Methods for assessing sleep and sleepiness in healthy adults and patients with respiratory sleep disorders

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Abstract

Scalp electroencephalography (scalp EEG) is an accurate method for measuring sleep. However, this procedure is cumbersome, costly, and cannot be conducted over an extended period. Recently, wearable pieces of equipment to monitor sleep have been developed, one of which is the in-ear EEG. Therefore, the first two aims of this thesis were to investigate whether a novel in-ear EEG could measure sleep accurately during daytime naps, and then during overnight sleep.

Clinically, excessive daytime sleepiness (EDS) is usually measured subjectively by use of the Epworth sleepiness scale (ESS). However, patients sometimes make errors and require assistance when they complete the ESS. A visual analogue scale (VAS) is a simple method that is used to measure subjective feelings such as pain, mood and breathlessness; we hypothesised that it could also measure sleepiness. Therefore, the third aim of this thesis was to investigate whether the VAS could be used as an accurate method to measure sleepiness in patients with respiratory sleep disorders, and in healthy adults.

In the first study, the in-ear EEG detected sleep onset and the results offered substantial agreement with the findings of scalp EEG, in healthy adults during daytime naps. In the second study, the in-ear EEG detected slow-wave sleep at a substantial level of agreement compared with scalp EEG, in healthy adults during overnight sleep. In the third study, the VAS detected sleepiness in healthy adults and patients with respiratory sleep disorders, before and after one month of continuous positive airway pressure (CPAP) treatment.

In summary, this thesis has shown that the in-ear EEG and VAS offer accurate and simple methods for the measurement of sleep and sleepiness, in both patients and healthy

participants. In future, it is speculated that these two methods could be integrated into smart phones to offer simple, fast and accurate measurement of sleep and sleepiness.

Table of Contents

Abstract 2

Declaration of Originality 8

Copyright Declaration 9

Acknowledgments 10

Publications arising from this thesis 11

Abstracts arising from this thesis 12

List of Figures 13

List of Tables 16

List of Appendices 17

Chapter 1: Introduction 18

1.1 What is sleep? 19

1.2 Neurological basis of sleep and wakefulness 19

1.2.1 Wake generating system 19

1.2.2 Sleep generating system 20

1.3 Methods used to measure sleep 21

1.3.1 Direct observation 22

1.3.2 Sleep diaries and questionnaires 22

1.3.3 Actigraphy 24

1.3.4 Electroencephalography 24

1.3.5 Other methods used to measure sleep 30

1.4 The in-ear EEG sensor 31

1.4.1 Motivations to build the in-ear EEG sensor 31

1.4.2 Developmental stages of the in-ear EEG sensor 34

1.4.3 Validation of the in-ear EEG sensor 38

1.5 Excessive daytime sleepiness (EDS) 42

1.5.1 Prevalence of EDS in the general population 42

1.5.2 Aetiology of excessive daytime sleepiness 43

1.5.3 EDS among OSA patients 44

1.5.4 The cause of EDS in patients with OSA 47

1.6 Methods to measure sleepiness 47

1.6.1 Epworth sleepiness scale (ESS) 47

1.6.2 Multiple sleep latency test (MSLT) 51

1.6.3 Maintenance of wakefulness test (MWT) 51
1.6.4 Oxford Sleep Resistance Test (OSLER) 52
1.7 Visual analogue scale (VAS) 52
1.8 Sleep deprivation 54
1.8.1 Definition of sleep deprivation 54
1.8.2 Acute versus chronic sleep restriction 55
1.8.3 Impact of sleep restriction on attention and memory 57
1.9 Aim of the thesis 58
Chapter 2: General Methods 59
2.1. Participants and hospital information 60
2.1. Ethical approval and conduct of research 60
2.2. Clinical assessment 61
2.3. Methods employed for the measurement of sleep 61
2.3.1. Nocturnal Oxygen saturation 61
2.3.2. Overnight home sleep study 64
2.4. Methods used for the measurement of sleepiness 68
2.4.1. Established subjective measure of sleepiness: Epworth sleepiness scale 68
2.4.2. Novel subjective measure of sleepiness: The visual analogue scale (VAS) 70
2.4.3. Objective measure of sleepiness: Multiple sleep latency test 71
2.6 In-ear EEG sensor 72
2.6.1 In-ear EEG construction 73
2.6.2 Electrical characteristics 75
2.7. Methods used for the measurement of cognitive function 76
2.7.1. Reaction time 76
2.7.2. Stroop test 77
2.8 Sleep restriction 79
2.9 Data collection 80
2.10 Data analysis 80
Chapter 3. A novel in-ear sensor to determine sleep latency during the Multiple Sleep Latency Test (MSLT) in healthy adults with and without sleep restriction 82
3.1 Introduction 83
3.2 Methods 85
3.2.1 Participants 85
3.2.2 Screening 85

3.2.3 Protocol 86
3.2.4 Measurement of functional outcomes of sleep restriction 88
3.2.5 Data analysis 89
3.2.6 Sample size and statistical analysis 89
3.3 Results 90
3.3.1 Comparison of EEG obtained in-ear versus that from the scalp 93
3.3.2 Changes in sleep latency, reaction time and cognitive function following sleep restriction 98
3.4 Discussion 99
3.4.1 Critique of the method 100
3.4.2 The in-ear EEG sensor 101
3.4.3 Significance of the findings 102
3.5 Conclusion 104
Chapter 4. The efficacy of an in-ear electroencephalogram sensor to measure non-rapid-eye-movement sleep in healthy adults overnight 105
4.1 Introduction 106
4.2 Methods 107
4.2.1 Participants 107
4.2.2 Screening 108
4.2.3 Protocol 108
4.2.4 Polysomnography 109
4.2.5 In-ear EEG sensor 110
4.2.6 Sleep scoring 111
4.2.7 Sample size and statistical analysis 112
4.3 Results 113
4.3.1 Comparison of the in-ear EEG findings with those from the scalp EEG 116
4.3.2 Intra-scorer reliability 122
4.4 Discussion 123
4.4.1 Critique of the method 123
4.4.2 Significance of the findings 124
4.5 Conclusion 126
Chapter 5: A Visual Analogue Scale for the assessment of sleepiness in patients who experience obstructive sleep apnoea and in healthy participants 127
5.1 Introduction 128
5.2 Methods 130

5.2.1 Participants 130
5.2.2 Measurements 133
5.2.3 Sample size calculation and statistical analysis 134
5.3 Results 134
5.3.1 Comparison between ESS and VAS results after one month 136
5.3.2 Comparison between ESS and VAS results 137
5.3.3 The ease of use and time taken to complete the ESS and VAS 142
5.4 Discussion 144
5.5 Conclusion 147
Chapter 6: Discussion and future direction 148
6.1. Summary of the aims 149
6.2. Summary of the main findings 149
6.2.1. The in-ear EEG sensor 149
6.2.1. The visual analogue scale 150
6.3. Limitations of the studies 151
6.3.1. Limitations of the in-ear EEG sensor 151
6.3.2. Limitations of the VAS 151
6.4. Future directions of the research 152
6.4.1. Hardware development of the in-ear EEG sensor 152
6.4.2. Software development for in-ear EEG 153
6.4.3. Digitisation of the visual analogue scale 154
6.4.4. Future research 154
6.5. Conclusion 155
References 157
Appendices 167
Appendix 1: Copyright of Figures 1.1 and 1.2. 167
Appendix 2: Copyright of Figure 1.6: 168
Appendix 3: Copyright for Chapter 3 169
Appendix 4: Ethical approval for Study 2 (Chapter 4): 170
Appendix 5: Ethical approval for Study 3 (Chapter 5) 171

Declaration of Originality

I declare that the contents of this thesis are my work except where otherwise acknowledged. The in-ear EEG sensor used for this work was made in collaboration with the Department of Electrical and Electronic Engineering at Imperial College London, Prof Danilo Mandic, Dr Valentin Goverdovsky, and Mr Takashi Nakamura. The studies described in this thesis were designed with the assistance of my supervisors Professor Mary Morrell, Prof Michael Polkey, and Dr James Moss. I conducted and collected data for all the studies presented in the thesis. I analysed all the data presented. Mr Aleksandar Dawidziuk also participated in the analysis of the VAS study as part of his summer research placement. No parts of this thesis have been submitted to any other institution to obtain a higher degree.

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T. Nakamura, T. Adjei, **Y. Alqurashi**, M. J. Morrell, and D. P. Mandic, (2017). 'Complexity science for sleep stage classification from EEG.' *Neural Networks (IJCNN)*, 2017, 4387-4394.

T. Nakamura, **Y. Alqurashi**, M. J. Morrell and D. Mandic, (2019). 'Hearables: Automatic overnight sleep monitoring with standardised in-ear EEG sensor.' *IEEE Transactions on Biomedical Engineering*, 22 April 2019. Available at: doi: 10.1109/TBME.2019.2911423. (ahead of print).

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List of Figures

Figure 1.1: Neurotransmitter systems that play the greatest role in the promotion of wakefulness. (Permission to reproduce image from Scammell et al., (2017))..... 20

Figure 1.2: Summary of the fast *n*eurotransmitter systems that contribute to sleep promotion. (Permission to reproduce image from Scammell *et al.,* 2017)..... 21

Figure 1.3: Timeline of milestones achieved during development of the usage of EEGs in sleep medicine. 27

Figure 1.4: Simplified illustration of extracellular currents (represented by current sinks and current sources), which originate due to post-synaptic activity in the dendrites of aligned pyramidal neurons. The generation of massive synchronised post-synaptic ac..... 28

Figure 1.5: The amount and duration of each sleep stage across the night (hypnogram). The boxes on the right of the diagram describe the EEG wave patterns that are associated with each sleep stage. 29

Figure 1.6: Changes in sleep stages across a lifespan. (Adapted with permission from Kryger *et al.,* 2005). 30

Figure 1.7: A participant wearing PSG equipment and an in-ear EEG sensor. Image from Study 2 (Chapter 4); participant consented to the inclusion of the image. 32

Figure 1.8: A customised in-ear EEG sensor that was used before the generic earpiece was developed. 35

Figure 1.9: In-ear EEG sensor used for the work described in this thesis. This figure shows the shape of the sensor (upper left); a 3D illustration of the sensor's fit inside the ear (upper right); the sensor attached to the wires that connect to the amplifier (lower left); and an actual fitting of the sensor in the ear (lower right). 37

Figure 1.10:The VAS used in the research described in this thesis to assess sleepiness 54

Figure 2.1: The picture (left) shows the pulse oximeter and its overnight configuration on a participant's wrist and finger. The waveform of oxygen saturation is shown (upper right) as is the pulse wave (lower right). The dips in saturation and associated increases in pulse rates highlighted in the black box suggest..... 63

Figure 2.3: The Epworth Sleepiness Scale used during the research conducted for this thesis. 69

Figure 2.4: Timeline of the developmental stages of the in-ear EEG sensors. 73

Figure 2.5: Variation of impedance of the in-ear EEG sensor over time (five hours) while worn by one person, from channel 1 (red) and channel 2 (black). Adapted from Goverdovsky *et al.,* 2016. 76

Figure 2.6: The OSLER device that was used to measure the reaction time test. 77

Figure 2.7: Example of the Stroop test. Depending on the task, participants are required to name either the colour in which the word is printed or the word itself. For example, in the conflicting word task, the participants should name the colour in which the word is printed, not the word itself. 79

Figure 3.1: MSLT protocol utilised in this study. Sleep duration in the prior night was estimated by asking the participants to log-in to a webpage every hour during the night and once when they woke up. Periods of naps during the sleep restriction visit are shown in orange, and periods of naps during the usual night sleep visit are shown in purple. RT=reaction time.....87

Figure 3.2: The in-ear EEG sensor. A person is shown wearing the scalp-EEG (C4) and in-ear EEG sensor with corresponding signals. The EEG shows a transition from alpha activity to theta activity during 10 seconds. GND=ground.....88

Figure 3.3: Consort flowchart. A) Consort diagram of the recruitment. B) Details of the naps excluded from the analysis: participant number, visits (1st or 2nd visit), sleep restriction (orange box) and usual night sleep (purple box) and nap numbers. Disconnection means that the electrodes did not record data due to technical problems.....92

Figure 3.4: Examples of signals from scalp EEG and in-ear EEG. A) Examples of in-ear EEG (black) and scalp EEG (blue) during 4 naps from one participant (26-year-old male) who did not remove the in-ear EEG sensor between naps. B) Examples of in-ear EEG (black) and scalp EEG (blue) during 4 naps from one participant (25-year-old male) who removed the in-ear EEG sensor between naps. Each EEG figure represents 30 second epoch. Note that the amplitude of the in-ear-EEG was less than that of the scalp EEG in figure 4A. However, inspection of the trends of power-spectral density showed that they were similar over all 23 participants, for both scalp and in- ear EEG channels. 95

Figure 3.5: Bland-Altman agreement for scalp EEG versus in-ear EEG. A) Bland-Altman agreement for individual naps (in-ear EEG minus scalp EEG), usual night sleep visit (left) and sleep restriction visit (right). Dashed lines show the confidence interval. B) Bland--Altman agreement for all naps combined (in-ear EEG minus scalp EEG), sleep restriction (orange) and usual night sleep (purple). Dashed orange lines show the confidence interval for sleep restriction while dashed purple lines show the confidence interval for usual night sleep. Note that several data points are overlapped.....97

Figure 3.6: Stroop test after sleep restriction and after usual night sleep. A) The number of mistakes in each task. The greatest number of mistakes was in the conflicting-word task after sleep restriction, and this change was significant compared with the results after usual night sleep. B) The mean time spent on each task (seconds). The time increased after sleep restriction in the conflicting colour, colour block, and monochrome set, but did not reach significance level. ** p =0.003. 99

Figure 4.1: A participant wearing the polysomnography equipment and in-ear EEG sensor during an overnight sleep study (left). An example of the in-ear EEG sensor inside the ear (right). 110

Figure 4.2: Example of EEG data during a 30-second epoch. A: An example of data that show slow-wave sleep from both the in-ear EEG sensor (red) and the corresponding scalp EEG sensors (blue). B: An example of data that show stage N2 sleep from the in-ear EEG sensor with the corresponding scalp EEG. Note that the amplitudes of the EEGs are different. 115

Figure 4.3: The 3*3 contingency table showing the comparison between the in-ear EEG and scalp EEG results. 116

Figure 4.4: The data for the seven epochs that were incorrectly scored from the in-ear EEG (red) and the corresponding scalp EEG (blue). A: five epochs incorrectly scored as SWS rather than wakefulness from four different participants. B: two epochs incorrectly scored as wakefulness rather than SWS from two different participants. Note that the alpha wave is overlapped with delta waves in the data obtained from the in-ear EEG sensor in both figures. This might be the cause of the incorrect scoring of the data obtained from the in-ear EEG sensor. 121

Figure 4.5: The 3*3 contingency table showing the comparison between the interpretations of the scalp EEG data before and after blinding (intra-scorer reliability). 122

Figure 5.1: The protocol followed for this study. ODI: oxygen desaturation index. 132

Figure 5.2: Consort diagram displaying method of recruitment and study of OSA patients and healthy participants. 135

Figure 5.3: Correlation between ESS and VAS results for patients with OSA (open circle) and healthy participants (closed circle) for Visit 1. B: Correlation between ESS and VAS results for patients with OSA (open circle) and healthy participants (closed circle) for Visit 2. Solid lines denote ESS score of 11, considered the minimum for excessive daytime sleepiness, and corresponding VAS result of 40 mm. 141

Figure 5.4A: Individual ESS and VAS results of OSA patients (n=31) collected at visits 1 and 2. 139

Figure 5.5: A: the mean changes in ESS in OSA patients (solid line) and healthy participants (dashed line). B: The mean VAS changes in OSA patients (solid line) and healthy participants (dashed line) before and after one month. 140

Figure 5.6: a screenshot of the online version of the VAS.....146

List of Tables

Table 1.1: Studies on the in-ear EEG sensor to date 39

Table 1.2: Methods employed to measure sleep and sleepiness 41

Table 1.3: Studies of the prevalence of obstructive sleep apnoea syndrome among the general population.....45

Table 1.4: Effects of acute and chronic sleep restriction on health and the brain. 56

Table 2.1: Signal sampling rates and filter settings for polysomnography 67

Table 3.1: Comparison between in-ear-EEG and scalp EEG in detection of sleep latency† 94

Table 4.1: The PSG values of overnight sleep parameters. 114

Table 5.1: Baseline characteristics of the participants, and the CPAP adherence statistics of patients treated for OSA.....136

Table 5.2: ESS and VAS scores of healthy participants (n=32) and OSA patients (n=31) 143

List of Appendices

Appendix 1: Copyright for Figures 1.1 and 1.2

Appendix 2: Copyright for Figure 1.6

Appendix 3: Copyright for Chapter 3

Appendix 4: Ethical approval for Study 2 (Chapter 4)

Appendix 5: Ethical approval for Study 3 (Chapter 5)

Chapter 1: Introduction

1.1 What is sleep?

Historically, sleep has been defined as 'an intermediate state between wakefulness and death' (McNish, 1834, p. 2). Sleep continued to be portrayed as a passive state until the discovery of electroencephalography (EEG). This can be used to record electroencephalograms (also known as EEG, or in this case EEGs) for analysis. Between 1875 and 1939, a series of studies demonstrated that sleep was characterised by slow-wave and high-amplitude neural activity, whereas wakefulness was characterised by beta and alpha-wave and low-amplitude EEGs. Since then, sleep has been regarded as an active process of slow, synchronised neural activity. It is a reversible state in which the sleeper's responsiveness is reduced, mobility is limited, and the ability to react to a stimulus is decreased. The reversibility distinguishes sleep from a coma, or even death (Kryger, Roth, & Dement, 2017).

1.2 Neurological basis of sleep and wakefulness

1.2.1 Wake generating system

Although the neurophysiological foundations of wakefulness and sleep are interrelated, there are some distinct differences. Wakefulness is regulated by the ascending reticular activating system (RAS), which originates in the brainstem. In the 1940s, Moruzzi and Magoun showed, using a cat model that the RAS was responsible for arousal from sleep (Moruzzi & Magoun, 1949). Following this seminal study, several other investigations demonstrated that arousal extended to the cortex via two main pathways, each of which utilised different neurotransmitters. The first was the dorsal pathway through the thalamus. The second was the ventral pathway through the lateral hypothalamus and basal forebrain (Moruzzi & Magoun, 1949; Schwartz & Roth, 2008). More recently, hypocretin (also called orexin) has been found to play a role in wakefulness. The cells that are responsive to orexin project to the

cortex to produce arousal (Eriksson, Sergeeva, Brown, & Haas, 2001). A summary of the wake-generation system is illustrated in Figure 1.1.

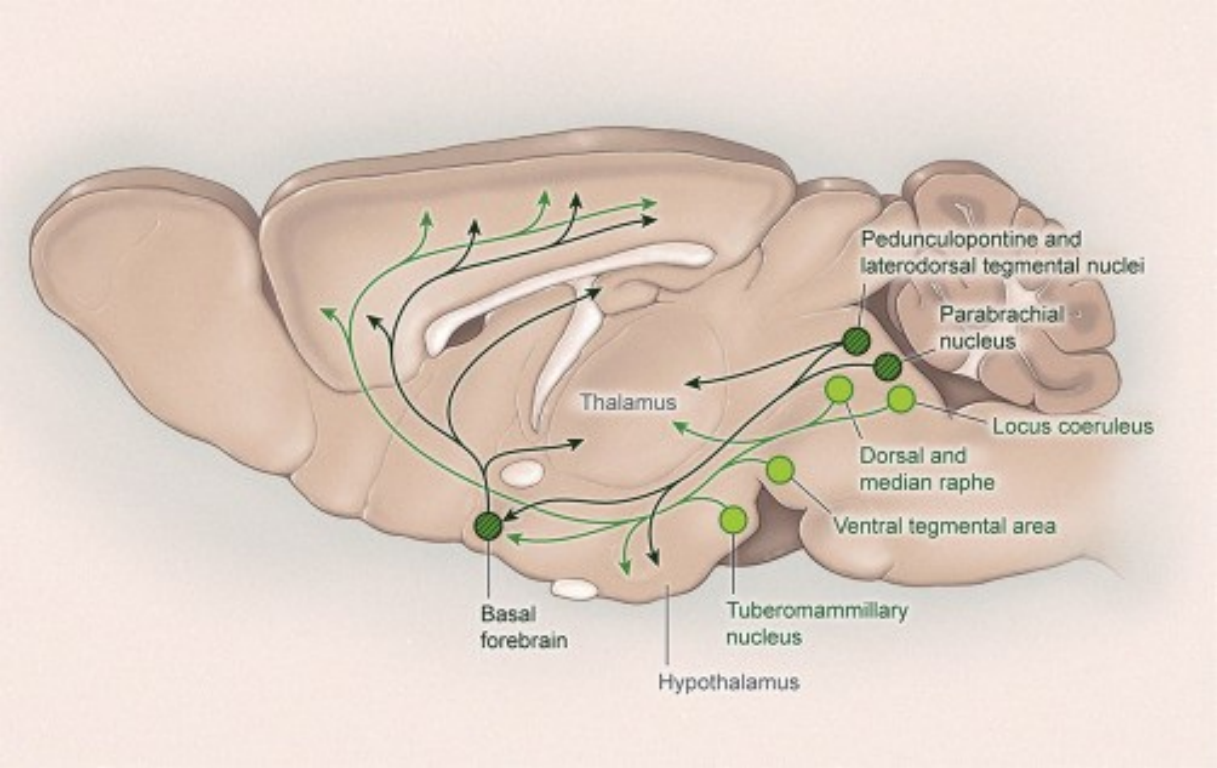


Figure 1.1: Neurotransmitter systems that play the greatest role in the promotion of wakefulness. (Permission to reproduce image from Scammell *et al.*, 2017)

1.2.2 Sleep generating system

Sleep is promoted actively by a group of neurons in the ventrolateral preoptic area (VLPO), anterior hypothalamus and basal forebrain. Neurons of the VLPO contain inhibitory gamma-aminobutyric acid (GABA) neurotransmitters. These neurotransmitters have been shown to play a major role in the inhibition of the wake-generating regions of the ascending RAS. This activation occurs only during sleep onset and the period of non-rapid eye movement (NREM). Another area within the hypothalamus, the median preoptic area (MnPO), has also been identified as active during sleep onset and NREM sleep (Suntsova, Szymusiak, Alam, Guzman-Marin, & McGinty, 2002). Therefore, sleep is initiated by GABAergic neuronal activity and by the inhibition of arousal neurons (Eriksson *et al*., 2001).

A summary of the sleep generation system is illustrated in Figure 1.2.

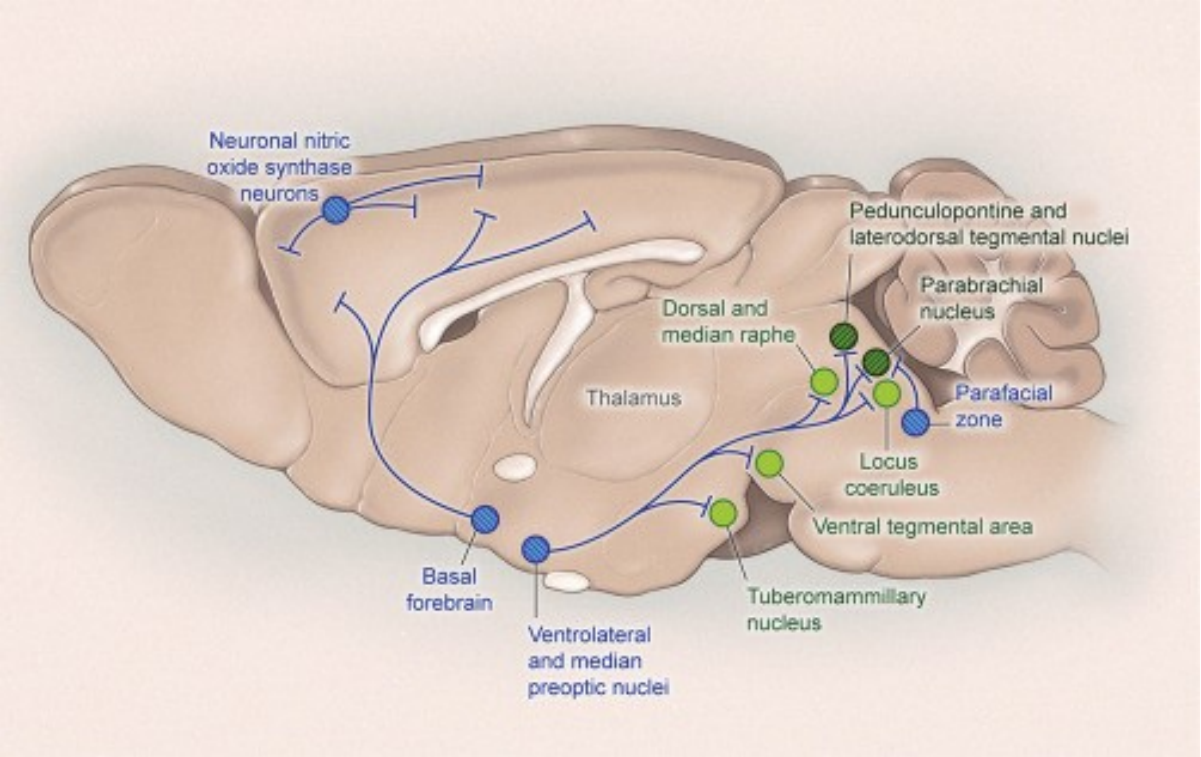


Figure 1.2: Summary of the fast neurotransmitter systems that contribute to sleep promotion. (Permission to reproduce image from Scammell *et al.,* 2017)

REM sleep is generated by different neurotransmitters. The REM-generating neural system was identified by transection studies of animals in the 1960s. As cited by Luppi (2017), Jouvet *et al*., (1962), found that the EEG signals of REM sleep were usually accompanied by muscle atonia. Subsequent localisation studies, conducted in humans, confirmed that the region between the caudal medulla and the rostral midbrain was essential for the generation of REM sleep (Luppi, 2017). Imaging studies of patients with brainstem lesions also demonstrated that the pons was important for the generation of REM sleep (Braun *et al*., 1997).

1.3 Methods used to measure sleep

This section presents the theoretical background of four methods that are widely used to measure sleep. Further details regarding ways in which each method specifically measures sleep are presented in General Methods (Chapter 2).

1.3.1 Direct observation

Sleep can be estimated based on direct observation of the number of hours that a person has been asleep. This is the traditional way to measure sleep among people from different cultures as it is simple and easy. However, when people ask: 'How many hours did you sleep last night?', they usually refer to the total period spent in bed, which is unlikely to be the same as the total period of sleep. It is important to distinguish total sleep time, from total bed time, as sleep efficiency relies on these terms (sleep efficiency = total bed time/total sleep time × 100). Some studies define sleep efficiency as the ratio of total 'recording' time to the total sleep time (recording refers to the device that records the sleep, whether polysomnography (PSG) or actigraphy) (Guimond & Lemelin, 2008). A meta-analysis by Baglioni *et al.,* (2014), found that only six out of 18 studies had explicitly defined the sleep efficiency calculation they had employed. This inconsistency in definition of sleep efficiency has a direct impact on diagnosis of sleep disorders, especially in insomnia where the term sleep efficiency is used frequently.

1.3.2 Sleep diaries and questionnaires

One of the methods most widely used in sleep research and clinical practice is the sleep diary. This is a self-report that records sleep hour-by-hour throughout the day and night. It contains information regarding time of going to bed, sleep onset, number of hours asleep, number of times the subject wakes, feelings before and after sleep, and the occurrence of any daytime naps. It has long been regarded as the gold standard for subjective sleep assessment (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006). Recently, a consensus sleep diary has been developed to minimise the variability between different sleep diaries used in different studies (Carney *et al*., 2012).

Several studies have assessed the sensitivity and specificity of the sleep diary and compared it with the best-regarded method, the PSG. Sensitivity has been found to range between 73% and 93% and specificity between 50% and 96%, depending on the type of sleep diary used (Ibáñez, Silva, & Cauli, 2018). Sleep diaries are available in paper and digital format. One study found that the results were similar when subjects used digital or paper sleep diaries, and the digital version was recommended as patients reported that it was easier to use than the paper version (Tonetti, Mingozzi, & Natale, 2016).

There are also many types of sleep questionnaire; some are generic and others are disease-specific (Fedson, Pack, & Gislason, 2012). Most studies of each sleep disorder now employ at least one preferred questionnaire (Kryger *et al.*, 2017). These questionnaires usually assess the quality of sleep rather than the quantity. One of the most commonly used is the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). It is a self-completed questionnaire that is used to evaluate overall sleep quality. It consists of seven subcategories: subjective sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbances; use of sleeping medications; and daytime dysfunction. The patient's bed partner is asked to respond to five additional questions for clinical purposes, but they are not scored. The sensitivity and specificity of the PSQI in the original study were reported as 90% and 86% respectively (Buysse *et al.,* 1989). A recent systematic review has indicated that the PSQI shows strong reliability in both patients and healthy people of between 70% and 83%, and it is recommended for use in clinical and non-clinical populations (Mollayeva *et al*., 2016).

1.3.3 Actigraphy

An actigraph is a watch-like device, typically worn on the wrist of the non-dominant hand, which measures hand movement, using accelerometer. The method assumes that lack of movement indicates sleep. It has been used in sleep research for more than two decades (Sadeh, Hauri, Kripke, & Lavie, 1995). Since the development of actigraphy in the early 1970s, many studies have assessed its validity. The American Academy of Sleep Medicine (AASM), the professional organisation responsible for setting diagnostic standards in sleep medicine in the United States (US), recommends the use of actigraphy as a valid tool to measure sleep-wake states (Smith *et al.,* 2018). However, because it is based on the assumption that lack of movement indicates sleep, it has been reported to be poor for the detection of wakefulness (specificity, 0.35), but excellent for the detection of sleep (sensitivity, 0.90) (Kushida *et al.*, 2001). Although actigraphy is very helpful to assess circadian–related sleep disorders, it cannot be used in isolation to diagnose other sleep disorders, such as sleep-related breathing disorders. In clinical practice, actigraphy is used as a first-line screening tool. If the actigraphy test suggests that a sleep disorder may be present, then this is usually followed by full-night PSG (Smith *et al*., 2018).

1.3.4 Electroencephalography

History of electroencephalography

Modern sleep research began in 1870, when two German researchers (Gustov Fritsch and Eduard Hitzig) found that the brain was responsive to an electrical current; they stimulated electrically the sensory motor cortex of a dog and produced a movement in the dog. Similar reports were published in 1875 by an English physician, Richard Caton, and in 1912 by Polish physiologist, Napoleon Cybulski. During this period, the term 'electrocerebrogram' was

coined to refer to the process of brain stimulation. In 1910, German physician Hens Berger developed a 'string galvanometers' device that exploited the principle of a magnetic coil. It set up a vibration when a current was passed through a quartz fibre. Berger attached a mirror to a string to obtain a record of the vibrations with time markers. When the device vibrated, a reflection of this vibration appeared on a strip of photographic paper that moved at a constant speed inside a light-tight chamber. Berger used this technology for almost 14 years until he recorded brain waves from a human in 1924. This was the first time brain waves had been recorded. Five years later, he published his first report: *On the Electroencephalogram of Man* (Berger, 1929). The delay of five years, from initial recording to subsequent publication, was attributed to Berger's need to confirm that the waves produced were not artefacts. Since this discovery, EEG recordings have been widely used in the non-invasive recording of brain waves (La Vaque, 1999).

EEGs were used in sleep research by Loomis, Harvey and Hobart (1937). Following extensive analysis of more than 600 hours of EEG recordings taken from 60 individuals, they reported the existence of a 'very definite state of sleep which changes suddenly from time to time'. They reported that these changes correlated with movements, dreams and external stimuli (Loomis, Harvey, & Hobart, 1937). In this work, they described five states of sleep: A, B, C, D, and E.

- A referred to 'alpha', which represented eight to 13 waves per second with slow eye rolling.
- B referred to 'low voltage', which represented straight brain-wave activity with no alpha.

- C referred to ‘spindles’, which showed 14 spindles per second of 20-40 microvolts (μV).
- D referred to ‘spindles plus random’, which showed a continuation of spindles plus large random waves of frequencies between 0.5 and 3.0 waves per second and amplitude of 300 μV.
- E referred to ‘random’, which represented 4.0 waves per second with no appearance of spindles.

This work was fundamental to all of the explanations that followed regarding the EEG frequencies observed in NREM sleep. In 1953, Aserinsky and Kleitman observed another state of sleep that was characterised by rapid, jerky eye movements associated with an increase in heart and respiratory rates; this became known as the REM stage (Aserinsky & Kleitman, 1953). In 1968, a group of sleep experts under the leadership of Allan Rechtschaffen and Anthony Kales met to develop a consensus regarding criteria to measure sleep stages and scoring in healthy humans and published a summary of these rules. This was the first sleep-scoring manual (Kales, 1968). Subsequently the AASM published a detailed manual of scoring of sleep stages, which included specifications of ways to score movements and breathing abnormalities (Iber & Iber, 2007). This was updated in 2012 (Berry, Budhiraja, *et al.,* 2012). Figure 1.3 illustrates a timeline that shows milestones achieved during the development of EEG and sleep medicine to date.

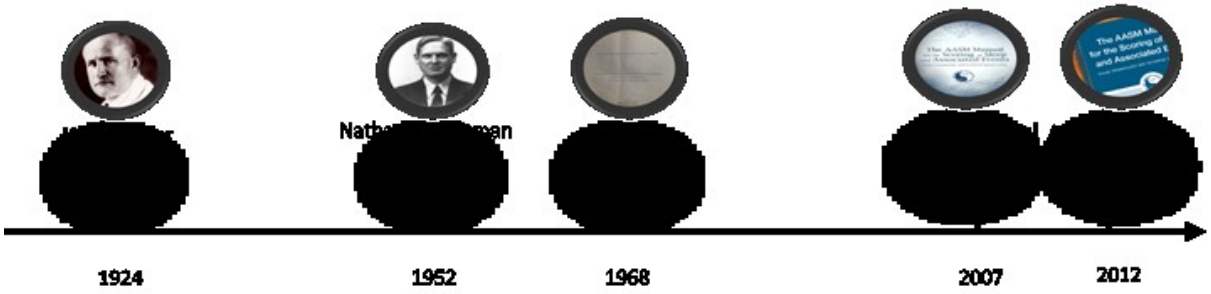


Figure 1.3: Timeline of milestones achieved during development of the usage of EEGs in sleep medicine.

How does EEG work?

The EEG is an electrophysiological method to record the electrical activity of the neurons in the human brain. Each neuron in the brain is connected to thousands of other neurons through chemical synapses. A synapse is formed between the axon of a neuron and a synaptic ending on a dendrite of another neuron. An action potential in the axon causes the pre-synaptic terminal to release neurotransmitters. During the excitatory post-synaptic potential (EPSP), there is an influx of positive ions into the cell, while the corresponding negative ions remain outside, and this makes the extracellular space negative. Conversely, during the inhibitory post-synaptic potential (IPSP), the cell becomes negative and the extracellular space becomes positive (Britton *et al.,* 2016). As this process occurs on thousands of neurons, it creates dipoles that can be measured through use of EEG (Figure 1.4).

An electroencephalogram is recorded through several electrodes that are placed on specific sites over the scalp, and these sites for detection of brain-wave activity are known as the 10-20 system (Jasper, 1958). Based on the frequency and amplitude of the recorded waves, different sleep stages can be identified. The current practice of sleep medicine and diagnosis of sleep disorders is based on EEGs (Pelayo & Dement, 2017).

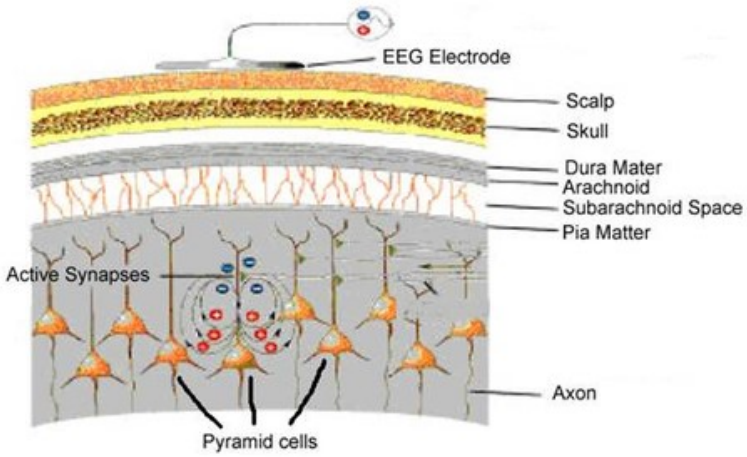


Figure 1.4: Simplified illustration of extracellular currents (represented by current sinks and current sources), which originate due to post-synaptic activity in the dendrites of aligned pyramidal neurons. The generation of massive synchronised post-synaptic activity causes electrical fields that are measurable on the scalp surface. Adapted from Abhang *et al.*, (2016).

EEGs and sleep stages

The first phase of sleep is normally NREM sleep, which is characterised on an EEG by low-voltage high-frequency waves and slow eye movement represented on an electrooculogram (EOG). REM sleep begins approximately 80 minutes after sleep onset. Periods of REM and NREM sleep alternate through the night in a cyclical fashion and every sleep cycle lasts for approximately 90 to 110 minutes (Figure 1.5).

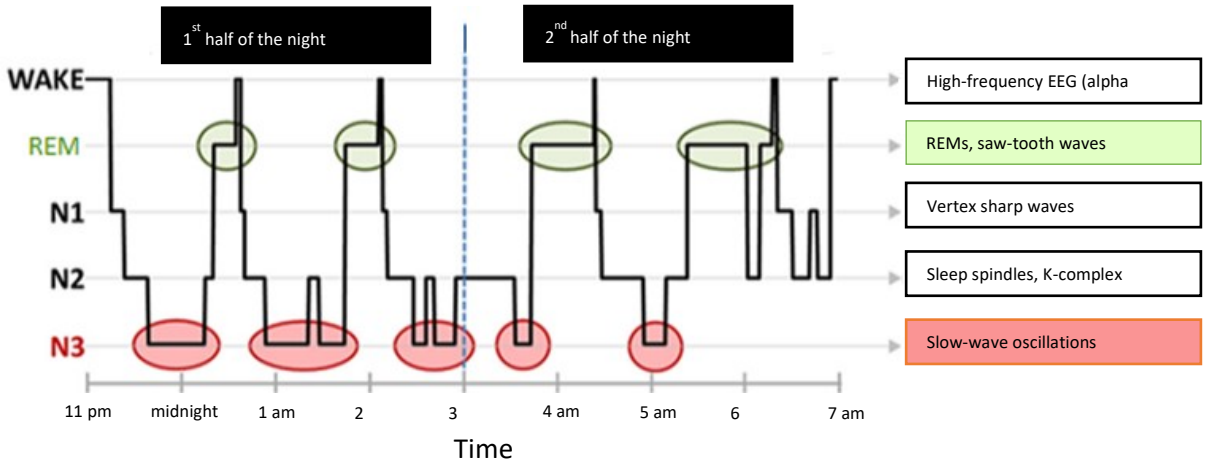


Figure 1.5: The amount and duration of each sleep stage across the night (hypnogram). The boxes on the right of the diagram describe the EEG wave patterns that are associated with each sleep stage.

NREM sleep consists of three stages, N1, N2, and N3. Each stage represents a particular depth of sleep (Kryger *et al.,* 2017). Stage 1 (N1) lasts for approximately one to seven minutes at the start of the night, and represents the transition from wakefulness to sleep. A key feature of this stage is a low threshold of arousal; the sleeper can be awakened easily during this stage, for example by the soft closure of a door. This is followed by Stage 2 (N2), which lasts for approximately 10 to 25 minutes. During this stage, K-complex and sleep spindles are shown on the EEG, and these form the main biological markers. Stage 2 accounts for approximately 50% of the total sleep time. Stage 3 represents the deepest stage of NREM sleep and lasts for approximately 20 to 40 minutes. Investigators usually refer to Stage 3 as slow-wave sleep or sometimes as deep sleep. NREM sleep predominantly occurs early in the sleep period, while REM sleep occurs later in the period. The preferential distribution of the NREM sleep towards the beginning of the night is thought to be a response to the prior length of wakefulness (Borbély, Baumann, Brandeis, Strauch, & Lehmann, 1981; Werth, Dijk, Achermann, & Borbély, 1996). The occurrence of REM sleep towards the end of the night is thought to be related to the body's circadian rhythm and a drop in the body temperature (Czeisler, Zimmerman,

Ronda, Moore-Ede, & Weitzman, 1980). The amount of NREM and REM sleep differs significantly according to the age of the subject (Kryger *et al.,* 2017) (Figure 1.6).

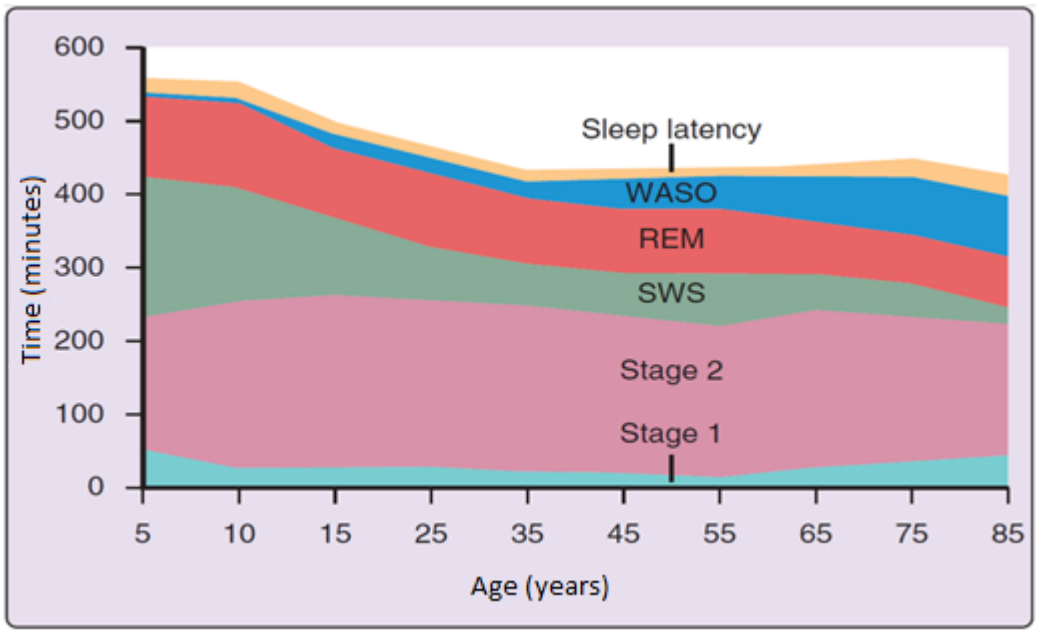


Figure 1.6: Changes in sleep stages across a lifespan. (Adapted with permission from Kryger *et al.,* 2005). WASO: wake after sleep onset, REM: rapid eye movement, SWS: slow wave sleep.

1.3.5 Other methods used to measure sleep

Sections 1.3.1 to 1.3.4 of this thesis present the methods that are commonly used in sleep research and practice to measure sleep. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are occasionally used in sleep research to measure sleep indirectly. Both methods are used in a few cases to identify the brain regions that become active during sleep. In contrast with EEG, which measures brain-wave activity from the cortex, fMRI and PET measure the blood flow of the deep-brain regions. This is an indirect measure of brain activity. These technologies advance our understanding of ways in which deep-brain regions interact during sleep. For example, it is now more clearly understood why patients with obstructive sleep apnoea (OSA) usually suffer from memory loss (Rosenzweig *et al.,*

2015, Emamian *et al.,* 2016). A recent study that used fMRI showed that patients with OSA exhibited greater β-amyloid deposition. This is thought to be linked with Alzheimer's disease (Osorio *et al*., 2015; Sharma *et al.*, 2018). This finding was possible through the use of fMRI technology. However, these methods are not used routinely to measure sleep directly in clinical applications.

Recent advances in the development of wearable technology have also facilitated the production of several devices that monitor sleep indirectly. These include wearable devices such as the Fitbit and the Apple Watch; sensors that are placed under the mattress; and non-contact sleep sensors which include mobile phone applications (apps). Each type of device uses a different algorithm to measure sleep. However, a critical review by Baron *et al*., (2018), showed that the majority of these devices overestimated sleep time and they performed poorly in the patient population.

In conclusion, the methods employed to measure sleep vary widely from simple subjective techniques, such as sleep diaries, to more complex and cumbersome, yet objective, methods, such as scalp EEGs. One of the aims of this thesis is to close the gap between these two methods in sleep research by the assessment of a method that combines the objectivity of the EEG with the wearability of other less accurate devices: the in-ear EEG sensor.

1.4 The in-ear EEG sensor

1.4.1 Motivations to build the in-ear EEG sensor

The in-ear EEG sensor was developed by Professor Mandic in the Department of Electrical and Electronic Engineering at Imperial College London, in collaboration with Professor Morrell from the National Heart and Lung Institute (NHLI). There were four reasons for building the in-ear EEG sensor:

1. The current conventional scalp EEG, as described above, is gained through complex and cumbersome equipment. The method requires ten wired electrodes to be placed on the scalp after measurements performed according to the 10/20 system (Jasper, 1958). To achieve a good-quality signal, the site on the scalp is usually cleansed of dead skin using an abrasive cream and the electrode is prepared with a conductive and adhesive gel so that the electrode can stay in place throughout the recording. The electrodes are then connected to an amplifier to amplify and record the signal (Figure 1.7). This process is cumbersome for both the technician and the patient.

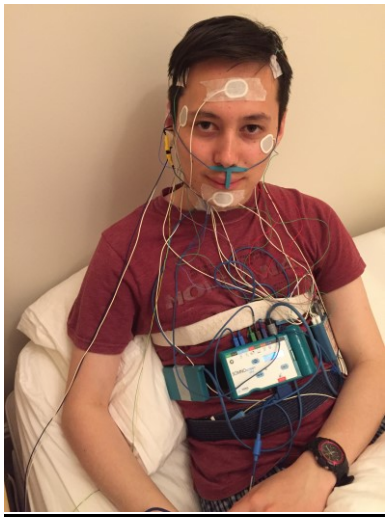


Figure 1.7: A participant wearing PSG equipment and an in-ear EEG sensor. Image from Study 2 (Chapter 4); participant consented to the inclusion of the image.

2. The application of the electrodes is time consuming; it can take up to one hour from the first measurement to the placement of the final electrode and the impedance check.
3. The application of scalp EEG sensors requires a controlled environment, so its use is limited to the collection of in-laboratory recordings or home recordings with close supervision to apply the electrodes. Some vulnerable populations such as older

people, or military personnel, truck drivers and those in high-risk occupations such as the security industry, require use of EEG measurement over the long term and in ambulatory and domiciliary environments (Goverdovsky *et al.,* 2017). Measurements of sleep can predict decreases in performance. For example, it is estimated that 20% of crashes that involve trucks are related to driver drowsiness (Burks *et al*., 2016).

4. It is important clinically to determine the total sleep time in order to diagnose sleep disorders. In the past decade many trials have been conducted to assess the efficacy of methods other than scalp EEG for the diagnosis of sleep disorders. These trials have used polygraphy and/or single-electrode recordings, such as pulse oximetry and heart-rate variability analysis (Berry, Hill, Thompson, & McLaurin, 2008; Kuna *et al.,* 2011; Ward *et al.,* 2012). These studies have resulted in some positive outcomes in certain situations, but problems still occur. For instance, polygraphy (a device that is frequently used to diagnose sleep apnoea which consists of a flow sensor, chest and abdominal bands, and oxygen saturation) can be used to diagnose sleep apnoea at a lower cost than through the performance of tests in the laboratory, but it cannot be used to define arousal from sleep due to an apnoeic event, because it lacks EEG electrodes. Overnight pulse oximetry can detect desaturation, and an apnoeic event can be predicted; however, arousal from sleep cannot be measured. Ward *et al*., (2012), assessed the utility of pulse oximetry and heart-rate variability techniques to rule out sleep-disordered breathing in patients with congestive heart failure. They found that the heart-rate variability test failed to detect arousal from sleep, whereas the PSG test detected it (Ward *et al.,* 2012). This can affect the diagnosis and treatment options offered to these patients.

1.4.2 Developmental stages of the in-ear EEG sensor

The in-ear EEG system uses breakthrough technology to enable continuous measurement of the signals through a wearable sensor. To develop such a system, which can overcome the issues of the conventional scalp EEG described above, the in-ear EEG sensor must meet several criteria: the quality of the recording must be good; the sensor must be convenient for a patient to use; it must offer privacy; it must not be obtrusive; and it needs to be cost-effective. Looney *et al*., (2012), suggest that a fully wearable EEG system must exhibit the following characteristics:

- *Discreet:* meaning that the system should not be clearly visible.
- *Unobtrusive*: meaning that the system should be comfortable to wear and hinder the user as little as possible. This feature is relevant to this thesis in that the in-ear EEG sensor should not alter sleep habits so that an accurate diagnosis can be made.
- *Robust:* meaning that the system should be embedded into a device that ensures the electrodes do not dislodge easily from the ear.
- *User-friendly*: meaning that users should be able to insert the device themselves without the assistance of a trained person.
- *Feasible:* meaning that the implementation of the system should be realistic so that it can retain maximum quality of the recording and use a small number of channels, taking into consideration the cost-effectiveness and quality of the recording.

To meet these requirements, the in-ear EEG system underwent two stages of development:

- ***Production of a customised earpiece:*** This prototype was based on a hearing-aid model, which was based on a wax impression of the participant's concha and outer-ear canal. This model was produced using three-dimensional (3D) printers. The

earpiece employed three electrodes made from silver wires and was placed in the right or left ear according to the participant's preference (Mikkelsen, Kappel, Mandic, & Kidmose, 2015) (Figure 1.8).

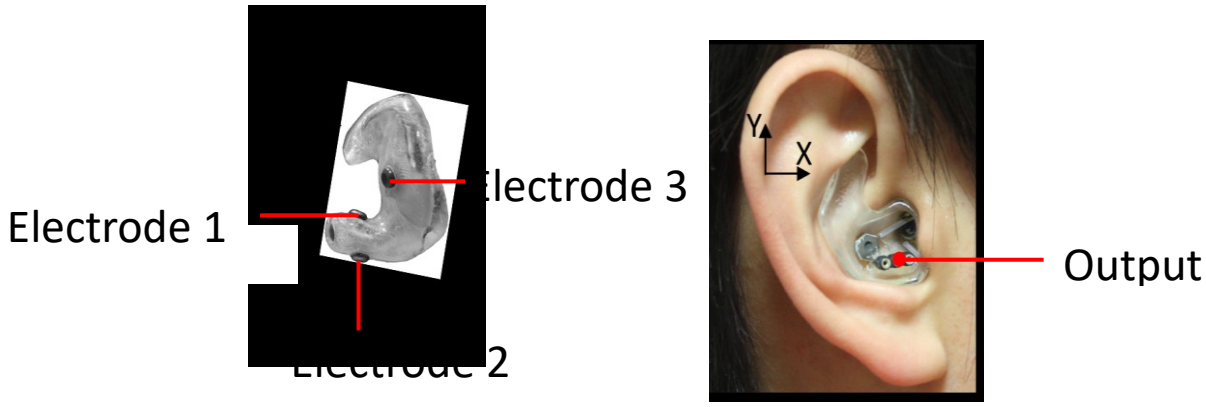


Figure 1.8: A customised in-ear EEG sensor that was used before the generic earpiece was developed.

- ***Generic earpiece:*** After some experiments (Kidmose, Looney, Ungstrup, Rank, & Mandic, 2013; Looney *et al.*, 2012; Looney *et al.*, 2011), it was found that production of the customised earpiece could not be scaled up due to frequent difficulties of fitting and cost. To address these issues, a generic earpiece was developed (Figure 1.9). All studies conducted during this PhD used this model.

Full details of the in-ear EEG sensor are explained in the general method section (Chapter 2). In brief, electrodes are embedded in an earpiece made of viscoelastic material. Two key components have been incorporated to make this sensor easy to use and cost-effective. These two features are the memory-foam and cloth-conductive electrode. The memory-foam is critical to fit the sensor inside the ear in a secure and safe manner. The device needs to be squeezed from all sides to make the insertion into the ear easy and painless. Then, the sensor distributes and expands evenly following insertion. The memory-foam material enables the sensor to absorb the motion and accordingly minimise movement artefacts that are usually seen during recordings for scalp EEG. The conductive cloth is flexible and soft for comfort. A

small amount of gel is required to achieve low impedance. All of the in-ear EEG sensors were made by the Department of Electrical and Electronic Engineering at Imperial College. (Goverdovsky, Looney, Kidmose, & Mandic, 2016).

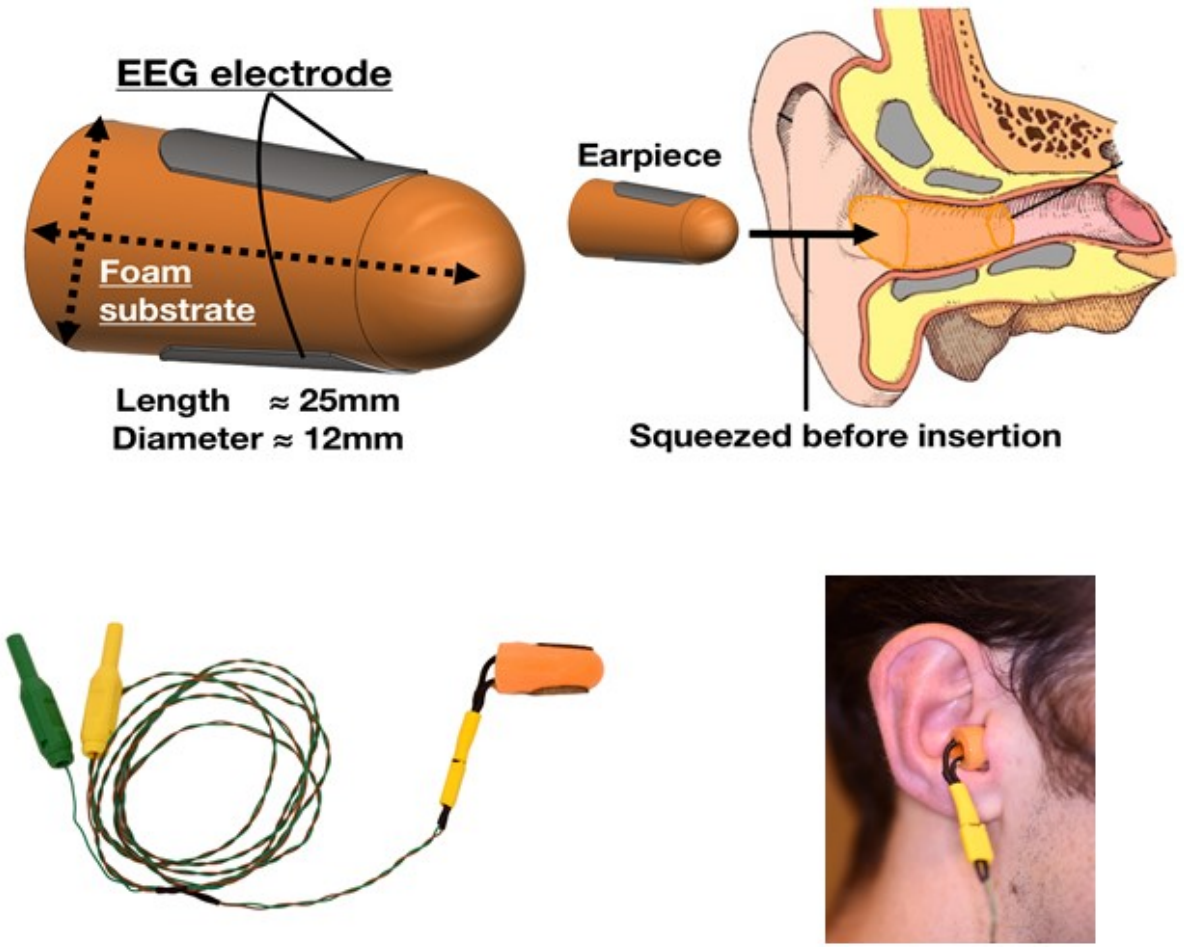


Figure 1.9: In-ear EEG sensor used for the studies described in this thesis. This figure shows the shape of the sensor (upper left); a 3D illustration of the sensor's fit inside the ear (upper right); the sensor attached to the wires that connect to the amplifier (lower left); and an actual fitting of the sensor in the ear (lower right).

1.4.3 Validation of the in-ear EEG sensor

The first validation study of the in-ear EEG method was published in 2011 (Looney *et al.,* 2011). This small study showed that the in-ear sensor could detect the alpha attenuation, which was defined as the suppression of the alpha wave (8-11 Hz) when the participants in the study opened their eyes. The alpha attenuation is a well-known response in an EEG system and is often exploited to test EEG recording equipment (Alloway, Ogilvie, & Shapiro, 1997). After this proof of concept study, Kidmose *et al*., (2013), published a second validation paper, which tested the auditory evoked potential (AEP). AEP is a modulated pattern observed in EEG signals that is usually produced when the participant presents with an auditory stimulus (Burkard, Eggermont, & Don, 2007). This study demonstrated that the in-ear EEG sensor could provide similar signal-to-noise ratios to those produced by conventional scalp EEG. This was the foundation study for the use of the in-ear EEG sensor in practical applications (Kidmose *et al*., 2013). After these two validation studies, a preliminary study was conducted during a daytime nap (Looney, Goverdovsky, Rosenzweig, Morrell, & Mandic, 2016).

Chapter 3 of this thesis presents results of a nap study conducted on 25 healthy participants before and after sleep restriction (Alqurashi *et al.,* 2018). Chapter 4 presents results of the first overnight sleep study conducted using this in-ear EEG sensor. Table 1.1 summarises the studies on the in-ear EEG sensor published to date.

Table 1.1: Studies on the in-ear EEG sensor to date

Study title	Authors and year	Purpose of study	Sample size	Methodology	Key findings
An In-The-Ear Platform for Recording Electroencephalogram. (case study)	Looney *et al*., (2011)	To discover the feasibility of the in-ear EEG concept compared with conventional scalp EEG electrodes.	One healthy participant.	Participants were instructed to keep their eyes open, until instructed by an auditory stimulus to close their eyes after 15 seconds.	Use of the in-ear EEG sensor leads to extraction of alpha attenuation and has shown excellent correlation with scalp EEG.
Auditory Evoked Responses from Ear-EEG Recordings. (case study)	Kidmose *et al*., (2013)	To observe whether auditory evoked potential (AEP) can be detected by the in-ear EEG sensor.	One healthy participant.	A sound stimulus was presented binaurally to the participant using headphones.	The in-ear EEG sensor detects the AEP. The evoked responses from the in-ear EEG sensor are lower in amplitude compared with the scalp EEG.
Wearable In-Ear Encephalography Sensor for Monitoring Sleep. Preliminary Observations from Nap Studies.	Looney *et al.*, (2016)	To determine the agreement between the in-ear EEG and scalp EEG sensors when used to detect wakefulness, light and deep sleep.	Four healthy participants.	Participants were instructed to sleep for 90 minutes during the afternoon with simultaneous recording of EEG through scalp and in-ear sensors.	Use of the in-ear sensor enables wakefulness and deep sleep to be distinguished at moderate to substantial levels compared with the scalp EEG sensor.

A Novel In-Ear Sensor to Determine Sleep Latency During the Multiple Sleep Latency Test (MSLT) in Healthy Adults With and Without Sleep Restriction.	Alqurashi *et al*., (2018)	To compare the sensitivities of the in-ear EEG sensor and the scalp EEG sensors to detect sleep latency during MSLT, before and after sleep restriction.	25 healthy participants.	Two MSLTs with simultaneous recording of the scalp and in-ear EEG results. Each test followed a randomly assigned period of sleep restriction or usual sleep.	Use of the in-ear sensor enabled detection of reduced sleep latency following sleep restriction that was sufficient to impair both the reaction time and cognitive function.

In the previous sections, the background of the methods used to measure sleep was explained. These methods were employed in two studies described in this thesis (Chapters 3 and 4). It has long been documented that sleepiness, which is a common symptom of sleep disorders, is difficult to measure. The next sections describe excessive daytime sleepiness (EDS) and its prevalence among the general population and patients with OSA. The theoretical background of methods used to measure sleepiness is also covered in detail, as they relate to the third study explained in this thesis (Chapter 5). This third study investigates the utility of a new method for measuring sleepiness in patients with OSA and in healthy participants. This method is the visual analogue scale (Table 1.2).

Table 1.2: Methods employed to measure sleep and sleepiness

<table>
<tr><th></th><th colspan="2">Established methods</th><th>New methods</th></tr>
<tr><td rowspan="4">Sleep</td><td rowspan="2">Subjective methods</td><td>Questionnaires</td><td rowspan="4">In-ear EEG</td></tr>
<tr><td>Direct observation</td></tr>
<tr><td rowspan="2">Objective methods</td><td>Actigraphy</td></tr>
<tr><td>Scalp EEG</td></tr>
<tr><td rowspan="4">Sleepiness</td><td>Subjective methods</td><td>Questionnaires</td><td rowspan="4">Visual analogue scale of sleepiness</td></tr>
<tr><td rowspan="3">Objective methods</td><td>Multiple sleep latency test</td></tr>
<tr><td>Maintenance of wakefulness test</td></tr>
<tr><td>Oxford sleep resistance test</td></tr>
</table>

1.5 Excessive daytime sleepiness (EDS)

1.5.1 Prevalence of EDS in the general population

EDS can be defined as a tendency to fall asleep during periods of anticipated wakefulness. EDS usually occurs during inappropriate situations while subjects undertake tasks for which they lack motivation. These can include reading, participation in a meeting or driving a vehicle (Ioachimescu & Collop, 2012). The prevalence of EDS among the general population is hard to estimate due to the subjectivity of this condition and the absence of an accurate, objective measure of sleepiness. Hence the prevalence of EDS has been estimated in the general population through either self-report questionnaires or subjective measures such as the Epworth Sleepiness Scale (ESS) (Johns, 1991). This scale assesses sleepiness by asking subjects to rate their likelihood of falling asleep in different situations. The scale ranges between zero (no daytime sleepiness) and 24 (severe daytime sleepiness).

Ford *et al*. (2015), estimated the prevalence of EDS to be 12.7% among the general population based on this question: 'During the past 12 months, have you regularly had excessive sleepiness during the day?' (Ford, Cunningham, Giles, & Croft, 2015). The American Sleep Foundation (ASF) has estimated the prevalence of EDS to be 18% based on the ESS (Swanson *et al.*, 2011). Another study found that the prevalence of EDS in the Japanese population was 2.5%. This was based on answers to the question 'Do you fall asleep when you must not sleep (for example when you are driving a car?)' (Kaneita *et al*., 2005). A recent Canadian study found that the prevalence of EDS in the general population of that country was estimated to be 33% based on the ESS (Jaussent, Morin, Ivers, & Dauvilliers, 2017). Taken together, these studies show that there is considerable variation in estimates of the prevalence of daytime sleepiness. This variation is due to the use of different subjective measures to assess this

symptom, inconsistencies in study design and sample size, and cultural and geographical factors; it is possible that different populations perceive the symptoms of sleepiness in different ways. However, there are other factors that make sleepiness a challenge to measure. These include but are not limited to age of the subject, time of the day when assessing sleepiness, total sleep time during the previous night, confusion between what is fatigue and what is sleepiness, sleep disorders that cause sleepiness, drugs, and diet. These issues illustrate ways in which estimates of sleepiness can be influenced by the measurement techniques that are used.

1.5.2 Aetiology of excessive daytime sleepiness

Lifestyle

In a 24/7 society, many factors prevent people from going to bed early. These include shopping hours, long commutes, and caffeine-rich drinks and foods (Czeisler, 2013). Excessive use of mobile phones, social media, and TV streaming systems are also new contributors to EDS. Indeed, 32% of Netflix viewers have been reported to have poor sleep quality, sleep fragmentation and EDS (Sexton-Radek, 2018). The Chief Executive Officer of Netflix once said that sleep was the company's number one competitor, and that the company was winning (The Guardian, 2017). The feeling of mild sleepiness usually disappears once people are motivated or engaged in a task. However, severe sleepiness can be overwhelming. The consequences of EDS are discussed in the introduction of study 1 (Chapter 3).

Clinical disorders

Clinical disorders such as periodic limb movement (PLM), narcolepsy, and OSA can cause EDS. Some patients with OSA experience daytime sleepiness, although some do not. Details regarding EDS and OSA are explained below.

1.5.3 EDS among OSA patients

OSA is a common sleep disorder characterised by repetitive occlusion of the upper airway during sleep. When OSA coexists with EDS, it is called obstructive sleep apnoea syndrome (OSAS). The prevalence of OSAS reported in the literature varies significantly depending on variables such as population studied, the methods used, the severity of OSA, age and gender. A study performed on a sleep cohort in Wisconsin, US, estimated that EDS among OSA patients occurred in 4% of male cases and 2% of female cases (Young *et al*., 1993). At around the same time in the United Kingdom (UK), Davies *et al*., (1996), estimated the prevalence of OSAS to be 1% to 5% among adult men (Davies & Stradling, 1996). Later, Peppard *et al*., (2013) reconsidered the study of the Wisconsin sleep cohort and found that 14% of men and 5% of women had OSAS (Peppard *et al*., 2013). However, recent estimates predict that 42% of patients with OSA have EDS (Ye *et al*., 2014). The increase in the prevalence of OSAS over time may be related to the increase in the prevalence of obesity, as this is a risk factor for OSAS. Table 1.3 below summarises some of the studies performed since 1993 that have estimated the prevalence of OSAS.

Table 1.3: Studies of the prevalence of obstructive sleep apnoea syndrome among the general population

Study region (Author, Year)	**Sample size (n)**	**Age (Years)**	**AHI ≥ Five events/hour**	**AHI ≥15 events/hour**	**OSAS**	**Methodology**
Wisconsin, US (Young *et al.,* 1993)	M: 352 W: 250	30-60	M: 24% W: 9%	M: 9% W: 4%	M: 4% W: 2%	Supervised PSG
Australia (Bearpark *et al.,* 1995)	M: 294	40-65	NA	M: 10%	M: 3.1%	Home nasal flow and oximetry
Pennsylvania, US (Bixler, 1998; Bixler, 2001)	M: 741 W: 1000	20-100	M: 17% W: 5%	M: 7% W: 2%	M: 3.3% W: 1.2%	Supervised PSG
Spain (Duran *et al.,* 2001)	M: 325 W: 235	30-70	M: 26% W: 28%	M: 14% W: 7%	M: 3.4% W: 3.0%	Supervised PSG
Hong Kong, China (Ip *et al.,* 2001; Ip *et al.,* 2004)	M: 154 W: 106	30-60	M: 8.8% W: 3.7%	M: 5.3% W: 1.2%	M: 4.1% W: 2.1%	Supervised PSG
Korea (Kim *et al.*, 2004)	M: 309 W: 148	40-69	M: 27% W: 16%	M: 10.1% W: 4.7%	M: 4.5% W: 3.2%	Supervised or home PSG
India (Udwadia *et al.,* 2004)	M: 250	30-60	M: 19.5%	M: 8.4%	M: 7.5%	Home PSG
India (Sharma *et al.,* 2006)	M:88 W:63	30-60	M: 19.7% W: 7.4%	NA	M: 4.9% W: 2.1%	Supervised PSG

Brazil (Tufik *et al.,* 2010)	M:466 W:576	20-80	M: 21.7% W: 20.9%	M: 24.8% W: 9.6%	M: 40.6% W:26.1%	Supervised PSG
Australia (Simpson *et al.,* 2012)	M:381 W: 412	38-70	NA	M: 12.4% W :5.7%	NA	Nasal flow and oximetry
US (Peppard *et al.,* 2013)	1520	30-70	M: 84% W: 43%	M: 28% W: 13%	M: 33% W: 11%	Supervised PSG
Iceland (Ye *et al*., 2014)	M: 666 W: 156	44-64	NA	44%	42%	Nasal flow and oximetry
Switzerland (Heinzer *et al.,* 2016)	M: 1024 W: 1097	49-68	M: 40% W: 42%	M: 32% W: 25%	M: 14% W: 10%	Home PSG
Saudi Arabia (Wali *et al.,* 2017)	M: 1303 W: 1379	30-60	M: 12.8% W: 5.1%	NA	M: 4.0% W: 1.8%	In-lab or home PSG (patient preference)
US (Huang *et al.*, 2018)	M: 22,896 W: 143,326	48-93	11%	58%	47%	Self-reported answers to the question: 'Have you ever been diagnosed with sleep apnoea by a sleep study?'

AHI: apnoea-hypopnea index.

1.5.4 The cause of EDS in patients with OSA

Two theories have been proposed to explain the causes of EDS in patients with OSA: the number of nocturnal arousals and intermittent hypoxaemia. These two theories have been tested against the cognitive dysfunction usually seen in these patients. Some studies show that the number and type of nocturnal arousals play essential roles in subsequent EDS exhibited by patients with OSA (Stepanski, Lamphere, Badia, Zorick, & Roth, 1984). The OSA in turn leads to cognitive dysfunction. If this is the case, the cognitive impairment should disappear after a short-term (one month) treatment (Rosenzweig *et al.*, 2016). However, some evidence seems to support the theory that intermittent hypoxaemia is a cause of EDS and leads to long-term changes in the brain (Koch *et al.,* 2017; Xu *et al.,* 2004). Recently, Garbarino *et al*., (2018), argued that both hypoxaemia and nocturnal arousal were substantial causes of EDS. However, there remains a debate about which of these theories, if any, explains EDS in patients with OSA (Bucks, Olaithe, Rosenzweig, & Morrell, 2017).

1.6 Methods to measure sleepiness

The previous sections have outlined the findings that EDS is a common symptom in both the general and the patient populations, leading to various conditions. However, this relationship is usually confounded by the lack of an accurate and simple method to measure sleepiness. The methods available to measure sleepiness are now presented. This is followed by an introduction to a new measure, the visual analogue scale (VAS) for sleepiness, and discussion of ways in which this might be used in the assessment of sleepiness.

1.6.1 Epworth sleepiness scale (ESS)

Several questionnaires have been used to measure sleepiness, such as the Karolinska sleepiness scale (KSS) (Åkerstedt & Gillberg, 1990) or the Stanford sleepiness scale (SSS)

(Hoddes, Zarcone, & Dement, 1972). However, the most frequently used scale is the ESS (Johns, 1991). It has been used extensively in many countries and translated into many languages (Ahmed *et al.,* 2014; Banhiran, Assanasen, Nopmaneejumruslers, & Metheetrairut, 2011; Beiske, Kjelsberg, Ruud, & Stavem, 2009; Bertolazi *et al.,* 2009; Bloch, Schoch, Zhang, & Russi, 1999; Chen *et al.,* 2002; Cho *et al.*, 2011; Izci *et al.,* 2008; Kopitovic *et al.,* 2011; Pecotic, Dodig, Valic, Ivkovic, & Dogas, 2012; Rosales-Mayor, De Castro, Huayanay, & Zagaceta, 2012; Tsara, Serasli, Amfilochiou, Constantinidis, & Christaki, 2004; Vignatelli *et al.,* 2003). The ESS assesses sleepiness by asking participants to rate their likelihood of falling asleep in different situations. The scale ranges between zero and 24, with zero indicating no daytime sleepiness and 24 indicating severe daytime sleepiness.

Conceptual basis of the ESS

When Johns (1991) developed the ESS he stated that the level of sleepiness depended not only on the time of the day, or how long the subject had been awake, but also on other variables including position, location, and environment. He called these variables 'sleep-induced characteristics' (Johns, 1994). He suggested that 'sleep propensity can be measured only within the context of the subject's situation and activity, both physical and mental, at the time', and that the sense of sleepiness felt by a person in the same situation/posture repeatedly could be a situation-specific sleep propensity. Later, he reported that these situations or postures showed reliability in test-retest trials over periods of five months and could be scored independently by a spouse or a bed partner (Johns, 2002).

Therefore, the measures noted to calculate the ESS were developed with consideration of some of the activities or non-activities that were frequently experienced by most people during their daily routines, though not necessarily on a daily basis (Johns, 1991).

Validity and reliability of the ESS

The validity of the ESS was first established in comparison with the multiple sleep latency test (MSLT) performed on 30 healthy people and 150 patients who exhibited several sleep disorders, aged between 18 and 78 years (Johns, 1991). This study showed that the ESS scores of individuals were significantly related to their mean sleep latency in the MSLT (*r=0.4, p=0.01*), and the ESS score significantly distinguished the healthy participants from patients with sleep disorders. Later, Johns reported the internal consistency of the ESS measures and test-retest reliability when the ESS was calculated for each of 87 medical students, and for 150 patients who exhibited various sleep disorders. He showed that the internal consistency was 0.88 for the patients and 0.72 for the students. The reliability of the ESS calculations for the medical students before and after five months was 0.82, and the ESS scores returned to normal after three to nine months of treatment of patients with sleep disorders (Johns, 1992). This study was the foundation of the recognised validity and reliability of the ESS, and it was followed by numerous studies that reported similar estimates (Lapin, Bena, Walia, & Moul, 2018).

Concerns regarding the ESS

Several studies that have examined issues associated with the ESS have revealed four factors that challenge the reliability of the ESS.

1. *The contextual factors used in the ESS may not be reflected accurately in the total ESS score.* These include position of the subject during completion of the ESS, location, and level of interest. They are used redundantly in the ESS such as in item #1 (sitting and reading) and item #3 (sitting inactive in a public place). This

redundancy can inflate the overall score of the ESS in sleepy patients because they are counted twice (Kendzerska, Smith, Brignardello-Petersen, Leung, & Tomlinson, 2014).

2. *Some items are not well defined to the extent that the responder can make their own interpretation.* For example, item #8 (in a car, while stopped for a few minutes in traffic) and item #3 (watching TV). Regarding item #8, patients often ask whether they are to consider themselves as a passenger or as the driver. This can lead to increased variability of scores between patients with different levels of sleepiness.
3. *The literacy level of the ESS is high, so some patients have difficulty completing it without help.* Ghiassi *et al*., (2011), have shown that one-third of new patients and one-sixth of ESS-naive patients who experience OSA make errors or require assistance when they complete the questionnaire. Examples of errors include leaving a question blank, or writing 'yes' or 'no' instead of giving an item a score (Ghiassi, Murphy, Cummin, & Partridge, 2011).
4. *Some items of the ESS are not universal for all countries and languages.* Bindi *et al*., (2016), investigated the challenges of translating the ESS into various languages and found that item #7 in the ESS, 'sitting quietly after a lunch without alcohol' was ambiguous either syntactically, semantically or culturally in 66 languages (Bindi, Bayles, Acquadro, & Johns, 2016). Collectively, these studies show that the ESS is not precise in the measurement of sleepiness.

1.6.2 Multiple sleep latency test (MSLT)

The MSLT was designed to provide information regarding sleepiness and the presence of abnormal REM-onset sleep (Carskadon, 1986). It is an in-laboratory procedure that consists of at least four nap opportunities with two-hour intervals between each nap. EEG electrodes are placed on the scalp, and participants are requested to close their eyes and try to fall asleep. Sleepiness is measured by the speed at which a person falls asleep during each nap opportunity, as measured by the EEG. If no sleep is detected, the test is terminated after 20 minutes (Carskadon *et al.,* 1986).

When first described by Carskadon (1986), the MSLT was designed as a test for pathological sleepiness in patients who experienced narcolepsy. However, the MSLT was later adopted as the gold-standard objective measure of sleepiness in all patients with sleep disorders who experienced sleepiness (Littner *et al*., 2005), and then it became a measure for sleepiness in research protocols (Arand *et al*., 2005).

Previous research has criticised the MSLT as cumbersome and expensive to conduct, and time-consuming. Researchers argue that it falls short of gold standard (Arand *et al.,* 2005; Johns, 2000). In addition, the MSLT has also been criticised for its floor effect which renders it useless for very sleepy individuals (Arand *et al*., 2005).

1.6.3 Maintenance of wakefulness test (MWT)

The MWT is a measure of wakefulness that was established as an alternative to the MSLT to remove the difficulties of the MSLT floor effect. In contrast with the MSLT, the MWT was developed to test levels of alertness (Littner *et al.*, 2005). It requires the participant to stay in a chair in a dimly lit and quiet room, sit still and remain awake for as long as possible.

Whereas the MSLT demonstrates a floor effect in subjects who exhibit severe sleepiness, MWT results show evidence of a 'ceiling effect' in subjects with normal levels of wakefulness, as many subjects remain awake throughout each trial (Littner *et al.,* 2005).

1.6.4 Oxford Sleep Resistance Test (OSLER)

As discussed in previous sections, the collection of objective measurements of sleepiness is time-consuming, expensive, and uncomfortable. These issues have led to the development of new technologies that aim to overcome these disadvantages. One of these is the OSLER, which is a behavioural test that detects a subject's ability to maintain wakefulness and measures daytime vigilance. It takes the form of a device, which was invented in 1992 by a group of researchers and engineers in Oxford, UK. The aim of its production was to offer an alternative to the MWT. When its performance was compared with that of the MWT in healthy people, the OSLER showed a sensitivity of 100% and specificity of 87.5% (Bennett, Stradling, & Davies, 1997).

1.7 Visual analogue scale (VAS)

The VAS is a simple method to measure subjective feelings. The scale consists of a 100 mm horizontal line on which respondents are asked to mark their perceptions of their symptoms between two anchors. These two anchors range from zero (least extreme) placed on the left side of the scale, to 100 (most extreme) placed on the right side of the scale (Kuhlmann, Dantlgraber, & Reips, 2017). It is thought that this scale was first described by Hayes and Patterson in 1921, when these researchers introduced a graphic-rating method that has since been identified as the first scientific description of the VAS (Yeung & Wong, 2019).

The VAS has been used extensively in psychological and medical research, and has been validated for the assessment of chronic symptoms such as anxiety (Kindler, Harms, Amsler,

Ihde-Scholl, & Scheidegger, 2000), mood (Folstein & Luria, 1973), depression (Lees & Lloyd-Williams, 1999), and breathlessness (Mador & Kufel, 1992), although it is most commonly used to assess pain (Jensen, Karoly, & Braver, 1986; Reed & Van Nostran, 2014). Different studies that have utilised the VAS in pain measurement have shown that it offers good validity and reliability (Delgado *et al*., 2018). One of the initial studies that compared the VAS with other measures of pain showed that the VAS exhibited excellent correlation with a simple descriptive scale (SDS) (r=0.77) and with a numerical rating scale (r=0.91) (Downie *et al*., 1978). Later, studies that measured different types of pain (for example back pain or post-operative pain) were replicated and similar conclusions were drawn (Kindler *et al*., 2000). Recently, some studies evaluated the use of a digital VAS for tests of pain and found no difference between the paper-based VAS and the digital VAS (Delgado *et al.*, 2018).

Different versions of the VAS employ horizontal or vertical lines, numerical ratings, or a facial scale. However, the most widely used version is the horizontal line with no categories labelled on the line. When categories have been used (for example, no pain, mild pain, moderate pain, severe pain, very severe pain), and the value experienced by the subject has fallen between these categories, participants have shown a systematic bias either to the lower or higher score. It has also been found that this bias decreases as the number of categories increases (Schwarz, 1999).

Sleepiness is a subjective feeling, and therefore, as part of the work described in this thesis, there was a consensus decision (made by four consultants at the Royal Brompton Hospital, at least two physiologists, and several patients) that a VAS might be useful to measure sleepiness reproducibly. Therefore, a VAS for the assessment of sleepiness was developed with an endpoint that matched the ESS as closely as possible (Figure 1.10). More details regarding the

VAS and how it can measure sleepiness are given in the General Methods chapter (Chapter 2).

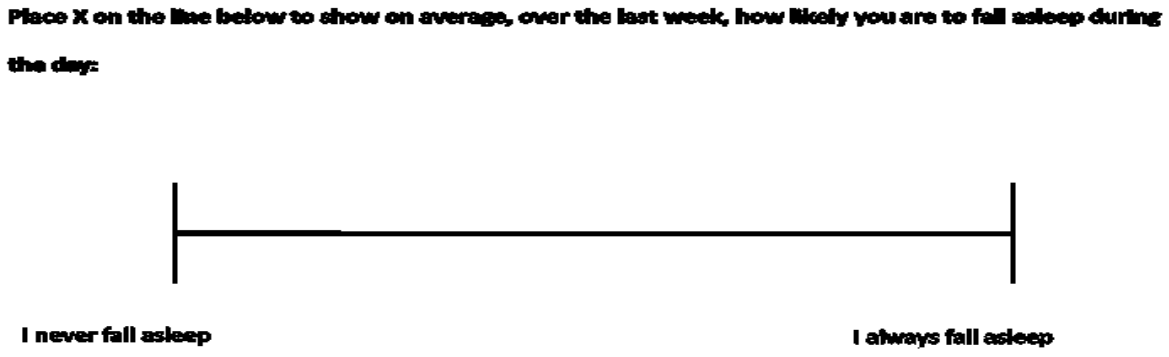


Figure 1.10:The VAS used in the research described in this thesis to assess sleepiness

1.8 Sleep deprivation

1.8.1 Definition of sleep deprivation

The term sleep deprivation has been used as a synonym for sleep loss or sleep debt in the early literature (Van Dongen, Rogers, & Dinges, 2003), and generally refers to sleep that does not reach the average basal level of seven to eight hours per night for adults (Altevogt & Colten, 2006) and approximately nine hours per night for adolescents (Carskadon, Acebo, & Jenni, 2004; Horne, 1988). This concept of a 'basal sleep need' is based on habitual sleep duration or the absence of a sleep debt (Dement & Greenberg, 1966). The concept was developed after a series of studies that showed significant implications for general health, brain and memory of sleep that lasted for fewer than five hours (Kryger *et al.,* 2017; Panel *et al.,* 2015). From these studies, two terms/concepts emerged: total sleep deprivation, and partial sleep deprivation or sleep restriction. Total sleep deprivation refers to the prevention or avoidance of sleep for 24 hours or more, whereas sleep restriction refers to the inability of a subject to undergo the recommended amount of sleep. Restricted sleep usually refers to

fewer than or approximately five hours for adults. For the purpose of this thesis, I will only describe sleep restriction and its impact on brain and memory as this is related to study 1 (Chapter 3) of this thesis.

1.8.2 Acute versus chronic sleep restriction

Acute sleep restriction refers to sleep that lasts for fewer than five hours a night for up to one week. This compares with chronic sleep restriction, which lasts for more than one week (Kryger *et al.,* 2017). Both have significant implications for health and the brain, as Table 1.4 shows. Recently, some evidence has shown that sleep restriction has definite effects on cognitive abilities, mood, attention, cardiovascular morbidity, and the immune system (Aidman, Jackson, & Kleitman, 2018; Hafner, Stepanek, Taylor, Troxel, & Van Stolk, 2016; Royal Society for Public Health, 2016). More details regarding the effect of sleep restriction on attention and memory are described below.

Table 1.4: Effects of acute and chronic sleep restriction on health and the brain.

	Acute sleep restriction	**Chronic sleep restriction**
Implications	• Perseveration/reduced flexibility in thinking (Harrison & Horne, 2000) • Impaired sense of humour (Killgore *et al.,* 2008) • Increased risk-taking (Venkatraman *et al.,* 2007) • Poor mental judgement (Killgore *et al.,* 2008) • Reduced emotional intelligence (Van der Helm *et al.,* 2010) • Negative mindset (Van der Helm *et al.,* 2010) • Increased calorific intake (Broussard *et al.,* 2016)	• Increased reaction time/psychomotor vigilance test time (Lim & Dinges, 2008) • Impaired memory performance (Van Dongen *et al.,* 2003) • Increased rate of accidents while using driving simulators (Dorrian *et al.,* 2007) • Decreased antibody titres (Spiegel *et al.,* 2002) • Increased insulin resistance (Broussard *et al.,* 2012) • Increased frequency of cardiovascular events and cardiovascular morbidity (Borel *et al.,* 2013)

1.8.3 Impact of sleep restriction on attention and memory

Attention is a fundamental aspect of cognitive performance; it is usually measured by the Psychomotor Vigilance Test (PVT). It has been shown in several studies that the PVT is a sensitive measure of any sleep loss (Basner, Mollicone, & Dinges, 2011; Lim & Dinges, 2008). PVT measures the time taken to respond to a visual stimulus in random time through either a hand-held device or a computer. The participant is usually asked to press a button as fast as possible when the stimuli appear. Previous studies have shown consistently that sleep restriction increases the PVT responses (that is, it increases reaction times) (Banks & Dinges, 2007; Basner *et al.,* 2017; Basner, Rao, Goel, & Dinges, 2013; Dinges & Kribbs, 1991; Goel, Rao, Durmer, & Dinges, 2009; Lim & Dinges, 2008; Short, Weber, Reynolds, Coussens, & Carskadon, 2018). The mechanism by which sleep restriction impairs attention is thought to involve monotony and boredom that lead to decreased motivation, which eventually leads to microsleep (Horne, 1991). This theory is based on studies in which a reward (monetary or the promise of the removal of sleep restriction) is introduced. In such studies, the attention levels of participants were improved to levels near to the baseline (Horne & Pettitt, 1985).

It is suggested that lapses of attention increase in duration and frequency as a function of the severity of sleep restriction; this hypothesis is known as 'wake-state instability', which is a condition caused by the interaction between the haemostatic drive of sleep, the endogenous circadian promotion of wakefulness, and the effort by the subject to perform well in the task (Doran, Van Dongen, & Dinges, 2001).

There is also a dose-response relationship between the duration of sleep restriction and impaired reaction time. The reaction time increases as the duration of sleep restriction increases. A study by Van Dongen *et al.,* (2003), showed that participants who were allowed

four or six hours in bed showed inferior performance in the PVT compared with those who were allowed eight hours in bed (Van Dongen, Maislin, Mullington, & Dinges, 2003). Recently, Mantua and Simonelli have argued that there is a linear relationship between the amount of sleep obtained by a subject and cognition; longer sleep duration leads to better cognitive performance (Mantua & Simonelli, 2019).

1.9 Aim of the thesis

The overall aim of this PhD thesis is to evaluate methods employed to assess sleep and sleepiness in healthy adults and in patients who experience respiratory sleep disorders.

When I first started my PhD in September 2015, there were no published studies that had examined the efficacy of the generic in-ear EEG sensor to assess sleep latency and sleep stages. Therefore, the first two aims of this thesis were:

- *To investigate the efficacy of the in-ear EEG in detecting sleep latency, compared to a scalp EEG in healthy participants during daytime naps, before and after sleep restriction.*
- *To investigate the efficacy of the in-ear EEG in detecting deep sleep (slow wave sleep) compared to a scalp EEG in healthy participants overnight.*

Clinically, no previous studies had been conducted that had assessed the efficacy of a VAS to detect sleepiness in patients with OSA before and after CPAP treatment.

Therefore, the third aim of this thesis was:

- *To investigate whether a new VAS would offer equivalent results to those obtained through the ESS, and would prove easier to use than the ESS, in the assessment of sleepiness in both patients newly diagnosed with OSA and in healthy participants.*

Chapter 2: General Methods

2.1. Participants and hospital information

All participants were recruited between December 2015 and August 2018 from the Royal Brompton and Harefield National Health Service (NHS) Foundation Trust and from Imperial College, London. Participants were identified from the Centre for Sleep at the Royal Brompton Hospital, or were students or staff of Imperial College. Participants were potentially eligible if they met the inclusion criteria and lived in London, UK. Participants were assessed for eligibility for the study initially by telephone call followed by face-to-face interview either at the college or at the Centre for Sleep. Participants recruited to take part in study 3 (Chapter 5) were asked to complete the sleepiness questionnaires at the Centre for Sleep after they had attended their CPAP set-up clinic.

2.1. Ethical approval and conduct of research

Study 1, (Chapter 3), titled 'A novel in-ear sensor to determine sleep latency during the Multiple Sleep Latency Test in healthy adults with and without sleep restriction', and study 2, (Chapter 4), titled 'The efficacy of an in-ear electroencephalography sensor to measure non-rapid-eye-movement sleep in healthy participants overnight', were approved by the Imperial College Research Ethics Committee (ICREC). The ICREC reference numbers are ICREC_12_1_1 and ICREC 17IC4150, respectively. Study 3, (Chapter 5), titled 'The measurement of sleepiness in patients with obstructive sleep apnoea pre and post CPAP using a Visual Analogue Scale', was approved by the South West - Cornwall & Plymouth Research Ethics Committee of the NHS Health Research Authority and was allocated the reference number 12/SW/0091. Copies of the approval letters from the representative ethics committees are shown in Appendices 4 and 5. All participants gave written informed consent to participate in the studies. All studies were conducted in accordance with the principles set out in the Good Clinical Practice (GCP)

guidelines and the Helsinki declaration on the principles of research conduct involving human participants.

2.2. Clinical assessment

Each patient who participated in study 3 (Chapter 5) underwent a medical review, which included a review of medical and drug history. A case report form (CRF) was used to collect medical and physiological data. Anthropometric measures of weight and height were recorded at the Centre for Sleep at the Royal Brompton Hospital. The medical reviews, completion of the CRF, measurements of physiological data, and data collection were all conducted by the author of the thesis.

2.3. Methods employed for the measurement of sleep

A discussion follows regarding each method used for the measurement of sleep in the research conducted for this thesis.

2.3.1. Nocturnal Oxygen saturation

During study 3 (Chapter 5), oxygen saturation was measured overnight in both patients with OSA, pre and post CPAP treatment and healthy participants. Oxygen levels and heart rates were recorded overnight in the participants' own homes using a pulse oximeter. This involved each participant wearing a small plastic clip on one finger. This plastic clip was attached to a watch-like device that recorded the oxygen saturation and pulse rate. All healthy participants underwent oximetry analysis on entry to the study to ensure that they did not show symptoms of sleep apnoea. All OSA patients underwent oximetry after one month of CPAP treatment, to evaluate the effectiveness of CPAP. To perform the pulse oximetry, the Konica Minolta Pulsox 300i Pulse Oximeter with Finger Probe was utilised. This device was either delivered to the participants by me or sent to them by post. Instructions

on the use and application of the oximeter were written, and explained, in a document attached to the device. After the recording of the oxygen saturation for the whole night, the device was returned by post for data analysis. Oxygen saturation analysis was performed automatically using the Konica Minolta Pulsox 300i software (Figure 2.1). The cut-off value of the oxygen desaturation index (ODI) was 7.5 events/hour for patients with OSA and 5.0 events/hour for healthy participants.



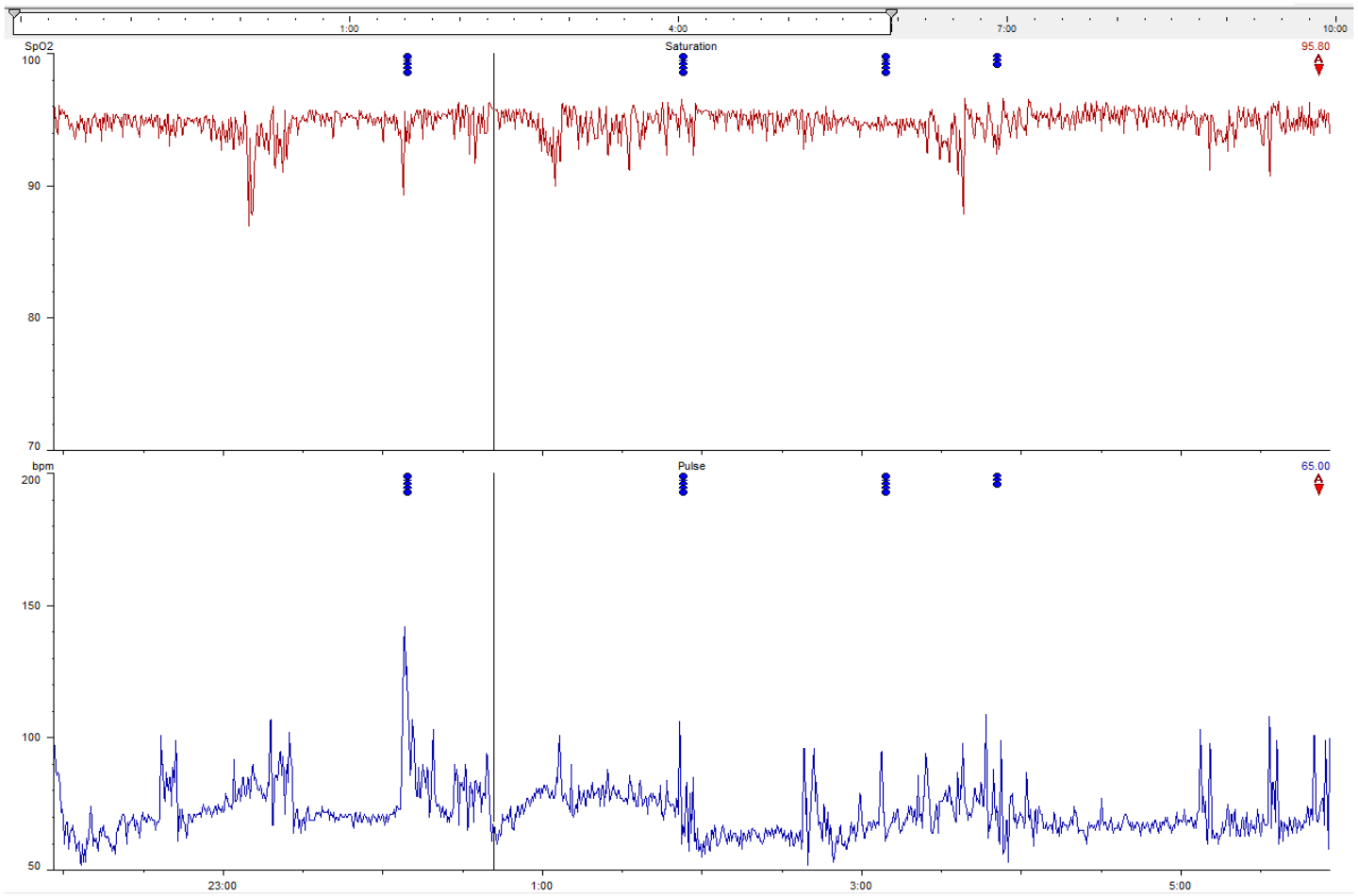


Figure 2.1: The picture (left) shows the pulse oximeter and its overnight configuration on a participant's wrist and finger. The waveform of oxygen saturation is shown (upper right) as is the pulse wave (lower right). The dips in saturation and associated increases in pulse rates highlighted in the black box suggest that an apnoea occurred during this time.

2.3.2. Overnight home sleep study

Overnight monitoring of sleep was conducted during study 2 (Chapter 4). Nocturnal unattended home polysomnography (PSG) tests (type II sleep study)(Collop *et al.,* 2007) were performed using portable monitoring equipment (SOMNOscreenTM Plus, SOMNOmedics GmbH, Germany). A survey conducted in our sleep and ventilation unit found that two-thirds of patients preferred the home PSG test (Ward, 2011). The home setting was selected in order to more robustly test the performance of the in-ear EEG sensor, by offering a real-world scenario. Participants were visited by the author at their homes approximately two hours before their usual bedtimes. Participants were asked to be prepared for their bedtime routines before my arrival. Upon arrival, the ESS was given to the participants to be completed and then the application of the PSG sensors was started. The set-up time of the PSG `was approximately one hour, which included the application of the PSG, bio-calibration, and impedance checking. The channels used in the montage of the sleep study were:

- Ten electroencephalography (EEG) channels, two reference electrodes and eight active electrodes. The three electrodes in the left hemisphere were referenced to the electrode in the right mastoid (A2) and vice versa. The electrode applied to the forehead was used as a ground electrode (Figure 2.2).
- Two electrooculogram (EOG) channels
- Three submental electromyogram (EMG) channels and two additional EMG channels, one placed on each of the tibialis anterior muscles of the left and right lower legs
- Two electrocardiography (ECG) channels
- Respiratory signals were also collected (measurement of airflow, chest and abdominal movements, oxygen saturation, snore)

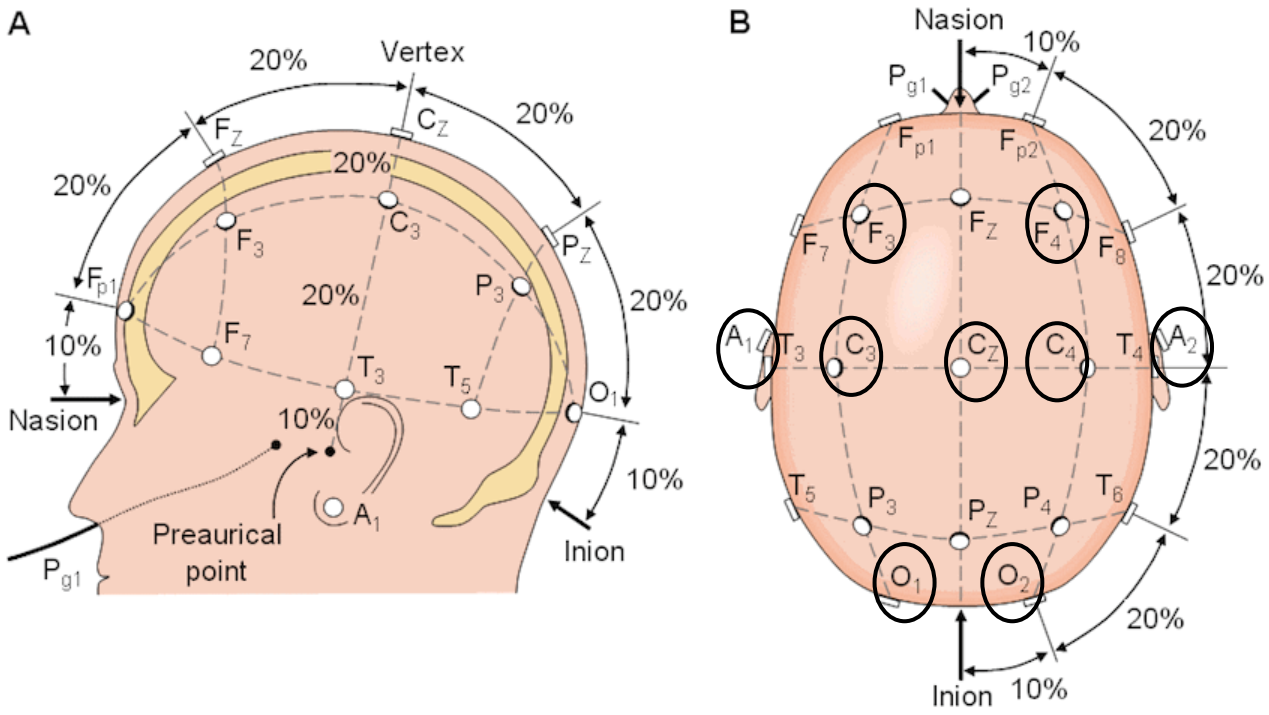


Figure 2.2: A: Positions of electrodes for sleep study 2 (Chapter 4) viewed from the side of the head. The electrodes are placed at 10% and 20% of the distance from nasion to inion and from the left and right preauricular points. B: The positions of electrodes used in sleep study 2 (Chapter 4) viewed from above. The odd numbers are in the left hemisphere and the even numbers are in the right hemisphere. F: frontal, C: central, O, occipital, T temporal, P: parietal. An additional ground electrode was placed on the forehead 10% of the distance from the nasion to inion (not shown in this diagram). The figure is adapted from the American Academy of Sleep Medicine scoring manual, Version 2.0.

Sleep was measured through data collected that showed the electrical activity of the brain (EEG), movements of the eyes (EOG) and measurement of muscle activity (EMG). The EEG data was collected through a combination of 10 mm gold-cup electrodes (Grass Technology, Rhode Island, US) and pre-gelled self-adhesive electrodes (Neuroline 720, Ambu Ltd, Cambridgeshire) placed on the scalp according to the 10/20 system. Gold-cup electrodes were placed on the scalp at positions C3, C4, Cz, F3, F4, O1 and O2. Neuroline electrodes were placed at positions A1, A2, EOG left and right, ground electrode and chin EMG (x 3). Before each electrode was positioned, the skin was prepared by cleaning the area with an abrasive paste (Neuprep, Weaver and Company, Colorado, USA) and subsequent wiping with an

alcohol swab. The gold-cup electrodes were filled with a conductive paste (Ten20 conductive paste, Weaver and Company, Colorado, US) and held in position on the scalp with an adhesive (Collodion, SLE Ltd., South Croydon, UK). The self-adhesive Neuroline electrodes were held in position by micropore tape. Once the electrodes had been attached, impedance was checked and physiological and mechanical calibrations were conducted. The physiological calibration was conducted by asking the participant to perform the following tasks to check the electrodes were working properly:

- keep the eyes open,
- look straight ahead for 30 seconds (s),
- close the eyes,
- look straight ahead for 30 s,
- look to the left and right,
- repeat up and down,
- hold head still,
- blink eyes slowly five times,
- grit teeth, clench jaw or smile,
- inhale and exhale,
- hold breath for 10 s,
- flex right foot,
- flex left foot,
- turn head and body to either side.

Mechanical calibration was performed by pressing the calibration button on the SomnoScreen software.

The electrical potentials between each pair of EEG, EOG and EMG electrodes were measured in voltage in AC mode. The raw data were recorded using the sampling rates and low- and high-pass filters shown in Table 2.1. The impedance of the EEG, EOG, and EMG networks was kept below 5KΩ.

Table 2.1: Signal sampling rates and filter settings for polysomnography

	Sampling rate (Hertz (Hz))	**Frequency, range (Hz)**	**High-pass filter (Hz)**	**Low-pass filter (Hz)**
EEG	256	Delta (0.5 – 3.0) Alpha and beta (8.0 – 32.0)	0.3	30
EOG	128	0.2 – 35.0	0.3	10
EMG	256	1.0 – 128.0	10.0	75
ECG	256	1.0 – 128.0	1.0	75

The data from the polysomnography tests were recorded on an integral memory card on the SOMNOscreen plus device (1GB Compact Flash card SOMNOmedics). The data were also simultaneously transmitted wirelessly to a computer in real time (Hewlett-Packard**;** hp, EliteBook, 850 G3, Palo Alto, California, US). SOMNOscreen software (DOMINO, Version 2.7.2) was used for signal processing and analysis.

2.4. Methods employed for the measurement of sleepiness

A discussion follows regarding each method used for the measurement of sleepiness in the research conducted for this thesis.

2.4.1. Established subjective measure of sleepiness: Epworth sleepiness scale

The ESS was used to assess daytime sleepiness (Johns, 1991). The ESS is the most widely used subjective scale in clinical and research practice. It takes the form of a short, self-administered questionnaire that comprises eight questions which require participants to rate the likelihood of them dozing or falling asleep during eight different soporific everyday situations (Figure 2.3).

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. a theatre or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

© **M.W. Johns 1990-97**

Figure 2.2: The Epworth Sleepiness Scale used during the research conducted for this thesis.

Patients are asked to rate their chances of falling asleep as never, slight, moderate or high, and these categories correspond with a scale from 0 to 3. The sum of the responses provides the score, which can therefore range from a lowest possible score of zero, which indicates a low level of sleepiness, to a highest possible score of 24, which indicates a high level of sleepiness (Johns, 1994). A reduction in the score after completion of subsequent questionnaires represents an improvement. The ESS has been validated extensively in diverse patient populations and in healthy participants who speak different languages, as described in Chapter 1, section 1.6.1.

The ESS was used in the research conducted for this thesis for all studies (Chapters 3, 4, and 5). The author administered the questionnaire before the application of the EEG electrodes in studies 1 and 2 (Chapters 3 and 4) and during the CPAP set-up visits in Study 3 (Chapter 5). Participants were asked to complete the ESS questionnaire themselves with no input from the partner, and the instructions given were: "This questionnaire assesses your level of sleepiness. Please read the instructions carefully and fill in the questionnaire. If you do not understand how to fill it in, or find it ambiguous, feel free to ask me". The ease of use was assessed by a Likert scale (zero to 10, with zero being most difficult and 10 being most easy) and this was also recorded. The ESS was administered in a paper format.

2.4.2. Novel subjective measure of sleepiness: The visual analogue scale (VAS)

The VAS was used in Study 3 (Chapter 5). It was developed as a self-administered scale that consisted of two opposing statements joined by a 10-cm line (see Chapter 1, Figure 1.10). Participants were asked to mark on the line how likely they were to doze off or fall asleep in different situations. The two opposing statements used were: 'I never fall asleep' and 'I always fall asleep'. These two statements were selected to resemble the scores on the ESS. The

opposing statements, or anchors, were developed by a consensus of experts (four consultants from the Royal Brompton Hospital, two sleep physiologists, and a group of patients).

Participants were asked to complete the VAS questionnaire themselves with no input from the partner, and the instructions given were: “This questionnaire assesses your level of sleepiness. Please read the instructions carefully and fill in the questionnaire. If you do not understand how to fill it in, or find it ambiguous, feel free to ask me.” The ease of use was assessed through use of a Likert scale (zero to 10, with zero being most difficult and 10 being most easy) and these data were also recorded. The VAS was administered in paper format. The actual score was measured using a ruler; the distance (in cm) from the left anchor to the point at which a participant made their mark was used as the VAS score for that participant.

2.4.3. Objective measure of sleepiness: Multiple sleep latency test

The multiple sleep latency test (MSLT) is an objective test for excessive daytime sleepiness. It measures how quickly a person can fall asleep in a quiet environment during the day. During the work performed for this thesis, the MSLT was conducted during Study 1 (Chapter 3) twice, before and after acute sleep restriction. The instructions given to the participants before the day of the test were:

- Refrain from caffeine and alcohol during the day of the test
- Avoid smoking 30 minutes prior to each nap
- Avoid vigorous activity during the day
- Avoid falling asleep in between naps
- Avoid lying down in between naps
- Avoid bright lights and direct sunlight
- Light breakfast and lunch are permitted but at least one hour prior to the next nap.

Participants were asked to arrive at the engineering department's EEG laboratory at 9 am. Upon arrival, each participant was asked to sit in a chair for the application of the EEG electrodes. The EEG electrodes applied on the scalp were C3, C4, A1, and A2. The in-ear EEG sensor was then placed in the ear. The reference and ground electrodes were placed on the helix and ear loop, respectively. After the EEG electrode application, the participant was instructed: "Please lie quietly, with your eyes closed, and try to fall asleep." The light was switched off and the curtains were closed. The participant was allowed four 20-minute naps, with a two-hour interval between each nap. The first nap time started at 10:00 am and the last nap was finished by 16:20 pm.

2.6 In-ear EEG sensor

In the introduction (Chapter 1) the theoretical background of the in-ear EEG sensor was explained. It was explained that the sensor passed through two stages of development: production of customised sensors similar to hearing-aids; and a generic earpiece similar to commercially available earplugs. Currently the engineering department is working on a wireless model to assess the performance of the ear sensor in real-world scenarios (Figure 2.4).

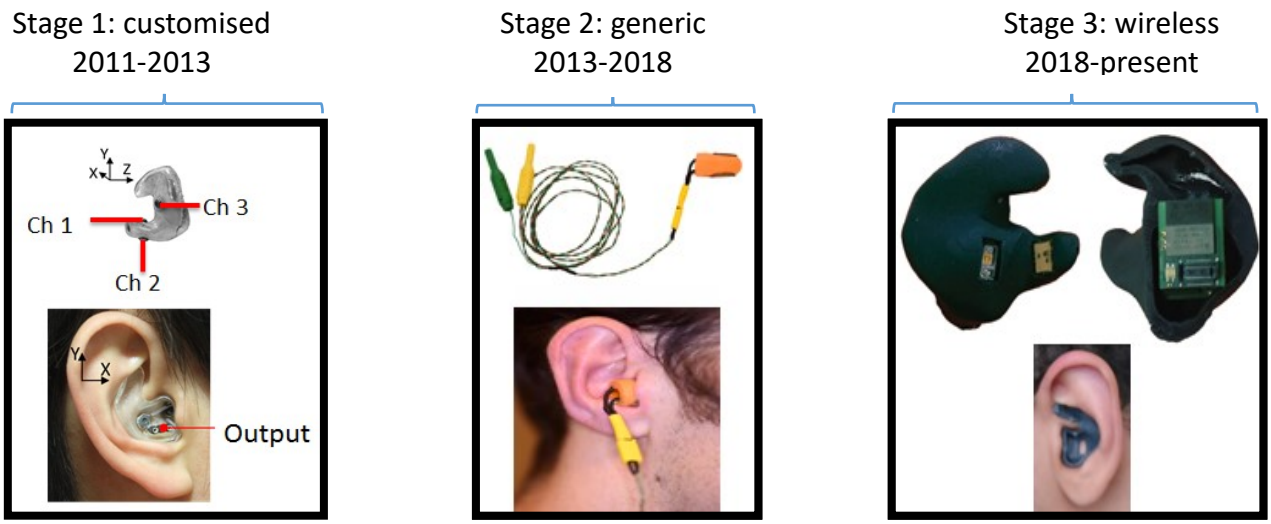


Figure 2.3: Timeline of the developmental stages of the in-ear EEG sensors.

Here, I will explain the development and construction of the in-ear EEG sensor and its electrical characteristics. It should be noted that the in-ear EEG sensor used for the research described in this thesis was constructed by Dr Valentine Goverdovsky and Takashi Nakamura of the engineering department of Imperial College. My involvement in the construction was limited to the observation of Dr Goverdovsky as he developed 10 sensors step by step on one occasion in early November 2015. On that occasion I built one sensor under his supervision.

2.6.1 In-ear EEG construction

The materials used for the customised in-ear EEG sensors (silicone and plastic) proved to be too stiff and rigid for efficient use. These physical characteristics prevented the provision of equally distributed pressure in the outer surface of the sensor, and therefore the electrode-skin contact was loose and intermittent. To overcome this issue, the earpiece material was required to be soft, easy to fit, robust and suitable for self-administration (Goverdovsky *et al.*, 2016). Such a material is now widely used in sound-blocking earplugs, and is gaining popularity for in-ear headphones. This material is usually referred to as memory foam, which

has characteristics of elastic; it does not deform when squeezed, stretched or twisted, and instead slowly returns to its original shape. It was evident to the researchers that this memory-foam material exhibited many of the key characteristics required for the in-ear EEG sensor. It enabled significant compression without loss of the original shape, which was a requirement for comfort and easy insertion.

The pressure on the outside surface of the foam earplug could be uniformly distributed and created excellent contact with the skin at any point on the earpiece, which provided a robust electrode-skin interface and comfort during long-term wear. The material was also cheap and could be moulded into different shapes as necessary. To accommodate the high levels of compression required prior to insertion into the ear, the electrodes were required to be made from similarly sturdy and flexible material. Different options were tested: polyurethane-based silver-loaded flexible adhesive; conductive copper paint; silver-loaded silicone rubber; and stretchable conductive fabric. The adhesive and the paint were found not to possess the required sturdiness when dry, and they cracked even under minor compression, and therefore were eliminated. Silicone rubber and the wires were found to be extremely difficult to attach to the substrate. They also exhibited high levels of impedance after several cycles. Stretchable fabric proved to offer the best performance: it accommodated all the required deformations, provided low impedance even after several months of use, and was straightforward to attach to the substrate and wires.

The conductive cloth chosen was made from silver-coated nylon interwoven with elastic fibres. It could stretch in both directions and showed very low impedance of only 0.5 Ohm/sq. cm. To create electrodes, stainless-steel thread was sewn into strips of fabric that were cut to the size 4 mm wide and 1 cm long. Standard wires could then be soldered directly to the

thread. The whole electrode remained resistant to corrosion since the thread was made from stainless steel and the cloth was silver-plated.

The fabric strips were then evenly placed on two sides of the memory-foam earplug opposite one another and were attached to the substrate using 3M adhesive transfer tape. Stainless-steel thread attached to the electrode was insulated through the use of heat-shrink tubing and was passed through the bulk of the earplug to exit through the flat face of the earpiece (Goverdovsky *et al.,* 2016). This construction created an in-ear EEG sensor with two electrodes diametrically opposed to each other as shown previously in Chapter 1, Figure 1.9.

2.6.2 Electrical characteristics

The two key aspects of the electrical characteristics of the proposed sensor were: 1) good electrode-skin contact to achieve low impedance and 2) the stability of such contact over time without abrasion to the user. It was verified that the desired low impedance was achievable with just a saline solution and normal cleaning of the ear canal to remove any excess ear wax. Long-term stability of such contact was investigated through the following experiment:

A user was asked to wear the earpiece for a period of five hours and to record electrode impedances at approximately half-hour intervals using a portable amplifier. Prior to insertion of the sensor, the ear was cleaned with cotton buds and water, no abrasion was performed, and small quantities of saline solution were applied to both electrodes. The results of this experiment indicated that the impedance was constant throughout the experiment (Figure 2.5) (Goverdovsky *et al.,* 2016).

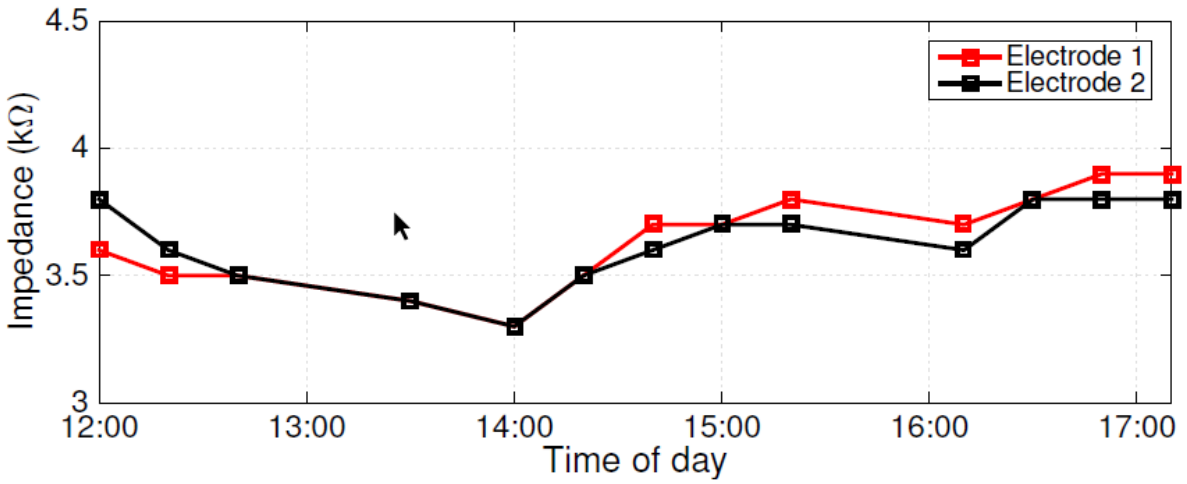


Figure 2.4: Variation of impedance of the in-ear EEG sensor over time (five hours) while worn by one person, from channel 1 (red) and channel 2 (black). Adapted from Goverdovsky *et al.*, 2016.

The in-ear EEG data collected during Study 1 (Chapter 3) and study 2 (Chapter 4) were recorded using a 16-channel, 24-bit biosignal USB amplifier (g.tec medical engineering GmbH, Schiedlberg, Austria). Data were acquired with a sampling rate of 1.2 kS/s. A fourth-order Butterworth bandpass filter with passband 3–14 Hz was applied to the in-ear EEG sensor.

2.7. Methods employed for the measurement of cognitive function

2.7.1. Reaction time

The reaction times measured during Study 1 (Chapter 3) were tested through the Oxford Sleep Resistance Test (OSLER). The OSLER device has two modes of measurement: the OSLER test, which is a behavioural version of the Multiple Wakefulness Test (MWT); and the Multiple Unprepared Reaction Time test (MURT). The MURT measures how fast a person responds to visual stimuli. During a MURT, the subject is instructed to hold the OSLER box with the dominant thumb over the middle button marked X (Figure 2.6). The LED light is repeatedly turned on at (pseudo) random intervals during a period of approximately 10 minutes, and the subject is required to press the button as rapidly as possible when the LED lights. Every time the button is pressed, the light goes out, and the reaction time is displayed on the screen. If

four seconds pass without the button being pressed, this is counted as a 'miss'. The average reaction time for all trials is shown at the end of the test.



Figure 2.5: The OSLER device that was used to measure the reaction time test.

The test was carried out in the EEG laboratory of the engineering department at Imperial College. The instruction that I gave to the participants before the start of the test was: "This is a reaction time test, which measures how fast you can respond to a visual stimulus. Please hold the box and put your dominant thumb over the X. I want you to press the X button as fast as possible every time you see the LED light. The LED light will appear at random intervals. The test will last for approximately 10 minutes." The participants were asked to sit in a stationary chair during the test.

2.7.2. Stroop test

The Stroop test was used during Study 1 (Chapter 3). It is a neuropsychological test used extensively for both experimental and clinical purposes. It assesses the ability to inhibit cognitive interference, which occurs when the processing of a feature of a stimulus affects the simultaneous processing of another attribute of the same stimulus. This is called the Stroop effect (Stroop, 1935). To complete the Stroop test, the participant is required to complete four sets of tests:

1- Conflicting words set: The participant is asked to read words printed in various colour patches of ink, but name the colour rather than read the word aloud (e.g., the word 'green' may be printed in blue ink; the participant is required to name the colour of the word, not the word itself) (Figure 2.7).

2- Conflicting colour set: The participant is asked to read the words printed in different colour patches (e.g., the word 'green' may be printed in blue ink; the participant is required to read aloud the word itself, not state the colour in which it is printed).

3- Colour blocks: the participant is asked to name the colour of rectangular boxes with no letters in these boxes (e.g., a 2X4 cm rectangular box may be printed in green; the participant is asked to name the colour of the box).

4- Monochrome set: the participant is asked to read the words printed in black ink (e.g.; the word 'green' may be printed in black ink; the participant is required to read aloud the word).

The colour-block and monochrome sets are the controls for the conflicting word and conflicting colour sets. Two types of quantitative results are generated from each set: the number of errors that the participant makes; and the time taken to complete each set.

The Stroop test was used during Study 1 (Chapter 3) that is described in this thesis. The use of the Stroop test in that study was due to the inconsistent results of the impact of sleep restriction on Stroop test. Bratzke *et al*. showed no variation in Stroop test after 40 hours of wakefulness (Bratzke *et al.,* 2012). However, Hartley and Shirley (1976) reported that there was an increase in interference in the evening compared with the morning (Hartley and Shirley, 1976). The use of Stroop test in this thesis was to investigate the effect of sleep

restriction on Stroop test and whether this impact can be predicted by the in-ear EEG.

The Stroop test was applied after the third nap that was undertaken during the MSLT. The author employed a laminated hard copy of the Stroop test, whereas each set for presentation to the participants was printed in A4 paper. I asked the participant in each set to name the colours as per the instructions described above. The number of mistakes and time taken to perform each set was recorded according to the answer key I was holding during the test. The total time to complete the test was approximately seven minutes.

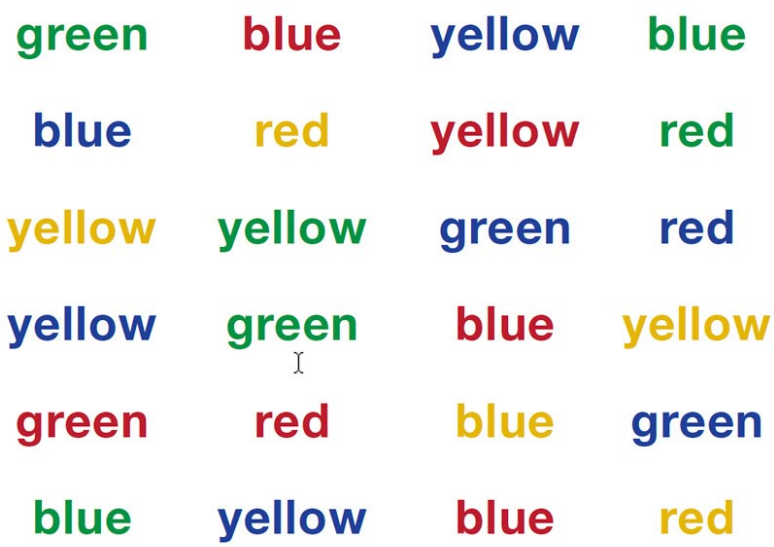


Figure 2.6: Example of the Stroop test. Depending on the task, participants are required to name either the colour in which the word is printed or the word itself. For example, in the conflicting word task, the participants should name the colour in which the word is printed, not the word itself.

2.8 Sleep restriction

Sleep restriction was used as an intervention during Study 1 (Chapter 3) in the work described in this thesis. Participants were asked to restrict their sleep to five hours per night before the day of the test. The goal of this intervention was to investigate whether cognitive function worsened after sleep restriction and how this related to the changes observed in the recorded EEG (sleep latency). To confirm whether participants had adhered to the protocol, they were

asked to log in to a Google webpage every hour from 6pm until the bedtime.

2.9 Data collection

The data from the polysomnography measurements were recorded on an integral memory card on the SOMNOscreen plus device (1GB Compact Flash card SOMNOmedics). The data were also simultaneously recorded on a laptop computer (Dell LATITUDE E6510) via telemetry. SOMNOscreen software (DOMINO, Version 2.7.2) was used for signal processing and analysis. The data collected by the in-ear EEG sensor were recorded online through use of a laptop computer (Lenovo X230).

2.10 Data analysis

Details of the data analysis are described in the appropriate experimental chapter. In brief, all statistical analysis was performed using SPSS v19 and v23 (IBM, USA). A summary of the analysis is described here. Statistical significance is considered as $p<0.05$. Data are described by means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables, depending on the sample size and distribution. Categorical variables are described as number and percentage. Normality testing of distributions is examined both visually (histogram and Q-Q plots) as well as by Shapiro-Wilk testing. Correlations are examined by Pearson tests.

All polysomnography studies were scored by the author blindly. The anonymisation of the data were performed by the engineering team (Mr Takashi Nakamura). The studies were all scored according to the American Academy of Sleep Medicine (AASM) standards manual 2012. Sleep stages were scored according to the table below:

Table 2.2. Sleep stages recorded during polysomnography and the scoring system employed during research conducted for this thesis.

Sleep stage	EEG	EMG	EOG
Wake	Fast beta activity >13Hz, high amplitude. With eyes closed there is alpha activity at 8 – 13Hz.	High tone	Rapid eye movements, blinks
N1	Theta activity 4 – 7Hz	Reduced tone compared with the awake state	Eye rolling and no rapid eye movements
N2	Spindles (fast bursts [0.5 – 2 seconds] of 12 – 15Hz activity) K-complexes (negative EEG deflections followed by positive) Both K-complexes and spindles occur on a background of low-voltage, mixed-frequency EEG	Lower tone than in N1 and the awake state.	Occasional slow eye movements
N3	Slow (delta) waves (0-3Hz, ≥75µV in amplitude) in more than 20% of the epoch.	Low tone	No eye movement
REM	Low-voltage, mixed-frequency EEG	Atonia	Burst of rapid eye movement

EEG = Electroencephalogram, EMG = Electromyogram, EOG = Electrooculogram, and REM = Rapid eye movement.

Chapter 3. A novel in-ear sensor to determine sleep latency during the Multiple Sleep Latency Test (MSLT) in healthy adults with and without sleep restriction

This chapter was published in *Nature and the Science of Sleep* journal in November 2018

3.1 Introduction

Excessive daytime sleepiness (EDS) is a common problem that affects approximately 12% of the general population (Jaussent *et al.,* 2012; Kim & Young, 2005; Pallesen *et al.,* 2007). The causes of EDS include both primary sleep disorders and secondary medical conditions that disrupt sleep, for example, those causing pain. In addition, poor sleep habits, whether chosen by the patient or imposed by occupational circumstances, can cause EDS. The consequences of EDS also vary widely, ranging from underperformance at school in the young population, to fatal road traffic accidents (RTA) in adults. A recent Cochrane Review suggested that EDS was associated with school absenteeism and poor academic performance (Marx *et al.,* 2017). Among drivers, EDS is thought to be a contributing factor in 5-7% of all RTA (McNicholas & Rodenstein, 2015; Tefft, 2012). For example, in the US alone, RTA due to sleep or drowsiness while driving was reported to have resulted in 8,952 deaths and 220,000 serious injuries between 2004 and 2013 (Burks *et al.,* 2016). Similar underperformance and accident issues arise among other occupations too. Reis *et al.* have shown that the prevalence of EDS among pilots is around 60% (Reis, Mestre, Canhao, Gradwell, & Paiva, 2016) and Cotrim *et al.* found that EDS was highly prevalent among train drivers, peaking at 72% during night shifts (Cotrim *et al.,* 2017).

Currently, evaluation of EDS in real-world situations is limited to subjective measures of sleepiness, with objective tests, such as the Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT), mainly being undertaken in sleep laboratories (Johns, 2000; Mitler, Gujavarty, & Browman, 1982; Richardson *et al.,* 1978) (see Chapter 2, section 2.4.3.) In both these tests, the EEG recorded from the scalp is used to detect sleep latency, a standard measure of sleepiness. These are the standard diagnostic tests for patients

with hypersomnia of central origins, such as narcolepsy. However, neither the MSLT nor the MWT has achieved universal acceptance because they require patients to stay in the laboratory for the whole day; this renders the investigation inconvenient, relatively costly and not representative of real-world situations. A common subjective measure of sleepiness is the Epworth sleepiness scale (ESS) (Johns, 1991) which has been used extensively in many countries (Ahmed *et al.,* 2014; Banhiran *et al.,* 2011; Beiske *et al.,* 2009; Bertolazi *et al.,* 2009; Bloch *et al.,* 1999; Chen *et al.,* 2002; Cho *et al.,* 2011; Izci *et al.,* 2008; Kopitovic *et al.,* 2011; Pecotic *et al.,* 2012; Rosales-Mayor *et al.,* 2012; Tsara *et al.,* 2004; Vignatelli *et al.,* 2003). (See Chapter 1, section 1.5) However, the ESS is known to be poorly correlated with objective measures of sleepiness (Chervin & Aldrich, 1999) and functional outcomes (Waller *et al.,* 2016). Therefore, the development of a robust, non-invasive, wearable EEG-based method to detect sleep latency could be of significant value to facilitate the measurement and understanding of EDS.

Our group have previously reported a wearable sensor that measures EEG from the external auditory meatus (in-ear EEG) (Goverdovsky *et al.,* 2016; Looney *et al.,* 2012). In preliminary studies, we have shown that an in-ear EEG sensor can be used to detect slow-wave sleep during short sleep studies (<1 hour) in four healthy adults (Looney *et al.,* 2016). The aim of the present study was to evaluate the efficacy of the EEG obtained in-ear to detect sleep latency during MSLT in healthy adults. I tested the hypothesis that the EEG obtained in-ear was not inferior to that obtained from the scalp to detect sleep latency during MSLT. For robustness, I used the intervention of voluntary sleep restriction, and confirmed that this was a stimulus of appropriate magnitude by measuring reaction time and cognitive impairment associated with our sleep-restriction intervention.

3.2 Methods

3.2.1 Participants

I recruited 25 healthy adults (eight female), who were identified using advertisements posted on campus at Imperial College London, UK; the majority of participants were students or employees. The inclusion and exclusion criteria were as follow:

- ***Inclusion Criteria***

1. Aged ≥ 18

- ***Exclusion Criteria:***

1. Any significant neurological conditions.
2. Shift workers.
3. International flight in the past two weeks.
4. Any kind of sleep disorder.
5. Significant use of sleep aids.
6. Inability to give fully informed consent.
7. Inability to commute to the sleep lab.

Participants gave written informed consent and the study was approved by Imperial College London Research Ethics Committee (ICREC_12_1_1).

3.2.2 Screening

Communication with potential participants was conducted initially through emails and then by face-to-face interviews, in order to ensure that the inclusion and exclusion criteria were met and to familiarise the participants with the in-ear EEG sensor. If participants met the

criteria and agreed to participate, they were assigned dates for the study (two daytime laboratory visits). The order of the studies (sleep restriction and usual night sleep) was randomised.

3.2.3 Protocol

A prospective, randomised crossover design was used, for which the participants were asked to come to the Imperial College signal processing EEG sleep laboratory after either a single night of sleep restriction (≤5 hours), or usual night sleep (≥7 hours). Adherence to the study protocol on the night before the MSLT was confirmed by asking participants to log in to a webpage every hour from 18:00 until the bedtime, and again when they first woke. Participants were asked to refrain from taking caffeine or any stimulants on the day of the study.

The MSLT protocol is shown in Figure 3.1. Participants arrived at the lab at 09:30 and the first nap time (nap 1) was started at 10:00; naps then occurred every two hours and the fourth nap (nap 4) was finished by 17:00 (Arand *et al.,* 2005; Carskadon *et al.*, 1986). The set-up time was approximately 30 minutes for attachment of both the scalp and in-ear EEG. The impedance was checked before each nap to maintain the quality of the signals. The scalp EEG electrodes were firmly attached throughout the study. The in-ear EEG sensor was also attached throughout the study unless the participant requested to remove it between naps. If the in-ear sensor was removed between naps, the sensor then was re-inserted before each nap and impedance was checked again. The scalp EEG electrodes were placed at the C3 and C4 positions according to the 10-20 montage, with the ground electrode placed on the forehead. The electrooculogram (right/left EOG) and electromyogram (chin EMG) were not recorded.

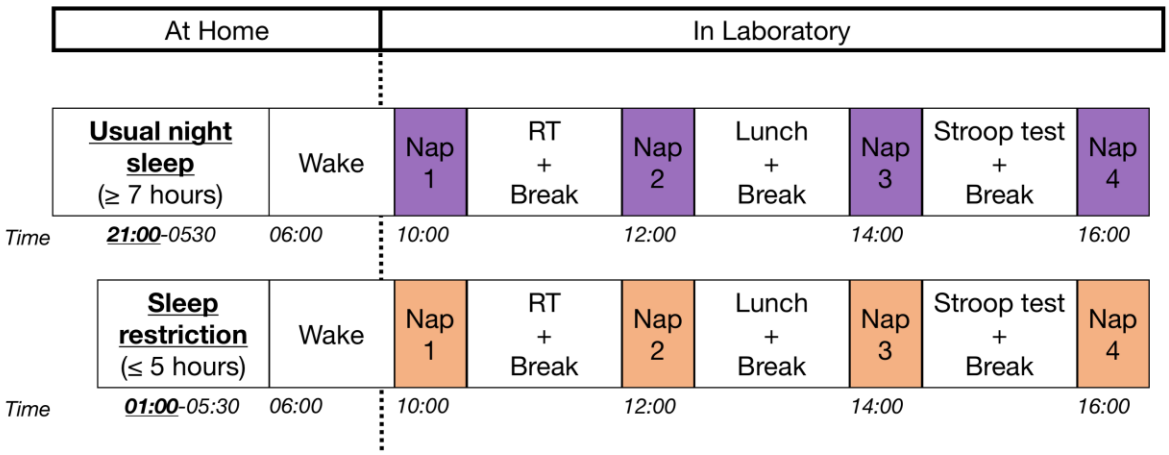


Figure 3.1: MSLT protocol utilised in this study. Sleep duration in the prior night was estimated by asking the participants to log in to a webpage every hour during the night and once when they woke up. Periods of naps during the sleep restriction visit are shown in orange, and periods of naps during the usual night sleep visit are shown in purple. RT=reaction time.

Full details of the in-ear EEG sensor are given in Chapter 2, General Methods. In brief, the in-ear EEG sensor was of approximately 25 mm length and 12 mm diameter. The two EEG electrodes were embedded onto the sensor diametrically opposite one another. The flexible viscoelastic sensor was inserted into the external auditory meatus by squeezing it to fit into the ear canal. The left or right ear was used for placement, according to participants' preference. The reference and ground electrodes for the in-ear sensor were placed on the helix and earlobe, respectively, using gold-cup electrodes (Bio-medical, MI, US). An example of a participant wearing scalp and in-ear EEG sensors and the corresponding signals recorded are shown in Figure 3.2. Prior to the application of gold-cup electrodes, skin was prepared using abrasive gel (Nuprep, Bio-medical, MI, US). Ear wax was removed from the ear using ear cotton buds, and Signa Gel was applied on the in-ear EEG sensor before insertion to the ear (Parker laboratories, Inc, USA). Scalp and in-ear EEG signals were recorded simultaneously using g-USBamp, a 24-bit biosignal amplifier (g.tec medical engineering GmbH, Schiedlberg,

Austria). Data were acquired with a sampling rate of 1.2kS/s. The impedance was checked before the start of the recording from both the in-ear and scalp EEG sensors, and the aim was to keep these below 10 KΩ. Fourth-order Butterworth bandpass filter with passband 3-14 Hz was applied to signals received from both the scalp- and in-ear EEG sensors.

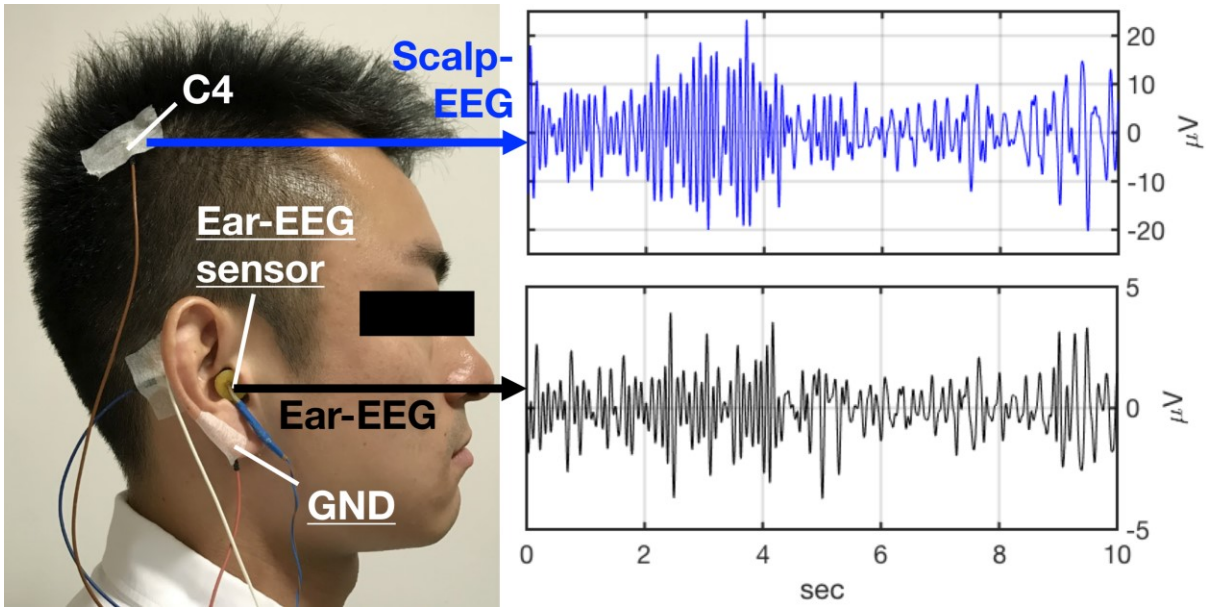


Figure 3.2: The in-ear EEG sensor. A person is shown wearing the scalp EEG (C4) and in-ear EEG sensor with corresponding signals. The EEG shows a transition from alpha activity to theta activity during 10 seconds. GND=ground.

Once the EEG electrodes were placed, participants were asked to sleep on a comfortable bed in a quiet and dark room following standardised instructions (Arand *et al.*, 2005; Carskadon *et al.,* 1986). Each nap was of 20-minutes duration, and if the participant slept they were allowed to continue for the duration of the nap.

1.9.1 3.2.4 Measurement of functional outcomes of sleep restriction

More details of the measurements are explained in General Methods (Chapter 2). In brief, after nap 1, participants performed a Multiple Unprepared Reaction Time (MURT) test using the Oxford Sleep Resistance Test (OSLER; Stowood Scientific, Oxford, UK) (Bennett *et al.,*

1997). After nap 3, participants performed a Stroop test (Stroop, 1935). Results were recorded in the form of the number of mistakes performed and the duration taken to complete the task.

3.2.5 Data analysis

Data were analysed blinded to the order allocation (sleep restriction or usual night sleep) and the mode of measurement (scalp EEG or in-ear EEG). The EEG scoring was performed by a single scorer according to the American Academy of Sleep Medicine (AASM) criteria, 2012 version 2.0 (Berry, Brooks *et al.,* 2012). Sleep latency was defined as the start of the first epoch scored as any stage other than the wake stage. This included the attenuation of the alpha rhythm (8-13 Hz) of more than 50% of an epoch and replaced by a low-amplitude, mixed-frequency activity (4-7 Hz). For participants who did not generate alpha activity, sleep latency was defined as the first appearance of sleep spindle and/or K-complex. Epochs were labelled as 'unable to analyse' if > 50% of the EEG signal (obtained via scalp or in-ear) showed artefacts that prevented the scorer from clearly distinguishing the stage, or if the electrodes did not record data due to technical problems. Naps were then removed from the analysis if more than 50% of the nap could not be scored. When the scoring was completed, the datasets were un-blinded, to enable statistical analysis.

3.2.6 Sample size and statistical analysis

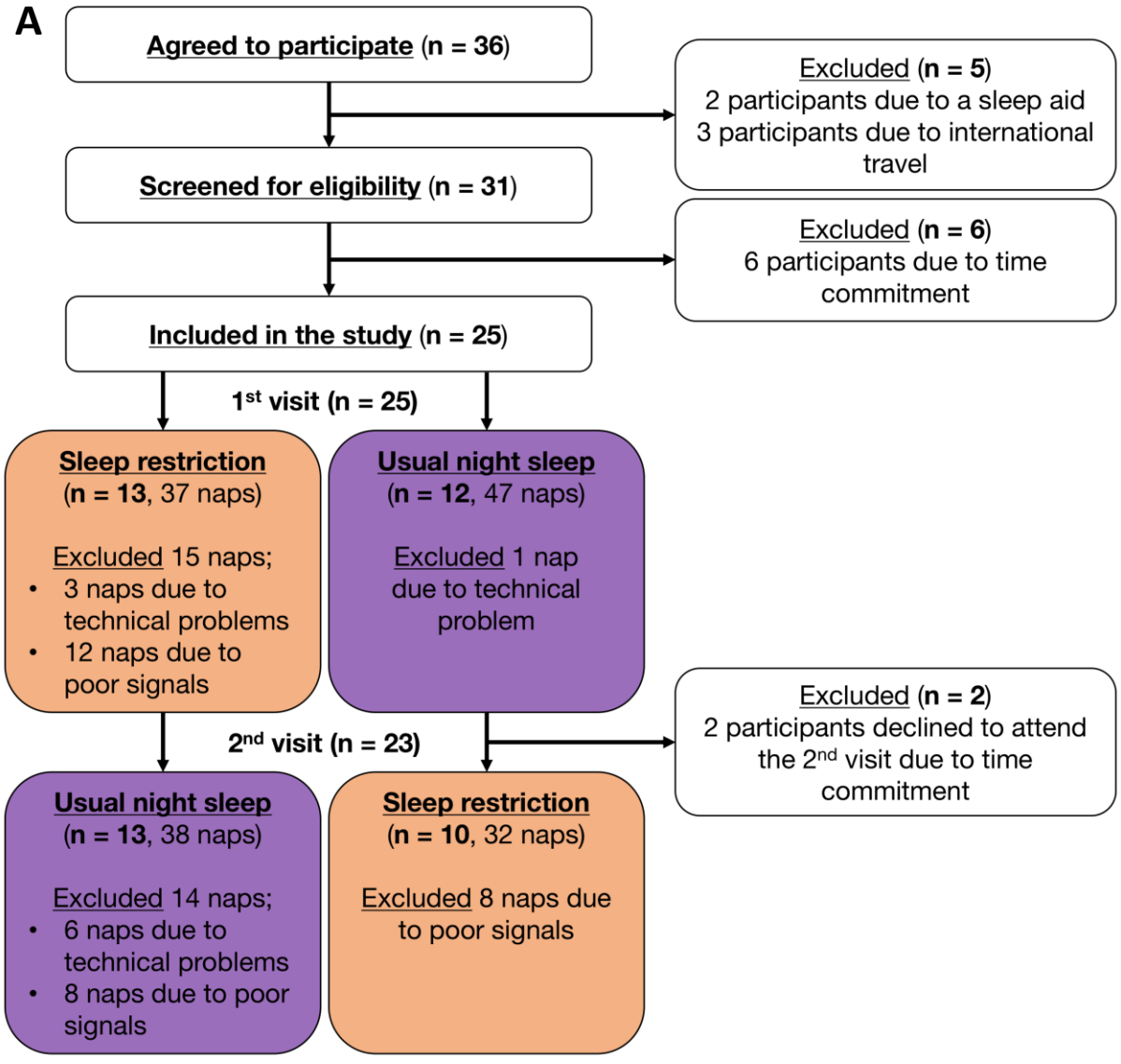
The sample size was calculated using the null hypothesis that the EEG obtained in-ear was not inferior to that obtained from the scalp, with a non-inferiority margin of three minutes and population variance of four minutes. The margin of three minutes was selected, as sleep latency had previously been reported to be reduced by three minutes following sleep restriction (Pejovic *et al.,* 2013). To reach a 5% significance level and 80% power, I estimated that 25 participants were required for this study.

The primary outcome of this study was measurements of the sleep latency obtained through in-ear EEG compared with scalp EEG, with and without sleep restriction. Data were evaluated by the mean and standard deviation (SD) or number and percentage (%) for categorical variables. The sleep latency measured through scalp and in-ear EEGs was compared using either a paired T-test or Wilcoxon signed rank sum test, as appropriate to the distribution of the data. Any nap that did not have a 'pair' (measured either by scalp or in-ear EEG) was deleted from the comparison (pair-wise deletion). Given the non-inferiority nature of this study, a confidence interval for the mean difference was constructed using the non-inferiority margin of three minutes, in order to assess whether indeed the EEG obtained in-ear was not inferior to that obtained from the scalp. To evaluate the sensitivity and specificity of the in-ear EEG sensor against the scalp EEG, the sleep-latency score was categorised as 'positive' or 'negative' for both devices, and that categorisation was used to assess the sensitivity and specificity. Agreement between scalp and in-ear EEG data to detect sleep latency was performed using the Bland-Altman method (Bland & Altman, 1986). The limits of agreement were defined as mean ± 1.96 SD. All statistical tests other than the non-inferiority test were two-sided and the statistical significance was set at $\underline{p} < 0.05$. IBM SPSS 23.0 software and Excel 2013 were used for statistical analysis, while GraphPad Prism 7 and Matlab 2016b (MathWorks, Inc) were used to generate the figures.

3.3 Results

I screened 36 healthy adults of whom 25 (eight female) were included in the study; details of recruitment are shown in the consort diagram (Figure 3.3a).

The mean age of the participants was 28.5±5.3 years. By design, since I sought healthy adults, the mean ESS score was normal (6±3) prior to the study.



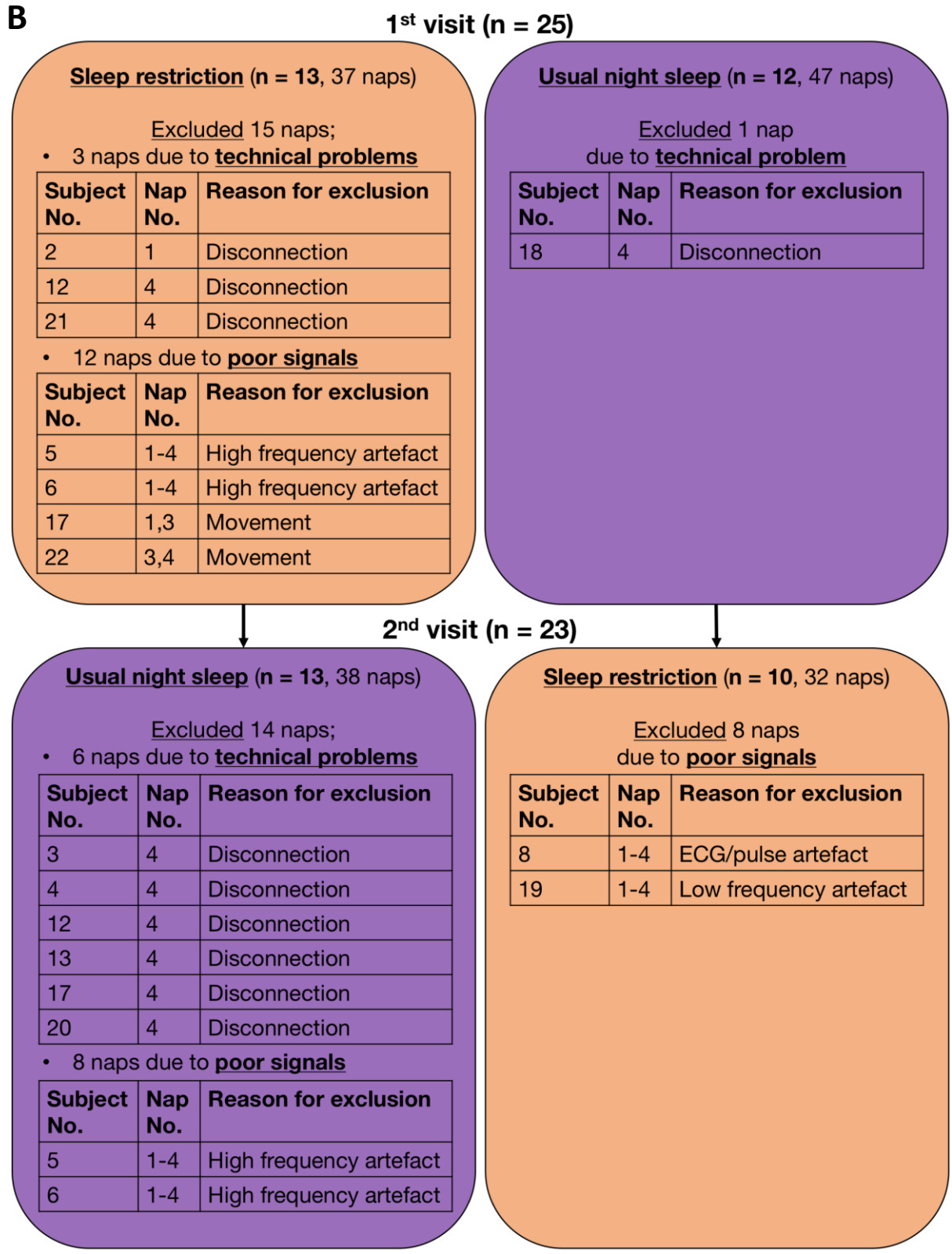


Figure 3.3: Consort flowchart. A) Consort diagram of the recruitment. B) Details of the naps excluded from the analysis: participant number, visits (1st or 2nd visit), sleep restriction (orange box) and usual night sleep (purple box) and nap numbers. Disconnection means that the electrodes did not record data due to technical problems.

3.3.1 Comparison of EEG obtained in-ear versus that from the scalp

Technically acceptable data were obtained from 23 adults during 69/92 naps in the sleep restriction condition and 25 adults during 85/100 naps in the usual night sleep. Naps were excluded from the analysis either because signals could not be scored (28 naps) or due to technical problems (10 naps). Specific details regarding which naps were excluded are given in Figure 3.3b. Signals that could not be scored included: I) high-frequency artefacts (16 naps, all of which were observed from the same participants, n=2 [4 naps × 2 conditions × 2 participants = 16 naps]), II) electrocardiogram (ECG)/pulse artefacts (four naps), III) low-frequency artefacts consistent with respiratory frequency (four naps), IV) movement (four naps). The majority of naps excluded due to technical problems were from nap 4 in the usual night-sleep condition. The group mean comparison between scalp EEG and in-ear EEG in detecting sleep latency is shown in Table 3.1.

Table 3.1: Comparison between in-ear EEG and scalp EEG in detection of sleep latency†

	Usual night sleep				**Sleep restriction**			
	n	**Scalp**	**In-ear**	***P value***	n	**Scalp**	**In-ear**	***P value***
Sleep latency of nap 1 (minutes)	23	11.1±6.2	11.7±6.2	*0.40*	17	9.6±5.9	10.7±6.2	*0.14*
Sleep latency of nap 2 (minutes)	23	12.0±6.4	11.9±6.4	*0.10*	19	11.6±6.7	12.2±6.9	*0.59*
Sleep latency of nap 3 (minutes)	23	12.7±7.0	12.4±6.7	*0.50*	17	8.4±5.1	9.1±5.7	*0.14*
Sleep latency of nap 4 (minutes)	16	15.6±5.7	15.6±5.7	*0.81*	16	12.5±6.5	12.7±5.2	*0.27*
Mean sleep latency all naps (minutes)	23	12.4±5.2	12.7±4.9	*0.38*	19	10.4±4.8	10.9±5.1	*0.26*
Mean sleep latency of nap 1-3 (minutes)*	23	12.4±5.3	12.7±5.1	*0.49*	19	10.0±4.7	10.5±5.1	*0.37*

†Data are presented as mean ± standard deviation.

***This measure of sleep latency is calculated to show that the data missed on nap number 4 due to technical problems did not change the group mean sleep latency.

The majority of our participants (22 out of 25) wore the in-ear sensor throughout the MSLT, including hours between naps, and only one participant commented negatively regarding the comfort of the in-ear sensor. Individual examples of scalp and in-ear EEG data during four naps for a participant who retained the in-ear sensor in place throughout the test, and a participant who removed the in-ear sensor between naps, are shown in Figures 3.4a and 3.4b, respectively.

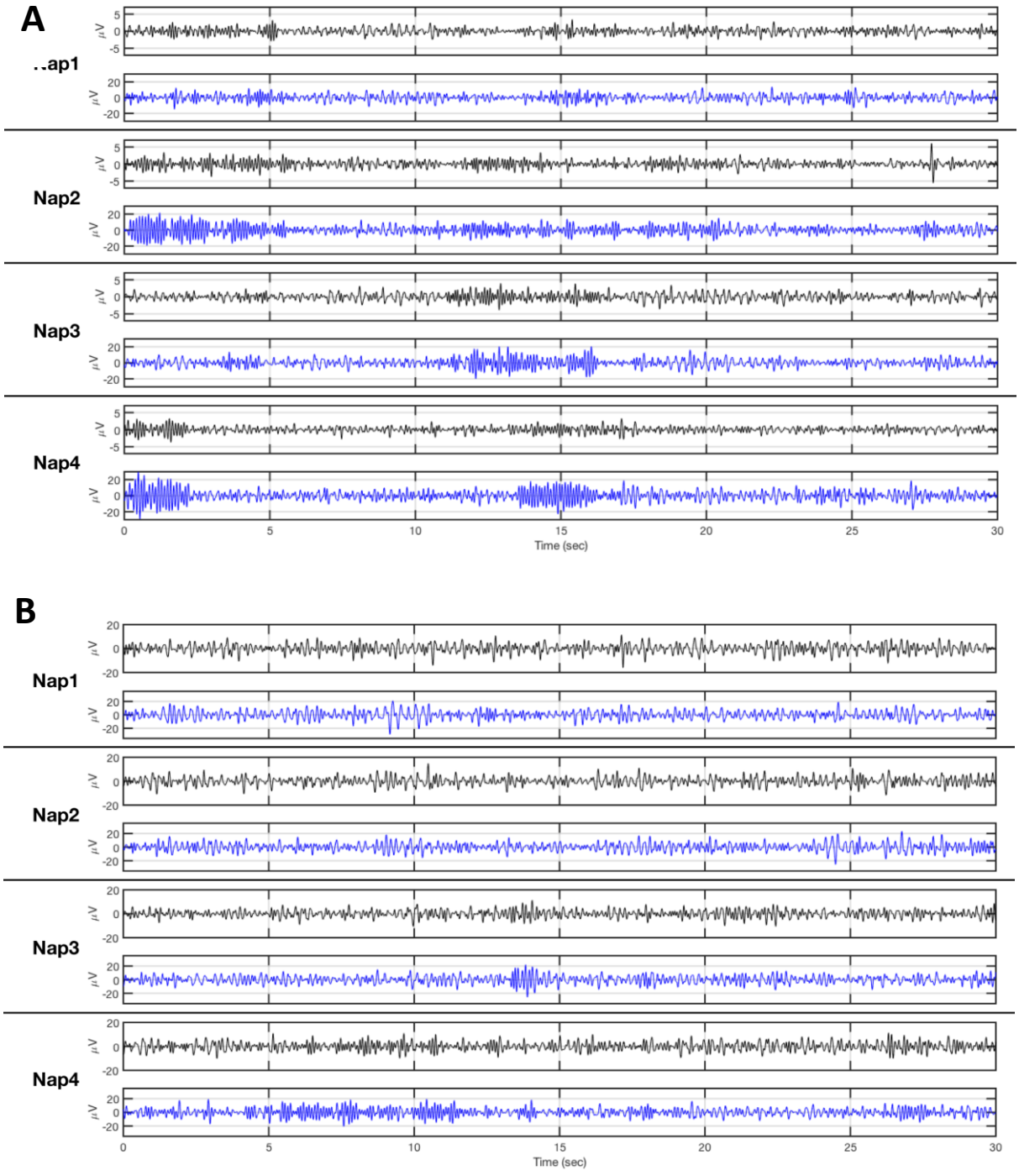


Figure 3.4: Examples of signals from scalp EEG and in-ear EEG. A) Examples of in-ear EEG (black) and scalp EEG (blue) during 4 naps from one participant (26-year-old male) who did not remove the in-ear EEG sensor between naps. B) Examples of in-ear EEG (black) and scalp EEG (blue) during 4 naps from one participant (25-year-old male) who removed the in-ear EEG sensor between naps. Each EEG figure represents 30 second epoch. Note that the amplitude of the in-ear EEG was less than that of the scalp EEG in Figure 4A. However, inspection of the trends of power-spectral density showed that they were similar over all 23 participants, for both scalp and in- ear EEG channels.

The difference between the scalp and in-ear EEGs in detection of sleep latency was <3 minutes in 84% of participants (58 out of 69) following sleep restriction and 94% of participants (80 out of 85) after usual night sleep. In the sleep-restriction condition, the in-ear EEG sensor exhibited a sensitivity of 0.93 and specificity of 0.80 for detection of sleep latency, with a substantial agreement (κ=*0.71*), while after the usual night sleep, the in-ear EEG sensor exhibited a sensitivity of 0.91 and specificity of 0.89, again with a substantial agreement (κ=*0.79*), compared with data obtained from the scalp EEG sensors. Bland-Altman analysis (Figure 3.5a) revealed good agreement between the two methods (in-ear EEG minus scalp EEG) for all naps combined (Figure 3.5b).

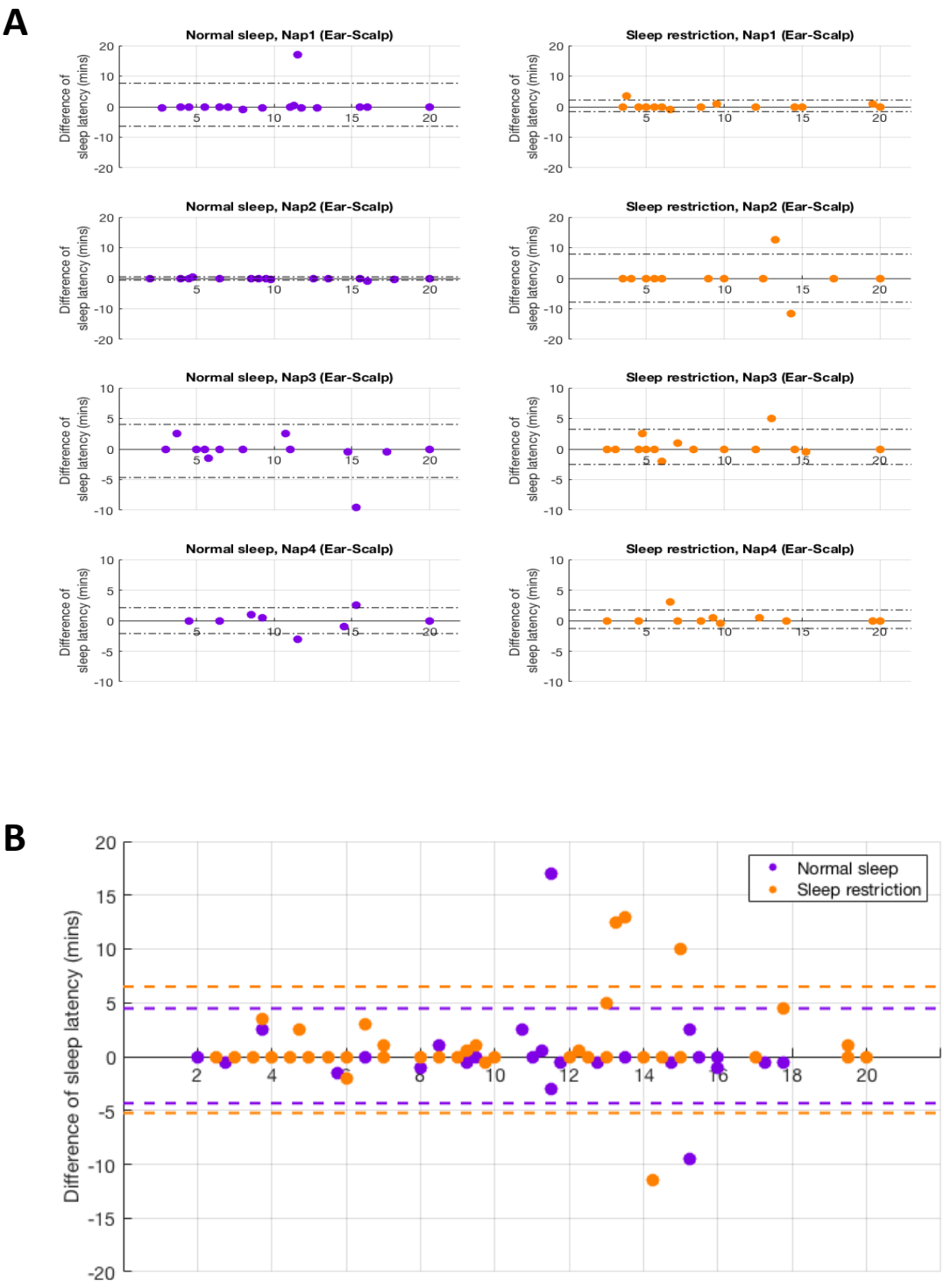


Figure 3.5: Bland-Altman agreement for scalp EEG versus in-ear EEG. A) Bland-Altman agreement for individual naps (in-ear EEG minus scalp EEG), usual night sleep visit (left) and sleep restriction visit (right). Dashed lines show the confidence interval. B) Bland--Altman agreement for all naps combined (in-ear EEG minus scalp EEG), sleep restriction (orange) and usual night sleep (purple). Dashed orange lines show the confidence interval for sleep restriction while dashed purple lines show the confidence interval for usual night sleep. Note that several data points are overlapped.

3.3.2 Changes in sleep latency, reaction time and cognitive function following sleep restriction

The mean sleep latency decreased significantly after sleep restriction compared with after usual night sleep in the scalp EEG measurements (10.4±4.8 minutes, 12.4±5.2 minutes; $\underline{p}$=0.014) and in-ear EEG measurements (10.9±5.1 minutes, 12.7±4.9 minutes; $\underline{p}$=0.019).

Participants fell asleep during 83% (57 out of 69) of the offered nap periods after sleep restriction and in 64% (55 out of 85) of the offered nap periods after usual night sleeps. Comparison of individual naps showed that nap 3 and nap 4 exhibited greater differences between sleep restriction and usual night sleep ($\underline{p}$*=0.004,* $\underline{p}$*=0.005)* compared with naps 1 and 2 ($\underline{p}$*=0.115,* $\underline{p}$*=0.792)*.

There was a modest but statistically significant increase in reaction time after sleep restriction compared with after usual night sleeps (238.4±30.4ms, 228.5±27.1ms; $\underline{p}$*=0.045*). When completing the Stroop test, the number of mistakes in the conflicting word task increased significantly after sleep restriction compared with after usual night sleep (2±2, 1±1, $\underline{p}$*=0.003)*. No significant increases were observed in the conflicting colour, colour block, or monochrome tasks (Figure 3. 6a). The period taken to complete each task increased for the conflicting colour, colour block, and monochrome tasks after sleep restriction, but this was not statistically significant (Figure 3.6b).

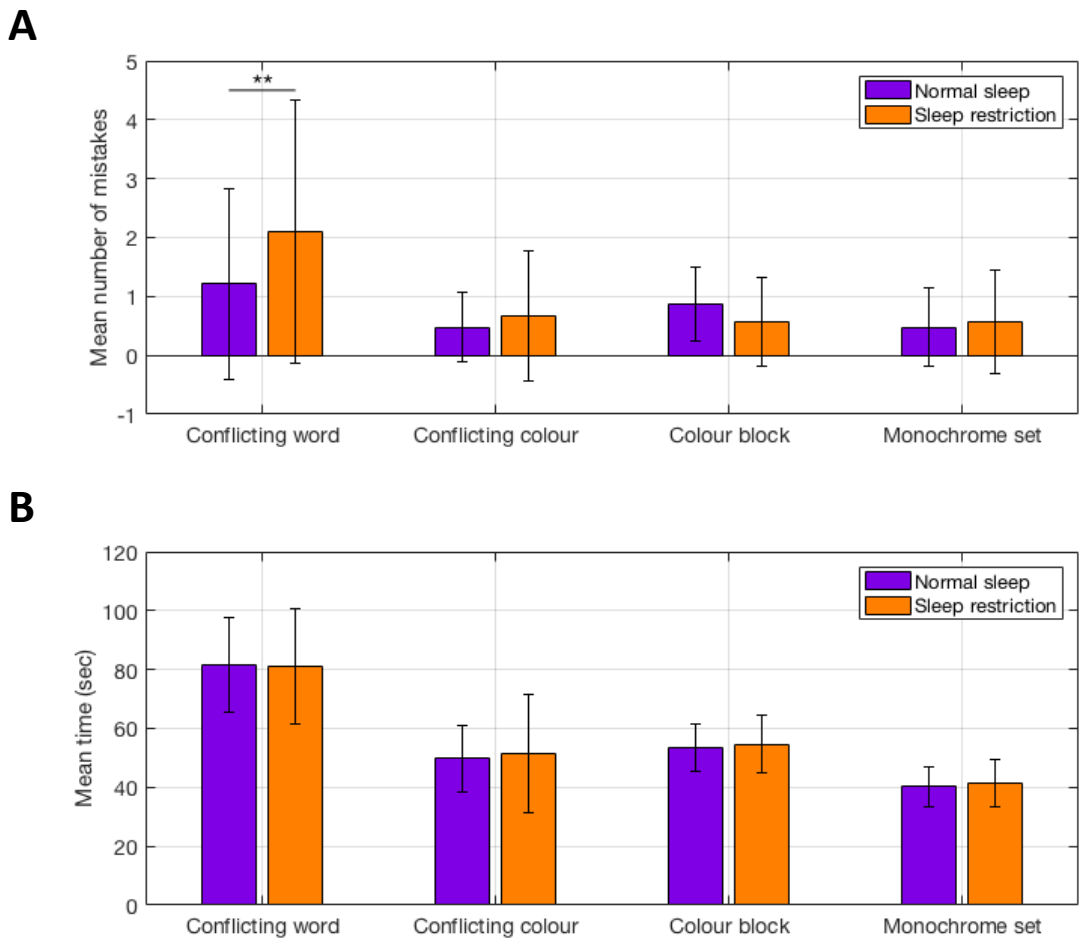


Figure 3.6: Stroop test after sleep restriction and after usual night sleep. A) The number of mistakes in each task. The greatest number of mistakes was in the conflicting-word task after sleep restriction, and this change was significant compared with the results after usual night sleep. B) The mean time spent on each task (seconds). The time increased after sleep restriction in the conflicting colour, colour block, and monochrome set, but did not reach significance level. ** p =0.003.

3.4 Discussion

The main finding of this study was that use of the in-ear EEG sensor enabled detection of sleep latency with substantial agreement, compared with the scalp EEG. As a consequence, use of the in-ear EEG sensor also enabled detection of the shortened sleep latency, induced by sleep restriction, which was associated with measurable functional impairment, as indicated by the reduced reaction time, and cognitive function.

3.4.1 Critique of the method

The participants in this study were all healthy adults. The performance of the in-ear EEG sensor in patients with sleep disorders is yet to be examined, therefore at the moment I cannot comment on the applicability of the current data, compared with that obtained from patients with sleep disorders. The same applies to discussion related to older people with more fragmented and less well-defined sleep architecture.

Another limitation of our study was that an overnight polysomnography was not carried out prior to the MSLT, as defined by the standard protocol (Carskadon *et al.,* 1986). Therefore the sleep restriction was not objectively documented. Conceptually it was possible that the participants slept between the times of logging into the website during the sleep restriction, and/or may have stayed awake during the usual night-sleep duration. However, the reaction times and cognitive abilities measured by the Stroop test were significantly impaired following the sleep restriction, which suggested that our participants adhered to the protocol. Previous studies, which utilised acute sleep restriction ≤ 5 hours, found a decreased sleep latency of two minutes (Belenky *et al.,* 2003). The sleep restriction in our study also produced a reduction in sleep latency of two minutes. In addition, reaction time was increased, and cognitive ability was impaired (Lim & Dinges, 2008). Our finding that the number of errors on the conflicting-word task increased following sleep restriction was also consistent with previous studies (MacLeod, 1991). In our study, the Stroop test was performed after nap 3, which enabled us to test the maximum impact of the decline in cognitive abilities as this seemed to deteriorate as cumulative time awake increased (Doran *et al.*, 2001). Previous studies also showed that the time of the day (morning vs. afternoon) impacted the cognitive abilities after sleep restrictions due to the circadian dip (Mollicone, Van Dongen, Rogers, Banks, & Dinges, 2010).

The current study extends our previous findings that use of the in-ear sensor enables detection of the non-REM (N3) stage (Looney *et al.,* 2016), but it does not extend to the detection of REM sleep. Indeed, I am not claiming the applicability of the sensor in the evaluation or diagnosis of specific sleep stages beyond sleep latency or sleep disorders.

3.4.2 The in-ear EEG sensor

In this study, the in-ear sensor was made from viscoelastic material, to enable expansion to fit tightly in the ear canal (Goverdovsky *et al.,* 2016). The size of the in-ear sensor was the same for all participants, even though the size of the ear canal may have been different in some participants, so the in-ear EEG sensor may not have fitted properly with the ear canal. Therefore, naps were removed from the analysis due to poor signal quality from the in-ear EEG sensor; specifically ECG artefacts, high-frequency artefacts, low-frequency artefacts, or movement artefacts may have been observed as a consequence of conduction difficulties between the skin and the in-ear sensor. A potential development would be to make the in-ear EEG sensor available in different sizes, and this could increase the retention of the in-ear sensor. This may be important when studying women in whom the average ear diameter is smaller (8.5±0.7 mm) than that of males (9.7±1.1 mm), and when studying different ethnicities, as European people typically have a larger ear canal diameter than those of Asian descent (Staab, Sjursen, Preves, & Squeglia, 2000).

In our study, the in-ear EEG analysis was carried out offline, since capture and analysis of data in real time would have required an automated algorithm. The development of such algorithms has proved elusive for PSG. However, this might be made easier through use of an in-ear EEG sensor since the interference from the EEG recorded from the ear canal is minimal (Kappel, Looney, Mandic, & Kidmose, 2017; Nakamura, Goverdovsky, Morrell, & Mandic,

2017; Tonoyan, Looney, Mandic, & Van Hulle, 2016).

Recording the EEG from within the ear has been investigated by different research groups (Kaare B Mikkelsen, Villadsen, Otto, & Kidmose, 2017; Nguyen *et al.*, 2017). However, there are distinct differences between our in-ear EEG device and other devices. Nguyen *et al.* used off-the-shelf foam-based earplugs that could be inserted in both ears simultaneously, one of the earpieces incorporated two passive electrodes, and the reference and ground electrodes were placed on the other earpiece. The two earpieces were connected with a wire cable. The device used by Mikkelsen *et al.* was a custom-made hard-shell in-ear EEG sensor. The earpiece incorporated four electrodes in total, two active electrodes, ground, and reference electrodes, and all were embedded in the same earpiece. Therefore, our device made from a viscoelastic earplug based on 'one-size-fits-all', and used only in one ear (left or right), shows significant differences. Additionally, the reference and ground electrodes of our in-ear EEG device were placed on the helix and earlobe, respectively, using gold-cup electrodes.

3.4.3 Significance of the findings

The in-ear EEG sensor exhibits at least two characteristics that make it convenient to use. First, the memory-foam mounting enables the sensor to be fitted comfortably and safely inside the ear after it has been squeezed from all sides. It also allows the sensor to expand evenly so it remains in place. Secondly, the sensor incorporates a conductive cloth cover, which is flexible and soft to make the sensor comfortable to wear. The present data confirm that use of the in-ear EEG sensor enables identification of sleep latency accurately enough to detect the short sleep latency elicited by sleep restriction in healthy adults. Further development is needed to understand how this can become a useful tool to capture recordings of sleepiness in the real-world (Goverdovsky *et al.,* 2017).

In our study, the majority of our participants wore the in-ear EEG sensor throughout the MSLT, including during the hours between naps. The qualities of the EEG signals obtained from a participant who wore the sensor throughout the MSLT and from a participant who removed the sensor were almost the same (Figures 4a and 4b). These figures demonstrate that the transition from alpha activity to theta activity observed in the scalp EEG is very similar to that observed in the EEG obtained in-ear. Therefore the quality of the signals does not change over time and this suggests that the in-ear EEG sensor is applicable for long-term recordings, such as overnight recordings (see Chapter 4).

A logical development of our study would be to develop a real-world MSLT. However, unless functionally significant data could be obtained from fewer than four naps, the procedure would be time consuming for the participant, even if less so for the investigator. Sunwoo *et al* have shown that, compared with four naps, a single nap subjected to a MSLT can detect reasonably well individuals with sleep latency of less than eight minutes (Sunwoo *et al.*, 2012).

Another potential use of our sensor could be domiciliary measurement of sleep latency. This cannot be performed easily for practical reasons. However, sleep latency measured at home on several consecutive nights, for example, might lead to improved understanding of idiopathic hypersomnia, which is currently typically monitored by actigraphy (Sateia, 2014). A further potential development for the in-ear EEG sensor would be in real-time detection of sleep, for example, as part of a system to detect sleepiness during driving. This would entail development of an automated, and rapid, scoring algorithm. Nakamura *et al.* have developed an algorithm to classify sleep stages with 90% agreement, compared with conventional scoring (Nakamura, Adjei, *et al.*, 2017). In this context, an advantage of the in-ear EEG sensor is that it allows free movement of the wearer, and is not visibly obtrusive; it may be possible

to modify its use for environments where PSG is not feasible.

Finally, although not tested in this study, our findings suggest that in-ear EEG data could also be used to simplify MSLT/MWT. This could be useful for some high-risk occupations in which participants are required to remain alert. For example, military pilots with hypersomnia in the US are advised by the United States Air Force to be tested for alertness through use of MWT (Grossman, Barenboim, Azaria, Sherer, & Goldstein, 2004). Similarly, in Australia, MWT has been recommended to assess the fitness for driving of patients with sleep disorders (Austroads, 2003). One can imagine a scenario in which a modified, simple MSLT/MWT is used to screen employees in high-risk occupations before they start their shifts.

3.5 Conclusion

Our findings show that detection of sleep latency is possible through use of the in-ear EEG sensor, during MSLT with and without sleep restriction, with substantial agreement compared with the results using the gold standard scalp EEG. The majority of participants in our study found the in-ear EEG sensor to be comfortable, and were able to keep it *in situ* all day. Also, our data show that the sleep restriction imposed was sufficient to shorten the sleep latency, with a decline in cognitive ability elicited by sleep restriction. I believe that the in-ear EEG sensor will provide new opportunities in clinical and occupational medicine to monitor real-world sleep.

Chapter 4. The efficacy of an in-ear electroencephalogram sensor to measure non-rapid-eye-movement sleep in healthy adults overnight

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4.1 Introduction

Polysomnography (PSG) remains the gold-standard technique for sleep assessment. However, attachment of all the required sensors can take a significant amount of time, and the subject can find these sensors uncomfortable to wear for an extended time because they are incompatible with any activity. One component of the PSG is the scalp EEG, which is used to distinguish wakefulness from non-rapid-eye-movement (non-REM) sleep and to subcategorise non-REM sleep into light and deep sleep. Rapid-eye-movement (REM) sleep is hard to distinguish electroencephalographically from wakefulness. Thus, other sensors, such as electrooculogram (EOG) and chin electromyogram (EMG) sensors, are needed to determine REM sleep. Nevertheless, since REM does not generally occur during the first hour after sleep onset, documentation of sleep onset and offset and assessment of the quantity of slow-wave sleep (SWS) could be obtained in large part from scalp EEG data alone.

Recently, wearable devices to monitor EEGs have been developed; typically sensors placed in the ear (Looney *et al.*, 2012). For more details see Chapter 1, section 1.4 and Chapter 2, section 2.6, but in brief this approach of using in-ear EEG has been tested for the detection of sleep against use of the conventional scalp EEG by different research groups (Kidmose *et al.*, 2013; Mikkelsen *et al.*, 2018; Mikkelsen *et al.*, 2017; Nguyen *et al.,* 2017; Stochholm, Mikkelsen, & Kidmose, 2016). These studies show substantial agreement between the in-ear EEG and scalp EEG sensors in experiments to detect all sleep stages. All these research groups used systems with two or more electrodes, but with different construction techniques. For example, Nguyen *et al.* used an in-ear sensor made from viscoelastic materials (similar to commercial earplugs)(Nguyen *et al.*, 2017), whereas Mikkelsen *et al.* used a customised in-ear EEG sensor made from hard-shell materials with six sensors in the earpiece (Mikkelsen *et*

al., 2017).

As described in Chapter 1&2, our group has developed an in-ear sensor which is mounted in a single generic earpiece that provides monaural (from one ear) recordings (Goverdovsky *et al.*, 2016). In Chapter 3, the sensor was tested during daytime naps (Looney *et al.*, 2016) with and without sleep restriction, and has been employed to produce functional cognitive measures of the impact of the sleep restriction. We showed that it could detect sleep onset (i.e. typically stage N1 sleep) accurately (Alqurashi *et al.*, 2018). In the study described in this Chapter, we sought to extend the findings from Chapter 3, by testing our in-ear EEG sensor during overnight sleep, with simultaneous recording of scalp EEG. We tested the hypothesis that there would be a good agreement between the in-ear and scalp EEGs for the detection of slow-wave sleep (SWS) in healthy participants overnight. We also investigated whether use of the in-ear EEG sensor would enable detection of stage 2 sleep (N2) and wakefulness as secondary outcomes.

4.2 Methods

4.2.1 Participants

Twenty-two healthy participants were recruited from among the body of students of Imperial College London. The inclusion and exclusion criteria were as follows:

- ***Inclusion criteria:***

1. Age ≥ 18 years
2. No reported sleep problems
3. Currently not taking prescribed sleep medicines or antidepressants
4. No major illnesses in the past 18 months for which the participant has seen a specialised doctor

- ***Exclusion criteria:***

1. Shift workers
2. International flight in the past two weeks
3. Medication that affects sleep quality or duration
4. Any significant neurological conditions such as seizure
5. Poor hearing
6. Pregnancy
7. Inability to give a fully informed consent

The exclusion criteria comprised: any self-reported sleep disorder, shift work, use of sleep medication, a hearing impairment or an ear infection. Participants gave written informed consent and the study was approved by the Imperial College Research Ethics Committee: (ICREC no: 17IC4150). See Appendix 4 for a copy of the approval.

4.2.2 Screening

Communication with potential participants was conducted initially by email, with subsequent face-to-face interviews to familiarise the participants with the in-ear EEG sensor. If participants met the criteria and agreed to participate, they were assigned a date for an overnight home PSG.

4.2.3 Protocol

Participants were visited at their home approximately two hours before their usual bedtime. Participants were asked to be prepared for their bedtime routine before the arrival of the sleep physiologist. Upon arrival, the ESS questionnaire was given to be completed by the participant, and then the application of the in-ear EEG and scalp EEG sensors was started. The set-up time of the PSG was approximately one hour; this included the application of the PSG, bio-calibration and impedance checking. The time for the application of the in-ear EEG electrode was approximately 30 minutes; this included ear wax removal using cotton buds,

preparation of the electrode with the conductive gel (Parker Laboratories, Inc, Fairfield, NJ, US), and impedance checks.

Prior feasibility studies had demonstrated that a low impedance (<10KΩ) was critical to achieve good-quality signals from the in-ear EEG. Therefore, if the impedance of the in-ear EEG was >10KΩ then the electrode was re-inserted. This process was repeated until good impedance was reached. Once the equipment was attached, the sleep physiologist left the participant's home, having asked the participant to sleep as usual. Each participant was given the sleep physiologist's contact number should they encounter any unforeseen issues. Participants were also asked to remove the sensors should they feel any discomfort. In the morning, the sleep physiologist visited each participant's home to collect the equipment.

The recording of the in-ear EEG and the PSG data was conducted simultaneously using two separate systems, through amplifiers and computers (see polysomnography and in-ear EEG sections below). The agreement between the times of these two systems was checked before each recording. The recording from the two computers was started simultaneously (manually) and the end of the recording was pre-set according to the participant's wake-up time.

4.2.4 Polysomnography

PSG recording was carried out using Somnomed screen diagnostic equipment (SOMNOmedics GmbH, Randersacker, Germany). The nocturnal PSG recordings included: scalp EEG data from electrodes placed on C3/M2, C4/M1, O1/M2, O2/M1, F3/M2, and F4/M1 according to the 10/20 system; EOG; EMG of the chin and both legs; continuous finger pulse oximetry; chest and abdominal movements (thoracic and abdominal belts); airflow (thermistor); and snoring (microphone). Data were acquired at a sampling rate of 256 Hz and bandpass filters were set between 0.2Hz and 35 Hz. Data were transmitted to a computer

wirelessly in real time (Hewlett-Packard**;** hp, EliteBook, 850 G3, Palo Alto, California, US).

4.2.5 In-ear EEG sensor

Full technical specifications of the in-ear EEG sensor can be found in the General Methods chapter (Chapter 2). In brief, the in-ear EEG sensor was made from a viscoelastic memory foam, similar to a commercial earplug. This produced a flexible and generic ear sensor, which could be squeezed and shaped to fit within any ear shape. Two flexible cloth EEG electrodes were constructed out of stretchable knitted fabric and embedded onto the sensor diametrically opposite one another. After the in-ear EEG sensor had been placed inside the ear canal, the memory foam relaxed and redistributed throughout its outer surface. Either ear could be selected for placement, according to each participant's preference. The ground and reference electrodes for the in-ear EEG sensor were placed on the earlobe and helix, respectively, using gold-cup electrodes (Bio-medical, MI, US). Data were acquired with a sampling rate of 1.2kS/s using a g.tec g.USBamp amplifier with 24-bit resolution (g.tec medical engineering GmbH, Schiedlberg, Austria). An example of a participant wearing both the scalp EEG and in-ear EEG sensors is shown in Figure 4.1.

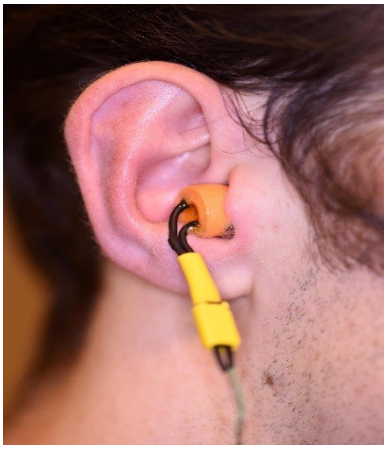


Figure 4.1: A participant wearing the in-ear EEG sensor, showing how it fits inside the ear during an overnight sleep study.

4.2.6 Sleep scoring

PSG data (all electrodes) were firstly scored un-blinded for the entire night for all participants by a single scorer according to the sleep stages specifications of the American Academy of Sleep Medicine (AASM) 2012 criteria (Berry, Brooks, *et al.,* 2012). Then, 20-minute periods (40 epochs) of uninterrupted (no movement) SWS, N2, and wakefulness were selected from the scalp EEGs. Note that REM sleep was not chosen, since the current criteria for scoring REM required EMG and EOG data. These 20 minutes were selected from electrodes C3/A2 and C4/A1 only due to their proximity to the ear, with the assumption that the EEGs obtained from these two places would most resemble that received from the in-ear sensor. Each 20-minute period was preceded by three minutes of consolidated sleep. Where possible, consecutive 20–minute periods for each sleep stage were selected: in other words, where no arousal occurred between the periods. If arousal occurred, sampling was not restarted until consolidated sleep had been maintained for three minutes. Therefore, these 20-minute periods were not always continuous. The scalp EEG data were then sent to a second investigator who was not involved in the sleep analysis described above (researcher TN) to extract the corresponding 20-minute periods from the in-ear EEG recordings. The 20-minute sections of EEG data from each device were then randomised and blinded; that is, periods of SWS, N2, and wakefulness were not consecutive and there was no identification of the participant. There were data for 120 epochs (40 epochs*3 sleep stages) for each participant from each device. These blinded data that showed SWS, N2, and wakefulness recorded by both in-ear EEG and scalp EEG were then returned to the author, YA, to be reanalysed blindly. The second scoring of the scalp EEG data provided intra-scorer reliability data. At the end of the analysis, data were un-blinded to enable statistical analysis.

The in-ear EEG data from channels 1 and 2 were analysed in combination; that is, each channel was not scored separately. This was also the case for C3/A2 and C4/A1 from the scalp EEG. If an epoch could not be visually scored according to the AASM criteria, then that epoch was scored as an artefact.

4.2.7 Sample size and statistical analysis

An *a priori* sample size was estimated based on a study by Bhat *et al.* in which they found a difference of 11% in SWS between two devices with a standard deviation of 10% among healthy participants (Bhat, 2015). Using these data at 5% significance level and 80% power, a sample size of 12 participants was required for this study.

The primary outcome of this study was the measurements of SWS obtained from the in-ear EEG sensors during an overnight sleep study and which could be compared with results from scalp EEG. The agreement between the in-ear and scalp EEGs in detection of stage N2 sleep and wakefulness was also investigated as a secondary outcome. To evaluate the sensitivity and specificity of the in-ear EEG sensor against the scalp EEG sensors, the number of epochs scored as SWS, N2, and wakefulness were categorised as 'positive' or 'negative' using a 3*3 contingency table, and that categorisation was used to assess the sensitivity and specificity. The agreement between the scalp EEG and in-ear EEG sensors in the detection of SWS, N2, and wakefulness was calculated using the Kappa agreement method. The limits of agreement were interpreted thus: values ≤ 0 were taken as no agreement; 0.01-0.20 as slight agreement; 0.21-0.40 as fair agreement; 0.41-0.60 as moderate agreement; 0.61-0.80 as substantial agreement; and 0.81-1.00 as almost perfect agreement.

The IBM SPSS 23.0 software and Excel 2013 were used for statistical analysis and to generate the graphs.

4.3 Results

Out of 22 participants who screened, technically acceptable data were obtained from 12 participants (five females) aged 22±2 years (mean±SD).

The EEG data that were excluded from the analysis either due to high-frequency noise from the PSG (n=1), total sleep time of less than 2 hours (n=1) or high impedance from the in-ear EEG (n=8). High impedance from the in-ear EEG was defined as any impedance of more than 10KΩ from the reference electrode.

The ESS score prior to the sleep study was 8±5. All participants reported that this was the first time they had experienced an overnight sleep study, but two participants had previously worn our in-ear EEG sensor in a previous study.

Table 1 shows the PSG values of overnight sleep parameters. The participant slept for more than six hours and exhibited sleep efficiency of more than 70%. The sleep latency was high (>30 minutes) and this might have been due to the new experience of the overnight sleep study (first-night effect).

Table 4.1: The PSG values of overnight sleep parameters.

Sleep parameters	Value (m ± SD)
Total bed time (hour)	8.5 ± 0.6
Total sleep time (hour)	6.8 ± 0.8
Sleep efficiency (%)	77.3 ± 9.9
Sleep latency (min)	46.4 ± 25.5
N1 sleep (%)	2.6 ± 1.3
N2 sleep (%)	58.7 ± 6.6
N3 sleep (%)	23.0 ± 6.4
REM sleep (%)	15.7 ± 7.1

An example of data that show a 30-second epoch of SWS from the in-ear EEG sensor with corresponding signals from the scalp EEG sensors are shown in Figure 4.2A. Another example of data that show a 30-second epoch of stage N2 sleep from the in-ear EEG sensor with corresponding signals from the scalp EEG sensors is shown in Figure 4.2B.

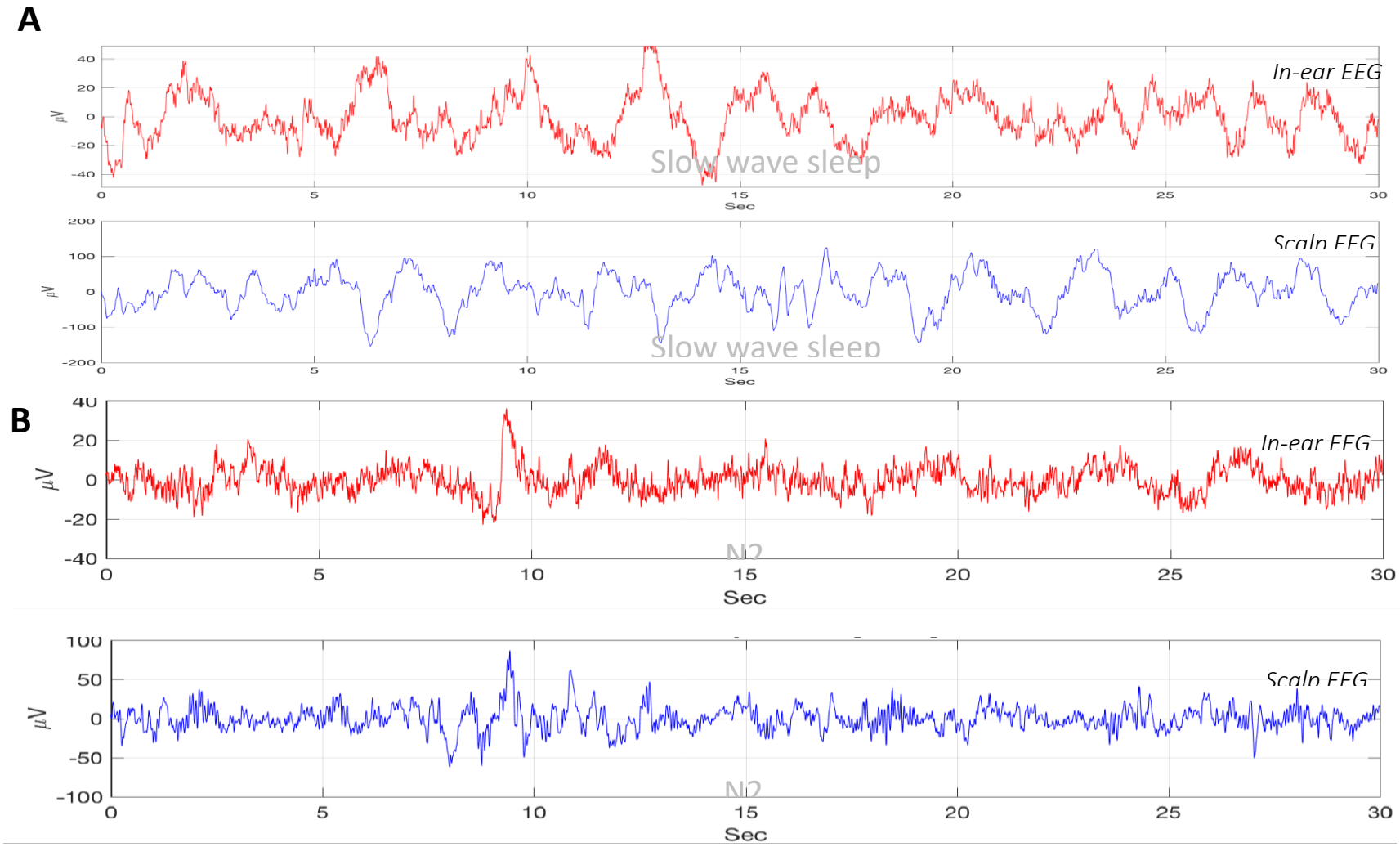


Figure 4.2: Example of EEG data during a 30-second epoch. A: An example of data that show slow-wave sleep from both the in-ear EEG sensor (red) and the corresponding scalp EEG sensors (blue). B: An example of data that show stage N2 sleep from the in-ear EEG sensor with the corresponding scalp EEG. Note that the amplitudes of the EEGs are different.

4.3.1 Comparison of the in-ear EEG findings with those from the scalp EEG

The accuracies of the in-ear EEG sensor in the detection of SWS, N2 sleep, and wakefulness (W) were 90%, 80%, and 88%, respectively, with an overall accuracy of 86%, and kappa agreement of 0.79, which indicated substantial agreement. The numbers of epochs that were incorrectly scored are shown in the 3X3 contingency table (Figure 4.3).

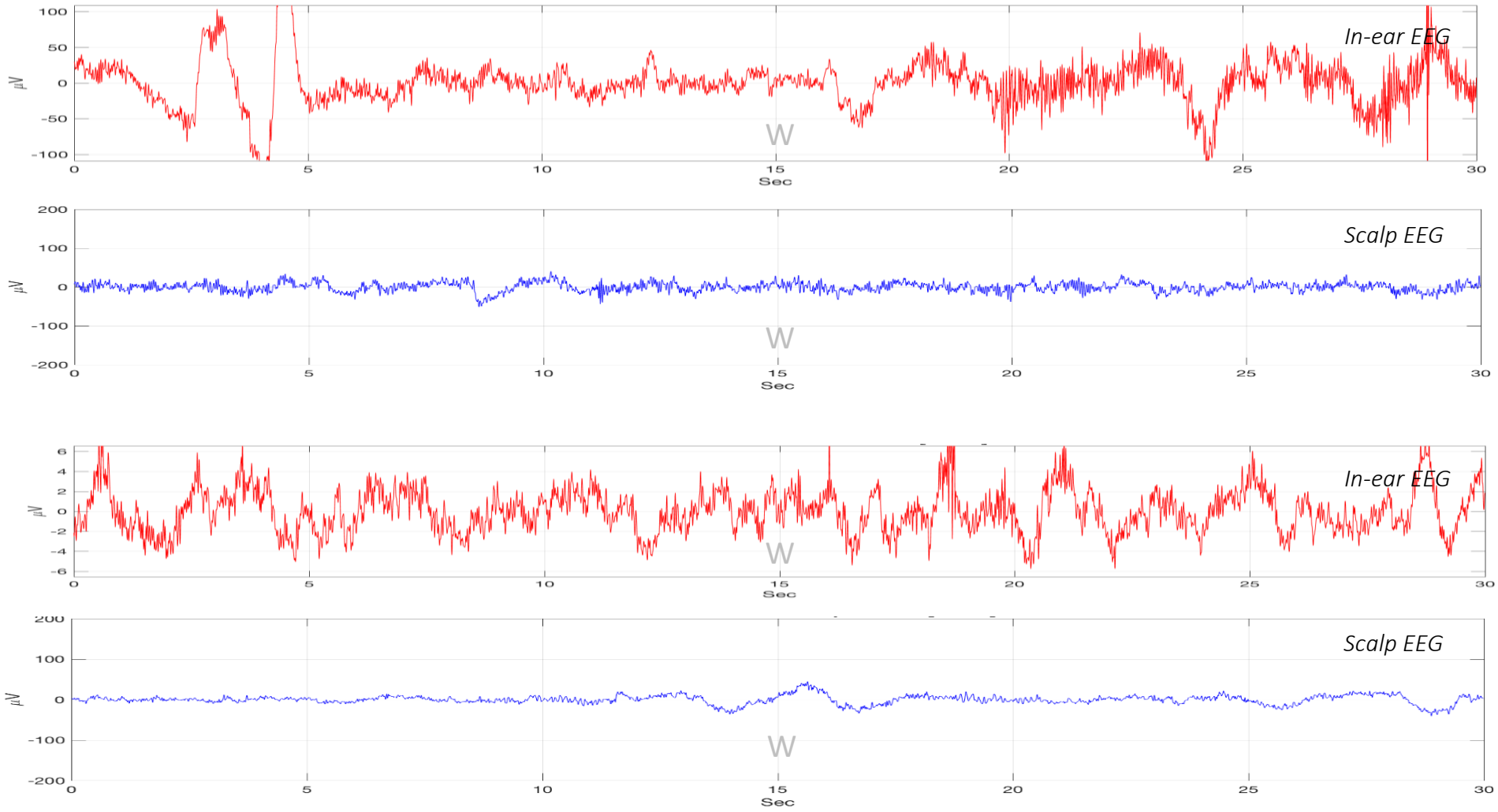
		In-ear EEG Number of epochs (%)			
		SWS	**N2**	**W**	**Total**
Scalp EEG	**SWS**	**426 (90%)**	47 (9%)	2 (1%)	**475 (100%)**
	N2	36 (8%)	**367 (80%)**	58 (12%)	**461 (100%)**
	W	5 (1%)	50 (11%)	**404 (88%)**	**459 (100%)**
	Overall accuracy	**1197/1395= 86% (*κ*= 0.79)**			

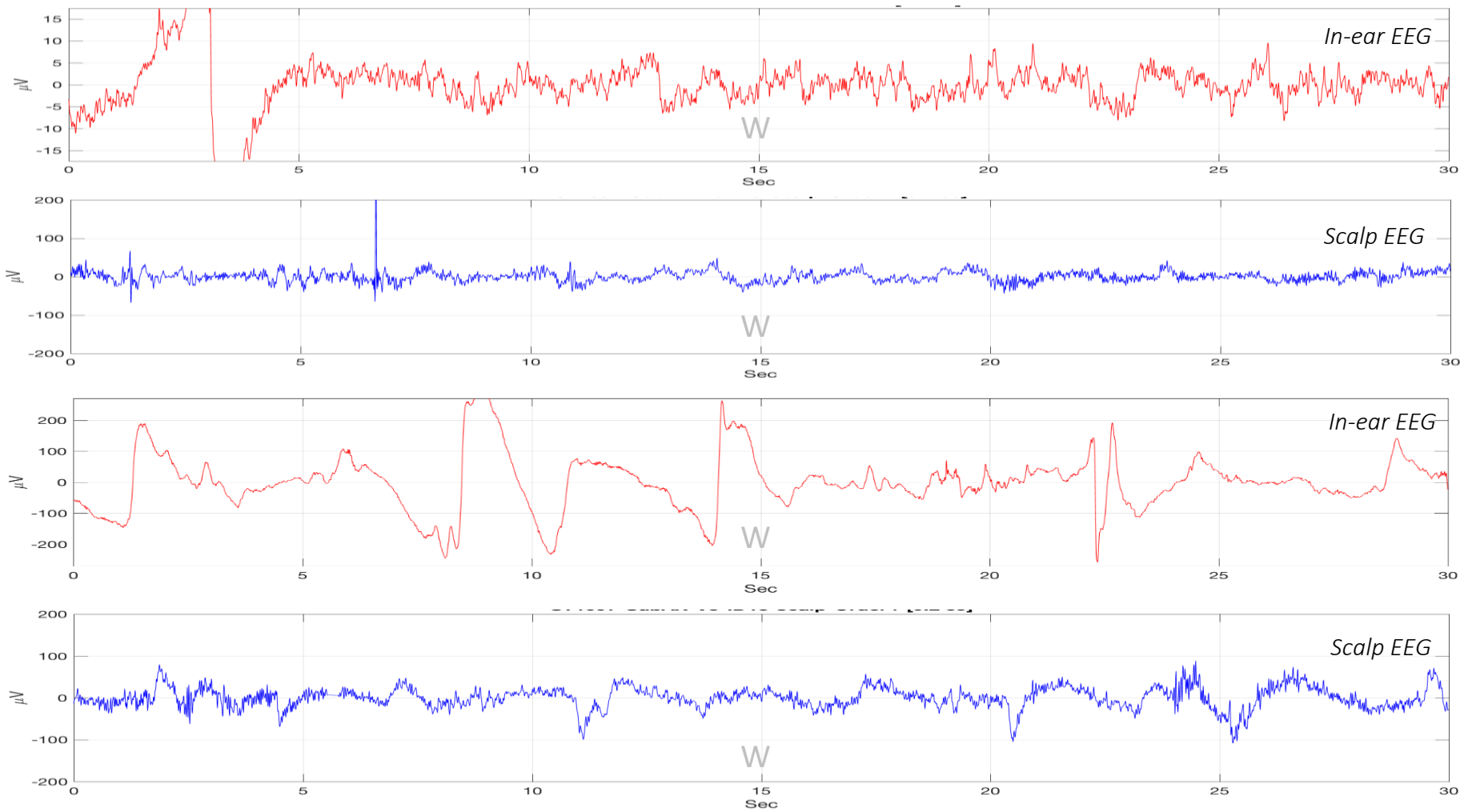
Figure 4.3: The 3*3 contingency table showing the comparison between the in-ear EEG and scalp EEG results.

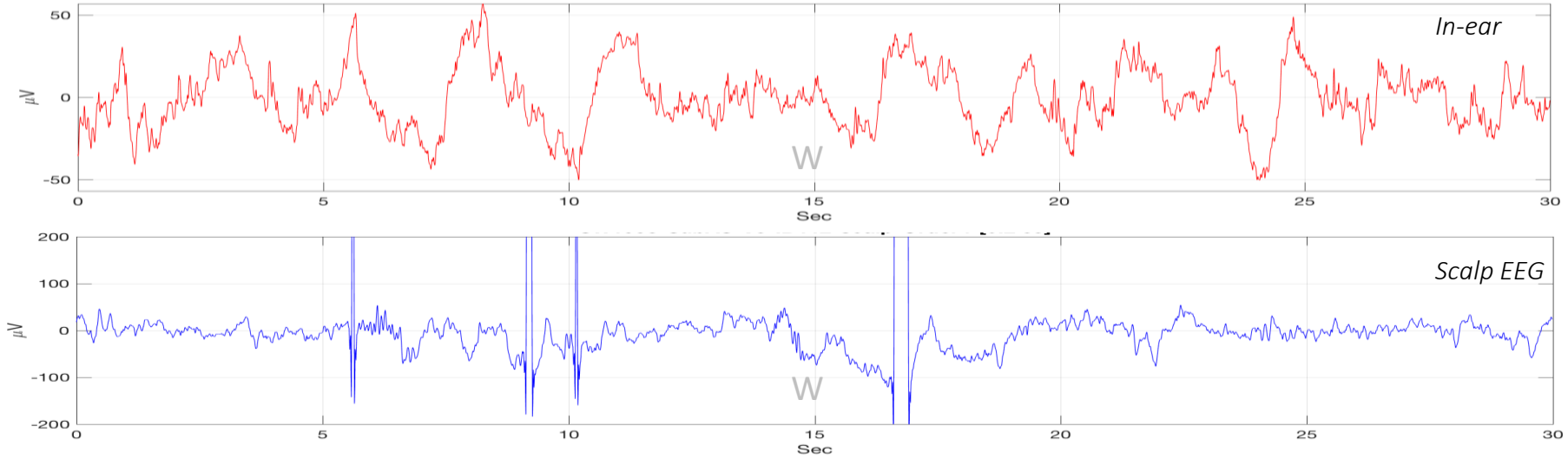
Five epochs of wakefulness were incorrectly scored as SWS from the results obtained through the in-ear EEGs from four participants. Paradoxically, two epochs of SWS were incorrectly scored as wakefulness after analysis of the in-ear EEG results from two different participants. To understand how this had occurred, epochs were inspected and compared with the

corresponding epochs obtained from scalp EEG. It seems that the main reasons for the incorrect scoring were the superimposed alpha and delta waves seen in the data obtained from the in-ear EEG data (see Figures 4.4A and 4.4B).

A




In-ear EEG
Scalp EEG
In-ear EEG
Scalp EEG
μV
Sec
W


In-ear
50
0
-50
μV
W
0
5
10
15
20
25
30
Sec
Scalp EEG
200
100
0
-100
-200
μV
W
0
5
10
15
20
25
30
Sec

B

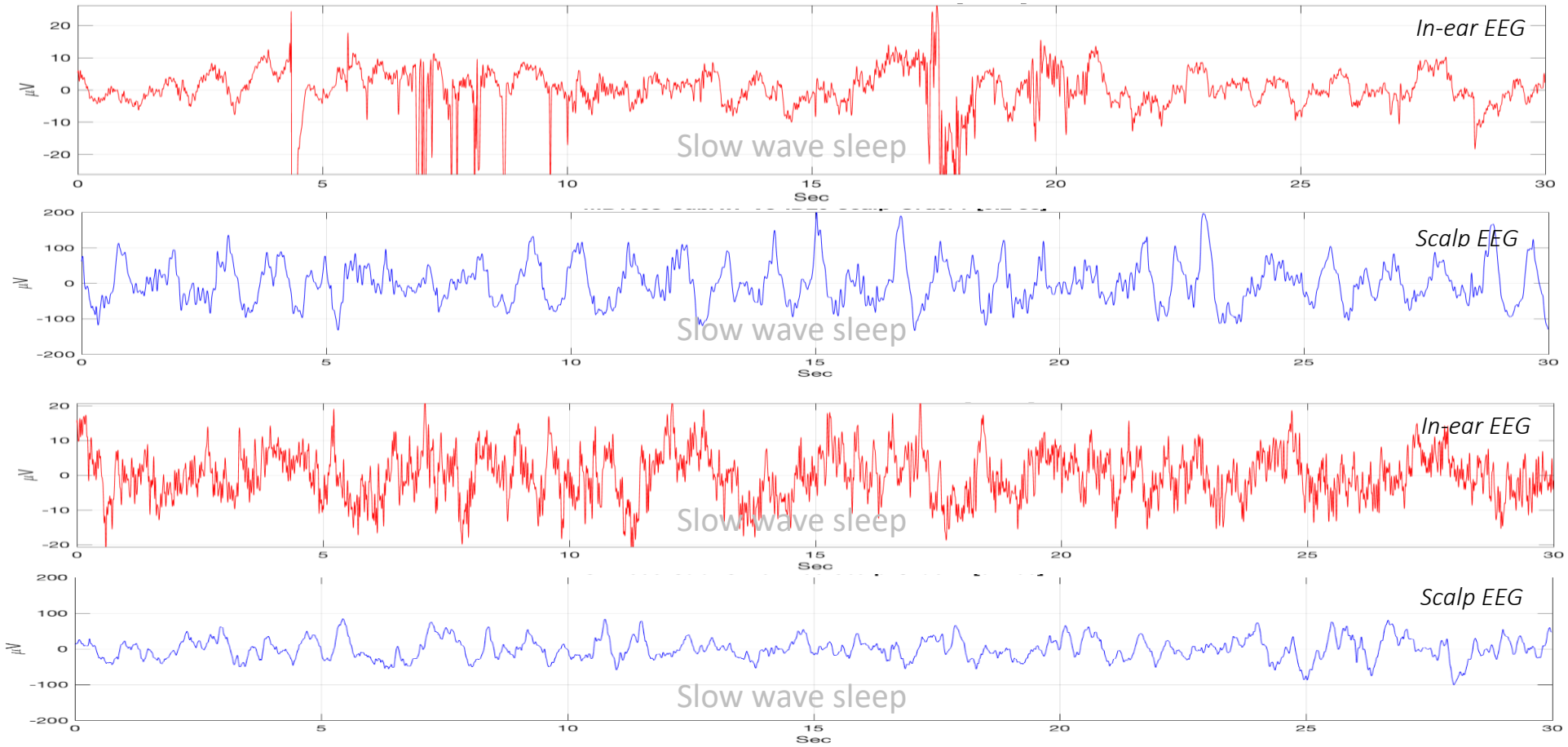


Figure 4.4: The data for the seven epochs that were incorrectly scored from the in-ear EEG (red) and the corresponding scalp EEG (blue). A: five epochs incorrectly scored as SWS rather than wakefulness from four different participants. B: two epochs incorrectly scored as wakefulness rather than SWS from two different participants. Note that the alpha wave is overlapped with delta waves in the data obtained from the in-ear EEG sensor in both figures. This might be the cause of the incorrect scoring of the data obtained from the in-ear EEG sensor.

As a sleep monitor (wakefulness vs. N2 and SWS combined) the sensitivity and specificity of the in-ear EEG sensor were 87% and 94%, respectively.

4.3.2 Intra-scorer reliability

The second scoring of the data obtained from the scalp EEGs after blinding enabled the assessment of the intra-scorer reliability. The reliability of scoring the scalp EEG data was 93%, which exhibited almost perfect agreement (κ= 0.88). The numbers of epochs that were incorrectly scored are shown in the 3X3 contingency table (Figure 4.5).

		Re-analysis of scalp EEG data Number of epochs (%)			
		SWS	**N2**	**W**	**Total**
<u>Original</u> analyses of scalp EEG data	**SWS**	**462 (96%)**	18 (4%)	0 (0%)	**480 (100%)**
	N2	13 (3%)	**430 (90%)**	37 (7%)	**480 (100%)**
	W	0 (0%)	39 (8%)	**441 (92%)**	**480 (100%)**
	Overall accuracy	**1333/1440= 93% (κ= 0.88)**			

Figure 4.5: The 3*3 contingency table showing the comparison between the interpretations of the scalp EEG data before and after blinding (intra-scorer reliability).

4.4 Discussion

The main finding of this study was that use of the in-ear EEG sensor enabled detection of non-REM sleep, specifically SWS and N2 sleep, and wakefulness, at a substantial level of agreement compared with scalp EEG sensors. These results, taken with our previous findings (Chapter 3) dealt primarily with N1 sleep (Alqurashi *et al.*, 2018), offer new opportunities in clinical and occupational sleep medicine to monitor overnight sleep objectively using a simple and wearable device.

4.4.1 Critique of the method

One limitation of this study was that the number of participants excluded from the analysis because of the poor signals from the in-ear EEG was relatively high (n= 10; 41%). Previous studies have shown that poor quality signals from type 2 sleep studies (full PSG at home) occurred in 4-23% of studies depending on where the set-up was conducted (home vs. hospital). The nature and/or mode of fixation of the in-ear EEG is different to that of the scalp EEG. The in-ear EEG used in this study was made from viscoelastic material, and one issue was the dislodgment of the sensor from the ear. Unlike scalp EEG, the in-ear EEG was not fixed by tape/adhesive material, and it could be that the in-ear EEG was displace during the overnight sleep.

Another limitation is that the EEG data from each channel were not analysed separately. Instead, the EEG data from pairs of scalp electrodes (C3/A2 and C4/A1) were analysed together. This was performed to mirror the data obtained from the in-ear sensor (channel 1 and channel 2). This analysis protocol did not enable any assessment of whether the EEG data from the left hemisphere of the brain showed superior agreement with the data obtained from the in-ear EEG sensor if the in-ear sensor was inserted in the left ear compared with

insertion in the right, and vice versa. However, previous studies have assessed similarities between EEG data obtained from different sites of the 10/20 system. These studies showed that the EEG data correlated better (*r* above 0.85) for inter-hemispheric places compared with intra-hemispheric (Guevara & Corsi-Cabrera, 1996). For example, the EEG correlation between sites C3 and C4 during SWS was 0.96, whereas the correlation between data obtained from sites C3 and T3 was 0.68. Therefore, it can be argued that the agreement would be the same in both scenarios, whether comparing the left ear with site C3 or the left ear with site C4.

4.4.2 Significance of the findings

As outlined in Chapter 1, section 1.4, several studies have used an in-ear EEG sensor (Looney *et al.,* 2012; Mikkelsen *et al.*, 2017; Nguyen *et al.*, 2017). However, only the present study has compared the manual scoring of data obtained from scalp EEG with those obtained from in-ear EEG during overnight sleep. Manual scoring is the current gold-standard method to analyse EEG scans, but it is a time-consuming procedure and requires trained personnel to enable the visual recognition of the signals (Berry, Brooks, *et al.,* 2012). With recent advances in machine learning, automatic algorithms to score EEG data have also been popular in sleep research, and they offer a promising way to remove the need for manual scoring. Our in-ear EEG data have previously been published in the validation of an automated algorithm (Nakamura, Alqurashi, Morrell, & Mandic, 2018; Nakamura, Goverdovsky, Morrell, & Mandic, 2017). Nakamura *et al.* have shown that the automatic algorithmic analysis of in-ear EEG data can correctly predict sleep compared with wakefulness, and light sleep (N1 and N2) compared with SWS, with a substantial level of agreement. This solution may facilitate several real-world applications for the measurement of sleep and the symptoms of sleepiness, especially in cases

where it is desired to take measurements in the workplace. Presently signals from our sensor must be analysed offline, but conceptually these signals could be transmitted to a device that contained sufficient computing power to analyse these signals in real time. For an individual this could be a smart phone, but it would also be possible to build this system into the working environment for a sleep-critical occupation (for example the cab of a heavy-goods vehicle or an air-traffic-control tower).

Interestingly, there are potential limitations to the use of this type of technology. For example, for obstructive sleep apnoea syndrome, respiratory polygraphy is considered adequate in many jurisdictions to rule in or confirm a diagnosis. Conversely, where the issue is one of limb movement or parasomnia, we anticipate that most clinicians will still wish to know whether the patient is in REM sleep, which cannot be calculated with the use of EEG alone (whether classical or in-ear EEG).

As noted above, we are cautious regarding proposals of clinical applications; patients who experience obstructive sleep apnoea are often diagnosed through the use of portable monitoring devices such as home polygraphy and/or pulse oximetry rather than full PSG due to cost and accessibility of facilities. However, in a few patients it is hard to know how much sleep the patient has experienced during the night, and this can influence the apnoea-hypopnoea index (AHI). It is sometimes possible to estimate this effect through the use of the posture or movement sensor that is supplied with most respiratory polygraphy devices, but the determination of this aspect non-invasively and at low cost, using, for example, the in-ear EEG sensor, might enhance the accuracy of these systems.

4.5 Conclusion

Through use of the in-ear EEG sensor, we were able to detect non-REM sleep and wakefulness in healthy participants overnight, and the results compared favourably with those obtained through use of scalp EEG. These data offer new opportunities to monitor overnight sleep accurately using wearable and objective measures. Future investigations are needed to determine whether use of the in-ear EEG sensor enables detection of other sleep stages such as REM sleep, in different populations such as patients with sleep disorders, and in different settings such as during driving.

Chapter 5: A visual analogue scale for the assessment of sleepiness in patients with obstructive sleep apnoea and healthy adults

5.1 Introduction

Excessive daytime sleepiness (EDS) is a common symptom in patients who experience obstructive sleep apnoea (OSA) (Benjafield *et al.*, 2018). EDS is also known to be a risk factor for a reduced quality of life (Kim *et al.*, 2017; Kim & Young, 2005; Lee, Lee, Ryu, Chung, & Kim, 2016), impaired cognitive function (Bucks *et al.*, 2017), motor vehicle and occupational accidents (Bioulac *et al.*, 2017; Uehli *et al*., 2014), as well as cardiovascular mortality in patients with OSA (Ng, Shaw, & Peeters, 2018). It is also important clinically to determine the amount of EDS that patients experience, because patients with OSA and symptoms of EDS seem to adhere to and benefit more from continuous positive airway pressure (CPAP) treatment compared with those who do not complain of EDS (Chai-Coetzer *et al.,* 2013; Craig *et al.*, 2012; McMillan *et al.*, 2014).

The Epworth sleepiness scale (ESS) is the method most frequently used to quantify subjective EDS (Johns, 1991). However, clinical studies have reported difficulties associated with its use (see Chapter 1, section 1.6.1). Briefly, these include, but are not limited to, challenges in the accurate completion of the scale due to illiteracy, ambiguity of items, and cultural applicability (Kendzerska *et al.,* 2014).

As discussed in Chapter 1, section 1.6.1, a study by Ghiassi *et al.* reported that one-third of new patients and one-sixth of ESS-naive patients with OSA made errors or required assistance when completing the scale; examples of errors included leaving a question blank, or writing ‘yes’ or ‘no’ instead of giving an item a score (Ghiassi *et al*., 2011). Some patients also needed help to read the items because they could not read or write or had vision impairments. Bindi *et al.* investigated the challenges of translating the ESS into different languages and found that item seven in the ESS (‘Sitting quietly after a lunch without alcohol’) was ambiguous

either syntactically, semantically or culturally in 66 languages (Bindi *et al*., 2016). Moreover, item eight in the ESS ('in a car, while stopped for a few minutes in the traffic') does not make a clear distinction regarding whether the respondents should imagine themselves as drivers or passengers. This is important as the association between EDS and OSA is now well-recognised (Rizzo *et al.*, 2018). Another study found that the contextual factors such as location, position, and level of interest during completion of the questionnaire affected the report of the ESS score, and this led to high variability between patients (Sharafkhaneh & Hirshkowitz, 2003). Lastly, the question that addresses the likelihood of dozing off in a theatre may be ambiguous even to Anglophones, since a 'theatre' in the UK is a venue for plays, whereas in Australia where the ESS originated it is a venue for films (that is, a cinema).

The visual analogue scale (VAS) is a simple method employed to measure subjective feelings (Folstein & Luria, 1973). It has been used and validated for the assessment of chronic symptoms such as anxiety (Kindler *et al.,* 2000), mood (Folstein & Luria, 1973), depression (Lees & Lloyd-Williams, 1999), pain (Jensen *et al.,* 1986), and breathlessness (Mador & Kufel, 1992). Sleepiness is a subjective feeling; therefore, it may be measured reproducibly using a VAS (Thorarinsdottir *et al.,* 2019). We therefore developed a VAS for the assessment of sleepiness, with endpoints that matched the ESS as closely as possible (see chapter 1, section 1.7).

The primary aim of this study was to determine the relationship between the ESS and a VAS in patients with OSA and healthy participants. We hypothesised that there would be a good correlation between the results obtained through use of the ESS and VAS at baseline and after one month of follow-up, when patients with OSA had been treated with continuous positive airway pressure (CPAP). The secondary aims were: 1) to determine whether the VAS was

easier to use than the ESS and 2) to determine the reproducibility of the VAS over time in healthy participants.

5.2 Methods

5.2.1 Participants

Patients were recruited prospectively from the Centre for Sleep at Royal Brompton Hospital, London, UK, if they had a confirmed diagnosis of OSA through use of overnight respiratory polygraphy (Apnoea link, ResMed, San Diego, California, US). The inclusion and exclusion criteria were as follow:

- ***Inclusion criteria***
  - *OSA patients:*
    1. Untreated OSA – oxygen desaturation index >7.5/hour of sleep (Berry, Brooks, *et al.*, 2012)
  - *Healthy controls:*
    1. Oxygen desaturation index <5/hour of sleep
- ***Exclusion criteria***
  - *Both groups:*
    1. Current clinically diagnosed depression or anxiety disorder
    2. Psychotropic medications (including all sedating medications and strong opioids, antidepressants,
    3. Anxiolytics, major tranquillisers, antipsychotics, hypnotics, anticonvulsants)
    4. Coexistence of another sleep disorder
    5. History of alcohol abuse or current use of recreational drugs

Other exclusion criteria included, for all patients, inability to comprehend what was proposed

and inability to travel to the sleep laboratory.

Healthy participants were also recruited to the study from among the Royal Brompton staff and Imperial College colleagues.

All participants gave written informed consent and the study was approved by the National Research Ethics Services (NRES) Committee of South West-Cornwall & Plymouth NHS Health Research Authority 12/SW/0091 (see Appendix 5 for a copy of the approval).

The protocol followed in the study is illustrated in Figure 5.1.

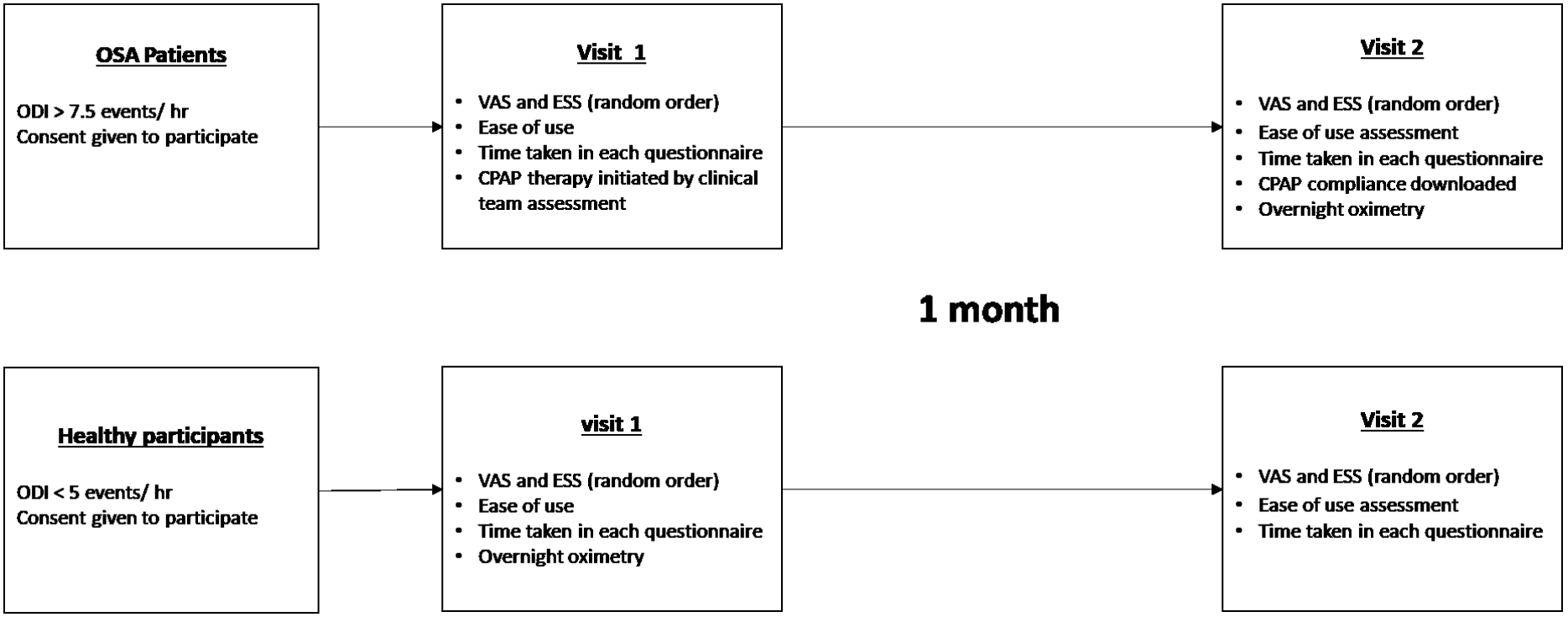


Figure 5.1: The protocol followed for this study. ODI: oxygen desaturation index.

5.2.2 Measurements

Details of the measurements are explained in the General Methods chapter (Chapter 2). In brief, participants were asked to complete the ESS and VAS questionnaires twice, at baseline and after one month. During this month, patients with OSA were treated with CPAP (ResMed, San Diego, California, US) and their adherence to the treatment was recorded using remote monitoring (Air view, ResMed, San Diego, California, US). Oxygen saturation was recorded overnight for all participants in their own homes using pulse oximetry (Konica Minolta Sensing Inc, Tokyo, Japan).

ESS: a self-administered questionnaire that yields a score between zero(least sleepy) and 24 (most sleepy) (Johns, 1991). Participants are asked to mark on a scale of 0 to 3, how likely they are to doze off or fall asleep during eight different situations.

VAS: a self-administered scale that consists of two opposing statements, joined by a 100-mm line. Participants are asked to mark on the line how likely they are to doze off or fall asleep during various scenarios. The two opposing statements are: “I never fall asleep” and “I always fall asleep”. These two statements have been selected to resemble the scores from the ESS. The VAS was developed by a consensus of experts (four consultants at the Royal Brompton Hospital, two physiologists, and several patients).

Both the ESSs and VASs were recorded on paper. Participants were also asked to rate the ease of use of both measures on the scale of zero (least easy) to 10 (most easy). The measurement of time taken to complete the ESS and VAS was included in the later phase of the investigation (after 13 participants had completed the study) to provide more comparison data between these scales.

5.2.3 Sample size calculation and statistical analysis

An *a priori* sample size was estimated based on a study by McMillan *et al.,* 2014 (McMillan *et al.,* 2014). These researchers investigated the efficacy of CPAP in the reduction of daytime sleepiness among older people who experienced OSA, through the use of ESS before and after CPAP treatment. They found a reduction in the ESS of two points following CPAP treatment (95% CI 2.8 to 1.2). Using these data, at 5% significance level and 80% power, a sample size of 64 participants was required for the author's study to show a similar reduction in the VAS after CPAP.

Normality of the data was investigated using Shapiro-Wilk's normality test.

For the purposes of comparison, the ESS and VAS results were converted to a percentage. For the ESS this was performed by the division of the true value of the ESS for each participant by 24 (that is, if the ESS score was 14, the percentage value was 14/24*100= 58.3%). Conversion of the VAS result was direct (that is, if the VAS result was 33 mm, the percentage value was 33%). A paired T-test was then performed to determine the difference between the percentage ESS and VAS scores. Pearson correlation was also performed to determine the correlation between ESS and VAS scores in both patients who experienced OSA and healthy participants. Ease-of-use ratings and time taken to complete the ESS and VAS papers were analysed through independent T-tests. All statistical analysis was conducted using IBM SPSS V.24 software.

5.3 Results

Sixty-seven participants were assessed for eligibility to participate in the study; of which 64 participants were included; 32 (10 female) patients diagnosed with OSA (age [Mean ± SD] 55.8 ± 13.4 years) and 32 (19 female) healthy participants (age: 36.74 ± 11.65 years). Details of the

recruitment are presented in the Consort diagram (Figure 5.2).

Baseline characteristics of the patients with OSA and healthy participants are presented in Table 5.1.

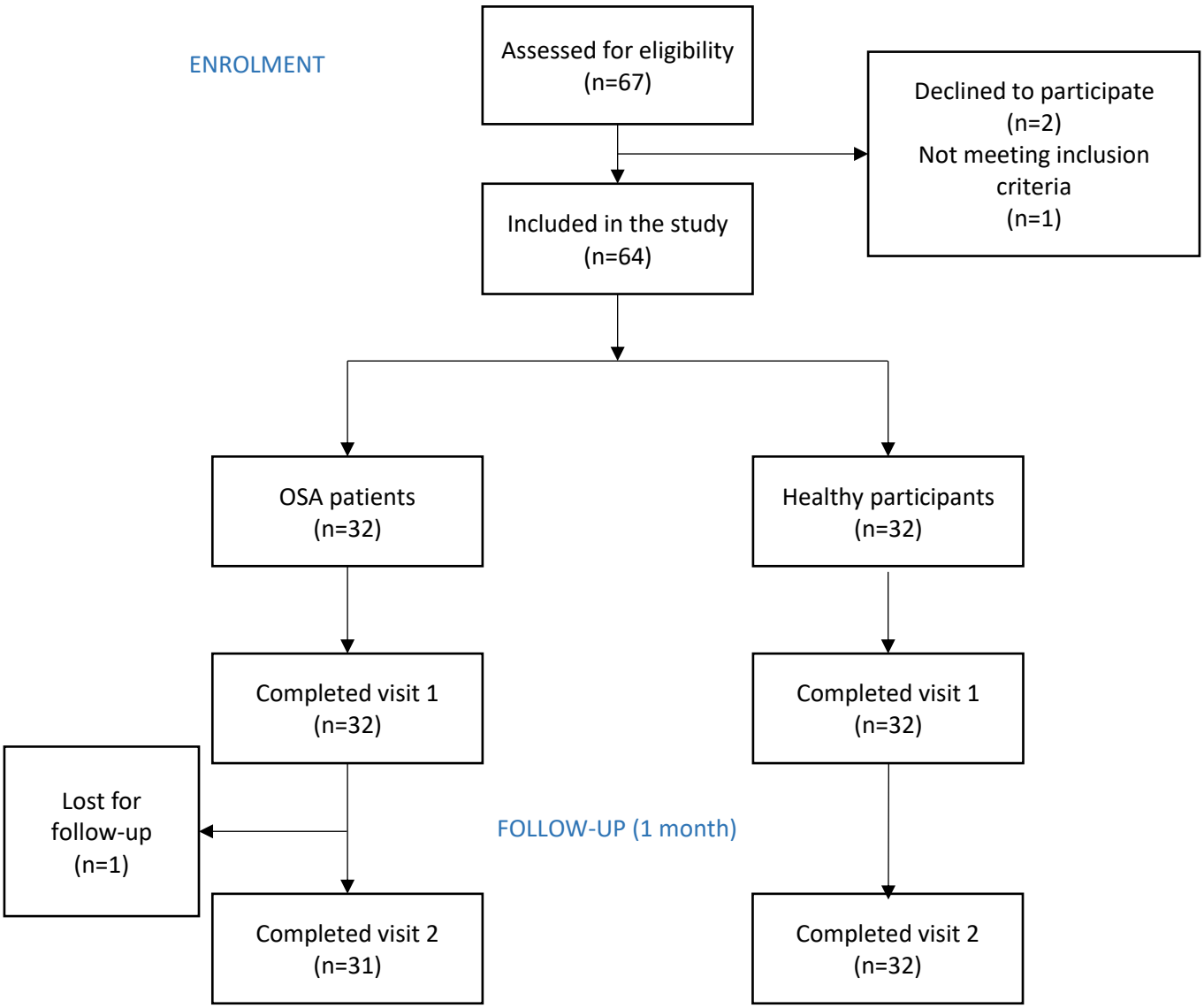


Figure 5.2: Consort diagram displaying method of recruitment and study of OSA patients and healthy participants.

Table 5.1: Baseline characteristics of the participants, and the CPAP adherence statistics of patients treated for OSA

	Mean ± SD		
	Total sample (n=64)	**Healthy participants (n=32)**	**OSA patients (n=32)**
Age (*years*)	46.27 ± 15.74	36.74 ± 11.65	55.80 ± 13.43
ODI > 4% at baseline (*events/hour*)	10.10 ± 9.36	1.73 ± 0.95	18.47 ± 5.70
ODI > 4% after CPAP treatment (*events/hour*)	N/A	N/A	5.89 ± 5.49
BMI (kg/m^2)	28.72 ± 5.83	26.26 ± 5.12	31.17 ± 5.52
Medical history (*n*)			
Hypertension	14	0	14
Heart failure	4	0	4
Other cardiac diagnosis	8	1	7
Epilepsy or other neurological diagnosis	2	0	2
Asthma	15	6	9
COPD or other respiratory disorders	10	0	10
Diabetes	7	1	6
Period between visits 1 & 2 (*days*)	34.19 ± 19.11	26.13 ± 10.09	42.25 ± 22.50

5.3.1 Comparison between ESS and VAS results after one month

In patients with OSA, the (mean ± SD) score of ESS at visit 1 was 11.16 ± 5.53, which indicated that the majority of our patients were mildly sleepy during the day. At visit 2, after one month of CPAP, the ESS score had decreased to 4.74 ± 5.01. The score of the VAS at visit 1 for patients with OSA was 50.22 ± 30.38 mm. At visit 2 after 1 month of CPAP, the VAS had decreased to 21.90 ± 26.92 mm (Figure 5.4A).

The mean percentage changes from visit 1 to visit 2 were 57.5% ± 35% and 56.4% ± 29.1% (p= 0.253*)* for ESS and VAS scores, respectively. These results indicate that use of both ESS and VAS detects the change in sleepiness at a similar level in patients with OSA after they have been treated with CPAP.

In healthy participants, the (mean ± SD) score of ESS at visit 1 was 3.91 ± 3.14. At visit 2, after one month of no intervention, the ESS score remained the same at 3.34 ± 3.27 (p = 0.48). The score of the VAS at visit 1 for healthy participants was 15.58 ± 21.21 mm. At visit 2, after one month of no intervention, the VAS score was 12.05 ± 14.75 (p = 0.44) (Figure 5.4B).

Figure 5.5 shows the mean changes in ESS (Figure 5.5 A) and VAS (Figure 5.5 B) before and after one month for patients who experienced OSA and healthy participants.

5.3.2 Comparison between ESS and VAS results

At visit 1, there were no significant differences observed between the percentage ESS and VAS scores for both OSA patients (ESS: 11.16 ± 5.53, VAS: 21.90 ± 26.92 mm, p= 0.252), and healthy participants (ESS: 3.91 ± 3.14, VAS: 15.58 ± 21.21 mm, p= 0.875). Similarly, at visit 2, there were no significant differences observed between the percentage ESS and VAS scores for both OSA patients (ESS: 4.74 ± 5.01, VAS: 21.90 ± 26.92 mm, p = 0.222) and healthy participants (ESS: 3.34 ± 3.27, VAS: 12.05 ± 14.75 mm, p = 0.094).

The VAS also correlated significantly with ESS among patients with OSA at both visits (visit 1: r = 0.77, p < 0.001, visit 2: r = 0.82, p < 0.001) and healthy participants (visit 1: r = 0.60, p < 0.001, visit 2: r = 0.71, p < 0.001). When the data for patients with OSA and healthy participants was combined, to examine the performance of the VAS scale at different levels of sleepiness, the correlation between the ESS and VAS was r = 0.82 (P < 0.001) for visit 1

and $r = 0.72$ ($p < 0.001$) for visit 2. Figure 5.2 shows the scatter plots for visit 1 (Figure 5.3A) and visit 2 (Figure 5.3B). The solid lines denote an ESS score of 11, which is considered the minimum that exhibits excessive daytime sleepiness. A corresponding measure of 40 mm on the VAS was proposed as indicatory of sleepiness.

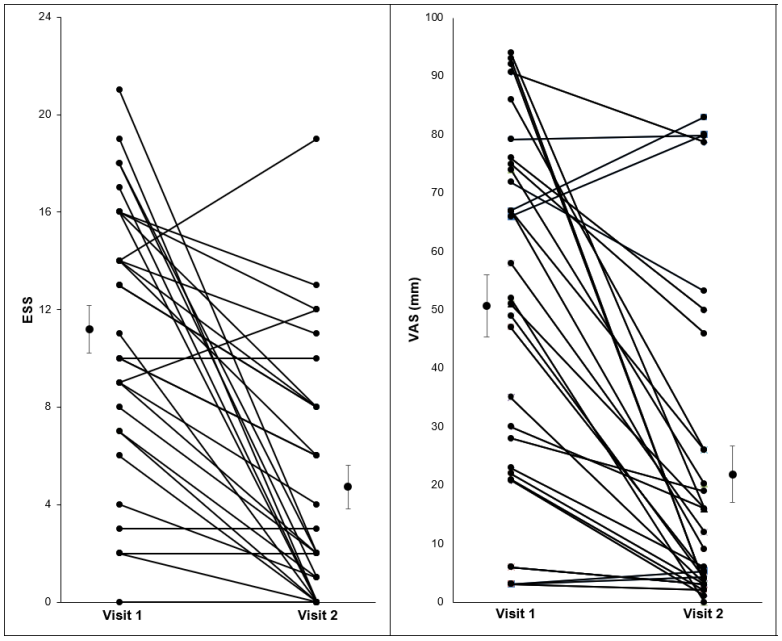


Figure 5.3A: Individual ESS and VAS results of OSA patients (n=31) collected at visits 1 & 2.

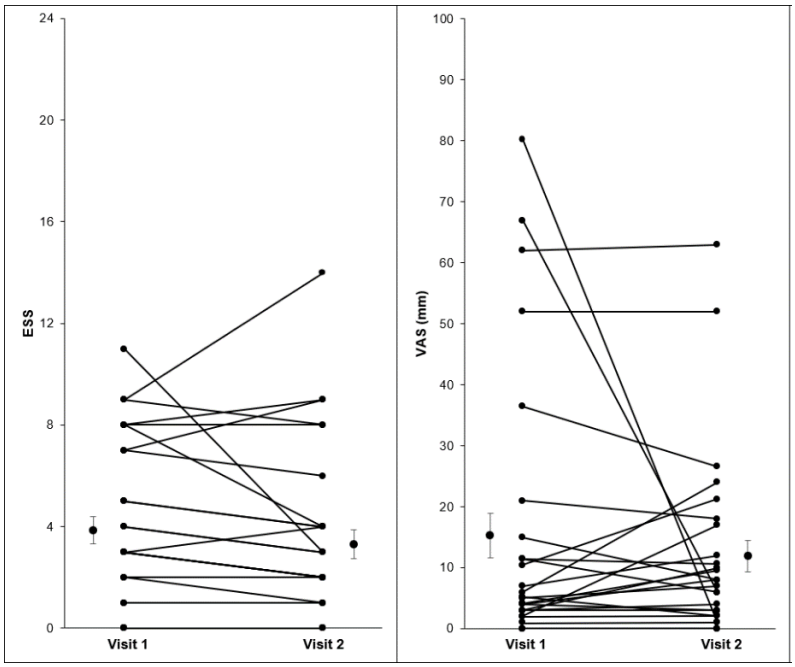


Figure 5.3B: Individual ESS and VAS results of healthy participants (n=32) collected at visits 1 & 2

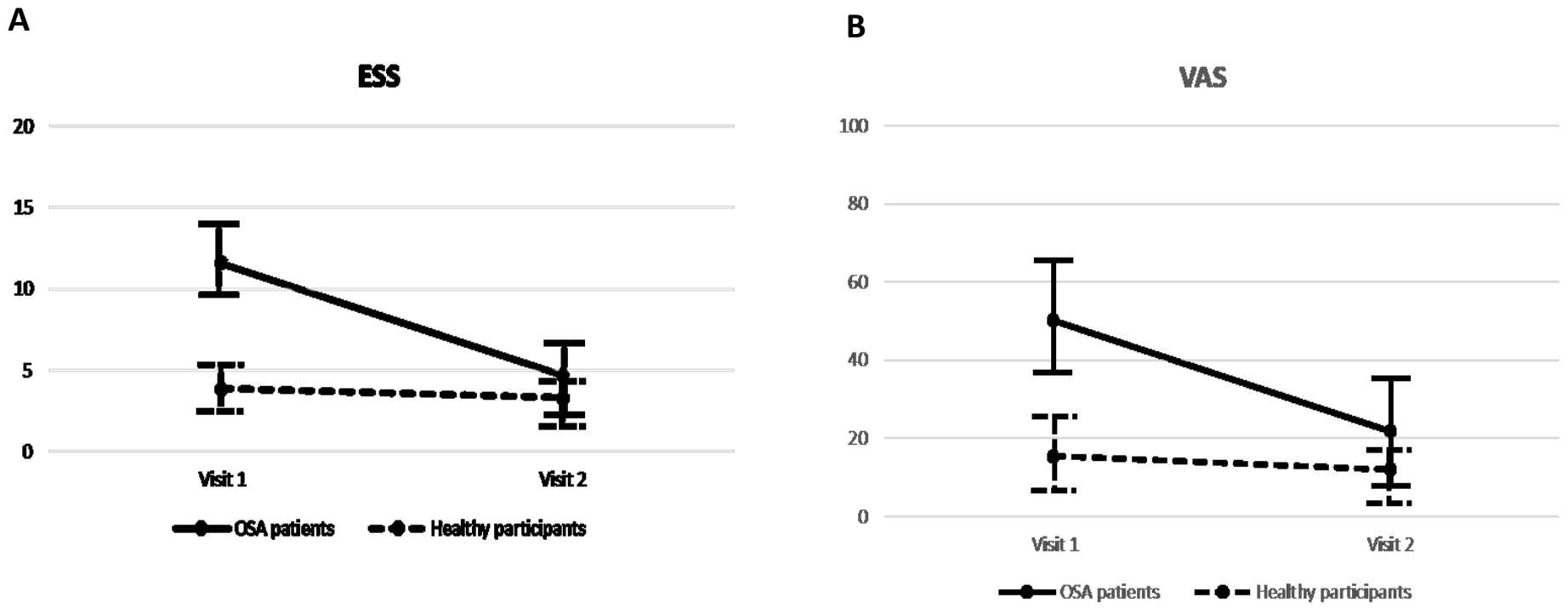
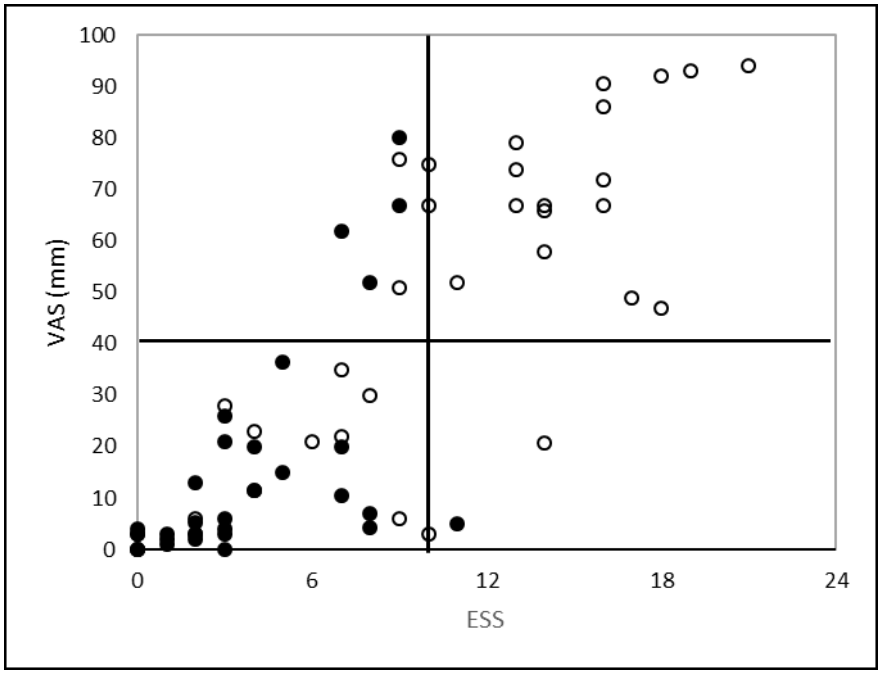


Figure 5.4: A: the mean changes in ESS in OSA patients (solid line) and healthy participants (dashed line). B: The mean VAS changes in OSA patients (solid line) and healthy participants (dashed line) before and after one month.

A



B

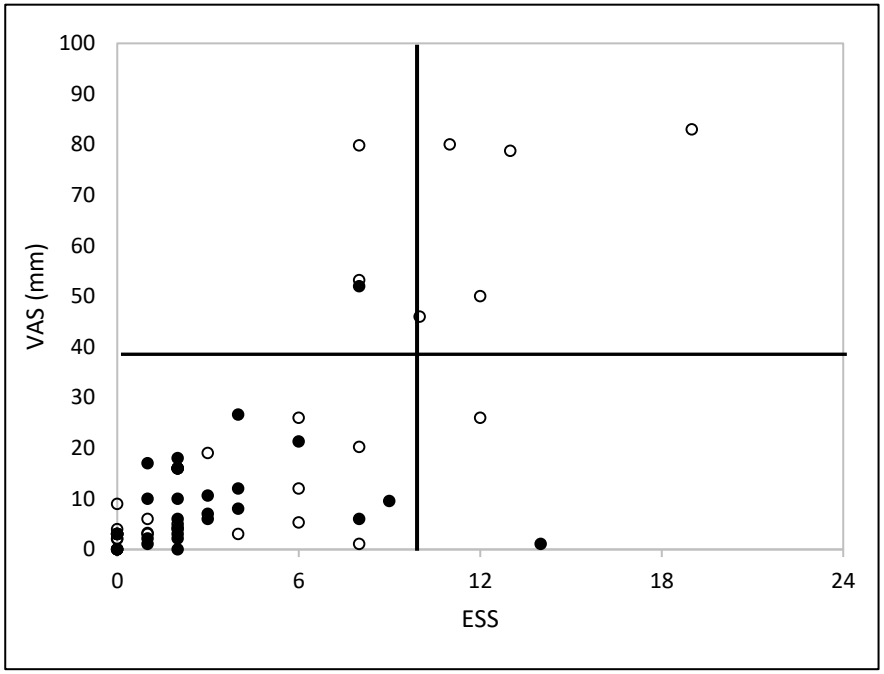


Figure 5.5: Correlation between ESS and VAS results for patients with OSA (open circle) and healthy participants (closed circle) for Visit 1. B: Correlation between ESS and VAS results for patients with OSA (open circle) and healthy participants (closed circle) for Visit 2. Solid lines denote ESS score of 11, considered the minimum for excessive daytime sleepiness, and corresponding VAS result of 40 mm.

5.3.3 The ease of use and time taken to complete the ESS and VAS

The VAS was easier to use compared with the ESS for both patients with OSA (Visit 1: VAS: 8.29 ± 2.34; ESS: 7.74 ± 2.84, $p< 0.001$, Visit2: VAS: 9.71 ± 0.59, ESS: 8.97 ± 1.22, $p<0.001$) and for healthy participants (Visit 1: VAS: 9.22 ± 1.43; ESS: 7.72 ± 2.34, $p< 0.001$, Visit2: VAS: 9.29 ± 1.94, ESS: 8.36 ± 1.75, $p<0.001$). The time taken to complete the VAS was also significantly shortened compared with the time taken to complete the ESS in patients with OSA (Visit 1: VAS: 14.92 ± 13.76 seconds, ESS: 38.75 ± 20.01 seconds, $p<0.001$, Visit 2: VAS: 5.67 ± 3.39 seconds, ESS: 31.33 ± 23.68, $p<0.001$) and in healthy participants (Visit 1: VAS: 17.32 ± 31.47 seconds, ESS: 62.32 ± 62.44 seconds, $p<0.001$, Visit 2: VAS: 10.16 ± 9.43 seconds, ESS: 38.00 ± 21.90, $p<0.001$) .

Table 5.2 below summarises the main results of the ESS and VAS for patients with OSA and healthy participants in both visits.

Table 5.2: ESS and VAS scores of healthy participants (n=32) and OSA patients (n=31)

	Epworth Sleepiness Scale (Mean ± SD)				Visual Analogue Scale (Mean ± SD)			
	Visit 1	**Visit 2**	**Difference 2 - 1**	***p-value***	**Visit 1**	**Visit 2**	**Difference 2 - 1**	***p-value***
OSA patients (n=31)								
Score (*ESS, VAS: mm)*	11.16 ± 5.53	4.74 ± 5.01	-6.42 ± 6.36	***<0.001****	50.22 ± 30.38	21.90 ± 26.92	-28.32 ± 28.16	***<0.001****
Percentage score (*%*)	46.51 ± 23.05	19.76 ± 20.89	-26.75 ± 26.50	***<0.001****	50.22 ± 30.38	21.90 ± 26.52	-28.32 ± 28.16	***<0.001****
Ease of use (*1-10*)	7.74 ± 2.84	8.97 ± 1.22	1.23 ± 2.64	***0.033****	8.29 ± 2.34	9.71 ± 0.59	1.42 ± 2.33	***0.002****
Time taken (s)	38.75 ± 20.01	31.33 ± 23.68	-7.42 ± 18.24	0.416	14.92 ± 13.76	5.67 ± 3.39	-9.25 ± 15.11	***0.043****
Healthy controls (n=32)								
Score (*ESS, VAS: mm)*	3.91 ± 3.14	3.34 ± 3.27	-0.56 ± 1.95	0.485	15.58 ± 21.21	12.05 ± 14.75	-3.58 ± 18.85	0.442
Percentage score (*%*)	16.28 ± 13.06	13.93 ± 13.62	-2.34 ± 8.12	0.485	15.58 ± 21.21	12.05 ± 14.75	-3.85 ± 18.85	0.442
Ease of use (*1-10*)	7.72 ± 2.34	8.47 ± 1.67	0.75 ± 2.08	0.145	9.22 ± 1.43	9.25 ± 1.87	0.03 ± 1.69	0.940
Time taken (s)	62.32 ± 62.44	38.00 ± 21.90	-24.32 ± 48.16	0.118	17.32 ± 31.47	10.16 ± 9.43	-7.16 ± 28.40	0.349

* Statistically significant difference

5.4 Discussion

The main finding from this study was that use of the VAS enabled detection of sleepiness in patients with OSA and in healthy participants compared with use of the ESS. The VAS was also sensitive, reproducible, and easier to use compared with the ESS over a one-month period during which patients with OSA were treated with CPAP and no intervention was applied to the healthy participants.

In this study, we used the visual analogue scale to assess sleepiness as it had been utilised in previous studies and had been proved to be a simple and reliable method to evaluate feelings such as anxiety (Kindler *et al.,* 2000), depression (Lees & Lloyd-Williams, 1999), pain (Jensen *et al.,* 1986), and breathlessness (Mador & Kufel, 1992). Various versions of the VAS are used in the literature: horizontal or vertical lines, numerical ratings, and a facial scale. However, the most widely used is the horizontal line version with no categories on the line. Where categories are used (for example, no pain, mild pain, moderate pain, severe pain, very severe pain), and the true value falls in between these categories, participants have shown a systematic bias either to the lower or higher score. It was also found that this bias decreases as the number of categories increases (Schwarz, 1999). See Chapter 1, section 1.7 for more details about the application of the VAS and how it has been used.

We have also shown that the VAS is sensitive to change in sleepiness levels before and after CPAP treatment, and the same was shown for the ESS. The sensitivity of the ESS to changes in levels of sleepiness before and after CPAP treatment has been well reported in previous research (Ballester *et al.*, 1999; Johns, 2000; Morrell, Finn, McMillian, & Peppard, 2012), and the majority of these studies found a change of two to three points in the ESS (Patel *et al.*, 2018). In our study, we observed a change of six points in the ESS score after CPAP

treatment. One explanation for the larger figure compared with that reported in the literature is that this was due to the short follow-up time (one month), and the results might have been different if patients had been followed for a longer period. McMillan *et al.* reported that the change in ESS after three months of CPAP treatment (-3.8) was greater than the change after 12 months (-3.4) (McMillan *et al.*, 2014). To what extent this change might by clinically significant is still a topic of interest in the field (Crook *et al.*, 2018; Patel *et al.,* 2018).

The reproducibility of the ESS scores has been discussed in Chapter 1, section 1.6.1. In this study the reproducibility of the ESS scores is in agreement with previous research. In the original study that validated the ESS, Johns reported that the reproducibility of the ESS in healthy participants was 82% (Johns, 1992). The reproducibility of the ESS reported in the present study was 81%. For the VAS, however, the reproducibility was moderate (53%). The lower reproducibility of the VAS can be attributed to the nature of the VAS, as it offers an open scale from 0 to 100 mm and participants have the freedom to indicate where they perceive their symptom to be anywhere in this scale. For example, the participant can indicate the level of sleepiness to be 45.3 mm in the first visit and 46.5 mm in the second visit. Therefore, participants might be reliable in scoring their sleepiness level, but because the VAS does not limit them to score it in a certain range, this might show variability in the score. To overcome this issue, a larger sample size is needed. However, this freedom to choose a score might be an advantage of the VAS as it offers participants the choice to put the true score.

Use of the internet and modern technology in recent years has not only enabled health promotion, but also has facilitated the collection of big data. A potential development of the

present study is to digitise the VAS and make it publicly available. We have moved towards this step by the development of an online version of the VAS (see Figure 5.6). Such development may aid awareness among the public regarding symptoms of sleepiness and therefore aid in the diagnosis of sleep disorders in a timely manner. A previous study by Boyes *et al.* has found that an online version of the ESS delivers fast, accurate and results comparable results with those obtained through use of the conventional ESS for a large number of participants (39,448 participants) (Boyes, Drakatos, Jarrold, Smith, & Steier, 2017). Future work will investigate the feasibility of using the online version of the VAS as a measure for sleepiness.

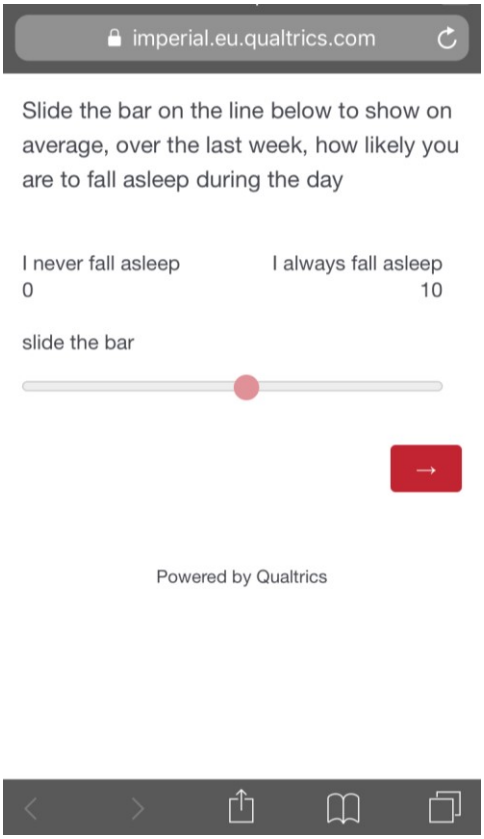


Figure 5.6: a screenshot of the online version of the VAS.

5.5 Conclusion

The findings of this study suggest that the new VAS is an effective measure of sleepiness in patients with OSA and healthy participants. The VAS is also able to detect changes in sleepiness among patients with OSA treated with CPAP. Future studies will investigate the efficacy of the VAS for patients with other sleep disorders.

Chapter 6: Discussion and future direction

6.1. Summary of the aims

The gold standard of sleep measurement techniques is polysomnography (PSG), which involves the attachment of several electrodes to the scalp to obtain an electroencephalogram which can be analysed to differentiate between sleep stages. However, the performance of scalp EEG is cumbersome, time-consuming and expensive. Our group at the sleep and ventilation unit, in collaboration with the Department of Electrical and Electronic Engineering at Imperial College London, has developed a wearable in-ear sensor to measure EEG within the ear. As stated in Chapter 1, **the first two aims of this thesis were:**

1) To investigate the efficacy of the in-ear EEG in detecting sleep latency, compared to a scalp EEG in healthy participants during daytime naps, before and after sleep restriction; and

2) To investigate the efficacy of the in-ear EEG in detecting deep sleep (slow wave sleep) compared to a scalp EEG in healthy participants overnight.

There had been no previous clinical studies that had assessed the efficacy of a visual analogue scale (VAS) to detect sleepiness in patients with OSA. Therefore, **the third aim of this thesis was to investigate whether a new VAS would offer equivalent results to those obtained through the ESS, and would prove easier to use than the ESS, in the assessment of sleepiness in both patients newly diagnosed with OSA and in healthy participants.**

6.2. Summary of the main findings

6.2.1. The in-ear EEG sensor

In collaboration with the electrical and electronic engineering department, we have successfully developed an in-ear EEG sensor. The sensor has passed extensive electrical and

electronic assessment to confirm that it collects EEG signals. The assessment included 10 hours' recording of impedance and Auditory Steady-State Response (ASSR) data (Goverdovsky *et al.,* 2016).

The first two studies of this thesis showed that in-ear EEG could be utilised to detect different sleep stages (N1, N2, slow-wave sleep, as well as wakefulness) with a substantial agreement (kappa coefficient > 0.61- 0.80) with the results obtained through scalp EEG. Sleep restriction imposed on participants in Study 1 (Chapter 3) was sufficient to impair the reaction time of participants and affect the Stroop test, which confirmed that the participants had adhered to the protocol.

These findings show that the in-ear EEG sensor can be used as a wearable and objective device to measure sleep. A future application of this sensor might be to enable self-administration of sleep studies in which participants can apply the in-ear EEG sensor to their ears and obtain sleep-stage analyses. This might offer a more accurate method to measure sleep than wearable devices such as the Fitbit, Apple Watch and mobile apps that are used by the public currently on a daily basis. Future directions of development of the sensor are explained in more detail in section 6.4.

6.2.1. The visual analogue scale

The VAS study shows that application of the VAS can detect sleepiness in patients with OSA and in healthy participants, and the results compare favourably with those obtained through use of the ESS. Use of the VAS also enabled detection of changes in sleepiness levels after CPAP treatment in patients with OSA. Patients with OSA have also rated the VAS as easier and faster to complete than the ESS.

These findings show that the VAS can be used in clinical and general populations to determine sleepiness. One future application might be as a digital version that can be made publicly available through the internet. Such a development may improve awareness regarding the symptoms of sleepiness and therefore aid in the diagnosis of sleep disorders in a timely manner.

6.3. Limitations of the studies

6.3.1. Limitations of the in-ear EEG sensor

Several limitations of the current prototype of the in-ear EEG sensor became apparent during my research. The first was the generic nature of the sensor (one-size-fits-all). Although advantages to this design were perceived during the design phase, it was found that the in-ear EEG sensor was uncomfortable for some participants, especially just before bedtime. This disadvantage was more apparent during Study 2 (Chapter 4), in which participants were asked to wear the sensor throughout the night. The second major limitation of the prototype sensor was the presence of wires that were attached to the earpiece. These wires were plugged into an amplifier, to enable recording of the signal on a laptop. A third limitation was that the sensor measured EEG only, and this did not enable measurement of data during, for example, the REM stage, which required EMG and EOG data.

6.3.2. Limitations of the VAS

One major limitation of the VAS study was the recruitment of patients with OSA who were attending the Centre for Sleep at Royal Brompton Hospital. This decision was based on the requirement that the studies should include patients with levels of sleepiness that ranged from mild through moderate to severe. However, the mean sleepiness level observed in the VAS study was 11 points, which indicated that the majority of participants did not experience

heavy sleepiness. Therefore, the performance of the VAS in patients with severe sleepiness remains unknown.

6.4. Future directions of the research

Further development of the in-ear EEG sensor and the VAS is required in four major areas: the hardware of the in-ear EEG sensor; software of the sensor; digitisation of the VAS; and future research.

6.4.1. Hardware development of the in-ear EEG sensor

- **Comfortable sensor:** as mentioned above, a generic in-ear EEG sensor was thought to confer advantages during the initial design. However, the generic sensor caused discomfort for some participants, especially those who took part in Study 2 (Chapter 4). The source of the discomfort was the requirement that the sensor must achieve good impedance (<10kΩ) in order to obtain good signals. This demand required participants to re-insert the sensor multiple times to achieve the necessary impedance. Discomfort was more apparent in those participants who exhibited narrow ear diameters. Although the discomfort elapsed approximately 10 minutes after the insertion, one can imagine the frustration and pain that could be caused by the need to insert an earpiece into the ear multiple times just before bedtime. This was difficult for the participants and the investigator, who needed to apply the electrode and recheck the signals after each insertion. Future development must consider the comfortable fitting of the sensor either through the testing of different materials for the sensor construction, or the production of different sizes. Two generic sizes, small and large, might be sufficient to overcome the difficulty.

- **Move towards wireless:** the second potential development of the hardware must be a move toward wireless sensors. Current technological advances have, for example, enabled the production of wireless in-ear headphones. Therefore, the production of a wireless in-ear EEG sensor should be possible. In fact, Professor Mandic, our engineering collaborator, has now established a collaboration with Bose company to explore various projects, one of which is the development of a wireless sensor.
- **Multiple channels:** the future development of the in-ear EEG sensor should consider the recording of multiple channels from one sensor (for example, EEG, EOG, microphone, oxygen saturation and others as necessary). Such development will increase the usability of the sensor. A Colorado research group has developed an in-ear sensor to measure EEG, EOG, and EMG. This sensor, therefore, can be used to detect all sleep stages, including REM, with 95% accuracy, which compares favourably with the accuracy of results that can be obtained through PSG (Nguyen *et al.,* 2017).

6.4.2. Software development for in-ear EEG

During the term of this thesis, data obtained through the performance of in-ear EEG has been processed using Matlab 2013b (MathWorks, Natick, MA, US), and this requires signal-processing skills. A future development of in-ear EEG should include production of software that offers user feedback. For example, this could take the form of a mobile app which offered a sleep score, through which a user could obtain a sleep score out of 100 and feedback regarding stages of sleep, the number of minutes spent in each stage, and number of awakenings experienced.

The software might also include a mode that could be activated when the wearer of the sensor was driving a vehicle. This could be set up to send an alert from the software if the driver started to fall asleep. It also might include an instruction to forward an alert during such situations to an emergency contact pre-determined in the software.

6.4.3. Digitisation of the visual analogue scale

The visual analogue scale utilised for the work described in this thesis was used in paper format. A development of the VAS that should be considered is its use digitally in hand-held devices such as mobile phones or tablets. Such a development might increase the usability of the scale among the general population and lead to increased early detection of sleepiness. I have created a link to obtain the VAS digitally through use of the Imperial Qualtrics survey tool (see Figure 5.6). However, this link was produced as a trial and has not been rigorously tested and reviewed by Imperial College regulatory bodies.

6.4.4. Future research

The in-ear EEG sensor: I have established in the research performed for this thesis that in-ear EEG measurement can be used as an objective measure of sleep in a healthy population. Therefore, once the challenges stated above have been overcome, it is important to continue with further studies to test the utility of the in-ear EEG sensor in patient populations. One subsequent study that would further develop applications of the sensor would be to investigate the utility of the in-ear EEG sensor in the detection of sleep latency during simulated driving in healthy participants and in patients with OSA. Such a study could form the basis of an investigation of whether

in-ear EEG could be used as a sensor for sleepy drivers. In the medium- to long-term, another study should investigate whether the in-ear EEG sensor combined with a user feedback system, such as a mobile phone app, during driving could reduce the incidence of near-miss crashes. This study could be conducted in real situations among drivers who undertake long journeys and for whom sleepiness during driving is an issue, such as patients with OSA.

The VAS: I have established in the work performed for this thesis that the VAS can detect sleepiness compared with the ESS among healthy participants, and among patients with OSA, before and after CPAP treatment, and who exhibited mild levels of sleepiness. Therefore, it is important to continue with further studies to investigate whether the VAS can detect sleepiness in OSA patients who experience severe levels of sleepiness. A future study could compare results obtained from mildly and severely sleepy patients, and compare these results with those obtained through use of the ESS. In the medium- to long-term, results obtained through use of the VAS should be compared with an objective measure of sleepiness such as the MSLT.

6.5. Conclusion

Current measures of sleep and sleepiness are either inaccurate or cumbersome to conduct. To close this gap in clinical research and practice in sleep medicine, this thesis has reviewed the latest studies of the current measures of sleep and sleepiness. Novel methods for the assessment of sleep (in-ear EEG) and sleepiness (VAS) have been developed and tested in healthy participants and among patients with respiratory sleep disorders. The performance of in-ear EEG was found to be an accurate method for the detection of different sleep stages. The VAS was also found to be an accurate method for the detection of mild sleepiness in

patients with OSA and in healthy participants. However, future research is required to test the accuracy of the in-ear EEG sensor in patient populations and to test the accuracy of the VAS in severely sleepy individuals.

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Appendices

Appendix 1: Copyright of Figures 1.1 and 1.2.

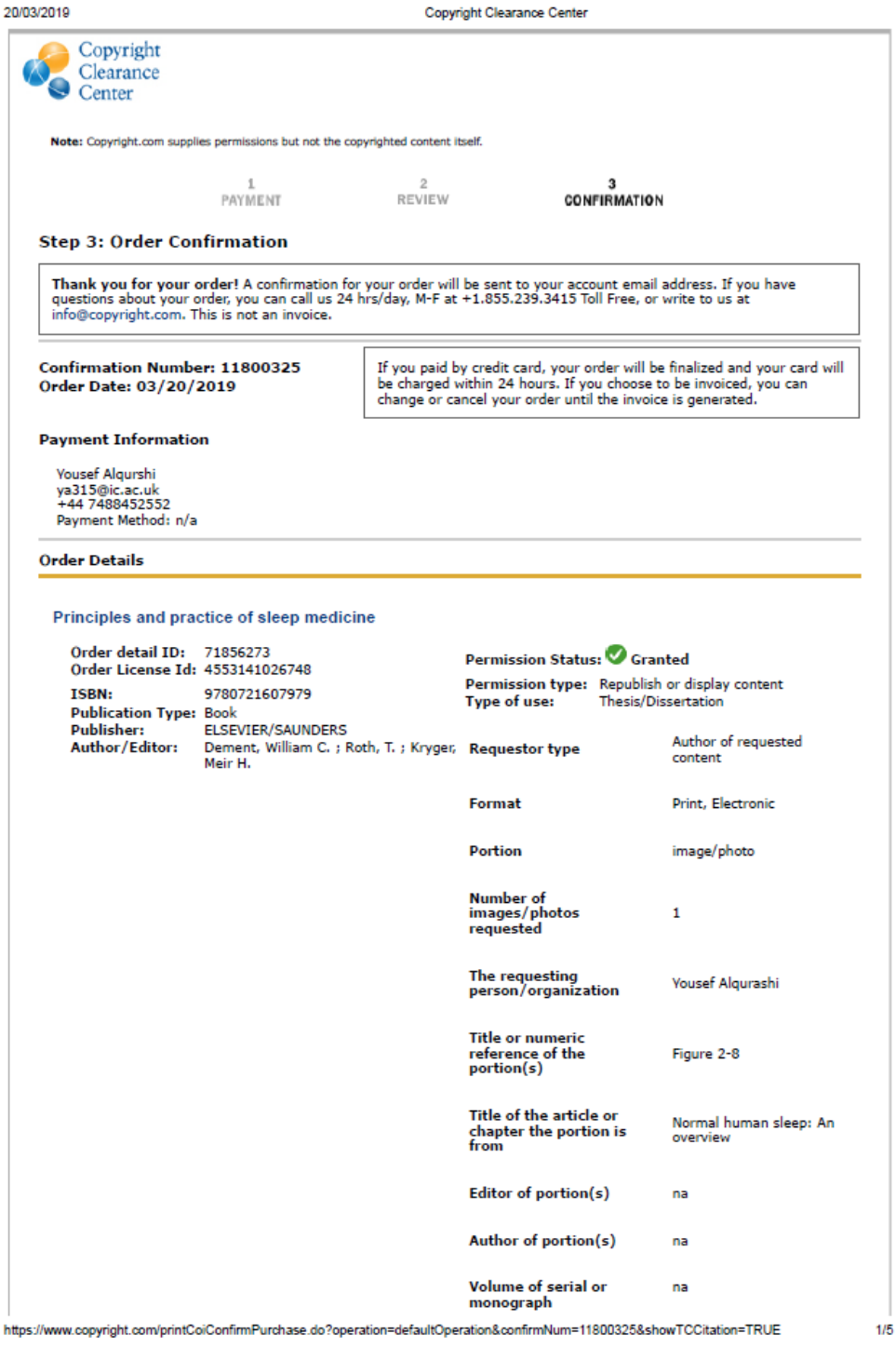
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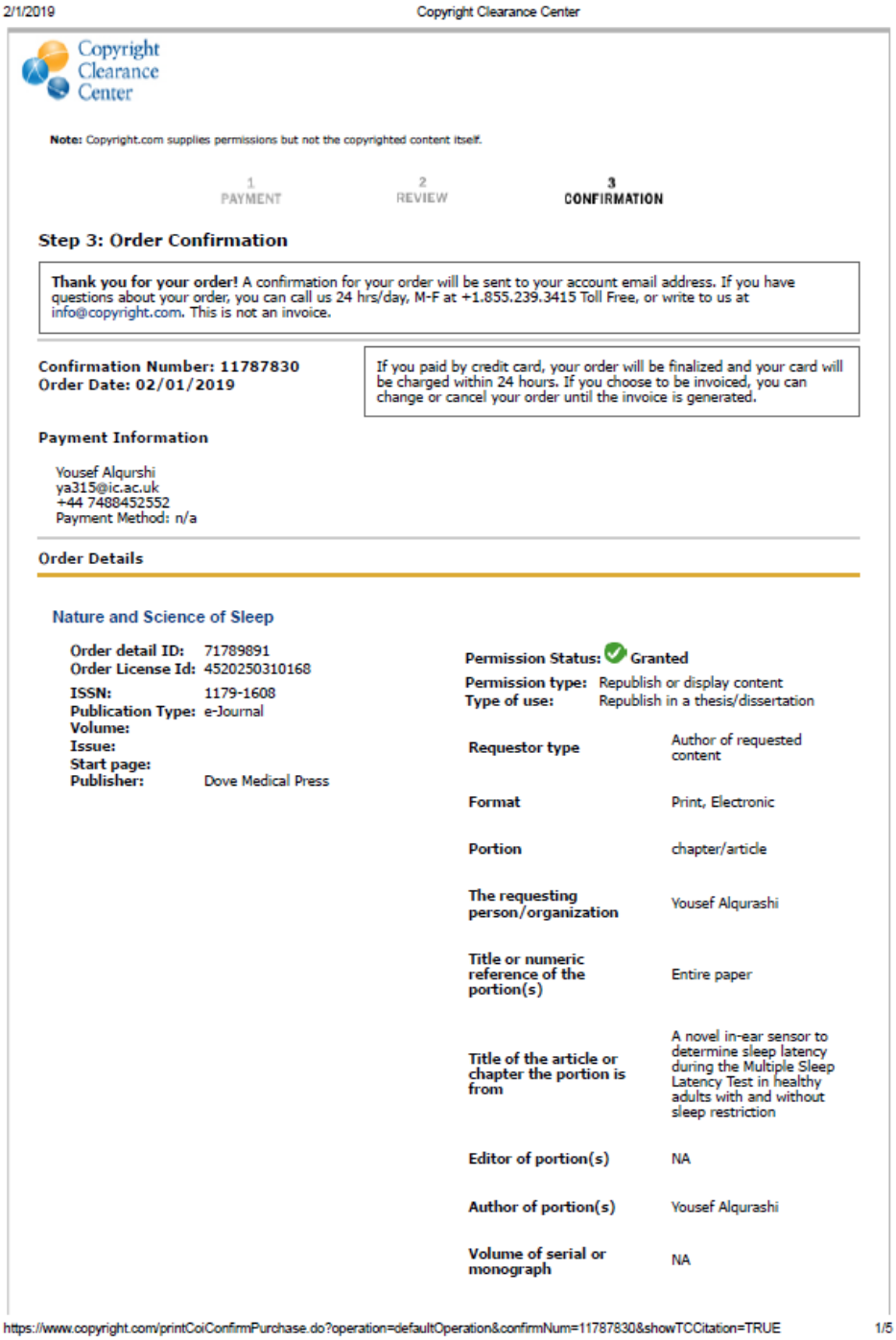
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Appendix 4: Ethical approval for Study 2 (Chapter 4):

Imperial College
London

Imperial College Research Ethics Committee
Imperial College London
Room 221
Medical School Building
St Marys Campus
London
W2 1PG
Tel: +44 (0)207 594 9484

researchethicscommittee@imperial.ac.uk

Professor Mary Morrell
Imperial College London
Royal Brompton Hospital
Sydney Street
London
SW3 6NP

20/09/2017

Dear Prof Morrell

Study Title: A proof-of concept study to investigate the efficacy of ear electroencephalography (EEG), to monitor overnight sleep, compared to scalp EEG, in healthy participants.

ICREC reference: 17IC4150

The above study was approved by your Head of Department on 25/08/17 and by the Joint Research Compliance Office on 20/09/17.

Under the Imperial College Research Ethics Committee process, a study that has been reviewed by the Joint Research Compliance Office and Head of Division/Department (or Principal), where no significant ethical issues have been identified in the protocol or ethics application, can be approved without requiring it to go to full committee.

Documents
The documents reviewed were:

- ICREC Application form
- Protocol (v2 18/09/17)
- Case report form (v2 28/07/17)
- Epworth Sleepiness Scale (v1.0 28/07/17)
- Informed Consent Sheet (v2 18/09/17)
- Participant Information sheet (v2 18/09/17)
- Pittsburger Sleep Quality index (v1 28/07/17)
- Quality of life short form (v1 28/07/17)
- Sleep study flyer (v1 28/07/17)

Yours sincerely,

Gary Roper,
Head of Regulatory Compliance,
Imperial College London

Appendix 5: Ethical approval for Study 3 (Chapter 5)

NHS
Health Research Authority

South West - Cornwall & Plymouth Research Ethics Committee

Level 3
Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

03 July 2017

Professor Mary Morrell
Professor of Sleep and Respiratory Physiology
Imperial College London
Academic Unit of Sleep and Breathing
2nd Floor, Fulham Wing
Royal Brompton Hospital
SW3 6NP

Dear Professor Morrell

Study title:	**A Visual Analogue Scale for the Assessment of Sleepiness in Obstructive Sleep Apnoea**
REC reference:	**12/SW/0091**
Protocol number:	**1**
Amendment number:	**1**
Amendment date:	**30 May 2017**
IRAS project ID:	**88752**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The Sub-Committee reviewed the following amendment:

1. Update to the study management group