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**Using EEG measures to quantify reduced  
daytime vigilance in patients diagnosed  
with obstructive sleep apnoea using a novel  
electroencephalogram analysis method**

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**MBBS, FRACP**

A thesis submitted in fulfilment of the partial requirements  
for the degree of Master of Philosophy

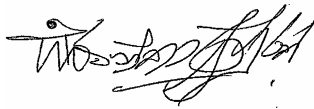
Department of Medicine  
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2013

## STATEMENT OF ORIGINALITY

This work is submitted to the University of Sydney for the partial fulfilment of requirement of the degree of Master of Philosophy.

I declare that the work presented in this thesis is original and that the material here had not been fully or partially included in any other degree at the Sydney University or any other institution.

A handwritten signature in black ink, appearing to read 'Samantha Herath', with a stylized flourish at the end.

Dr Samantha Herath

31 May 2013

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## **PREFACE**

This project used data previously collected by our group for the project titled ‘Neurobiological effects of sleep apnoea and sleepiness’, Protocol No. X06-0299.

Data was processed and analysed by the student to compare artefact removal methodologies and validation of a novel EEG measurement that could be used in patients with sleep apnoea to assess daytime performance objectively.

Approval was obtained from the governing ethics committee to include the student in the above project as an associate investigator for the purposes of this analysis.

## **ABBREVIATIONS AND ACRONYMS**

CPAP	Continuous Positive Airway Pressure
DASS	Depression and Anxiety State
DFA	De-trended Fluctuation Analysis
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalogram
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes of Sleep
ICA	Independent Component Analysis
ICC	Intra-Class Correlation Coefficient
KDT	Karolinska Drowsiness Test
KSS	Karolinska Sleepiness Scale
MSLT	Mean Sleep Latency Testing
MVA	Motor Vehicle Accident
MWT	Maintenance of Wakefulness Testing
NREM	Non-Rapid Eye Movement Sleep
OSA	Obstructive Sleep Apnoea
PSA	Power Spectral Analysis
qEEG	Quantitative Electroencephalogram Analysis
REM	Rapid Eye Movement Sleep
SE	Scaling Exponent

# **ABSTRACT**

## **Introduction**

Vigilance in obstructive sleep apnoea (OSA) does not correlate well with measures of severity of the disease or symptoms. There is a need for a simple objective test to identify patients with reduced vigilance. One such method could be quantitative analysis of the awake electroencephalogram (qEEG).

qEEG is conventionally analysed using Power Spectral Analysis (PSA) looking at different EEG frequencies of delta, theta, alpha and beta. A novel method of analysing the qEEG: De-trended fluctuation analysis (DFA) provides a single value: the scaling exponent (SE), which measures the fluctuations in the EEG signal. DFA SE and PSA are two different measurements (measuring fluctuations of EEG versus EEG frequencies respectively) used to examine the same effect: EEG slowing, which implies increased drowsiness.

Artefact removal from EEG is of utmost importance with the gold standard being manual scoring. Another method of automated artefact removal is independent component analysis (ICA).

## **Objective**

1. Investigate the role of conventional and newer methods of EEG analysis as an objective and quantitative measure of testing vigilance in patients diagnosed with OSA by comparing it with subjectively rated sleepiness, as well as a battery of neurobehavioral performance testing.
2. Validate the use of ICA in a group of patients diagnosed with OSA.

## **Methodology**

Retrospective cross-sectional study of untreated OSA patients.

## **Results**

ICA and manual artefact removal gave well-correlated interchangeable results in the DFA scaling exponent, but not PSA measurements.

EEG slowing measured by PSA metrics and DFA did not correlate to impaired performance during a battery of 14 separate performance tests, as well as AusEd driving task in this group.

## **Conclusion**

ICA and manual artefact removal can be interchangeably used in extracting DFA measurements with confidence. PSA metrics have shown to be highly influenced by artefact, therefore, the use of ICA may not be reliable.

The novel EEG measurement, DFA scaling exponent was superior to that of power spectrum measurements in withstanding artefact.

DFA is complementary to the currently used PSA metrics and will be valuable during circumstances of increased artefacts, for example, EEG measurements during a driving task.



# TABLE OF CONTENTS

<b>STATEMENT OF ORIGINALITY</b>	<b>I</b>
<b>ACKNOWLEDGEMENTS</b>	<b>II</b>
<b>PREFACE</b>	<b>III</b>
<b>ABBREVIATIONS AND ACRONYMS</b>	<b>IV</b>
<b>ABSTRACT</b>	<b>V</b>
Introduction	v
Objective	v
Methodology	vi
Results	vi
Conclusion	vi
<b>TABLE OF CONTENTS</b>	<b>VII</b>
<b>LIST OF TABLES</b>	<b>X</b>
<b>LIST OF FIGURES</b>	<b>XII</b>
<b>1. INTRODUCTION</b>	<b>1</b>
<b>1.1 An overview of obstructive sleep apnoea (OSA)</b>	<b>1</b>
1.1.1 Pathophysiology of OSA	1
1.1.2 OSA epidemiology	2
1.1.3 Clinical symptoms of OSA	2
1.1.4 OSA impact on health	3
<b>1.2 OSA and Vigilance</b>	<b>4</b>
1.2.1 OSA and vigilance	4
1.2.2 Existing methods for testing for vigilance	5
1.2.3 Problems with existing methods	5
1.2.4 Using awake EEG as test for vigilance (qEEG)	6
1.2.5 Power spectral analysis of qEEG and its use in sleep disorders	7
1.2.6 Novel method of EEG analysis: De-trended fluctuation analysis	9
1.2.7 Use of DFA in non-sleep disorders	9
1.2.8 Use of DFA in sleep disorders	10
1.2.9 Advantages of using DFA in place of PSA	10
<b>1.3 Introduction to artefact removal in EEG</b>	<b>11</b>
1.3.1 Manual artefact removal	11
1.3.2 Independent Component Analysis (ICA)	12
<b>2. OBJECTIVE</b>	<b>14</b>

<b>3.</b>	<b>METHODOLOGY</b>	<b>15</b>
<b>3.1</b>	<b>Study design</b>	<b>15</b>
3.1.1	Ethics approval	15
3.1.2	Participants	15
3.1.3	Protocol and measurements	16
3.1.4	Statistical analysis	17
<b>3.2</b>	<b>Measurements of vigilance</b>	<b>17</b>
3.2.1	Diagnostic polysomnography	17
3.2.2	Awake EEG (qEEG)	18
3.2.3	Self rating questionnaires	18
3.2.4	Performance testing	20
<b>3.3</b>	<b>Comparing EEG artefact removal methods (ICA vs manual scoring)</b>	<b>28</b>
3.3.1	EEG preparation for analysis	28
3.3.2	Manual method of EEG artefact removal	29
3.3.3	ICA for artefact removal	33
3.3.4	Analysing the EEG data to obtain PSA and DFA measurements by using both artefact removal methods	33
<b>3.4</b>	<b>Statistical methods used to compare the two methodologies of artifact removal (Manual vs ICA)</b>	<b>35</b>
3.4.1	Student's t-test	35
3.4.2	Effect size	35
3.4.3	Bland-Altman plots	36
3.4.4	Pearson's correlation coefficient	36
3.4.5	Intra-class correlation coefficient for agreement	36
<b>3.5</b>	<b>Comparing the EEG measurements (PSA and DFA) with vigilance testing</b>	<b>36</b>
<b>3.6</b>	<b>Assessing the relationship between PSA and DFA in awake EEG</b>	<b>37</b>
<b>4.</b>	<b>RESULTS</b>	<b>38</b>
<b>4.1</b>	<b>Participant Demographics</b>	<b>38</b>
<b>4.2</b>	<b>Comparing two methods of artefact removal (manual vs ICA)</b>	<b>38</b>
4.2.1	Checking data for normal distribution	38
4.2.2	Preparation of data for analysis	38
4.2.3	Paired t-tests	39
4.2.4	Effect size	40
4.2.5	Bland-Altman plots	41
4.2.6	Pearson's correlation coefficient	44
4.2.7	Intra-class correlation for absolute agreement	47
4.2.8	Correlation of manual and ICA artefact removal methods to performance test results	50
<b>4.3</b>	<b>Correlation of EEG parameters to vigilance testing</b>	<b>52</b>
4.3.1	Sleep study data	53
4.3.2	Questionnaires for sleepiness (ESS and KSS)	56

4.3.3	AusEd driving simulator	56
4.3.4	Questionnaire for anxiety and depression (DASS and FOSQ)	58
4.3.5	Tests for performance	59
<b>4.4</b>	<b>Assessing the relationship between PSA and DFA in awake EEG</b>	<b>60</b>
4.4.1	Comparing individual PSA frequencies to DFA scaling exponent	60
<b>5.</b>	<b>DISCUSSION</b>	<b>65</b>
<b>5.1</b>	<b>Summary of Findings</b>	<b>65</b>
<b>5.2</b>	<b>Comparing two methodologies of artefact removal</b>	<b>65</b>
5.2.1	Paired t-test	67
5.2.2	Effect size	68
5.2.3	Pearson's correlation coefficient	68
5.2.4	Intra-class correlation coefficient (ICC) (2-way mixed model for agreement)	69
5.2.5	Bland-Altman plots	70
5.2.6	Comparing manual and ICA measurements to performance test results	71
<b>5.3</b>	<b>Using EEG as a method of assessing performance in OSA patients</b>	<b>72</b>
<b>5.4</b>	<b>Comparing the use of the novel method of EEG slowing (DFA scaling exponent) with PSA metrics</b>	<b>75</b>
<b>5.5</b>	<b>Limitations</b>	<b>76</b>
<b>5.6</b>	<b>Future needs</b>	<b>77</b>
<b>6.</b>	<b>CONCLUSION</b>	<b>78</b>
<b>6.1</b>	<b>Comparison of manual versus ICA artefact removal methods</b>	<b>78</b>
<b>6.2</b>	<b>Comparison of EEG slowing with performance testing</b>	<b>80</b>
	<b>BIBLIOGRAPHY</b>	<b>82</b>

## APPENDICES

<b>Appendix 1</b>	<b>Tables</b>
<b>Appendix 2</b>	<b>RPAH Zone Ethics Approval</b>

# LIST OF TABLES

## Chapter 1

Table 1.1	EEG waveforms and frequencies	7
-----------	-------------------------------	---

## Chapter 1

Table 4.1	Defining EEG measurements compared between manual (n) and ICA (i) artefact removal methods	39
Table 4.2	Comparison of ICA (i) and manual (n) artefact removal measurements using paired t-test	40
Table 4.3	Effect size for changes observed between two artefact removal methods	41
Table 4.4	Pearson's correlation coefficient comparing the correlation between two different artefact removal methods	44
Table 4.5	Intra-class correlation coefficient for absolute agreement of the two artefact removal methods	48
Table 4.6	Summary of the results of statistical methods used in comparing the ICA and manual artefact removal methods	49
Table 4.7	Pearson's correlation of DFA scaling exponent versus individual power spectrum frequencies	61
Table 4.8	Pearson's correlation of DFA scaling exponent versus combined power spectrum frequencies	62
Table 4.9	Comparing three EEG slowing methods and the steering deviation test	63

## Appendix 1

Table 1	Factors predisposing to OSA	1
Table 2	Epworth Sleepiness Scale	2
Table 3	Karolinska Sleepiness Scale	2
Table 4	Depression and Anxiety Stress Scale (DASS)	3
Table 5	Functional Outcome of Sleep Questionnaire (FOSQ)	4
Table 6	Correlations between DFA with performance test (manual and ICA)	7
Table 7	Correlation between EEG slowing and AusEd driving simulation test	8
Table 8	Correlation between EEG slowing and sleep study data	9

Table 9	Correlation between measurements of EEG slowing and self-rated questionnaires on sleepiness	10
Table 10	Correlation between EEG slowing and depression and anxiety scale and functional assessment of sleep questionnaire	10
Table 11	(Part 1: Tests for attention) Correlation between EEG slowing and tests for performance	11
Table 12	(Part 2: Tests for intelligence) Correlation between EEG slowing and tests for performance	12
Table 13	(Part 3: Tests for memory and verbal fluency) Correlation between EEG slowing and tests for performance	13

# LIST OF FIGURES

## Chapter 1

Figure 1.1	ICA artefact removal method demonstrated in an ictal EEG	12
------------	--	----

## Chapter 3

Figure 3.1	International 10-20 system of electrode placement	17
Figure 3.2	Tower of London Task	22
Figure 3.3	Functional MRI enhancement in the frontal lobe while performing difficult tower of London task (Roth et al. (2006) Brain Imaging Laboratory, Dartmouth Medical School	23
Figure 3.4	Trail-marking test – Part A	24
Figure 3.5	Corsi block tapping test	26
Figure 3.6	Stroop test – incongruent text and colours	27
Figure 3.7	A screen shot of a 5-second epoch with marked artefacts ('noisy' epoch excluded during manual scoring)	30
Figure 3.8	A screen shot of a 5-second epoch with minimal artefacts ('clean epoch' included during manual scoring)	30
Figure 3.9	A screen shot of 5 second 'clean' epoch without artefact	31
Figure 3.10	A screen shot of the same 5 second epoch analysed by ICA (marked in green), demonstrating overlapping waveform without corrections	31
Figure 3.11	A screen shot of 5-second epoch showing a 'noisy' epoch with an eye blink artifact	32
Figure 3.12	A screen shot of the same 5 second epoch with ICA correction marked in green	32

## Chapter 4

Figure 4.1	Bland-Altman plots for delta power EO	42
Figure 4.2	Bland-Altman plots for delta power EC	42
Figure 4.3	Bland-Altman plots for theta power EO	42
Figure 4.4	Bland-Altman plots for theta power EC	42
Figure 4.5	Bland-Altman plots for alpha power EO	43
Figure 4.6	Bland-Altman plots for alpha power EC	43

Figure 4.7	Bland-Altman plots for beta power EO	43
Figure 4.8	Bland-Altman plots for beta power EC	43
Figure 4.9	Bland-Altman plots for DFA EO	43
Figure 4.10	Bland-Altman plots for DFA EC	43
Figure 4.11	Correlation between manual and ICA artefact removal methods in delta power (EO)	45
Figure 4.12	Correlation between manual and ICA artefact removal methods in delta power (EC)	45
Figure 4.13	Correlation between manual and ICA artefact removal methods in theta power (EO)	45
Figure 4.14	Correlation between manual and ICA artefact removal methods in theta power (EC)	45
Figure 4.15	Correlation between manual and ICA artefact removal methods in alpha power (EO)	46
Figure 4.16	Correlation between manual and ICA artefact removal methods in alpha power (EC)	46
Figure 4.17	Correlation between manual and ICA artefact removal methods in beta power (EO)	46
Figure 4.18	Correlation between manual and ICA artefact removal methods in beta power (EC)	46
Figure 4.19	Scaling exponent (EO) correlation between manual and ICA artefact removal methods in DFA (EO)	47
Figure 4.20	Scaling exponent (EO) correlation between manual and ICA artefact removal methods in DFA (EO)	47
Figure 4.21	Correlation between DFA extracted by ICA and finger tapping task	50
Figure 4.22	Correlation between DFA extracted manually and finger tapping task	50
Figure 4.23	Correlation between DFA extracted by ICA and 4-choice reaction time task	51
Figure 4.24	Correlation between DFA extracted manually and 4-choice reaction time task	51
Figure 4.25	Correlation between PSA extracted by ICA and mean reaction time	52
Figure 4.26	Correlation between PSA extracted manually and mean reaction time	52
Figure 4.27	Correlation between PSA extracted by ICA and median reaction time	52
Figure 4.28	Correlation between PSA extracted manually and median reaction time	52
Figure 4.29	Correlation between EEG slowing (delta+theta/alpha+ beta) EC and total AHI	54
Figure 4.30	Correlation between EEG slowing (delta+theta/alpha+ beta) EC and total AHI (following removal of two outliers)	54
Figure 4.31	Correlation between EEG slowing (delta+theta/alpha+ beta) EC and arousal index	55

Figure 4.32	Correlation between EEG slowing (delta+theta/alpha+ beta) and arousal (following removal of two outliers)	55
Figure 4.33	Correlation between EEG slowing (delta+theta/alpha+ beta) and NREM AHI	55
Figure 4.34	Correlation between EEG slowing (delta+theta/alpha+ beta) and NREM AHI (following removal of two outliers)	55
Figure 4.35	Correlation between mean reaction time and EEG slowing (delta+theta/alpha+delta)	57
Figure 4.36	Correlation between mean reaction time and EEG slowing (delta+theta/alpha+delta) (following removal of two outliers)	57
Figure 4.37	Correlation between median reaction time and EEG slowing (delta+theta/alpha+delta)	57
Figure 4.38	Correlation between median reaction time and EEG slowing (delta+theta/alpha+delta) following removal of two outliers	57
Figure 4.39	Correlation between EEG slowing (delta+theta/alpha+ beta) EC and DASS score for anxiety	58
Figure 4.40	Correlation between EEG slowing (delta+theta/alpha+ beta) EC and DASS score for anxiety (following removal of outliers)	58
Figure 4.41	EEG slowing measured by (delta+theta/alpha+beta) EC and spot the real word test	60
Figure 4.42	EEG slowing measured by (delta+theta/alpha+beta) EC and spot the real word test (following removal of two outliers)	60
Figure 4.43	Correlation between DFA and PSA measured by theta/alpha (EC)	62
Figure 4.44	Correlation between DFA and PSA measured by theta/alpha (EO)	62
Figure 4.45	Correlation between DFA and PSA measured by delta+ theta/alpha+beta (EC)	63
Figure 4.46	Correlation between DFA and PSA measured by delta+ theta/alpha+beta (EO)	63
Figure 4.47	Correlation between PSA (delta+theta/alpha+beta) EO and steering deviation	64
Figure 4.48	Correlation between PSA (theta/alpha) EO and steering deviation	64
Figure 4.49	Correlation between DFA scaling exponent (EO) and steering deviation	64



# 1. INTRODUCTION

## 1.1 An overview of obstructive sleep apnoea (OSA)

### 1.1.1 Pathophysiology of OSA

In obstructive sleep apnoea (OSA), the muscles of the upper airway collapse during sleep, causing a temporary obstruction. This cuts off the airflow to the lungs for a period of time causing a drop in oxygen saturation in the blood. This oxygen desaturation leads to an arousal response, causing the patient to wake up and take a breath, abolishing the cycle of obstruction. The level of desaturation that needs to occur to cause an arousal, as well as the length of the apnoea, varies markedly from one patient to another. However, as apnoeas become more frequent and oxygen desaturation becomes more pronounced, OSA is considered to be severe.

For technical purposes, apnoeic events are categorised in two groups according to the *American Academy of Sleep Medicine Guidelines* (1), as listed below:

1. Apnoea – A drop in airflow by  $\geq 90\%$  of pre-event baseline using an oro-nasal thermal sensor for  $\geq 10$  seconds.
2. Hypopnea – A drop in the airflow by  $\geq 30\%$  of pre-event baseline using nasal pressure for  $\geq 10$  seconds in association with either  $\geq 3\%$  arterial oxygen desaturation or an arousal.

There were two main factors that lead to the development of OSA (2) (Appendix Table 1.1): (i) acquisition of a small upper airway; and (ii) loss of upper airway dilator muscle activity.

A small upper airway could be the result of obesity, upper airway lesions such as enlarged tonsils or tumours, or hormonal factors, for example, acromegaly or hypothyroidism.

A loss of upper airway dilator muscle activity tends to occur due to extrinsic factors such as using sedatives and alcohol, as well as intrinsic factors, for example, cerebral vascular accidents and Arnold-Chiari malformations.

### **1.1.2 OSA epidemiology**

OSA is a common condition. Approximately 2-4% of middle-aged men and 1-2% of middle-aged women have clinically significant OSA (3). There is a strong association between obesity and the development of OSA (4). This is likely to become more pronounced in the coming decades due to the increasing rates of obesity worldwide.

OSA has an association with age. In children, it is commonest between the ages of two and six mainly due to the increased size of adenoids and tonsils during this period (5). In adults, OSA becomes more frequent with increasing age. The odds ratio of developing OSA doubles with every decade until age 60 (2). After 60 years of age, OSA becomes even more frequent. The prevalence rate in elderly patients has been recorded up to 24% (6). With the increase in the elderly population, OSA will become a common co-morbid condition in the future (7). There is a familial tendency for development of OSA where the risk of developing OSA is doubled if a parent or a sibling has OSA (8).

There is also an ethnic variation to OSA. For example, individuals with Polynesian and Chinese ancestry are reported to have a greater likelihood of developing sleep apnoea, even when adjusted to the body mass index (BMI) (2).

### **1.1.3 Clinical symptoms of OSA**

Patients with OSA can present with a variety of symptoms. Loud snoring, witnessed apnoeas and excessive daytime somnolence are the hallmark features of OSA. However, not all patients present with these symptoms. There is a marked individual variation in symptomatology. It is not uncommon to present with disrupted sleep at night-time, lethargy, insomnia or frequent nocturnal urination. OSA could also cause sleep fragmentation resulting in parasomnias and confusional arousals. Nocturnal angina and

nocturnal arrhythmias have also been linked to OSA. Other daytime symptoms are frontal headaches, sore throat, reduced libido and impotence.

The severity of OSA does not always co-relate well to the symptoms of the patients. Some patients may have mild OSA and yet complain of severe daytime functional impairment, while other patients present with severe OSA and have minimal daytime impairment. Hence, the measurement of daytime impairment has become a challenging task (9, 10).

#### **1.1.4 OSA impact on health**

Patients may have had the OSA for many years before they seek medical attention (11). Some patients adjust their lives to cope with the symptoms and most of the time they consider their ill-health to be ‘normal’ and are surprised to see how well they felt after initiating effective treatment (12).

Severe OSA is associated with cardiovascular morbidity and mortality (13), and hypertension (14). It may also be a risk factor for CVA and myocardial infarction (15). Patients with OSA are more likely to have diabetes mellitus and hyperlipidaemia. The link between OSA and increased metabolic risk is now well recognised (16).

Severe OSA may lead to low libido and erectile dysfunction (17). OSA in pregnancy may be associated with low birth weight (18).

The presence of severe OSA was associated with an increase in all-cause mortality. Middle-aged men with an Apnoea-Hypopnea Index (AHI) of more than 20 events per hour had mortality as high as 20% at five years and 35% at eight years. The cause of death ranged from accidents, cerebral vascular accidents, myocardial infarction, cardiac arrhythmias or hypertension associated conditions (19). However, this study had limitations of being a retrospective and uncontrolled trial.

More recent data of well controlled long term longitudinal studies have confirmed increased cardiovascular mortality in patients with OSA (20).

Beyond its impact on an individual, OSA is also an important public health issue. The most marked concern from a public health issue is daytime hypersomnolence and reduced vigilance in OSA patients, including its effect on others. This reduced neurocognitive function not only puts patients at risk, for example, accidents when operating heavy machinery, but also puts the individual patient at risk, for example, motor vehicle accidents (21).

## **1.2 OSA and Vigilance**

### **1.2.1 OSA and vigilance**

Patients with OSA experience neuropsychological deficits falling broadly into three areas of daytime sleepiness: (i) cognitive deficits; (ii) reduced driving competence; and (iii) impaired psychosocial well-being (22). Most OSA patients perform poorly compared to controls in vigilance and attention tasks such as continuous performance testing and driving simulator tests (23). These impairments are thought to be a result of sleep fragmentation and intermittent nocturnal hypoxia secondary to OSA (24, 25).

The risk of motor vehicle accident (MVA) in severe OSA is two to 10 times higher than that of the general population (26). A previous meta-analysis of nine observational studies examining the MVA of drivers with OSA before and after CPAP treatment found a significant reduction in risk with CPAP use (27). The rate of workplace accidents is at least doubled in patients with OSA (28). There is a high prevalence of minor psychiatric morbidity and reductions in functional and health status among patients with OSA (22).

Although daytime sleepiness is commonly associated with severe OSA, this is not true in all cases. Not all patients with OSA develop excessive daytime sleepiness (EDS); the severity of OSA is not directly proportional to the EDS in all patients and neither is there a consistent relationship between patient-reported EDS and measured tendency to sleep by objective testing, for example, maintenance of wakefulness testing (MWT) (29).

The relationship between reduced daytime performance in OSA and currently available and widely used measures of subjective self-reported sleepiness, for example, the Epworth Sleepiness Scale (ESS) has been documented to be elusive (30). Hence, there is a need for a test to measure impaired function in OSA patients so that we may target treatment, evaluate the response to treatment and assess safety at driving or work reliably and objectively.

### **1.2.2 Existing methods for testing for vigilance**

Daytime performances in OSA patients are conventionally measured using questionnaires and performance of tasks to test attention and concentration. The standard questionnaires used are the Epworth Sleepiness Scale (ESS) (31), Karolinska Sleepiness Scale (KSS) (32), Functional Outcomes of Sleep Questionnaire (FOSQ) (33) and Depression and Anxiety Stress State (DASS) (34). The routine performance tests that have been used in research previously are driving simulations (23, 35), four choice reaction time (36) and finger tapping test (37).

Two of the most commonly used ‘objective’ testing for vigilance in clinical practice to determine somnolence are the Mean Sleep Latency Test (MSLT) and Maintenance of Wakefulness (MWT) test (38).

### **1.2.3 Problems with existing methods**

Problems with the above questionnaires are that they are self-rated. Some patients with OSA may be excessively sleepy while they perceive themselves to be functioning well. Hence, they will underscore the severity of their symptoms. Sometimes a fear of consequences such as a loss of their driving license pushes patients to under-report certain components of the questionnaires. For example, the last question of the ESS: *Do you feel sleepy during driving?* is often marked as ‘0’ by most patients despite all other areas of the questionnaire having a disproportionately higher scoring for sleepiness.

This presents a barrier that is overcome with performance testing. However, the problem here is that the severity of daytime performance impairment does not correlate well with OSA severity. One individual with severe OSA may perform the driving task

well while another with mild OSA may be markedly poor in performance. There is also a question as to what extent a driving tests under laboratory circumstances could assess real world driving ability such as the risk of MVA. Furthermore, some patients would perform better at one test compared to another one. Hence, testing for vigilance is not uniformly available and applicable for all patients and does not give a good correlation between severity of the disease and symptoms.

The MSLT and MWT testing are the most objective testing currently used. The MSLT is aimed at measuring the physiological tendency to fall asleep in the absence of stimulating factors while the MWT measures the ability to stay awake under the same conditions during a predefined time duration of 20 or 40 minutes. However, MSLT and MWT tests have their own limitations. Both tests are affected by physiological, psychological and test protocol variables (38).

There is a wide variability in both MSLT and MWT sleep latencies in normal population which makes interpretation of an individual test result difficult (39).

It has been argued that ESS may be a better predictor of sleepiness than MSLT/MWT as the later measures only one situational sleep propensity while the former provides estimate of average sleep tendency (40).

There is a need for simple objective tests that can easily be administered to find which patients are more vulnerable to reduced daytime vigilance.

#### **1.2.4 Using awake EEG as test for vigilance (qEEG)**

Finding a reliable method of measuring vigilance would be very useful in assessing patients who may have impaired daytime performance. This will assist clinical decision-making when applying appropriate restrictions to driving or operating heavy machinery.

One possibility is a quantitative analysis of the awake electroencephalogram (qEEG) of individuals diagnosed with OSA. EEG consists of different frequency waveforms that are generated in the brain. During wakefulness, EEG patterns are different to those of sleeping. This difference could be utilised in assessing sleepiness in an individual.

During a full diagnostic sleep study, measuring EEG activity is a mandatory component of the montage. EEG leads were placed in accordance with an international system of 10-20 electrode placements (Figure 1.1). Each EEG recording can be divided into small sections called ‘epochs’ to help analysis. A conventional sleep study was scored visually with 30-second epochs. For this project, the qEEG was analysed in 5-second epochs.

There are many models developed to analyse EEG waveforms. Two methods discussed in this project were:

1. Power Spectral Analysis (PSA)
2. De-trended Fluctuation Analysis (DFA): Novel method of EEG analysis

### 1.2.5 Power spectral analysis of qEEG and its use in sleep disorders

Each 5-second epoch comprises of different EEG frequencies. Arbitrarily these frequencies are classified into bands of beta, alpha, theta and delta frequency (Table 1.1).

**Table 1.1 EEG waveforms and frequencies**

EEG waveform	Frequency Hz	Most prominently occurs in
Beta	12-25	Awake eyes open
Alpha	8-12	Awake eyes closed
Theta	4-8	Awake slightly drowsy (Eyes open or closed)
Delta	0.5-4	Very drowsy (Eyes Open or Closed)

In each 5-second epoch, there would be a different density in each of these waveforms. The relative power of each individual waveform can be calculated to obtain an objective measure of what waveform predominates. For example, the delta power density of a given epoch would be the absolute power of the delta frequency range (0.5-4Hz) divided by the sum of absolute powers in delta, theta, alpha and beta (0.5-25 Hz) frequency ranges.

Delta waves are low frequency larger waves that occur during periods of drowsiness when awake, as well as being the predominant waveform during slow wave sleep. Hence, higher delta power during awake periods should theoretically indicate increased drowsiness in an individual. Theta waves are not as large as delta waves and have a higher frequency than delta waves. During wakefulness, a higher amount of theta and delta power reflects increased drowsiness.

Alpha waves are the usual waveform that occurs during resting wakefulness when the eyes are closed. However, if alpha waves occur during wakefulness when the eyes are open, this may reflect increased drowsiness as well.

Beta waves are the usual waveform frequency occurring during the restful awake state when the eyes are open.

### **Use of power spectral analysis (PSA) in sleep disorders**

PSA was used to assess sleep-deprived healthy individuals. In healthy individuals who were subjected to 40 hours of extended wakefulness, the theta/alpha density seemed to progressively increase. Furthermore, there was a proportional increase in their self-rated fatigue score (41). This increase of PSA in low frequency (delta, theta) bands was shown again in extended wakefulness of 24 hours in both OSA patients and the healthy controls (42). However, the OSA group tended to underestimate their subjective sleepiness when both groups were assessed using the KSS (42).

In OSA patients, EEG slowing (higher ratio of delta and theta power to alpha and beta power) was observed in both wakefulness and REM sleep. During wakefulness all cortical areas had shown EEG slowing. This explains the reduced functional capacity attached to different cortical areas observed in OSA patients, and shows that the effect is not limited to the frontal area alone as sometimes speculated (43).

The same group had looked at whether initiating Continuous Positive Airway Pressure (CPAP) treatment for OSA patients would correct this EEG slowing. Following six



months of treatment with CPAP, the EEG slowing was corrected in the frontal and central cortical regions during REM sleep as well as wakefulness ([44](#)).

Another study shows that when OSA patients underwent treatment with CPAP for three months and then were exposed to a sustained awake period of 24 hours, they showed reduced theta power compared to pre-CPAP treatment ([45](#)).

EEG slowing seems to be more pronounced with age, as shown when comparing patients aged over 50 years, to less than 50 ([46](#)).

### **1.2.6 Novel method of EEG analysis: De-trended fluctuation analysis**

A newer method of analysing EEG is called de-trended fluctuation analysis (DFA), which is a method used to analyse the randomness of an event occurring. This method looks at fluctuations in EEG as a function of time after removing artefacts ([47](#)). DFA provides a single value called a scaling exponent (SE). The scaling exponent increases during transition from wake to sleep, continues to increase with deeper stages of non-rapid eye movement sleep (NREM) and correlates with traditional PSA metrics ([47](#)). Recently published data from our group that analysed resting awake EEG data at baseline and after 40 hours of sustained wakefulness by using DFA measurements found that the higher the scaling exponent recorded at baseline and while the eyes were open, correlated well with impaired driving performance after 24 hours of wakefulness in OSA patients. This baseline DFA measurement gives information as to how the subject would perform when they are sleep deprived. Subjects with higher DFA SE at baseline showed increased impairment of driving ability if subjected to sleep deprivation. Furthermore, the scaling exponent had positive correlation to the delta power (increased sleepiness) in PSA and negative correlation to beta power (increased alertness) ([48](#)).

### **1.2.7 Use of DFA in non-sleep disorders**

In anaesthesia, DFA had been used to measure the depth of anaesthesia. It was used to measure the difference between the awake, sedated and anaesthetised states as a non-invasive methodology allowing real-time implementation ([49](#)).

### **1.2.8 Use of DFA in sleep disorders**

The use of DFA has been looked at in narcolepsy patients. The overnight sleep study of 10 narcoleptic patients when compared to eight healthy controls showed that there was a higher DFA scaling exponent noted during deep sleep stages in narcoleptic patients compared with the controls, suggesting a potential application of DFA in diagnosing narcolepsy (47).

#### **Possible use of DFA in OSA patients to assess vigilance**

Preliminary work suggests that DFA of the qEEG recorded at rest may correlate with performance on a simulated driving task in patients with OSA. However, this is after 24 hours of extended wakefulness (48). These findings need to be confirmed in larger groups of patients.

The studies are sparse on the use of DFA in subjects with OSA to assess vigilance in non-sleep deprived conditions.

### **1.2.9 Advantages of using DFA in place of PSA**

The DFA scaling exponent has some advantages over the power spectral method of EEG analysis.

1. The limitation of PSA is that it assumes the EEG to be linear and stationary, which is not accurate (50).
2. The scaling exponent is the single measure that is extracted from the DFA method. This is in place of the four different waveforms explained earlier in the power spectral analysis. The frequency bands of each of these PSA waveforms are not strictly defined and sometimes have an overlap. For example, Beta frequency, in some instances, is defined as 12-25 Hz frequency and at other times divided into sigma frequency 12-15Hz and beta 16-25Hz.

3. The DFA scaling exponent would be more robust at withstanding artefacts like muscle movements and eye blinking that changes the waveforms in PSA.

If the DFA scaling exponent was found to have a good correlation to vigilance testing and performance tasks in patients with OSA, this would be a single metric appropriate for non-linear data and more robust to ‘noise’. As with the PSA method, DFA also requires a larger set of data to give a more accurate result (50). Hence, this would be a valuable method in analysing the overnight PSG with a large amount of EEG data.

### **1.3 Introduction to artefact removal in EEG**

To analyse an EEG accurately, the signal should be as clean as possible to represent waves that originate from the cerebral cortex. This is never easy as physiological signals such as muscle movements, eye blinking and heart beat may be superimposed on the EEG. There could also be artefacts due to equipment interference. Hence, removing artefacts or ‘noise’ is very important to get a clean signal for analysis. This can be done in two ways: (i) either manually removing the epochs that have artefacts; or (ii) using an automated method to identify epochs with artefacts.

#### **1.3.1 Manual artefact removal**

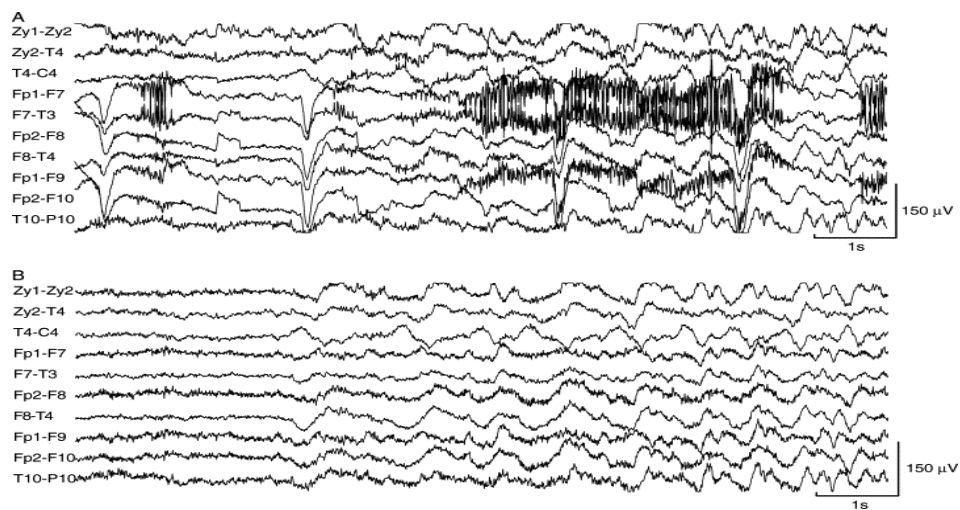
This is considered the ‘gold standard’ for artefact removal. The conventional method of artefact removal is done by an individual trained in this task, for example, a certified sleep technologist, and excludes the epochs that have eye blinking or muscle movements. While this is the gold standard method, it is time-consuming because each 5-second epoch needs to be examined. In terms of analysing lengthy timeframes, this is very tedious and not practical. The other disadvantage is that when manual artefact removal is used, ‘noisy’ epochs have to be excluded completely, thereby reducing the power of the recordings as fewer epochs can be included in the analysis. Furthermore, when epochs are excluded, valuable information about the artefacts will be lost and a full representation of the EEG activity during the examined time period is not obtained.

### 1.3.2 Independent Component Analysis (ICA)

Several methods of artefact removal from EEG recordings have been published before ([50](#), [51](#)). One such method of automated artefact removal is independent component analysis (ICA). Most of the work in ICA relates to epileptiform activity monitoring, as it is a complex task separating ictal waveforms from artefacts for accurate interpretation of the seizure activity ([53](#)). In ICA, a reference signal is used for an artefact (e.g. eye movement extracted from EOG channel), which is then subtracted from the EEG after scaling it by an appropriate factor determined by regression in the time or frequency domains ([53](#)).

Figure 1.1 illustrates the mechanism of artefact removal. Section A demonstrates a seizure contaminated by marked ocular activity on channels Fp1-F7, F7-T3, Fp2-F8, F8-T4, Fp1-F9, and Fp2-F10. To a lesser degree, there is muscle activity in channels Fp1-F7, F7-T3, and Fp1-F9.

In section B, the ICA is applied and most of the artefacts have been removed, preserving the underlying EEG activity ([53](#)).



**Figure 1.1 ICA artefact removal method demonstrated in an ictal EEG**

Our research group internally developed a program incorporating ICA to automatically ‘correct’ the EOG artefacts in the EEG components without excluding the epochs from

analysis. We had validated this artefact removal method previously ([48](#)). The EEG data of 17 individual healthy controls (each patient had five recordings consisting of 7.5 minutes of qEEG data) comprising of 85 EEG recording in total were analysed for artefact using three methods: (i) ICA; (ii) manual scoring; and (iii) raw data without artefact removal.

When values of DFA scaling exponent obtained by the manual scoring and ICA were compared to driving performance, the results did not show any significant difference between the two methods ([48](#)). For example, AusEd steering deviation ICA:  $r = 0.62$  and manual:  $r = 0.61$ .

Hence, using the ICA improved the power of the data as more data was preserved and was also less labour intensive and time efficient.

## **2. OBJECTIVE**

The aims of this project are to:

1. Investigate the role of conventional and newer methods of EEG analysis as an objective and quantitative measure of testing vigilance in patients diagnosed with OSA by comparing it with subjectively rated sleepiness, as well as a battery of neurobehavioral performance testing.
2. Validate the use of ICA in a group of patients diagnosed with OSA.

If validated, these techniques will enable the researcher to accurately quantify reduced vigilance in OSA patients and find characteristics that determine the patients who are at higher risk of drowsiness by using EEG recordings routinely collected as part of a polysomnogram used in the clinical evaluation of sleep apnoea.

### **3. METHODOLOGY**

#### **3.1 Study design**

The study design is a retrospective cross-sectional observational study of untreated OSA patients.

##### **3.1.1 Ethics approval**

The Sydney South West Area Health Services Human Research Ethics Committee (RAPH zone) granted the ethics approval for the initial project titled ‘Neurobiological effects of sleep apnoea and sleepiness’ Protocol No. X06-0299 (Appendix 4). The research student was included as an associate investigator for this project to enable student to extract the data from this study to use in this project.

The original study from which data was extracted was registered with the Australian Clinical Trials Registry as an observational study (ACTRN 012605000089639).

##### **3.1.2 Participants**

Previously collected data on patients with untreated OSA by our research group as per Protocol No. X06-0299 was used to validate this novel methodology.

The participants were adults aged 18-75, with diagnosed or suspected OSA but not commenced on treatment for OSA with reasonable fluency in written and spoken English enabling them to perform neurocognitive tasks satisfactorily.

Participants with sleep disorders other than OSA were excluded. Other exclusion criteria were epilepsy, previous stroke, significant uncontrolled co-morbidities like cardiac failure, respiratory failure or malignancy and regular use of medications known to affect sleep architecture or EEG (e.g. antidepressants and antipsychotic drugs).

### **3.1.3 Protocol and measurements**

The protocol explained here is that of the initial study (Clinical Trials Registry No. ACTRN 012605000089639) from which the student had extracted data for this project.

#### **Screening and recruitment**

Potential participants who were clinically suspected of OSA and booked for a diagnostic sleep study were contacted prior to the diagnostic study. The study rationale and procedure were explained and eligibility was determined. Those verbally consenting participants were requested to attend the overnight polysomnography during the usual time. Bookings were made at the Brain Resource Company for an neurocognitive functioning appointment.

#### **Sleep laboratory visit**

Testing was performed prior to the diagnostic sleep study and on the morning after the sleep study. Participants were requested to refrain from caffeine from 0900h of the date of the sleep study until all investigations were completed. They arrived at the sleep laboratory at 1630h, which is the usual requested time of arrival for preparing the overnight study. The study procedure was explained, written consent was obtained, and testing schedules were explained. External sensors used for overnight polysomnography were attached to the subject, including seven extra EEG leads. Additional leads were placed in the Fz, Cz, Pz and Oz regions, left lateral, right lateral and right supra-ocular electrooculogram (EOG).

After checking for signal accuracy, the waking EEG recording was performed for the above described five-minute duration. This was followed by the Tower of London task (3 minutes practice run and 8-12 minutes of test) and the AusEd driving task (5 minutes practice and 30 minutes of testing). After testing, dinner was provided (as per routine sleep unit practice). The participants were then administered questionnaires. The overnight polysomnography recording commenced at 2130h and terminated at 0600h. After breakfast, the participants were asked to attend neurocognitive testing at the Brain Resource Company (0900 to 1200h).



### 3.1.4 Statistical analysis

Data was analysed using SPSS statistics 21.0 for Mac (IBM SPSS, Somers, NY, USA). Statistical support was given by Ms Anne-Sophie Valliard (biostatistician) from Sydney University and Dr Keith Wong, Staff Specialist from Royal Prince Alfred Hospital, (Camperdown NSW).

## 3.2 Measurements of vigilance

### 3.2.1 Diagnostic polysomnography

Polysomnography was performed at the Sleep Unit of Royal Prince Alfred Hospital using Compumedics E series acquisition hardware. The setup was similar to a routine diagnostic sleep study. EEG leads were placed according to the international 10-20 specifications (Figure 3.1). Seven additional leads in the Fz, Cz, Pz and Oz regions, left lateral, right lateral, right supra-ocular electrooculogram (EOG) were placed. All EEG leads were sampled at a rate of 256Hz, with a high pass filter placed at 0.3Hz and low pass filter at 50Hz. Sleep staging and manual scoring of arousal and respiratory events were performed using standard criteria (1).

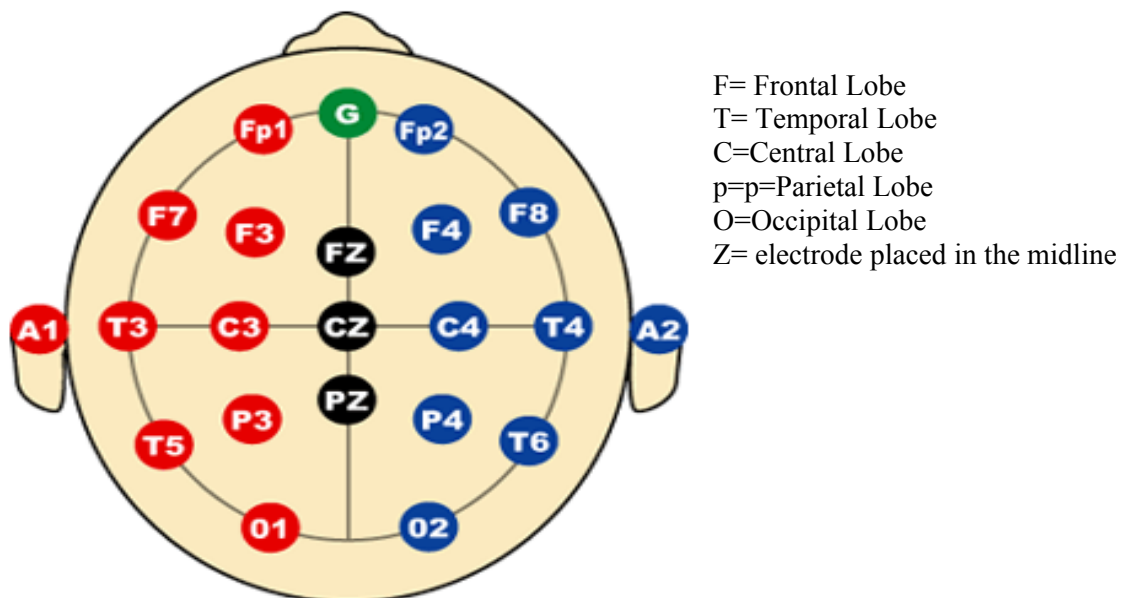


Figure 3.1 International 10-20 system of electrode placement

### **3.2.2 Awake EEG (qEEG)**

Awake EEG is acquired prior to commencing the sleep study. Patients would be attached to EEG scalp electrodes as above in preparation for their overnight study. The signal accuracy is checked when the patient is awake. All EEG acquisitions at the sleep laboratory used the same Compumedics E series hardware that was used for the polysomnogram. A five-minute resting awake EEG was performed using the above-described leads. This component of awake EEG measurement is named the Karolinska Drowsiness Test (KDT), and it may be used as a test to measure vigilance in patients.

During the KDT, patients were required to sit upright in bed in a quiet room with ambient indoor lighting. They were requested to fix their gaze on a dot placed two to three metres away at eye level on a wall, staying relaxed but awake. The signal integrity was checked before recording commenced. After two minutes, the subject was instructed to close their eyes. The recording was terminated after another two minutes.

### **3.2.3 Self rating questionnaires**

Questionnaires commonly used to assess vigilance were used to assess the impact of sleepiness.

#### **Epworth Sleepiness Score (ESS)**

The ESS is an eight scenario self-rated questionnaire used extensively in sleep research and clinical practice. It has been validated in healthy volunteers and in sleep apnoea (31). In each given scenario, the subject is asked to indicate their likelihood of falling asleep. The response for an individual item being a score of 0 indicates no chance of dozing, up to a score of 3 which indicates a high chance of dozing. The total score would be out of 24 (Appendix Table 2).

#### **Karolinska Sleepiness Scale (KSS)**

The KSS is a single item measurement of sleepiness in an individual at that moment. There are nine possible responses ranging from 1 indicating ‘very alert’ to 9 ‘very sleepy; great effort to keep awake; fighting sleep (Appendix Table 3). This scale is used

to indicate an individual's current state of sleepiness as opposed to a 'trait' of sleepiness.

The KSS has been validated against performance and EEG variables in a small group of healthy individuals (n=16). The variables of median reaction times and the number of lapses in the psychomotor vigilance task, as well as alpha and theta power density have shown significant increase with the increase of the KSS score (32).

### **Depression Anxiety Stress Scale (DASS)**

A questionnaire on depression and anxiety was included because both these conditions can make a subject feel sleepy, resulting in mood disorders becoming a compounding factor. At the same time, mood disorders can occur as a secondary consequence of OSA. The depression and anxiety score is a 21-item questionnaire (Appendix Table 4) to self-rate depression, anxiety and stress (a shorter version of the 42-item full DASS questionnaire). The DASS is a widely used instrument in research (34). Subjects are asked to use a 4-point severity/frequency scale to rate the experience of each state over the past week.

The scale has questions relating to three components: (i) depression; (ii) anxiety; and (iii) stress. Each sub-class has seven questions to rate that particular mood. Scores are calculated by adding the ratings from items belonging to each of the three subscales: (i) depression, items 3,5,10,13,16,17,21; (ii) anxiety, items 2,4,7,9,15,19; and (iii) stress, items 1,6,8,11,12,14,18.

The answers were added and multiplied by two to give a final score that was comparable to the 42 question standard DASS questionnaire.

### **Functional Outcome of Sleep Questionnaire (FOSQ)**

The functional outcomes of the FOSQ is a 30-item self-reported scale that explores the extent to which sleepiness affects five aspects of daily living (33) (Appendix Table 5).

1. General productivity (items 11-4 and 8-11)

2. Social outcome (items 12 and 13)
3. Activity level (items 5, 14-16, 22-26)
4. Vigilance (items 6-7, 17-21)
5. Intimacy and sexual activities (items 27-30)

The test requested subjects to mark the degree of difficulty experienced in performing each activity. The response was given a mark from 1 to 4 with smaller values representing greater difficulty. If participants indicated they did not engage in that activity, it was marked as 'missing'. The arithmetic mean of the non-missing responses formed the subscale results.

### **3.2.4 Performance testing**

#### **AusEd driving simulator**

The AusEd driving simulator assesses multiple performance areas, including attention, concentration and executive functioning. The AusEd driving task (Woolcock Institute of Medical Research, Sydney, Australia) ([35](#)) is a PC-based task simulating driving on a country road at night. It is sensitive to performance decrement from driver fatigue in the laboratory setting, potentially making it useful as a laboratory or office-based test for driver fatigue risk management.

The test was performed after satisfactory understanding of the instructions and controls were achieved on a 5-minute practice run. The practice run was supervised by the researcher who repeated the practice task if needed.

The actual test was 30 minutes in duration and comprised of alternating 2-minute winding and 5-minute straight periods. Participants were asked to drive in the centre of the left-hand lane. They were requested to maintain a speed between 60-80 km/h. A speedometer was available on the top left-hand corner of the display. Ten trucks were presented at random intervals during the task. As soon as trucks appeared, the participant was requested to remove his/her foot from the accelerator pedal and depress the brake pedal, followed by returning the foot to the accelerator panel and continue driving.

The measurements taken during this task were:

1. Steering deviation (stdvm)
2. Speed deviation (spdev)
3. Mean reaction time to braking (rtmn)
4. Number of crashes (crash)

Data from the first six minutes were excluded from analysis to reduce the effects of acclimatization to the task.

Previously published data demonstrated that patients with OSA had more lane variability, speed variability, steering rate variability and a higher number of crash frequency over a 60-minute driving task compared to the control ([55](#)).

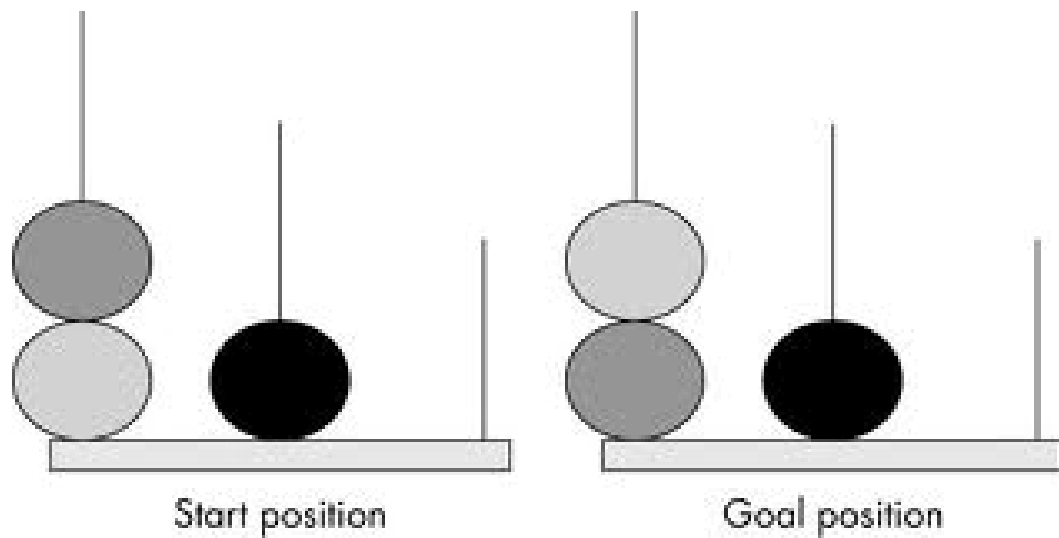
The AusEd simulator has shown to be a sensitive marker in measuring mean reaction time and speed deviation following 30 hours of extended sleep deprivation in OSA and healthy individuals ([56](#)). In another study, the AusEd task was used for 70 minutes and a small dose of alcohol was added to give a mean blood alcohol concentration of 0.037g/dl, in addition to one night's sleep restriction of five hours in bed. The result indicated a worsening of the steering deviation and mean reaction time to break when compared with sleep restriction alone ([57](#)).

### **Tower of London Task (Executive functioning)**

The Tower of London task was used to assess executive functioning. It has been shown to assess executive planning in healthy elementary students and young adults ([58](#)). The task involves moving coloured balls stacked on pegs into a goal position by using a minimal number of moves (Figure 3.2).

This test has not been used to assess vigilance in OSA patients in past research. However, functional MRI had shown that when comparing a hard condition relative to an easy task (difficulty based on the number of moves required to solve a problem) in a healthy adult, there was prominent frontal lobe activation (Figure 3.3). This is a region

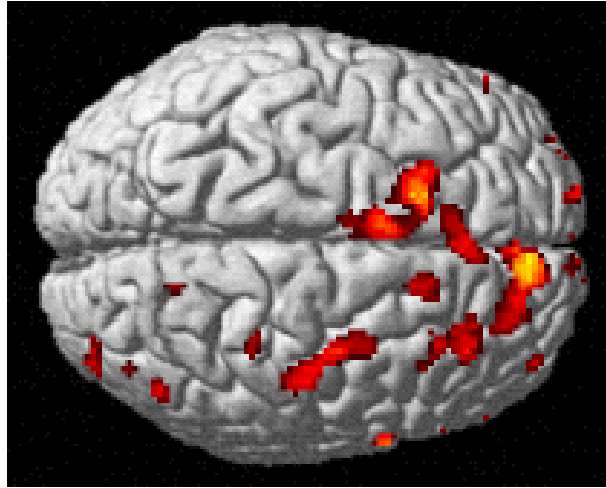
thought to be vulnerable to EEG slowing during wakefulness and sleep in OSA patients (44).



**Figure 3.2 Tower of London Task**

A computerised version of this task was administered (Colorado assessment tests, version 1.2, Colorado Springs, Colorado USA). The software automated the process of administering the test and produced written and spoken instructions at the start of the testing session. A brief practice session lasting three minutes was given prior to the actual test, which lasted 8-12 minutes. The subject had to move the coloured balls between pegs by using a computer mouse. Trials from the practice test were not repeated during the actual test, however, computer software automated the scoring. Measurements observed in this task were:

1. Total number of moves, above the minimum required to solve the problem (t.excess)
2. Average time taken per trial to solve the problem (t.avtrial)



**Figure 3.3** Functional MRI enhancement in the frontal lobe while performing difficult tower of London task (Roth et al. (2006) Brain Imaging Laboratory, Dartmouth Medical School

#### **Four choice reaction time test (Attention)**

This test assesses reaction time and is a measure of attention. There are four circles on the computer screen and one would randomly light up. The subject is instructed to touch that circle as quickly as possible. This test has been used in OSA patients. In a test of 90-minute duration, random appearance of a choice every 20-40 seconds showed that the reaction time was linearly correlated to the vigilance state (36). The measurement taken was the average speed of response (Ch\_avrt).

#### **Visual timing (Attention)**

This task determines visual attention and subjective sense of time intervals. When a circle appears on the screen for 1-12 seconds, the participant is requested to indicate how long the circle was visible. The time estimation task has been associated with changes in frontal brain of healthy aging adults (59).

The measurement from this task was the value of the average difference between the (actual lengths of the stimulus – subjects estimate) weighted by the actual length of the stimulus (t\_prbias).

### **Sustained attention task (Attention)**

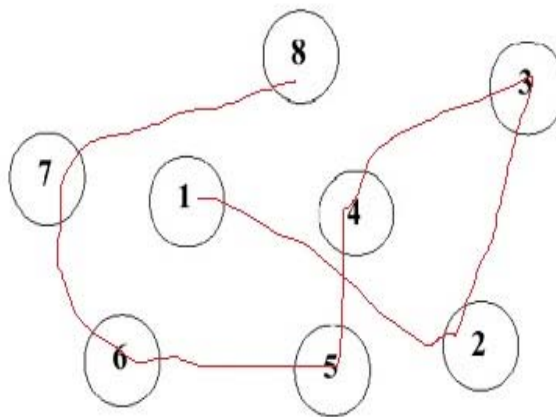
A series of letters (e.g. B, C, D and G) are presented for 200ms each. The participant is requested to press the button if the same letter appears twice in a row.

Measurements from this task were:

1. Number of incorrect responses, or false positives (Wmfp)
2. Number of targets the subject did not respond to, or false negatives (wmfn)

### **Switching of attention (Attention and executive functioning)**

This test has two components: (i) Part A: a participant is requested to touch a sequence of 25 numbers scattered across the screen in ascending order (Figure 3.4) (60); and (ii) Part B: the subject touches alternating numbers 1-13 and letters (A-L). The second part is dealing with executive functioning.



**Figure 3.4 Trail-marking test – Part A**

Measurements from these tests were:

1. Time to complete test A successfully (Swoadur 1)
2. Time to complete test B successfully (Swoadur 2)



### **Finger tapping test (Manual dexterity/attention)**

The manual dexterity test requires the participant to tap a circle with the index finger as many times as possible within 30 seconds. The task is performed using both hands. Slowing of the tapping has been associated with sleep onset drowsiness (37).

Measurements from this task were:

1. Number of taps over 30 seconds – dominant hand (tapdomn)
2. Number of taps over 30 seconds – non-dominant hand (tapndmn)

### **Memory recall and recognition (Memory)**

This is a test to determine delayed memory recall and memory recognition. A list of 12 words is read to the subject four times. The participant is asked to recall the words after each reading (recall trials 1-4). A second distracter list is presented that has to be memorised. Twenty minutes later, the subject is asked to recall the original list (memory recall). In the second part of the test, the participant is shown a list of words and asked if they belonged to the original set of words (memory recognition).

Measurements from the memory recall and recognition tasks were:

1. Total number of words recalled over trials 1-4 (memtot14)
2. Number of words recalled after the trial at 25 minutes (memrec7)
3. Words correctly recognised as from the original list (memrecco)

### **Digit span (Memory)**

This is a test of memory. After a hearing sequence ranging from 3 to 9 digits, the participant enters the numbers on a numeric keypad in the order they were presented. (Forward digit span). The reverse digit span is when the subject is asked to enter the digits in the reverse order of presentation (61).

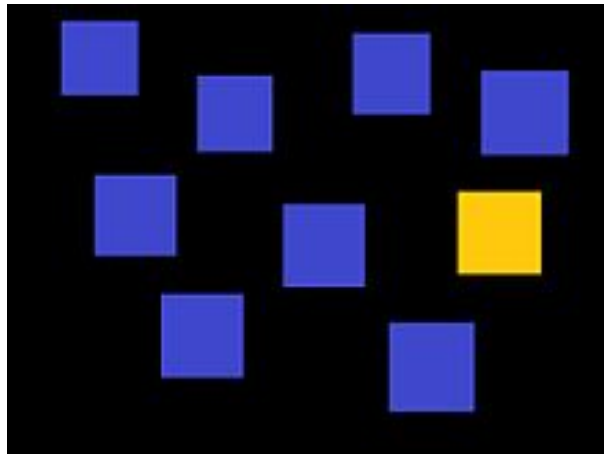
Measurements taken during this test were:

1. Forward digit span – Longest sequence correctly completed (digitot)
2. Backward digit span – Longest sequence correctly completed (rdigitot)

### **Span of visual memory (Memory)**

This task assesses the working memory. This is also known as the modified Corsi block-tapping test ([62](#)). Up to nine identical squares light up on the display in a random fashion. The participant has to tap the sequence in the order they lit up once they hear a tone. The sequence starts out simply, usually using two blocks, but becomes more complex until the subject's performance suffers (Figure 3.5).

The measurement from this test is the longest sequence correctly completed (Spvm)



**Figure 3.5 Corsi block tapping test**

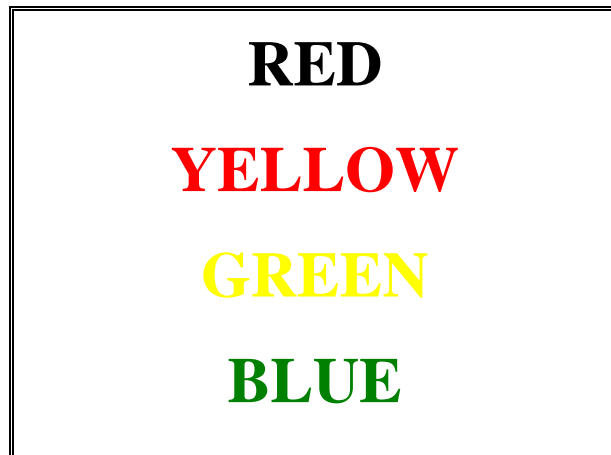
Note: Yellow is the current block in sequence.

### **Verbal interference (Verbal fluency)**

Also referred to as the Stroop test ([63](#)), this test consists of two parts. In the first part, a coloured word (red, yellow, green or blue) appears on the screen (Figure 3.6). The participant is requested to indicate the colour the word is spelling out by pressing a button allocated to the four colours mentioned. Then the participant is requested to indicate the colour of that word. The words and colours are always incongruent.

Measurements in these tests are:

1. Stroop (text) – number of words correctly identified (Vi\_scol)
2. Stroop (colour) – number of colours correctly identified (Vi\_sco2)



**Figure 3.6 Stroop test – incongruent text and colours**

#### **Word generation FAS test (Verbal fluency)**

Also known as the controlled oral word association test (FAS test), this test requests the participant to recall as many words as possible beginning with each of the letters F, A and S. One minute is allowed for each letter. Responses are recorded and manually scored.

The measurement taken from this test is the FAS score – Number of words recalled across the three letters (fas).

#### **Word generation animal test (Verbal fluency)**

In this task, the participant is requested to recall the names of as many animals as they can starting with a selected letter. The time allocated for this task is one minute. The measurement taken was the number of words recalled (animals).

### **Spot the real world (Intelligence)**

The participant is presented with two pairs of words (64): one has a true meaning; and (ii) the other is a non-word. The measurement of this task is the number of real words recognised (spotscor).

### **Maze task (Executive functioning)**

The task combines memory and planning with self-monitoring. The participant is required to remember a hidden path through a maze. The task is completed either when the participant traces the same path twice in a row successfully or when the time limit of eight minutes is reached.

Measurements from this task are:

1. The number of trials completed before the end of the task. (mazetrls)
1. The total number of off-path moves (mazeerr)

## **3.3 Comparing EEG artefact removal methods (ICA vs manual scoring)**

### **3.3.1 EEG preparation for analysis**

Each individual awake EEG recorded in Compumedics E series software was extracted into a universal viewing program called EDF viewer that was able to run the analysis using the software program developed by our group (47). Each 5-minute awake EEG segment would have a 2.5 minute ‘eyes open’ segment followed by a 2.5 minute ‘eyes closed’ segment. During the awake EEG recording, procedural instructions were given by the technician to the participant, to initiate each ‘eyes open’ and ‘eyes closed’ component. Consequently, 30 seconds at the beginning of each 2.5-minute segment was discarded. Hence, the final EEG data would have two minutes of eyes open (EO) and two minutes of eyes closed (EC) segments.

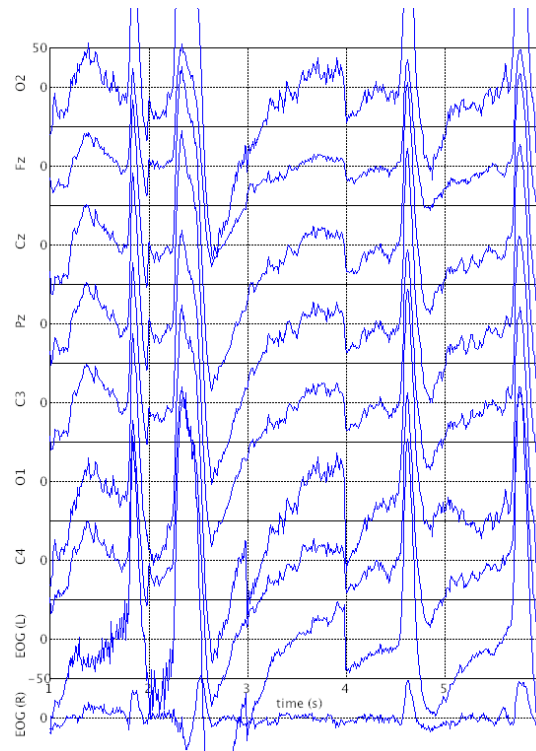
Eighty-three awake EEG recordings were extracted from the data set, each consisting of two minutes of 'eyes open' (EO) and two minutes of 'eyes closed' (EC) resting awake EEG extracted to a EDF viewer. For each recording, the Cz channel was selected for analysis. It was the preferred instrument because it was a midline channel that would not have been influenced by the hand dominance of the patient. All 83 awake EEG recordings were then manually screened in 5-second epochs to look at signal integrity and artefacts.

### **3.3.2 Manual method of EEG artefact removal**

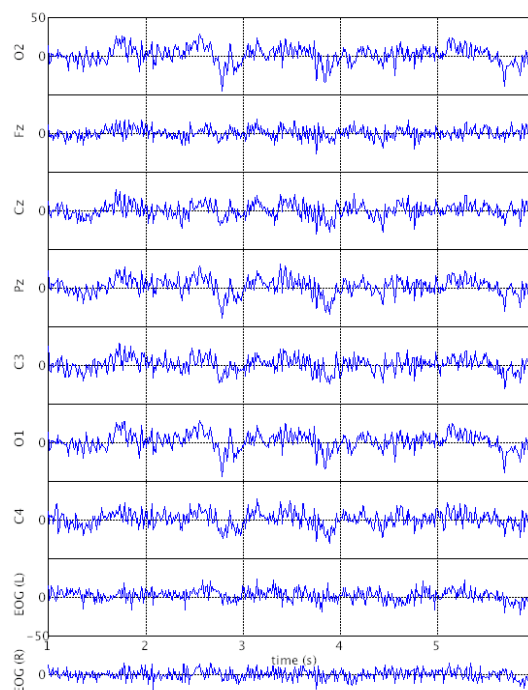
As mentioned above, artefact removal is of paramount importance for obtaining a clean signal in the awake EEG. This is especially important when EEG data are being used to correlate the testing of vigilance to assess drowsiness. Muscle movements and eye blinking can generate large low frequency waves that can be interpreted as delta waves if not correctly excluded.

Manual removal of artefacts is the gold standard. However, adequate training and pattern recognition is required to do this accurately. The manual artefact removal is time consuming and labour intensive. In this project data of 83 recordings of 4-minute duration for each recording, involving 3984 epochs in total was analysed for artefact by the student. The student was trained in EEG analysis for artefact removal prior to commencement of the study.

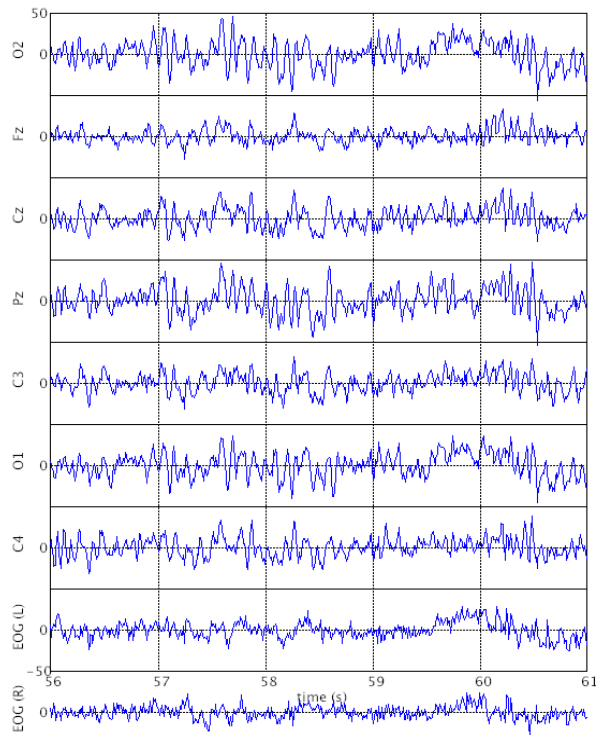
The student was requested to perform manual scoring of 20 randomly selected patient qEEG data from the 83 patient records to assess the adequacy of training prior to analysis of the entire data set. These EEG scoring was then discussed with the student in a group meeting by Dr Jon Wong Kim and Ms. Angela Denotti for agreement of marking of the 'noisy' epochs and discussion regarding ICA and manual scoring. The student was found to be scoring artefacts at the expected level.



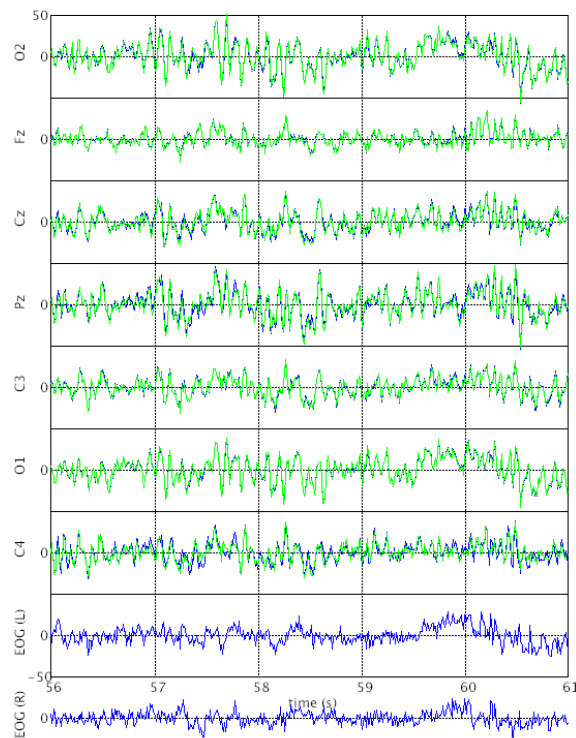
**Figure 3.7** A screen shot of a 5-second epoch with marked artefacts ('noisy' epoch excluded during manual scoring)



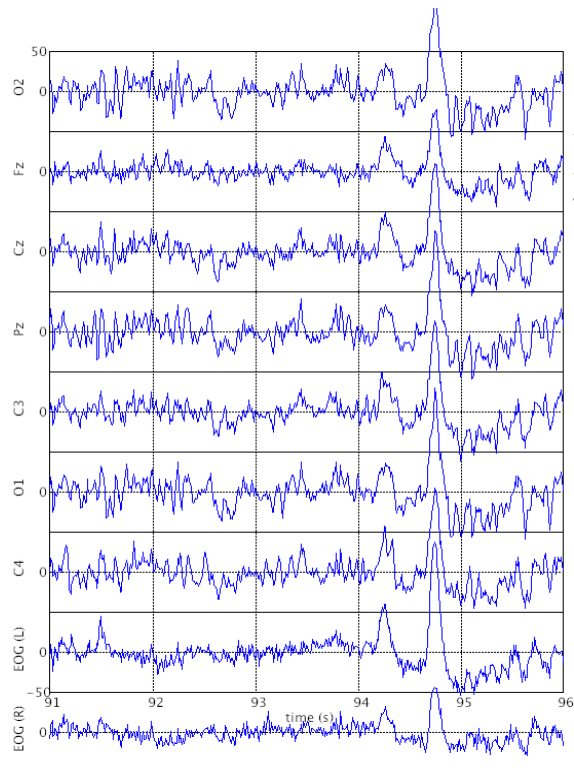
**Figure 3.8** A screen shot of a 5-second epoch with minimal artefacts ('clean epoch' included during manual scoring)



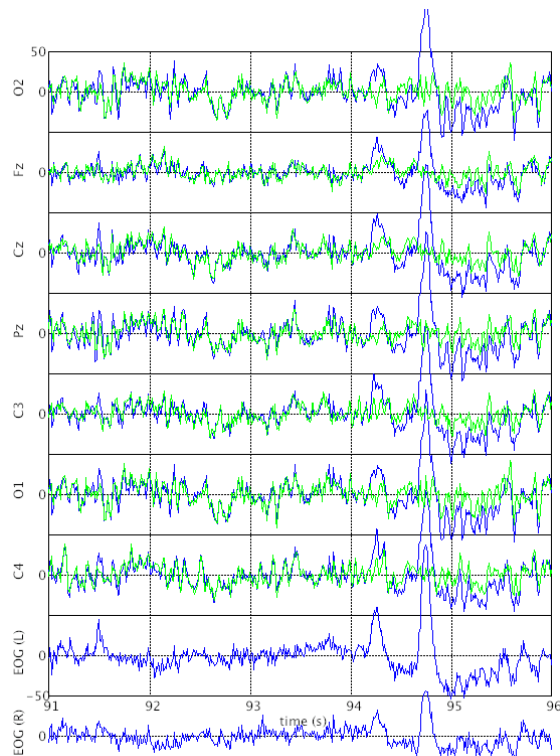
**Figure 3.9 A screen shot of 5 second 'clean' epoch without artefact**



**Figure 3.10 A screen shot of the same 5 second epoch analysed by ICA (marked in green), demonstrating overlapping waveform without corrections**



**Figure 3.11** A screen shot of 5-second epoch showing a ‘noisy’ epoch with an eye blink artifact



**Figure 3.12** A screen shot of the same 5 second epoch with ICA correction marked in green



During manual artefact removal each of the epochs are marked as ‘noisy’ (has artefact) (Figure 3.7) or clean (no artefacts) (Figure 3.8) and the software has the capability to store these changes. Once marking was completed for all four minutes, the manual artefact removal can be saved in the same patient folder. The epochs marked as ‘noisy’ were excluded from the analysis. Following this the analysis for both DFA scaling exponent and PSA can be run on the saved manual data by using the software developed by our group.

### **3.3.3 ICA for artefact removal**

The above process is made much simpler by using the automated ICA artefact removal method. Once the 4-minute qEEG was selected from a participant, then the software allows the operator to select ICA option for artefact removal (instead of manual), and then directly obtains the analysis for PSA and DFA measurements.

This ICA option automatically analyses each 5-second epoch and the noisy epochs identified, however they are not excluded. Instead they are normalised by removing the eye blink artefacts. Artefacts due to heart rate or other muscle movements were not removed by this method.

### **3.3.4 Analysing the EEG data to obtain PSA and DFA measurements by using both artefact removal methods**

Once artefacts have been removed the clean EEG segments was analysed for PSA and DFA measurements. This gives two sets of results; one for manual artefact removal and one for the ICA. During the PSA analysis, the results are displayed as individual absolute values of delta, theta, alpha and beta frequencies for each five seconds. Each of these waveforms are then individually summed across the 48 epochs of each patient to give final values for the previously mentioned delta, theta, alpha and beta for each of the eyes open (24 epochs) and eyes closed (24 epochs) segments.

DFA analysis however gives only one parameter called the scaling exponent for each 5-second epoch. These values of the DFA SE across the 48 epochs for each patient are

then summed to give the total scaling exponent during eyes open (24 epochs) and eyes closed (24 epochs) state.

During this study, EEG slowing was measured in three ways:

1. Using PSA ratio of delta power and theta power to alpha power and beta power, this was a ratio of slow frequencies: delta and theta (indicating sleepiness) to the faster frequencies: alpha and beta (indicating alertness). It was selected as a global index for EEG slowing. A higher value indicates reduced alertness. A study done by Morrison et al. ([43](#)) involving 21 OSA patients compared to 10 normal controls demonstrated increased EEG slowing using this method during REM sleep in frontal, central and parietal regions while EEG slowing during 46 wakefulness occurred in all cortical regions. This may explain the wider range of performance impairment seen in OSA patients and not limited to executive functioning.
2. Using PSA ratio of theta to alpha power waves (measuring the ratio between more drowsy waves to the more alert waves), a higher value indicated reduced alertness. A study by Greneche et al. ([41](#)) demonstrated increased theta/alpha density when nine healthy women were subjected to 40 hours of extended wakefulness. There was a correlated increase in the self-rated fatigue score as well.
3. Using DFA scaling exponent (higher the value of scaling exponent, more sleepier the subject), Rozeriaio et al. ([48](#)) demonstrated higher DFA scaling exponent and higher delta power during wakefulness in OSA patients than controls. The baseline DFA scaling exponent was found to be a marker for impaired driving performance after 24 hours of extended wakefulness in patients with OSA.

Each EEG slowing parameters were measured during eyes open and eyes closed state.

During the statistical analysis of multiple correlation testing for EEG slowing and performance testing there is a one in 20 chance of a false positive result. The results could also be falsely positive due to outliers in the given sample. Hence once the correlation tests are carried out they will then be plotted in a scatter plot to assess the validity of the results (65).

### **3.4 Statistical methods used to compare the two methodologies of artifact removal (Manual vs ICA)**

A literature review identified several statistical methods that measure the agreement between two measurements, as is the case with this study. One single statistical method was not superior or accurate in drawing conclusions, hence five statistical methods namely: (i) student t-tests; (ii) effect size measurement; (iii) Bland-Altman plots; (iv) Pearson's correlation coefficient; and (iv) intra-class correlation coefficient measurement were used to draw a combined inference.

#### **3.4.1 Student's t-test**

The paired sample student's t-test was used to ascertain whether there is a difference in the sample mean when using ICA and manual artifact removal method in each of the PSA wave densities and DFA scaling exponent measurements during EO and EC states. A P value <0.05 was considered to be the statistical significant level.

#### **3.4.2 Effect size**

Effect size was used to measure the clinical significance of the difference noted between two measurements as statistical significance does not automatically transform to clinical significance. This was measured by dividing the mean difference between the 2 groups of each EEG measurement by the standard deviation of the manually extracted data of the same measurement, e.g. effect size of delta power = mean difference of delta power (i-n)/SD of delta power(n).

### **3.4.3 Bland-Altman plots**

To further clarify the scatter of the difference between the measurements of the two artefact removal methods, Bland-Altman plots (B&A plots) were used. The mean of the two measurement methods were to be plotted against the standard deviation of the difference between the two methods to decide if the limits of agreement are narrow or wide, e.g. Bland-Altman plot for delta power would comprise of the X axis (delta power  $i+n/2$ ) plotted against the Y axis; the mean difference of the two values (delta power  $i-n$ ).

### **3.4.4 Pearson's correlation coefficient**

Person's co-relation was calculated to find out the strength of the association between the two methodologies of artifact removal. The results are then explored further for validity and outliers by use of scatter plots.

### **3.4.5 Intra-class correlation coefficient for agreement**

To test the absolute agreement between the two methods of artifact removal, intra-class correlation coefficient was performed.

## **3.5 Comparing the EEG measurements (PSA and DFA) with vigilance testing**

There is limited data on using PSA power spectrum EEG slowing to assess vigilance. Using DFA scaling exponent our group had recently published data on driving performance in patients with OSA after extended wakefulness with encouraging results.

The use of DFA is novel and data is unavailable on vigilance testing in non-sleep deprived OSA patients.

In the current project, four main domains were included for vigilance testing: (i) attention and concentration; (ii) memory; (iii) verbal fluency; and (iv) executive function.

The above vigilance testing elements were compared against PSA and DFA parameters to determine whether there was a good relationship that enabled awake EEG measures to be used as an objective method of assessing vigilance. The DFA and PSA measurements were then compared against each other to assess if they gave comparable results.

### **3.6 Assessing the relationship between PSA and DFA in awake EEG**

Previous studies done by our group showed that the conventional EEG PSA measures significantly correlated with DFA scaling exponent in both eyes open and eyes closed states. The DFA scaling exponent was positively correlated to delta power density (eyes open/eyes closed  $r=0.75$ ,  $p<0.0001$ / $r=0.86$ ,  $p<0.0001$ ) and negatively correlated to alpha power density ( $r=-0.56$ ,  $p<0.0001$ / $r=-0.73$ ,  $p<0.0001$ ) ([40](#)). This association would be explored further using this data set.

## **4. RESULTS**

### **4.1 Participant Demographics**

Eighty-three study participants completed satisfactory awake EEG testing prior to the overnight sleep study. The majority of the patients were male 67 (81%). Mean age was 45 years (SD  $\pm$ 11 years). The mean BMI was 32kg/m<sup>2</sup>. (SD  $\pm$ 5.5kg/m<sup>2</sup>). The mean Epworth Sleepiness Scale score in this group was 11 (range 0-22). The overnight diagnostic sleep study showed a mean total Apnoea Hypopnea Index (AHI) of 30/h (SD  $\pm$ 26/h). The range for AHI was 0-113.

### **4.2 Comparing two methods of artefact removal (manual vs ICA)**

#### **4.2.1 Checking data for normal distribution**

Extracted qEEG data were checked for the normality of the distribution by calculating the mean and median, as well as using boxplots and histograms. All qEEG measurements obtained either with manual artefact removal or ICA in alpha, delta, theta and beta power, as well as the DFA scaling exponent in eyes open and eyes closed status were suitable for parametric statistical analysis.

#### **4.2.2 Preparation of data for analysis**

For manual analysis of the 83 patient qEEG data, the student screened a total of 3990 epochs. If an artefact was identified, the epoch was marked as 'noisy' and was excluded from the manual analysis. During manual artefact removal of the EO section, 909 (46%) out of 1992 epochs were excluded as noisy. The EC section had 287 (14%) 5-second epochs removed from 1998 epochs.

During manual scoring, six patients did not have acceptable EEG data in the EO state due to gross contamination by eye blinks. Hence, in the manual analysis, data from 76 patients were used in the eyes open state and all 83 patient's data were used in the eyes closed state.

In the automated analysis, epochs with artefacts were not excluded, however, artefacts were ‘corrected’ by the ICA.

To explore the agreement and interchangeability of both methodologies of artefact removal, the following tests were conducted in each of the 10 EEG parameters measured below (Table 4.1).

**Table 4.1 Defining EEG measurements compared between manual (n) and ICA (i) artefact removal methods**

EEG frequency bands	Manual artefact removal result (n)	ICA artefact removal result (i)
Delta power Eyes Open	Delta EO n	Delta EO i
Theta power Eyes Open	Theta EO n	Theta EO i
Alpha power Eyes Open	Alpha EO n	Alpha EO i
Beta power Eyes Open	Beta EO n	Beta EO i
Delta power Eyes Closed	Delta ECn	Delta EC i
Theta power Eyes Closed	Theta ECn	Theta EC i
Alpha power Eyes Closed	Alpha ECn	Alpha EC i
Beta power Eyes Closed	Beta ECn	Beta EC i
DFA scaling exponent Eyes Open	DFA SE EO n	DFA SE EO i
DFA scaling exponent Eyes Closed	DFA SE EC n	DFA SE EC i

#### 4.2.3 Paired t-tests

Ten EEG parameters, namely, Delta power EO and EC, Theta power EO and EC, Alpha power EO and EC, Beta power EO and EC, and DFA scaling exponent EO and EC were tested for differences between the two artefact removal methods. Paired t-tests were performed using SPSS statistics software.

The eyes-open theta density ( $p=0.207$ ) and eyes open DFA scaling exponent ( $p=0.136$ ) did not show a statistically significant difference between the mean power densities when comparing manual artefact removal with ICA. However, rather surprisingly, the Delta density EO ( $p=0.034$ ), EC ( $p<0.001$ ), Theta density EC ( $p=0.006$ ), Alpha density

EO ( $p=0.03$ ), EC ( $p<0.001$ ) and Beta density (0.002) all showed statistically significant differences of the mean power density of each of the waveform frequencies.

The DFA scaling exponent EC also showed statistically significant differences between the values of manual and ICA scoring.

Higher power density values were observed in ICA artefact removal method in Delta EO, Beta EO, Theta EC, Alpha EC, Beta EC and DFA SE EC and EO. The manual scoring showed higher power density values in Theta EO, alpha EO and Delta EC. However, the absolute difference between the means obtained by the two methods of artefact removal for each EEG measurement was small (Table 4.2).

**Table 4.2 Comparison of ICA (i) and manual (n) artefact removal measurements using paired t-test**

EEG Pair	Comparison between ICA (i) And manual (n) EEG power spectrum and DFA during EO	Mean Difference	SD	t	df	Statistical Significance
Pair 1	Delta EO i -Delta EO n	0.036	0.14	2.16	76	$p<0.05$
Pair 2	Theta EO i – Theta EO n	-0.004	0.03	1.27	76	$p=0.207$
Pair 3	Alpha EO i –Alpha EO n	-0.014	0.05	2.20	76	$p<0.05$
Pair 4	Beta EO i – Beta EO n	0.089	0.08	8.76	76	$p<0.001$
Pair 5	Delta EC i- Delta EC n	-0.040	0.08	4.40	82	$p<0.001$
Pair 6	Theta EC i – Theta EC n	0.006	0.02	2.80	82	$p<0.01$
Pair 7	Alpha EC i – Alpha EC n	0.017	0.03	4.95	82	$p<0.001$
Pair 8	Beta EC i – Beta EC n	0.017	0.04	3.26	82	$p<0.01$
Pair 9	DFA SE EO i - DFA SE EO n	0.019	0.11	1.50	76	$p=0.136$
Pair 10	DFA SE EC i - DFA SE EC n	0.037	0.08	4.25	82	$p<0.001$

#### 4.2.4 Effect size

As there was a significant difference in means between the manual and ICA artefact removal methods in eight out of the 10 EEG parameters tested, the effect size was calculated to explore the magnitude of the difference between the two methods on each of the measurements.



Results showed delta power EO 0.2/EC 0.2, theta power EO 0.1/EC 0.15, alpha power EO 0.16/EC 0.16, beta power EO 1.0/EC 0.17. In the DFA scaling exponent, the effect size was EO 0.1/ EC 0.2 (Table 4.3).

**Table 4.3 Effect size for changes observed between two artefact removal methods**

Paired sample of EEG measurement	Effect size	Interpretation
Delta EO i -Delta EO n	0.2	small
Theta EO i – Theta EO n	0.1	small
Alpha EO i –Alpha EO n	0.1	small
Beta EO i – Beta EO n	1.0	large
Delta EC i- Delta EC n	0.2	small
Theta EC i – Theta EC n	0.1	small
Alpha EC i – Alpha EC n	0.1	small
Beta EC i – Beta EC n	0.1	small
DFA SE EO i - DFA SE EO n	0.1	small
DFA SE EC i - DFA SE EC n	0.2	small

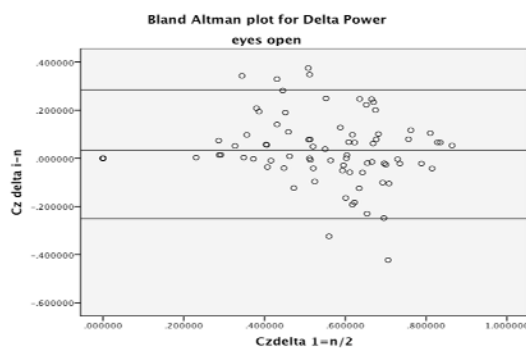
Although there was a significant difference in the mean power density in eight out of the 10 EEG parameters calculated for the two artefact removal methods, the effect size was found to be very small  $<0.2$ . Based on Cohen's rule of thumb for interpreting effect sizes, a 'small' effect size is considered to be  $<0.20$ , a 'medium' effect size is approximately 0.50 and a 'large' effect size is considered to be  $>.80$  (66). The beta power density during EO state demonstrated a large effect size.

#### 4.2.5 Bland-Altman plots

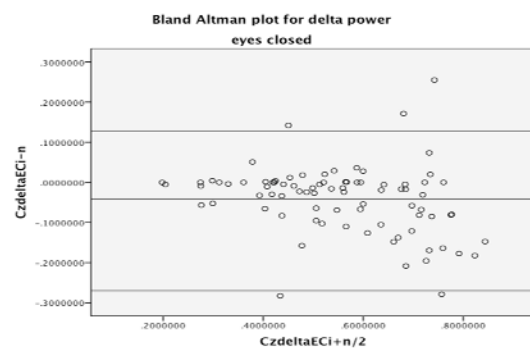
To further clarify the scatter of the difference between the measurements of the 2-artefact removal methods, Bland-Altman plots (B&A plots) were used to identify if the differences between the measurements were similar across a range of values and to decide if limits of agreement were narrow. The limitation with our measurements when using Bland-Altman plots was that the measurements for PSA and DFA scaling

exponents did not have an established measurement range, unlike other common physiological measurements, for example, blood pressure in mmHg or height in centimetres. However, a tighter scatter around the mean would imply that there were narrow-based limits of agreement.

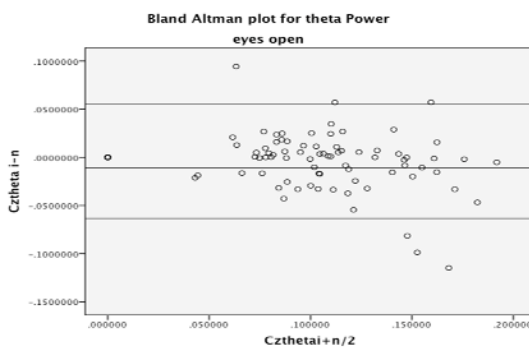
The Bland-Altman plots demonstrated a tight scatter around the mean during the eyes closed segment in comparison to the eyes open segment in all 10 EEG measures investigated. The beta power density during the eyes open segment had the most amount of scatter in keeping with the higher effect size noted during earlier testing.



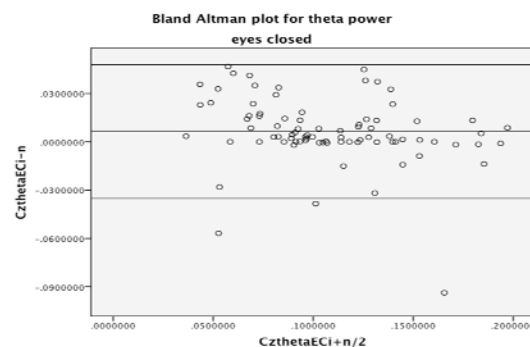
**Figure 4.1** Bland-Altman plots for delta power EO



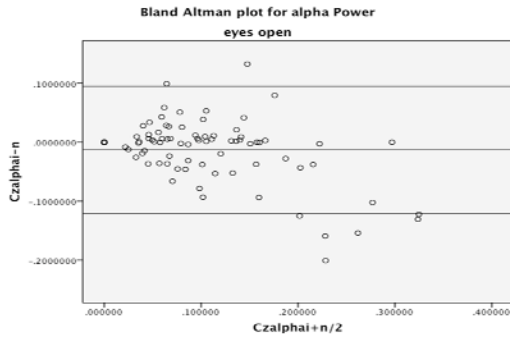
**Figure 4.2** Bland-Altman plots for delta power EC



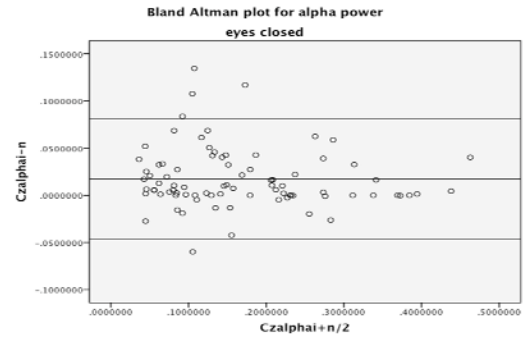
**Figure 4.3** Bland-Altman plots for theta power EO



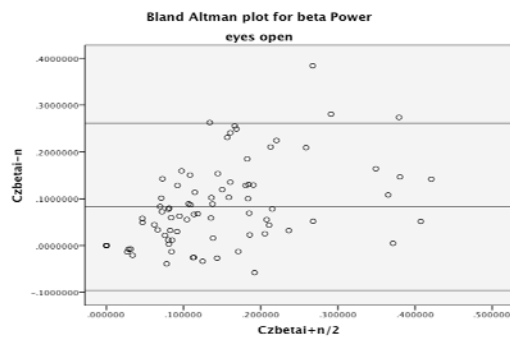
**Figure 4.4** Bland-Altman plots for theta power EC



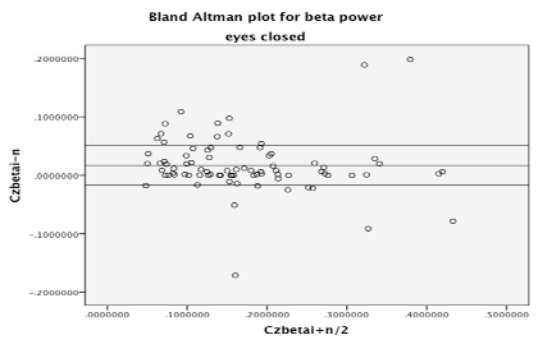
**Figure 4.5 Bland-Altman plots for alpha power EO**



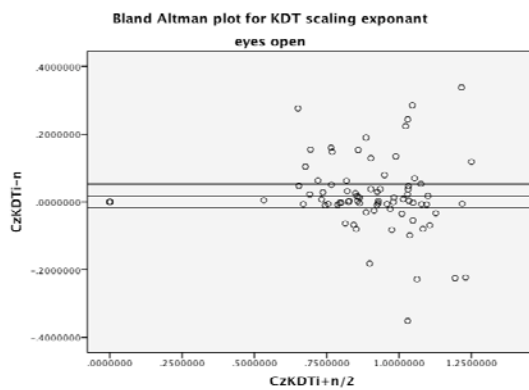
**Figure 4.6 Bland-Altman plots for alpha power EC**



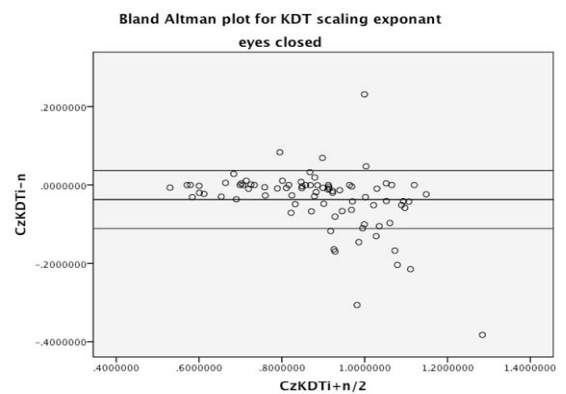
**Figure 4.7 Bland-Altman plots for beta power EO**



**Figure 4.8 Bland-Altman plots for beta power EC**



**Figure 4.9 Bland-Altman plots for DFA EO**



**Figure 4.10 Bland-Altman plots for DFA EC**

#### 4.2.6 Pearson's correlation coefficient

Given the small effect size, to further explore the correlation between the two methodologies of artefact removal, scatter plots were created for both manual and ICA methods in the 10 EEG measures explored above.

Pearson's correlation was calculated to find out the strength of the association between the two methodologies in each of the power densities of delta, theta, alpha and beta during the eyes closed and eyes open states, as well as scaling exponent both eyes open and eyes closed states. There was a very strong correlations displayed between all power densities across both eyes closed and open states, with the eyes closed state having an even tighter association.

The Delta power EO 0.609/EC 0.871, Theta power EO 0.666/EC 0.871, Alpha power EO 0.783/EC 0.954 and Beta power EO 0.664/EC0.874 associations were highly statistically significant ( $p<0.0001$ ).

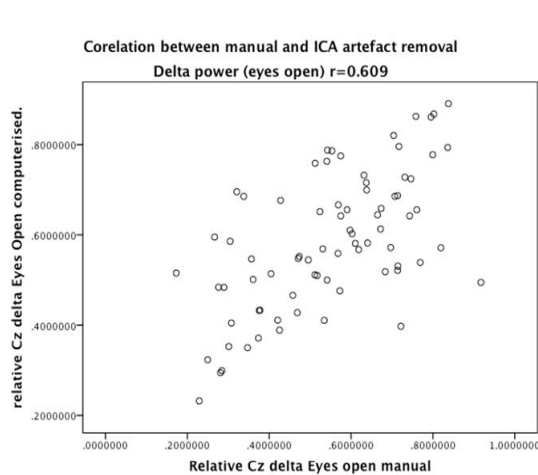
The DFA scaling exponent analysis in both eyes closed and open states showed an even tighter association between the two methods of artefact removal (DFA scaling exponent EO 0.773/EC 0.898). This association was highly statistically significant ( $p<0.0001$ ) (Table 4.4).

**Table 4.4 Pearson's correlation coefficient comparing the correlation between two different artefact removal methods**

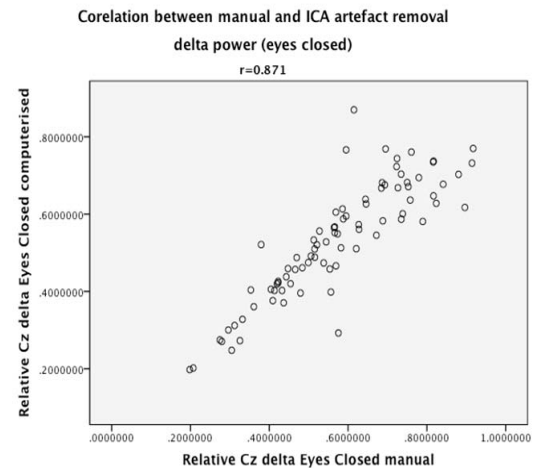
Paired sample of EEG measurement	N	Correlation	Sig.
Delta EO i -Delta EO n	77	0.609	$p<0.001$
Theta EO i – Theta EO n	77	0.666	$p<0.001$
Alpha EO i –Alpha EO n	77	0.783	$p<0.001$
Beta EO i – Beta EO n	77	0.664	$p<0.001$
Delta EC i- Delta EC n	83	0.871	$p<0.001$
Theta EC i – Theta EC n	83	0.871	$p<0.001$
Alpha EC i – Alpha EC n	83	0.954	$p<0.001$
Beta EC i – Beta EC n	83	0.874	$p<0.001$

DFA SE EO i - DFA SE EO n	77	0.773	p<0.001
DFA SE EC i - DFA SE EC n	83	0.898	p<0.001

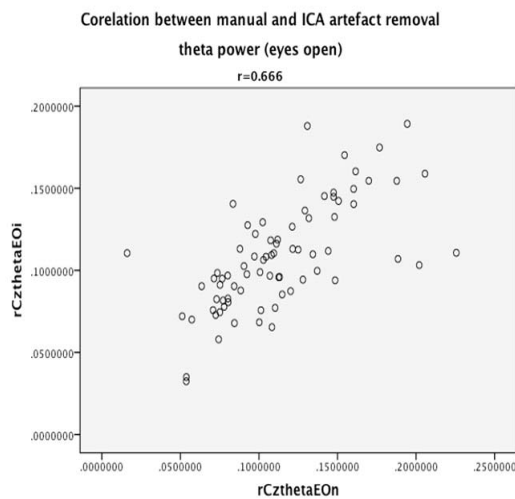
These associations were further explored with scatter plots.



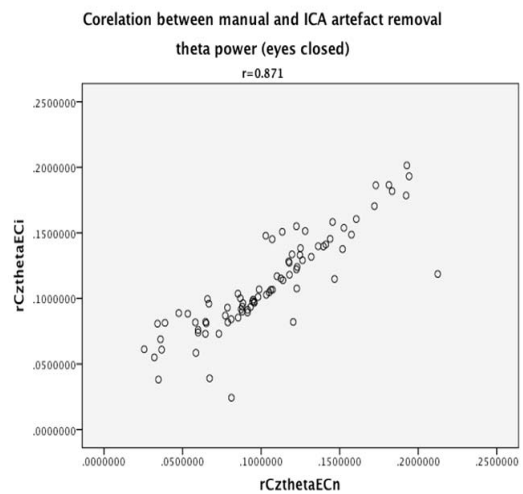
**Figure 4.11** Correlation between manual and ICA artefact removal methods in delta power (EO)



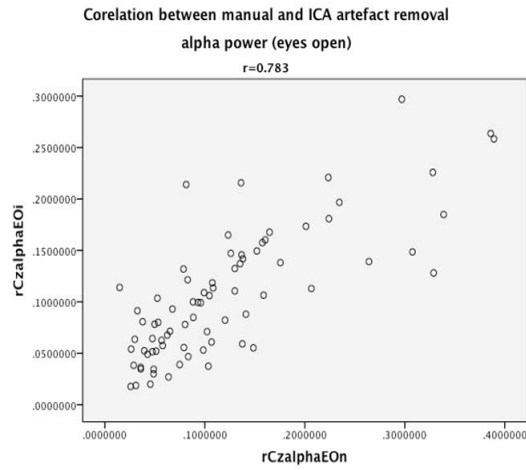
**Figure 4.12** Correlation between manual and ICA artefact removal methods in delta power (EC)



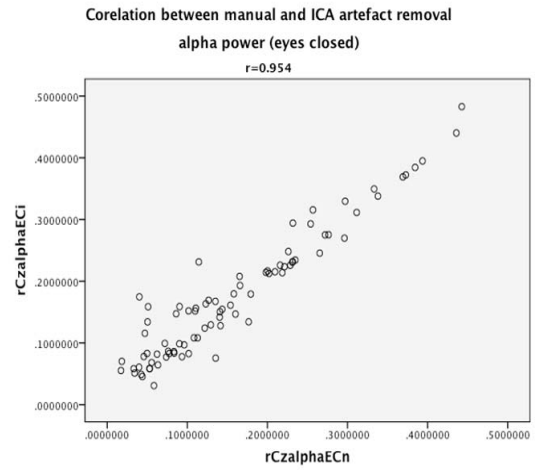
**Figure 4.13** Correlation between manual and ICA artefact removal methods in theta power (EO)



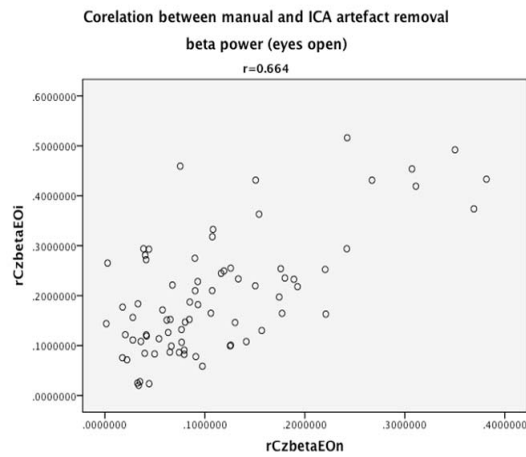
**Figure 4.14** Correlation between manual and ICA artefact removal methods in theta power (EC)



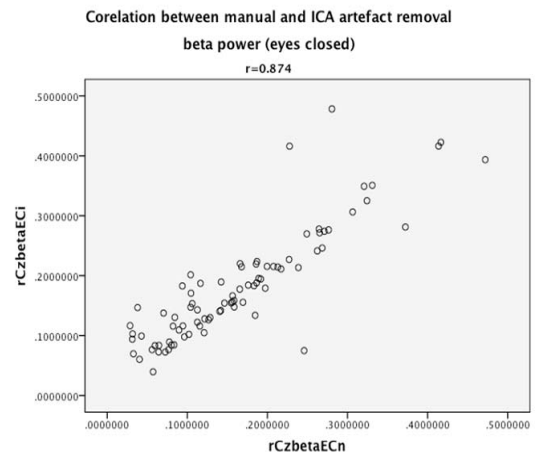
**Figure 4.15** Correlation between manual and ICA artefact removal methods in alpha power (EO)



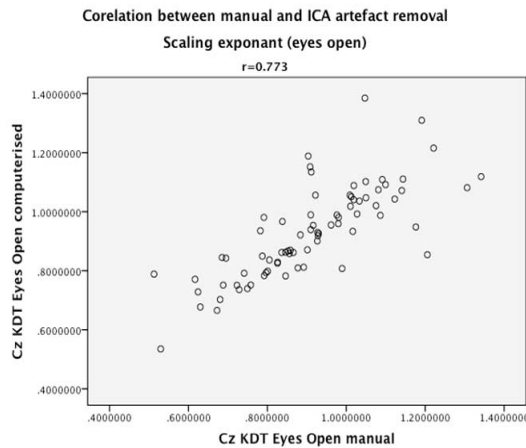
**Figure 4.16** Correlation between manual and ICA artefact removal methods in alpha power (EC)



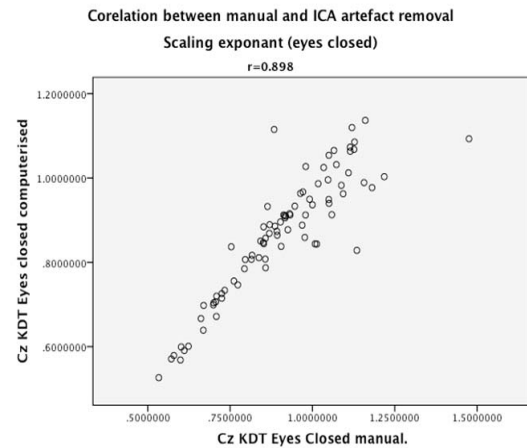
**Figure 4.17** Correlation between manual and ICA artefact removal methods in beta power (EO)



**Figure 4.18** Correlation between manual and ICA artefact removal methods in beta power (EC)



**Figure 4.19 Scaling exponent (EO) correlation between manual and ICA artefact removal methods in DFA (EO)**



**Figure 4.20 Scaling exponent (EO) correlation between manual and ICA artefact removal methods in DFA (EO)**

#### 4.2.7 Intra-class correlation for absolute agreement

By using the two artefact removal methods the results obtained for each EEG measurement essentially would be similar if the two methodologies had absolute agreement. If this was true, one method could be interchanged for the other without errors and with good reproducibility.

To test the absolute agreement between the two methods of artefact removal, intra-class correlation coefficient was performed. All PSA power densities and DFA scaling exponents in both eyes open and eyes closed states showed statistically significant absolute agreement (Table 4.5).

All PSA parameters obtained by the two methodologies showed good agreement although the degree of agreement varied between 0.2 and 0.8.

The DFA scaling exponents demonstrated a stronger agreement between the two artefact removal methods (0.6-0.9) with the eyes closed segment showing perfect agreement enabling good interchangeability (ICC 0.9; 95% CI 0.8-0.9).

**Table 4.5 Intra-class correlation coefficient for absolute agreement of the two artefact removal methods**

Pair	Absolute agreement and 95% CI	Significance
Delta EO i -Delta EO n	0.6 (0.4-0.7)	p<0.0001
Theta EO i – Theta EO n	0.7 (0.5-0.7)	p<0.0001
Alpha EO i –Alpha EO n	0.7 (0.6-0.8)	p<0.0001
Beta EO i – Beta EO n	0.6 (0.5-0.7)	p<0.0001
Delta EC i- Delta EC n	0.3 (0.2-0.5)	p=0.002
Theta EC i – Theta EC n	0.3 (0.1 - 0.4)	p=0.006
Alpha EC i – Alpha EC n	0.8 (0.7-0.8)	p<0.0001
Beta EC i – Beta EC n	0.2 (0.01-0.4)	p=0.02
DFA SE EO i - DFA SE EO n	0.8 (0.6 - 0.8)	p<0.0001
DFA SE EC i - DFA SE EC n	0.9 (0.8 - 0.9)	p<0.0001



**Table 4.6 Summary of the results of statistical methods used in comparing the ICA and manual artefact removal methods**

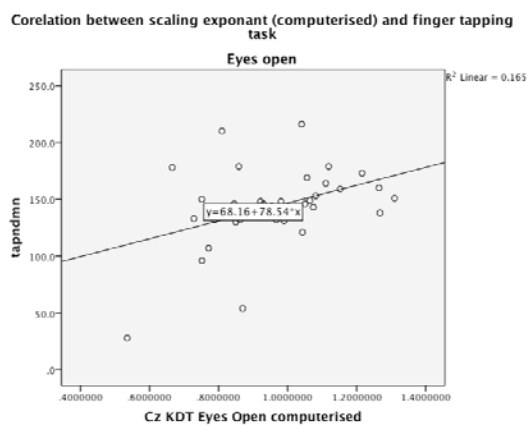
Pair	Paired T test		Effect size		Pearson's correlation coefficient		Intra class correlation coefficient		Bland Altman Plots	
	Mean difference	Sig.	Effect size	Interpretation	Correlation	Sig.	Absolute agreement	Sig.	Scatter around the mean	Limits of agreement
Delta EO i -Delta EO n	0.036	P<0.05	0.2	Small	0.609	P<0.001	0.6	P<0.0001	Tight	Narrow
Theta EO i – Theta EO n	0.004	P=0.207	0.1	Small	0.666	P<0.001	0.7	P<0.0001	Tight	Narrow
Alpha EO i –Alpha EO n	0.014	P<0.05	0.1	Small	0.783	P<0.001	0.7	P<0.0001	Tight	Narrow
Beta EO i – Beta EO n	0.089	P<0.001	1.0	Large	0.664	P<0.001	0.5	P<0.0001	Scatter around the mean is large	Broad
Delta EC i- Delta EC n	0.040	P<0.001	0.2	Small	0.871	P<0.001	0.3	P=0.002	Tighter	Narrower than EO
Theta EC i – Theta EC n	0.006	P<0.01	0.1	Small	0.871	P<0.001	0.3	P=0.006	Tighter	Narrower than EO
Alpha EC i – Alpha EC n	0.017	P<0.001	0.1	Small	0.954	P<0.001	0.8	P<0.0001	Tighter	Narrower than EO
Beta EC i – Beta EC n	0.017	P<0.01	0.1	Small	0.874	P<0.001	0.2	P=0.02	Tighter	Narrower than EO
DFA SE EO i - DFA SE EO n	0.019	P=0.136	0.1	Small	0.773	P<0.001	0.8	P<0.0001	Very tight	Extremely narrow
DFA SE EC i - DFA SE EC n	0.037	P<0.001	0.2	Small	0.898	P<0.001	0.9	P<0.0001	Very tight	Extremely narrow

#### 4.2.8 Correlation of manual and ICA artefact removal methods to performance test results

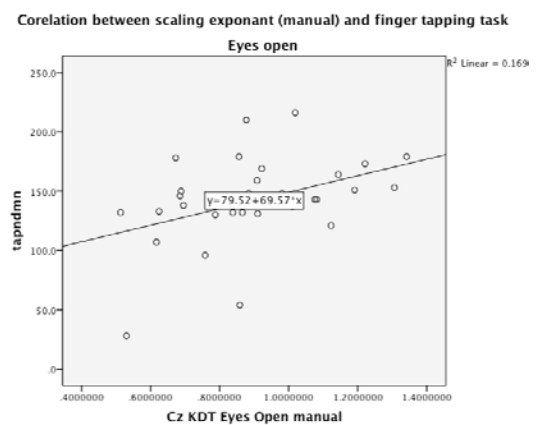
In this study, two artefact removal methods (manual and ICA) were compared with a battery of performance testing. The results obtained by both artefact removal methods were correlated to performance testing to identify if both methods gave similar results.

##### DFA scaling exponent: Comparison of DFA scaling exponent (manual vs ICA) and performance tasks

A significant correlation for using DFA scaling exponent was observed only during the finger tapping task and four-choice reaction time tasks. These two tasks were used to compare the results obtained by manual and ICA artefact removal (Appendix Table 6): (i) finger tapping test ICA EO  $r=0.41$ , manual EO  $r=0.41$  (Figures 4.21 & 4.22)' and (ii) four-choice reaction time ICA EC  $r=-0.26$ , manual EC  $r=-0.26$  (Figures 4.23 & 4.24).

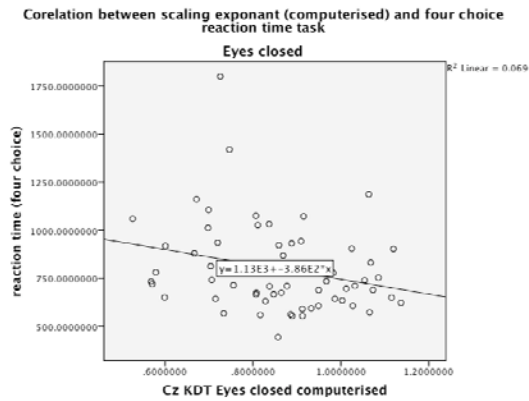


**Figure 4.21** Correlation between DFA extracted by ICA and finger tapping task

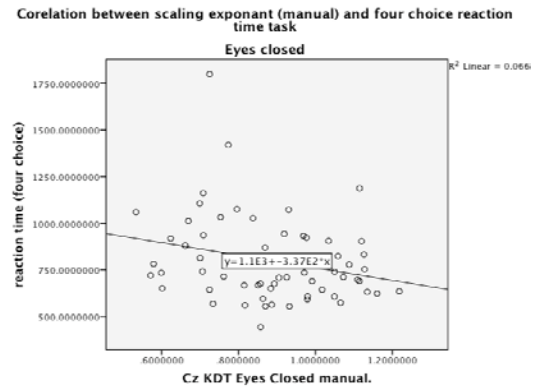


**Figure 4.22** Correlation between DFA extracted manually and finger tapping task

When a statistically significant result occurred, both artefact removal methods gave identical results with similar trends in DFA analysis. This was further explored using scatter plots.



**Figure 4.23 Correlation between DFA extracted by ICA and 4-choice reaction time task**



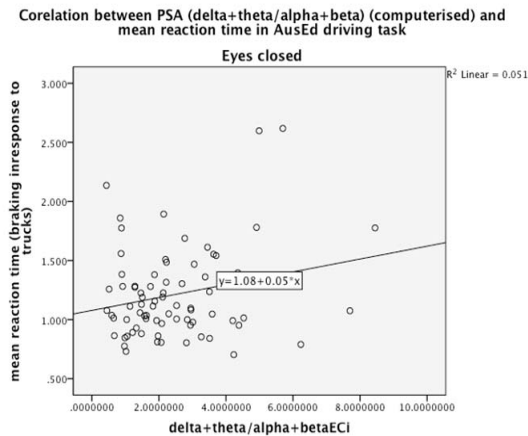
**Figure 4.24 Correlation between DFA extracted manually and 4-choice reaction time task**

### **PSA analysis: Comparison of PSA (manual vs ICA) and performance tasks**

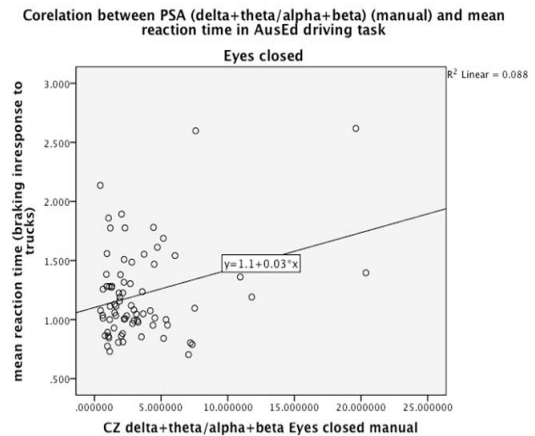
PSA analysis was done using combined frequencies to measure EEG slowing. One method used in this study to calculate EEG slowing was using delta and theta over the alpha and beta equation. In this study, two artefact removal methods were used to obtain separate PSA values for statistically significant results and to compare the agreeability.

PSA measurements had significant correlations only in mean reaction time and median reaction time in the AusEd driving task (Appendix Table 7). A comparison was made between the manual and ICA results. The mean reaction time to braking in response to trucks was ICA EC  $r=0.23$ , manual  $r=0.29$  and the median reaction time in response to trucks was ICA EC  $r=0.24$ , manual EC  $r=0.3$ .

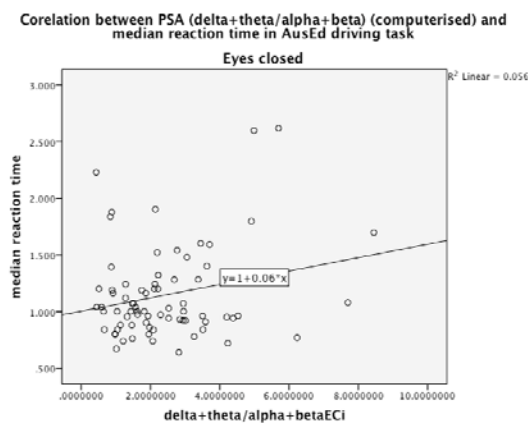
When a statistically significant result was obtained by PSA measurements, there was a correlation of a similar trend between manual and ICA artefact removal methods. However, the absolute numbers of the correlation coefficient were different. This was further explored using scatter plots (Figures 4.25 to 4.28).



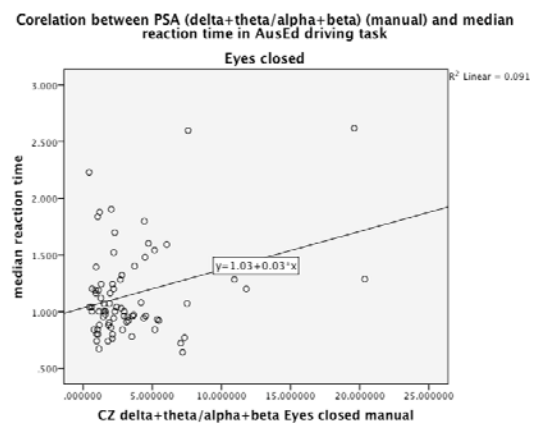
**Figure 4.25** Correlation between PSA extracted by ICA and mean reaction time



**Figure 4.26** Correlation between PSA extracted manually and mean reaction time



**Figure 4.27** Correlation between PSA extracted by ICA and median reaction time



**Figure 4.28** Correlation between PSA extracted manually and median reaction time

### 4.3 Correlation of EEG parameters to vigilance testing

The gold standard artefact removal method uses manual scoring. During manual scoring, very tight screening was done to rule out all muscle artefacts and eye blinks that could be interpreted as delta waves, thereby giving false high ‘sleepy EEG’ values. Due to the observed differences between the two artefact removal methods, as previously explained, from this point onwards all correlations to performance testing

was done using the manual artefact removal method alone as the gold standard. The full results of the comparison between EEG measurements and performance testing are described later in Section 4.2.5.

During this study, EEG slowing was measured in three ways:

1. *Using PSA ratio of delta power and theta power to alpha power and beta power*, this was a ratio of slow frequencies: delta and theta (indicating sleepiness) to the faster frequencies: alpha and beta (indicating alertness). It was selected as a global index for EEG slowing. A higher value indicates reduced alertness (43).
2. *Using PSA ratio of theta to alpha power waves* (measuring the ratio between more drowsy waves to the more alert waves) a higher value indicated reduced alertness (41).
3. *Using DFA scaling exponent* (higher the value of scaling exponent, more sleepier the subject) (48).

Each EEG slowing parameters were measured during eyes open and eyes closed state.

In the next step, Pearson's correlation coefficient was used to determine the correlations between EEG slowing and the results of sleep study data, self-rated questionnaires, AusEd driving simulator testing, anxiety and depression scales and vigilance testing.

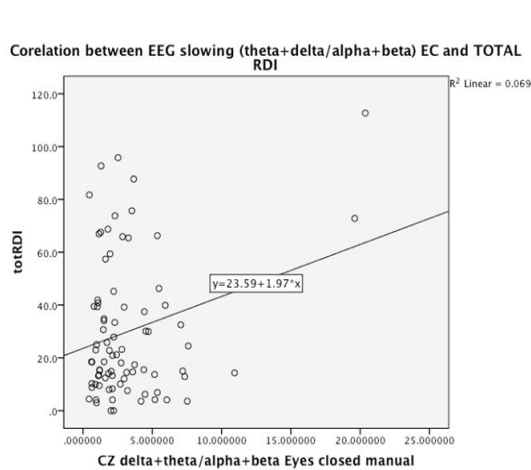
#### **4.3.1 Sleep study data**

Sleep study data looked at sleep efficiency, arousal index, proportion of time with saturations below 90%, total apnoea hypopnea index (AHI), non-rapid eye movement (NREM) AHI, rapid eye movement (REM) AHI and minimum saturations recorded during the sleep period. The sleep study parameters were correlated against the measurements for EEG slowing (Appendix Table 8).

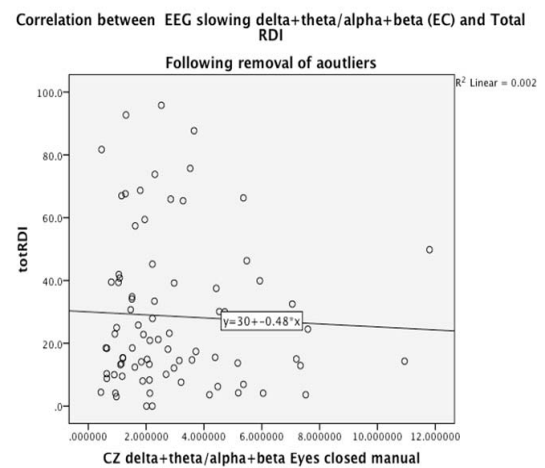
Only a single EEG slowing parameter: delta+theta/alpha+beta (EC) was associated with higher arousal index ( $r=0.299$ ,  $p<0.01$ ), increased NREM AHI ( $r=0.268$ ,  $p<0.05$ ) and total AHI ( $r=0.263$ ,  $p<0.05$ ). The correlations were statistically significant but weak.

To explore the validity of these results, scatter plots were constructed (Figures 4.29, 4.31 and 4.33). They suggested that the correlations seen were secondary to two outliers in the dataset.

The analysis was repeated following removal of these two outliers who had delta+theta/alpha+beta (EC) value  $>15.00$ . Following removal of the outliers, the EEG slowing measured by delta+theta/alpha+beta (EC) did not show significant correlations to total AHI ( $r=-0.05$ ,  $p=0.7$ ), arousal index ( $r=0.005$ ,  $p=0.96$ ) or NREM AHI ( $r=-0.024$ ,  $p=0.8$ ) (Figures 4.30, 4.32 and 4.34).

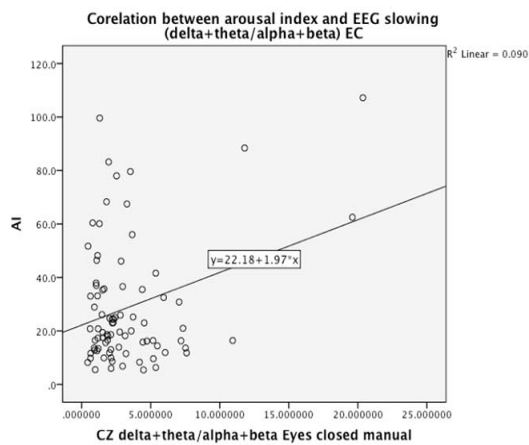


**Figure 4.29** Correlation between EEG slowing (delta+theta/alpha+beta) EC and total AHI

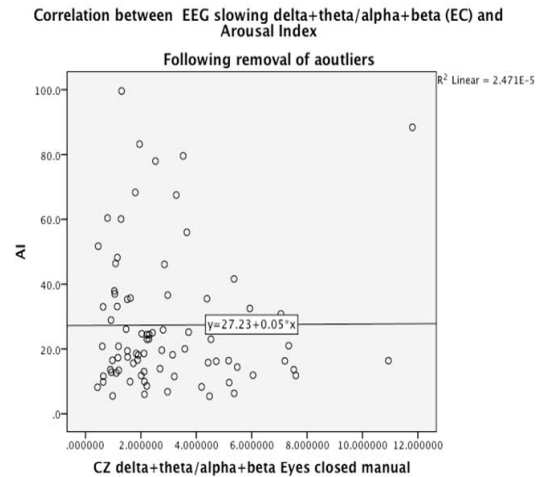


**Figure 4.30** Correlation between EEG slowing (delta+theta/alpha+beta) EC and total AHI (following removal of two outliers)

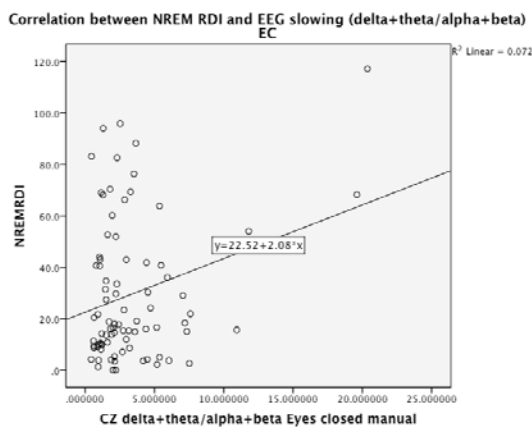
Sleep efficiency and nocturnal hypoxia did not have an association with EEG slowing. Other EEG slowing measurements of theta/alpha and DFA scaling exponent did not show any correlation for all tested sleep study parameters.



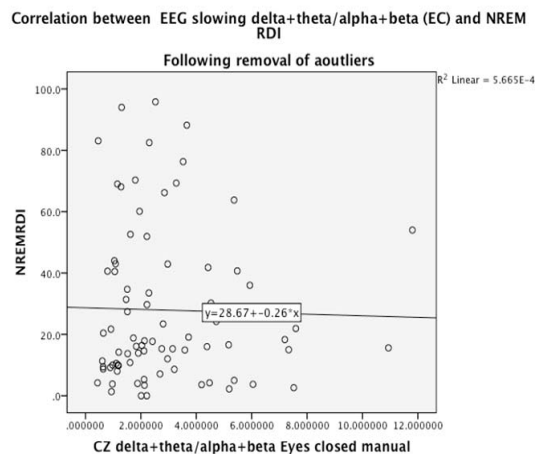
**Figure 4.31** Correlation between EEG slowing (delta+theta/alpha+beta) EC and arousal index



**Figure 4.32** Correlation between EEG slowing (delta+theta/alpha+beta) and arousal (following removal of two outliers)



**Figure 4.33** Correlation between EEG slowing (delta+theta/alpha+beta) and NREM AHI



**Figure 4.34** Correlation between EEG slowing (delta+theta/alpha+beta) and NREM AHI (following removal of two outliers)

In summary, EEG slowing did not show any significant correlation to sleep study data of total AHI, NREM AHI, arousal index, nocturnal hypoxia or sleep efficiency.

#### **4.3.2 Questionnaires for sleepiness (ESS and KSS)**

The EEG slowing measured by combined frequencies of delta+theta/alpha+beta EO ( $r=-0.2$ ,  $P=0.01$ ) and EC ( $r=-0.2$ ,  $p=0.07$ ) state or theta/delta during EO ( $r=-0.08$ ,  $p=0.4$ ) did not show any correlation with ESS. However, the theta/alpha densities during EC ( $r=-0.3$ ,  $p=0.01$ ) did show weak correlations but the direction of the association was opposite to what was expected. This was not clinically acceptable (worsened EEG slowing associated with improved sleepiness), therefore, it was not taken as a valid correlation. The DFA scaling exponent during eyes open ( $r=-0.2$ ,  $p=0.1$ ) and eyes closed ( $r=-0.13$ ,  $p=0.3$ ) states did not correlate with ESS (Appendix Table 9). Furthermore, the KSS score did not show correlations to PSA or DFA measurements of EEG slowing (Appendix Table 9)

In summary, there was no significant correlation noted between EEG slowing measured by PSA or DFA and subjective self-rated sleepiness scores.

#### **4.3.3 AusEd driving simulator**

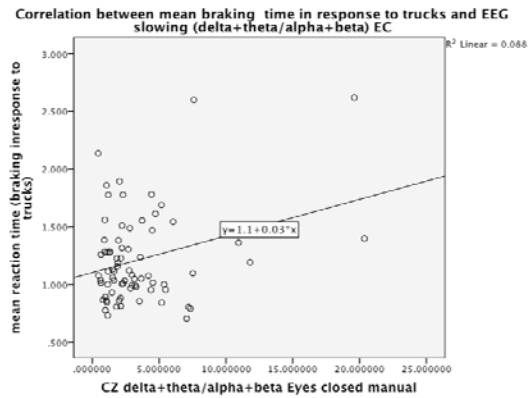
The AusEd driving simulator measured domains of steering deviation from the centre of the lane, steering deviation from the median lane position, speed deviation outside the 60-80 km/h zone, mean breaking time in reaction to trucks, standard deviation of the reaction time, median reaction time in response to trucks and the number of crashes (Appendix Table 7). These parameters were correlated to the three measurements of EEG slowing as outlined above during the EO and EC states.

Again, the same EEG slowing measurement as before (delta+theta/alpha+beta EC) had weak but statistically significant correlation to the mean reaction time in response to trucks ( $r=0.296$ ,  $p<0.01$ ) and the median reaction time ( $r=0.302$ ,  $p<0.01$ ). This relationship was explored further by using scatter plots (Figures 4.35 and 4.37).

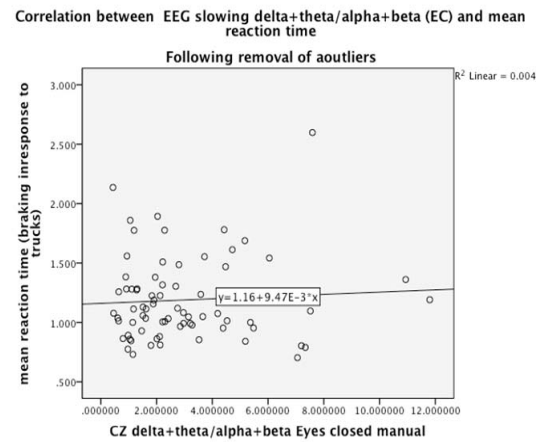
The same two outliers noted previously for the delta+theta/alpha+beta EC measurement also influenced these results. Following removal of the two outliers, the mean reaction time ( $r=0.063$ ,  $p=0.6$ ) and median reaction time ( $r=0.09$ ,  $p=0.4$ ) did not show significant correlations to the EEG slowing (Figures 4.36 and 4.38). The EEG slowing measured



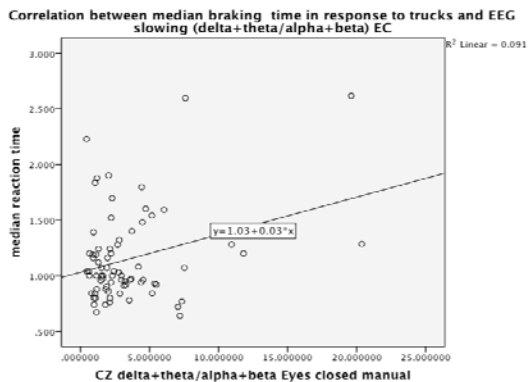
by theta/alpha and DFA scaling exponent during the EO and EC states did not correlate with driving performance.



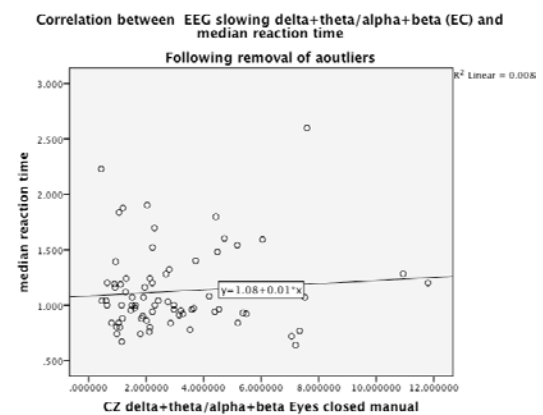
**Figure 4.35** Correlation between mean reaction time and EEG slowing (delta+theta/alpha+delta)



**Figure 4.36** Correlation between mean reaction time and EEG slowing (delta+theta/alpha+delta) (following removal of two outliers)



**Figure 4.37** Correlation between median reaction time and EEG slowing (delta+theta/alpha+delta)



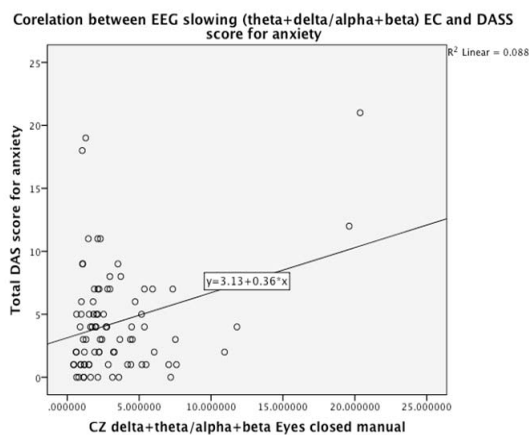
**Figure 4.38** Correlation between median reaction time and EEG slowing (delta+theta/alpha+delta) following removal of two outliers

In summary, EEG slowing measured by PSA and DFA did not show any correlation to driving performance.

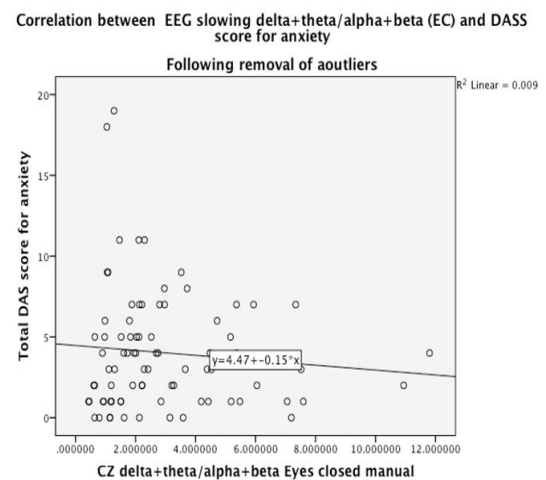
#### 4.3.4 Questionnaire for anxiety and depression (DASS and FOSQ)

The depression and anxiety questionnaire and the functional assessment of sleep questionnaire were compared with EEG slowing measured by PSA and DFA methods. Again, the same EEG measurement delta+theta/alpha+beta (EC) demonstrated statically significant correlation with the DASS score for anxiety ( $r=0.297$ ,  $p<0.01$ ) (Appendix Table 10). However, the scatter plot below (Figure 4.39) showed that the correlation was a result of two outliers identified before changing the slope of line for best fit.

Following removal of the outliers, the correlations of EEG slowing to DASS score for anxiety became non-significant ( $r=-0.09$ ,  $p=0.4$ ) (Figure 4.40). The other subgroups of the DASS questionnaire, including the score for stress and depression, did not show any correlations to the measurements of EEG slowing. The FOSQ score for vigilance did not show any correlation to EEG slowing either, as measured by all three methods during the EO and EC states.



**Figure 4.39** Correlation between EEG slowing (delta+theta/alpha+beta) EC and DASS score for anxiety



**Figure 4.40** Correlation between EEG slowing (delta+theta/alpha+beta) EC and DASS score for anxiety (following removal of outliers)

In summary, the EEG slowing measurements with PSA and DFA were not associated with the DASS questionnaire or FOSQ scores.

#### 4.3.5 Tests for performance

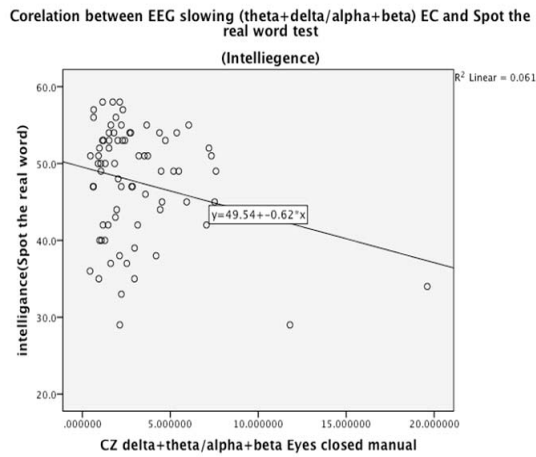
Fourteen individual tests were performed to assess daytime functioning (Appendix Tables 11, 12 & 13).

1. Attention: Four choice reaction test; finger tapping test; visual attention test; attention switching (trail marking test A) and sustained attention task.
2. Tests for memory: Digit span; memory recall; and span of visual memory.
3. Tests for executive functioning: Tower of London, trail marking test, Stroop test and Maze test.
4. Verbal fluency: Spot the real word test; word generation (FAS test); and word generation (animal test).

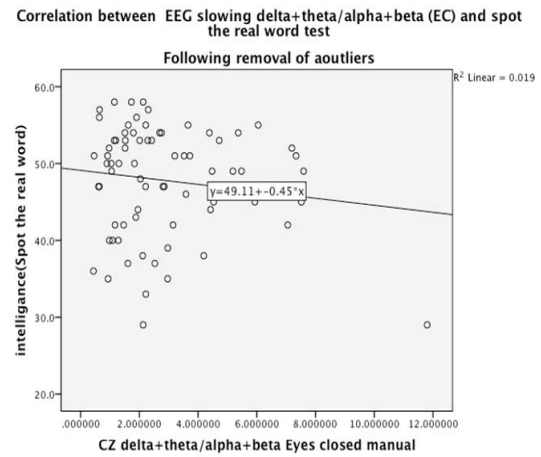
EEG slowing was measured using PSA measurements (delta+theta/alpha+beta and theta/ alpha) and DFA scaling exponent.

The only positive results obtained from Pearson's correlation coefficient were 'spot the real word' test. This test had a negative correlation to the EEG slowing measured by delta+theta/alpha+beta EC state ( $r=-0.247$ ,  $p<0.05$ ) (Figure 4.41).

However, the scatter plot demonstrates that this result is again secondary to the one extreme outliers noted with this EEG measurement during the previous analysis. Following removal of the outlier, the correlations became non-significant ( $r=-0.12$ ,  $p=0.24$ ) (Figure 4.42).



**Figure 4.41 EEG slowing measured by (delta+theta/alpha+beta) EC and spot the real word test**



**Figure 4.42 EEG slowing measured by (delta+theta/alpha+beta) EC and spot the real word test (following removal of two outliers)**

In summary, the measured performance tests did not show any correlation to EEG slowing when measured using PSA or DFA.

## 4.4 Assessing the relationship between PSA and DFA in awake EEG

The DFA scaling exponent and PSA measurements measured by individual frequency densities had previously been shown to correlate well with each other (48). All frequencies of the power spectrum were shown to be either positive (delta power) or negative (alpha power) correlated to the DFA scaling exponent in both eyes closed and eyes open states.

### 4.4.1 Comparing individual PSA frequencies to DFA scaling exponent

In this dataset, the DFA scaling exponent was compared with individual delta, alpha, theta and beta power densities and correlations assessed using Pearson's correlation coefficient (Table 4.6). There was a very strong positive correlation between the DFA scaling exponent and delta power during both eyes open ( $r=0.800$ ,  $p < 0.01$ ) and eyes closed ( $r=0.872$ ,  $p < 0.01$ ) states.

There was a strong negative correlation between the DFA scaling exponent and alpha power in both eyes open ( $r=-.672$ ,  $p<0.01$ ) and eyes closed ( $r=-.788$ ,  $p<0.01$ ) states, which was in keeping with the previous published data (48).

All other power spectrum densities were correlated significantly except for theta power when the eyes were open ( $r=0.064$ ,  $p=0.579$ ).

**Table 4.7 Pearson's correlation of DFA scaling exponent versus individual power spectrum frequencies**

Comparison between KDT SE and individual power densities		Pearsons correlation coefficient
KDT EO	Delta power EO	$r=0.80$ $p<0.01$
	Theta power EO	$r=0.06$ $p=0.56$
	Alpha power EO	$r=-0.67$ $p<0.01$
	Beta power EO	$r=-0.43$ $p<0.01$
KDT EC	Delta power EC	$r=0.87$ $p<0.01$
	Theta power EC	$r=-.26$ $p=0.02$
	Alpha power EC	$r=-.79$ $p<0.01$
	Beta power EC	$r=-.58$ $p<0.01$

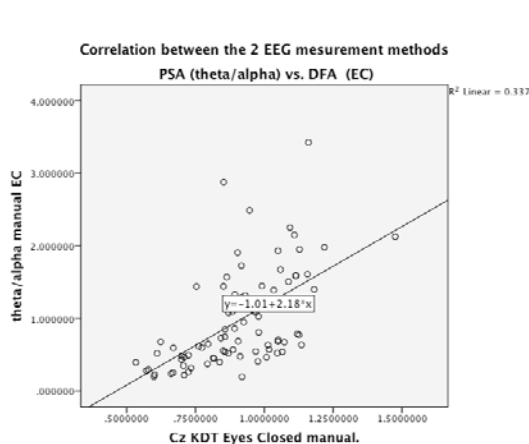
### Comparing combined PSA frequencies to DFA scaling exponent

Following this, the EEG slowing measured by combined PSA frequencies of delta+theta/alpha+beta and theta/alpha was correlated against the DFA scaling exponent to determine the correlations. This analysis was done for corresponding eyes open and eyes closed states of the DFA scaling exponent.

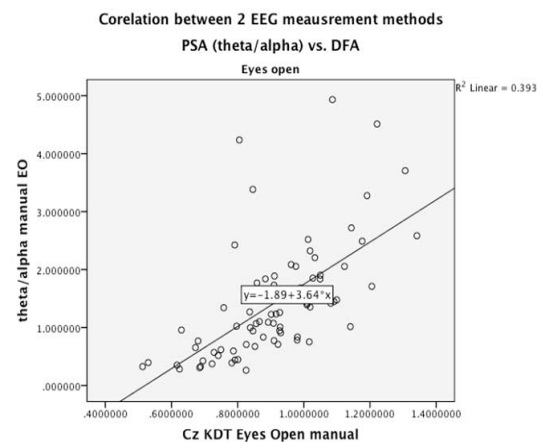
**Table 4.8 Pearson's correlation of DFA scaling exponent versus combined power spectrum frequencies**

EEG slowing measurement using PSA (EO)	DFA (EO)	EEG slowing measurement using PSA (EC)	DFA (EC)
Alpha/theta (EO)	$r=0.581$ $p<0.0001$	Alpha/theta (EC)	$r=0.627$ $p<0.0001$
Delta+theta/alpha+beta(EO)	$r=0.750$ $p<0.001$	Delta+theta/alpha+beta (EC)	$r=0.683$ $p<0.0001$

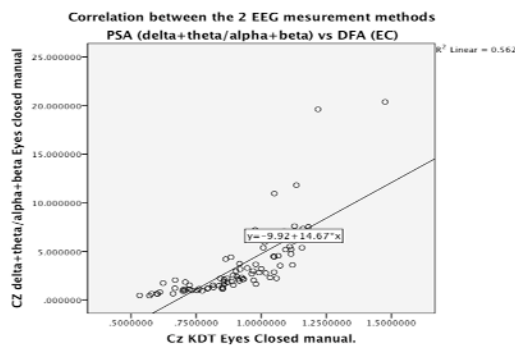
Comparing the relationship between the DFA scaling exponent and EEG slowing measured by PSA, there was an excellent correlation between the two measurements as demonstrated below. These relationships are consistent in both eyes open and eyes closed states (Table 4.7). A graphical representation of this correlation was made by using scatter plots and found the correlations to be robust (Figures 4.43, 4.44, 4.45 and 4.46).



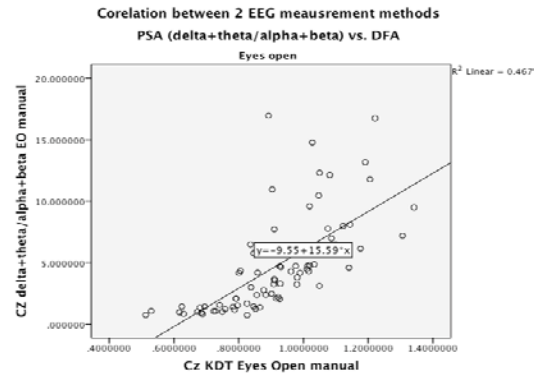
**Figure 4.43 Correlation between DFA and PSA measured by theta/alpha (EC)**



**Figure 4.44 Correlation between DFA and PSA measured by theta/alpha (EO)**



**Figure 4.45** Correlation between DFA and PSA measured by delta+theta/alpha+beta (EC)



**Figure 4.46** Correlation between DFA and PSA measured by delta+theta/alpha+beta (EO)

### Correlating three EEG slowing measurements to performance testing

Correlating to performance testing assessed the degree of agreement between three individual methods of EEG slowing. Steering deviation from the left lane was taken as a random outcome measure. All three methods of EEG slowing showed similar correlations although the numerical value for the correlation coefficient was not identical (Table 4.8) and the correlations were not statistically significant.

Scatter plots were used to demonstrate the similar trend between the three methods of EEG slowing even though the correlation was not significant (Figures 4.47, 4.48 and 4.49).

**Table 4.9** Comparing three EEG slowing methods and the steering deviation test

EEG slowing during	Steering deviation from the left lane.
Delta+theta/alpha+beta EO	$r = -0.14$ ,
Theta/alpha manual EO	$r = -0.15$
DFA Eyes Open	$r = -0.13$

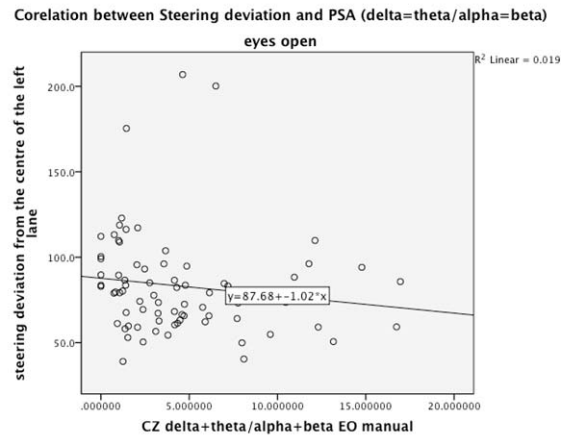


Figure 4.47 Correlation between PSA (delta+theta/alpha+beta) EO and steering deviation

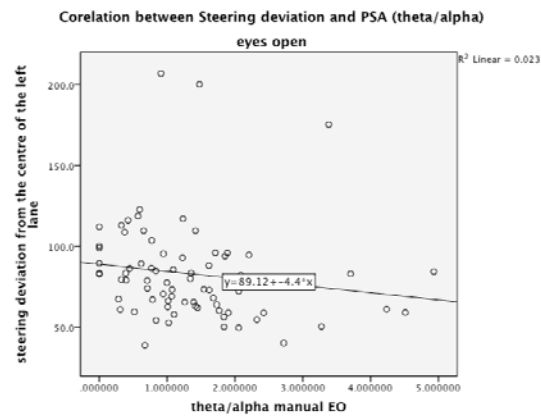


Figure 4.48 Correlation between PSA (theta/alpha) EO and steering deviation

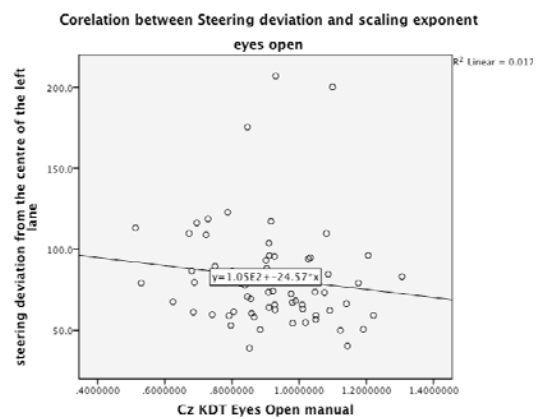


Figure 4.49 Correlation between DFA scaling exponent (EO) and steering deviation



## 5. DISCUSSION

### 5.1 Summary of Findings

Overall, DFA and PSA look at the same effect of EEG slowing in different ways, that is, measuring EEG fluctuations versus EEG frequencies respectively. During a comparison of the two artefact removal methods using multiple statistical tests, PSA metrics were found to be vulnerable to the influence of artefacts in contrast to the novel EEG analysis method DFA which was far superior to PSA metrics in withstanding artefact. When a statistically significant result was present, both manual and ICA artefact removal methods produced identical results with DFA but not with PSA.

The battery of performance testing gave statistically significant but weak correlations only with one measurement of EEG slowing:  $\delta + \theta / \alpha + \beta$  EC. Further exploration of these correlations using scatter plots demonstrated that positive results were due to two significant outliers. Following removal of the outliers, no significant association between EEG slowing and performance testing was found.

### 5.2 Comparing two methodologies of artefact removal

When drawing inferences from EEG parameters, artefact removal is of paramount importance, as we should ensure that the waves analysed to ascertain drowsiness originates from the brain and not an artefact that occurred due to muscle movements and eyes blinks.

Several methods of eye artefact removal have been noted in the literature. Berg and Scherg ([67](#)) in 1991 proposed a method of eye artefact removal using a spatio-temporal dipole model. In this method priori assumptions are made about the number of dipoles for blinks and other eye movements, which then led to inaccuracies in the dipole model that subsequently lead to inaccuracies in the contributions from EOG to EEG. To overcome this problem they later on proposed another technique for removing ocular artefacts, by using principal component analysis (PCA) ([68](#)). Here, EEG and EOG

signals were simultaneously collected while the subject performed standard eye movements and blinks. Then, a PCA of the variance in these calibration signals gave major components representing blinks and other eye movements. Corrected EEG data could be obtained by removing these components through the simple inverse computation. The PCA method was demonstrated to be superior to the spatiotemporal dipole model of removing eye artefacts ([68](#)).

The problem noted with PCA was that it cannot completely separate some artefacts from cerebral activity, especially when they both have comparable amplitudes ([69](#)).

The ICA method was originally proposed to solve this blind source separation problem to recover independent source signals ([70](#)). The ICA algorithms have since been used to separate neural activity from muscle and blink artefacts in spontaneous EEG data and had been shown to help tracking alertness ([71](#)).

The two EEG artefact removal methods analysed here were ICA (automated) and manual scoring. During the eyes open state, artefacts are more troublesome as expected due to the eye blinking more frequently.

With manual scoring, the ‘noisy’ epochs were stringently marked in order to obtain as ‘clear’ a signal as possible. While this resulted in a clean measure of the EEG waveforms, a larger number of epochs had to be excluded from the analysis. During the eyes open state, 45% epochs were rejected while during the eyes closed state, only 14% were rejected. This carries the disadvantage of having sparse data for some patients who have more artefacts in the EEG. Due to the sparse data, the mean value of the ‘clean’ epochs may not be a true representation of all EEG epochs. Furthermore, the ‘clean’ epochs alone may not be a true representation of all the EEG data of that patient.

This shows the obvious advantage in using ICA as an artefact removal method because ICA does not ‘reject’ epochs. Instead it identifies the artefactual waveforms by using a reference from the EOG and ‘corrects’ the EEG waveform. Therefore, all measured epochs were included, making the full use of the EEG data which would provide a more reliable EEG representation for that patient.

The gold standard measurement for artefact removal is by manually scoring individual epochs. Given the above advantage of increased power in measurements, as well as the ability to analyse large amounts of data in a short time in a consistent pattern, ICA could be an alternative to manual scoring of artefacts. Hence, it is important to establish the interchangeability and degree of agreement between ICA and manual scoring.

A literature review identified several statistical methods that measure the agreement between two measurements, as is the case with this study. Students' t-tests, effect size measurement, intra-class correlation coefficient measurement, Bland-Altman plots and Pearson's correlation coefficient were described as statistical methods that were used to compare agreement between two measurements. However, all statistical methods had their inherent limitations and a single superior method was not found. Because all methods for the measurement of agreement have limitations, the overall impression given from several statistical approaches were thought to give a better measure of reliability and agreement (72). However, it is also important to realise that there are specific drawbacks in every method. Hence, when interpreting the results of an individual statistical method, the applicability of that result depends on the clinical context (73).

Throughout this discussion the comparison is made between 10 EEG waveforms measured by ICA and manual artefact removal methods, namely delta power EO/EC, theta power EO/EC, alpha power EO/EC, beta power EO/EC and DFA scaling exponent EO/EC (Table 4.1).

### **5.2.1 Paired t-test**

The paired t-test was measured for 10 EEG waveforms, namely delta power, theta power, alpha power, beta power in EO and EC states, and the DFA scaling exponent EC and EO. Overall, there was a statistically significant difference in eight out of 10 waveforms measured. This showed a definite difference of the arithmetic mean in eight out of the 10 EEG measurements. However, the mean difference between the two methods in each waveform was very small, ranging from 0.006 to 0.089.

### 5.2.2 Effect size

The effect size of the above difference is important to make clinical decisions, as statistical significance does not automatically imply clinical significance. The effect size varies from 0 to 1.0 based on Cohen's article for interpreting effect sizes: a 'small' effect size is considered to be  $<0.20$  (66). Calculating an effect size is also a good measure for a clinician to understand the magnitude of the effect to make a clinical judgement over a statistical value. With prior knowledge of the scale of a measurement, an effect size could be calculated clinically to be small, medium or large. In this data set, nine out of the 10 EEG measurements had a small effect size statistically and clinically. This indicates that although there was a statistically significant difference between the variables measured with the paired t-tests, the magnitude of the difference was small.

Only beta power EO had a large effect size. Bland-Altman plots were used to explore if this large effect size of the beta power EO could be due to a random error or bias. However, beta waves (low amplitude, high frequency waves) are seen during wakefulness. When measuring drowsiness of an individual, the usual frequencies of interest are in the delta, theta and alpha ranges with beta activity being less relevant as it is a frequency of wakefulness rather than that of drowsiness. Beta activity is not commonly reported to be related to sleepiness, therefore, although there is a difference between manual and ICA markings of beta power, it may not be of relevance in the measurement of sleepiness.

### 5.2.3 Pearson's correlation coefficient

To explore this noted difference in means during the paired t-test, the Pearson's correlation coefficient was used. Pearson's correlation coefficient assesses the closeness of the data to the line of best fit (74). Between manual and ICA measurements in each of the 10 EEG measurements, there was a significant correlation  $<0.001$  in all waveforms measured. This was well demonstrated by the scatter plots showing a close relationship, which was stronger when eyes closed (range:  $r=0.871$  to  $0.954$ ) to eyes open (range:  $r=0.609$  to  $0.783$ ). This reflects a larger number of artefacts during the EO

state than the EC state. This correlation was much greater for DFA during both EO ( $r=0.773$ ) and EC ( $r=0.898$ ) than PSA metrics in keeping with the known robustness of the scaling exponent to withstand artefacts.

#### **5.2.4 Intra-class correlation coefficient (ICC) (2-way mixed model for agreement)**

The two artefact removal methods look at the same population, extracting the results for the same 10 EEG measurements. Hence, the results from the two methods should show agreement for them to be interchangeable in clinical practice. The intra-class correlation coefficient was used to assess this.

McGraw and Wong defined the intra-class correlation coefficient for assessing agreement. The measurement obtained could be ICC for consistency or ICC for absolute agreement; this was either by excluding or not excluding the observer variance from the denominator mean square, respectively (75). The systematic variability due to observers is irrelevant for 'ICC for consistency' and relevant for 'ICC for agreement'. The ICC ranges from 0 (no agreement) to 1 (perfect agreement), but it can be negative. Consequently, ICC values have no absolute meaning but the cut-off value of 0.75 proposed by Fleiss (76) is used to signify a good agreement. This cut-off value had been disputed by another group led by Lee who argued that the absolute agreement in interclass correlation coefficient is considered interchangeable only when  $r>0.75$ , as well as the lower limit of 95% of CI for ICC is  $>0.75\%$  (77).

All 10 EEG measurements showed statistically significant correlations between the two artefact removal methods used. The analysis of EEG frequencies in delta, theta, alpha and beta EC/EO states showed a variable correlation between 0.2 and 0.8 between the two methods. Both EO and EC states had similar correlations. The tightest correlations were noted during DFA analysis (EO 0.8, EC 0.85). Again, this is a measure of the robustness of DFA to withstand artefact, hence, giving comparable results irrespective of the methodology used for artefact removal.

An important limitation of ICC is that it is strongly influenced by the variance of the trait in the sample in which it is assessed (78). This may explain the lesser correlation

expressed by power spectrum parameters (lesser variability of the sample) versus the stronger correlation expressed by DFA measures showing a greater variance.

### **5.2.5 Bland-Altman plots**

To assess agreement between two methods of clinical measurement, Bland and Altman proposed the limits of agreement approach (79). They emphasised that neither the paired t-test nor the intra-class correlation is appropriate for validating the interchangeability of two measurement methods and proposed using the mean of the two measurement methods to be plotted against the standard deviation of the difference between the two methods.

Based on limits of agreement, deciding whether the agreement is acceptable or not is always clinical and not a statistical judgement because there is no measure of what a ‘good’ agreement is (73). In general, the tighter the scatter around the mean difference, which demonstrates a narrower 2SD for that measurement, shows smaller difference between the measurements.

The other important information that can be derived from the Bland-Altman plots are to ascertain if there is a systematic bias, as well as clarifying if the scatter about the mean difference increases as the magnitude of the measurement increases.

The PSA metrics show a tight scatter around the mean difference. This tightness is more during the EC state than the EO state, therefore, demonstrating increased artefacts occurring during the EO state and PSA metrics vulnerability to artefacts during the EO state. The beta power EO shows most scatter around the mean in keeping with wider limits of agreement. The beta power EO (Figure 4.7) also demonstrates that there is existence of systematic bias.

Once again, irrespective of the eyes closed or eyes open state, the DFA scaling exponent has very tight scatter around the mean with very small (95%) confidence interval of the mean difference. This shows the robustness of DFA to artefact. For the same reason, the EO and EC states give similar results in DFA.

### **5.2.6 Comparing manual and ICA measurements to performance test results**

All the above tests show that there is a significant arithmetic mean difference between the two methodologies of artefact removal in each of the EEG measurements. The effect size of this difference is small and a tight correlation exists between the two methodologies. This was explored further to identify if a statistically significant difference was clinically significant as well.

#### **PSA (using ICA and manual) versus a performance test with a significant association**

The results obtained for EEG slowing by using combination PSA frequencies of delta and theta over alpha and beta were correlated to performance testing. Positive results were obtained only from the AusEd driving simulator task domains of mean reaction time and median reaction time. (See Section 5.2 for EEG measurements and performance testing results.)

The statistically significant correlations to the performance testing measured by PSA using either manual or ICA artefact removal method demonstrated results of similar trend. For example, the mean reaction time to braking in response to trucks ICA EC  $r=0.23$ , manual  $r=0.29$ . Median reaction time in response to trucks ICA EC  $r=0.24$ , manual EC  $r=0.3$

#### **DFA (using ICA and manual) versus a performance test with a significant association**

When correlating the DFA to performance testing, a statistically significant result was noted only during the finger tapping test and four-choice reaction time (Section 5.2). The correlation was weak, however, when the DFA was obtained from the manual and ICA artefact removal methods were compared to the performance testing, identical correlations were obtained. There was no difference between the EO and EC states, and the trend was always the same, for example, finger tapping test ICA EO  $r=0.41$ , manual EO  $r=0.41$ ; four choice reaction time ICA EC  $r=-0.26$ , manual EC  $r=-0.26$ .

Hence, with both manual and ICA artefact removal methods used, the DFA gave similar results for correlation to performance tasks. This was in keeping with previous research published by our group in validating the use of ICA as an artefact removal method in calculating DFA ([48](#)).

This again showed how the novel EEG measurement DFA can withstand isolated artefacts like eye blinks without much influence on the outcome of the DFA measurement, hence, making it a very robust to artefacts.

### **5.3 Using EEG as a method of assessing performance in OSA patients**

Impairment of vigilance in OSA patients was shown to affect not just one specific task but impairment over a wide range of attention tasks. In this study, we used a range of performance tasks that could be categorised broadly into tasks of attention (AusEd driving simulator ([35](#)); four choice reaction test ([36](#)); finger tapping test ([37](#)); visual attention test ([59](#)); attention switching (trail making test A) ([60](#)) and sustained attention task), tasks of memory (digit span ([61](#)); memory recall, span of visual memory ([62](#))), executive tasks (Tower of London ([44](#)), trail making test, Stroop test and maze test), and verbal fluency (spot the real word test ([64](#)), FAS test and the animal test). The aim of this study is to investigate if there is a correlation between EEG slowing (indicative of drowsiness/lack of vigilance) and impaired performance.

For this component of the analysis, only the manual artefact removal method results were used due to the previously explained difference noted with ICA.

EEG slowing was calculated using the following three methods:

1. PSA – delta & theta power/alpha & beta power (EO and EC state)
2. PSA – theta power/alpha power (EO and EC state)
3. DFA – scaling exponent (EO and EC state)



In correlating the above-mentioned three EEG slowing measurements to performance testing only a few tests yielded correlations. All statistically significant correlations were noted only with PSA ( $\delta + \theta / \alpha + \beta$ ) EC measurements. Positive correlations were noted for total AHI, NREM AHI, arousal index, DASS score for anxiety, mean reaction time, median reaction time of the breaking in response to trucks during the AUSEd driving task and spot the real word test. All correlations were statistically significant but weak. When these correlations were explored further by using scatter plots, it was obvious that there was influence from two outliers, drastically changing the line of best fit. When the analysis was repeated after removing the two outliers, all the above results became non-significant. Hence, all three EEG slowing measurements of  $\delta + \theta / \alpha + \beta$ ,  $\theta / \alpha$  and DFA did not show any significant correlations over the 14 individual performance tasks and AusEd driving simulator task.

The battery of testing contained an array of tests that had been previously tested on OSA patients and had been found to be impaired compared to the controls ([35](#), [36](#), [37](#), [55](#), [56](#), [57](#), [81](#)). Therefore, the correct tests had been applied, but none of the performance tests showed any significant correlation to EEG slowing. The possible explanation for a negative finding is outlined below.

Firstly, performance testing was carried out the day after the awake EEG testing. Hence, the lag time between EEG testing from which we obtained measurements for EEG slowing and the actual performance test was about 15 hours. This may explain the lack of relationship.

Secondly, the tests were carried out between 9 am and 12 noon after a full night's sleep and at a time when the homeostatic drive for sleep was at its nadir, thus possibly contributing to improved performance during the testing period and attenuating the ability of a test to detect impairment.

Thirdly, the inter individual variability that could occur during neurocognitive testing may have contributed to a negative study ([80](#)).

Finally, because testing was done under ‘controlled’ conditions, it did not give a true indication of how a participant would behave in real life when participants could be sleep-restricted and possibly had varying degrees of alcohol consumption that would impair their performance the next day. Add to this personal factors such as children, pets and environmental noises that impair sleep. These conditions were artificially controlled during the testing period, possibly leading to improved performance. This assumption is not applicable to all patients. Furthermore, some patients may have done the test poorly due to the first night effect in the laboratory resulting in more fragmented sleep with less sleep efficiency.

The driving performance task did not yield positive results after dismissing the influential outliers, even though the driving performance task was executed soon after the 5-minute recording of awake EEG. Hence, the test was conducted in the evening (between 1600 and 1900 hours) when the participants have been awake throughout the day, the homeostatic sleep drive was high and the lag time between the EEG measurement and the tests was small.

It could be determined that the test was not sensitive enough because it lasted only 30 minutes. If the driving test was prolonged, a more positive result would be achieved as previously published data demonstrating significant driving impairment in OSA patients had utilised the driving task of more than 60 minutes (81). Another reason for a lack of positive results was that this was a simulated computer task and not a real life situation, hence, patients may not have the same level of motivation to perform at their best when their physical safety is not at risk. The breaking to trucks only appeared 10 times during the entire period, hence, this domain does not measure the attention during the total driving period.

Once again, measuring EEG activity at the time of the task would give a more accurate understanding in correlation to performance. However, the disadvantage would be the marked muscle and eye blink artefact that would be expected in the EEG when the subject is constantly moving his/her eyes and head.

The performance tests were correlated against the subjective sleepiness scores of KSS and ESS, both of which did not show any correlation to performance. The anxiety and depression score, as well as the FOSQ score, failed to show correlation to performance testing as well. All sleep study data that was compared, including the total apnoea/hypopnea index; arousal index and nocturnal hypoxia did not correlate significantly to performance testing.

#### **5.4 Comparing the use of the novel method of EEG slowing (DFA scaling exponent) with PSA metrics**

The EEG slowing measured by activity in individual PSA densities correlated well with DFA measurements. There were strong positive correlations to delta activity and a negative correlation to alpha activity in keeping with previously published research (40). This shows that the DFA scaling exponent increases with an EEG indicator of increased drowsiness, and decreases with increased alertness.

The EEG slowing measured by using combined PSA densities were then compared with the novel method of the DFA. DFA has very good correlation to both PSA measures of EEG slowing (delta+theta/alpha+beta) as well as (theta/alpha) when assessed using Pearson's correlation coefficient. The combined power densities of PSA showed consistently tighter correlation than the individual power densities measured.

There were not adequate statistically significant results to say which EEG slowing measurement is the most sensitive in detecting performance impairment.

The use of EEG as a measure of sleepiness or of performance ability should be explored further with more sensitive measures of performance, for example, extended driving tests as the results of this study did not yield adequate statistically significant results to draw a conclusion.

However, the results are sufficiently convincing to use the ICA in place of manual scoring for artefact removal during DFA measurements. This is not recommended for

PSA as identical results were not obtained for both scoring systems and further validation in a group of patients with more positive results are required.

## 5.5 Limitations

The limitations are as follows:

1. During manual scoring of the awake EEG, almost 50% of the epochs were excluded during the EO state. As there were only two minutes of recording in total per EO/EC state, 50% would include only one minute of recordings. This exclusion facilitated analysis of a clear signal but reduced the precision of the measurement.
2. For some tasks, a greater time separation between EEG recording and performance testing may have attenuated any association between EEG and measured performance. While some tasks such as the driving task were performed within minutes of the EEG recording, many other tests were performed the next morning approximately 12 hours later. Timing of the EEG acquisition may also influence the test results as there is evidence to suggest a presence of diurnal variation in the cortical quantitative EEG ([82](#), [83](#)).
3. Individual tests may not have been conducted in optimal conditions to show performance impairment in the patients tested. Firstly, some tasks were performed in the morning when the homeostatic and circadian drive to sleep was at its nadir. Secondly, the tasks may not have been sufficiently challenging. The AusEd task was applied for 30 minutes. While this testing duration has been shown to be sensitive to the effects of sleep loss ([35](#)), a recent study has found that a 90-minute drive to be better in revealing differences in performance between patients ([81](#)).
4. All tests were performed in laboratory conditions that do not simulate real life occurrences, therefore, the results may have been adversely affected.

## 5.6 Future needs

The future needs are as follows:

1. Using an effective CPAP for a period of time and measuring the EEG slowing, comparing the pre- and post-treatment values would give a good indicator as to the benefit of treatment in improving vigilance.
2. If manual artefact removal was to be used, increasing the duration of the awake EEG to 7.5 minutes as opposed to five minutes would give a larger sample of epochs to be included in the measurement, thus increasing the precision of the measurement.
3. This current study has identified DFA as a measure that is robust to artefacts sustained during a recording done at rest while awake, however, the EEG testing should be performed while the task is being performed in order to accurately plot how EEG slowing is associated with performance.
4. If a participant's usual circumstances can be simulated, for example, alcohol intake and the usual number of hours in bed, more realistic measures of the performance testing can be acquired.
5. More sensitive results would have been expected if the AusEd driving task was extended.
6. This study group had an AHI ranging from 0 to 112. Patients with AHI  $<5$  were not considered to have significant sleep disordered breathing. Hence, excluding patients with AHI  $<5$  may have given performance data of a more robust OSA group.
7. In this study, all patients diagnosed with OSA were invited to participate in the project. If a selective group was chosen with known daytime impairment such as previous MVA, higher ESS or higher AHI, the performance results may have been more significant.

## **6. CONCLUSION**

### **6.1 Comparison of manual versus ICA artefact removal methods**

In this study, two electroencephalographic artefact removal methods were compared: (i) manual ‘gold standard’; and (ii) automated method based on Independent Components Analysis. Ten EEG measurements were explored, of which eight used power spectral data measuring different EEG frequencies of delta (0.5-4Hz), theta (4-8Hz), alpha (8-12 Hz) and beta (12-25Hz) in both eyes open and eyes closed states. The other two EEG measurements were from a novel measure, the DFA scaling exponent, which measures the randomness or fluctuations of the EEG signal.

No single statistical method has been proven to be superior in identifying the interchangeability of two methods of measurement. Combined impressions from a number of statistical tests were encouraged to draw clinical conclusions. When comparing manual versus ICA artefact removal methods by using a paired t-test, there was a statistically significant difference between the two measurements in eight of the 10 EEG waveforms measured. However, the calculated effect sizes and the difference between the means were small. The only exception to this was the comparison for beta power EO state, which showed a large effect size. The Bland-Altman plots demonstrated a tight scatter around the mean difference in all EEG measurements except for beta power EO. The examination of the beta power EO plot showed that the measurements are scattered around the mean, but with a higher mean difference. There is also systematic bias that would explain the higher effect size noted previously. Since the beta frequency range is of less interest in investigating drowsiness with changes more frequently described in the lower frequencies, this would not affect the overall measurements of drowsiness, which is measured by slower waves of delta and theta.

Pearson’s correlation coefficient and intra-class correlation coefficient for agreement demonstrated good agreement between the manual and ICA artefact removal methods in all 10 EEG measurements. A tighter relationship was demonstrated during the EC state compared to the EO state, and correlation was greater for DFA than for PSA

measurements. This implies that the influence of artefact on the measured parameters was less during the eyes closed state, and also that DFA was a more robust measurement compared to PSA metrics in withstanding artefacts.

The intra-class correlation further strengthens this argument and showed a near perfect absolute agreement between the ICA and manual artefact removal methods in measuring DFA. This correlation was less strong for PSA metrics.

Overall, DFA and PSA look at the same effect (EEG slowing or drowsiness) in different ways, measuring fluctuations of EEG versus measuring EEG frequency respectively. PSA metrics are vulnerable to the influence of artefacts as eye blinks and muscle movements create larger waves with slower frequencies similar to the delta wave frequency. In contrast, the novel EEG analysis method, DFA, is far superior to PSA metrics in withstanding artefact. This robustness was proven during comparison of the two artefact removal methods that showed perfect interchangeability when measuring DFA with either artefact removal method, but not PSA.

Next, an attempt is made to look at the clinical applicability of the results obtained from the two artefact removal methods. To do this, each artefact removal method was correlated to the performance testing.

With use of PSA, when a statistically significant correlation was observed a similar trend was observed regardless of whether artefact removal was performed automatically by ICA or manually, although the exact correlation coefficient numerical value was slightly different.

With the use of DFA, when a statistically significant correlation is present, the manual and ICA methods derived identical results.

Our group had previously validated the use of ICA by comparing DFA to performance testing in a group of normal controls using both methods of manual scoring and ICA, demonstrating comparable results (48). The result of this study where the ICA was used

in 83 patients with OSA is consistent with the previous results, and strengthens the validation of ICA use in OSA patients in giving similar results when using DFA.

This current study shows that ICA and manual artefact removal can be interchangeably used in extracting DFA measurements with confidence.

The PSA metrics have shown to be highly influenced by artefact, hence interchangeability of artefact removal methods is not advisable. When analysing PSA metrics, only the manual artefact removal method should be used.

## **6.2 Comparison of EEG slowing with performance testing**

The battery of performance testing yielded weak but statistically significant positive results only with delta+theta/alpha+beta EC in tasks of AusEd driving test parameters of mean reaction time and median reaction time to trucks and spot the real word test, the total AHI, NREM AHI, arousal index and the DASS score for anxiety. When the correlations were explored further with scatter plots, it was evident that the above results were due to two influential outliers. Following removal of these outliers, no significant association between EEG slowing and the other variables was found.

Hence, there were no significant correlations between the 10 EEG metrics examined, 14 individual performance tests and the AusEd driving task. This is despite choosing a set of individual tests previously reported to demonstrate performance impairment in OSA patients. The lack of significant impairment in performance may be due to the lag time between the awake EEG recording that was done in the evening and performance tests that were conducted in the morning on the following day, the reduced homeostatic drive to sleep at the time of testing (9 am) and the modified laboratory conditions that would have either improved or disrupted the participant's sleep, as well as using the AusEd driving task that was too short in duration, therefore, reducing its sensitivity to detect performance impairment.

It is possible that measuring the awake EEG at a greater temporal proximity to task performance would give a better understanding of the electrophysiological state of the



brain at that time and hence provide a better indicator of the impairment of task performance. For example, if EEG were measured at the time of driving, a stronger association between EEG slowing and driving task performance may have been obtained. The main disadvantage of this strategy would be the increased artefacts that one would expect with eye blinking and head movement. We would expect data like this to be best analysed using a DFA scaling exponent due to its resilience to withstand artefacts.

It is not known what causes EEG slowing in OSA patients. This study found that there was no relationship to subjective sleepiness, sleep study measures of arousal, nocturnal hypoxia or sleep apnoea severity, as defined by the AHI that would explain EEG slowing.

The performance testing did not yield any statistically significant correlations with any measure of EEG slowing, hence, there is inadequate data to evaluate what method of EEG slowing is most sensitive to performance impairment.

The novel DFA measurement is a robust measurement with minimal influence from artefacts. It is complementary to the currently used PSA metrics, especially during circumstances with increased artefacts.

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# APPENDICES

## Appendix 1 –Tables

**Table 1 Factors predisposing to OSA**

Factors		Causes	Example
Small upper airway		Obesity	Menopause, lack of exercise, poor diet
		Hormonal factors	Hypothyroidism Acromegaly Cushing’s syndrome
		Supine position	
		Upper airway lesions	Enlarged tonsils and adenoids Congenital laryngeal cysts and webs Crico-arytenoid arthritis
		Skeletal abnormality	Retrognathia Micrognathia (Pierre Robin syndrome, Treacher –Collins syndrome) Marfan’s syndrome Mid face hypoplasia (Craniosynostoses, Achondroplasia, Down’s syndrome)
		Mucopolysaccharidoses	Hunter, Hurler and Hunter syndromes
Reduction of upper airway dilator muscle activity		Sleep deprivation and sleep fragmentation	
		Medication	Benzodiazepam Opioids
		Alcohol	
		Neuromuscular conditions	Strokes Cerebral palsy Arnold-Chairi malformations Prader-Willi Syndrome

**Table 2     Epworth Sleepiness Scale**

Situation	Chance of dozing 0 = no chance of dozing 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing
Sitting and reading	
Watching television	
Sitting inactive in a public place (e.g. a cinema or meeting)	
As passenger in a car for > 1 hour	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to a companion	
Sitting quietly after an alcohol-free lunch	
In a car, while stopped briefly in heavy traffic	
<b>Total Epworth Sleepiness Score</b>	

Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep, 14(6):540-545.)

**Table 3     Karolinska Sleepiness Scale**

1 = extremely alert
2 = very alert
3 = alert
4 = rather alert
5 = neither alert nor sleepy
6 = some signs of sleepiness
7 = sleepy, but no effort to keep awake
8 = sleepy, some effort to keep awake
9 = very sleepy, great effort to keep awake

**Table 4     Depression and Anxiety Stress Scale (DASS)**

1.	I found it hard to wind down	0	1	2	3
2.	I was aware of dryness of my mouth	0	1	2	3
3.	I couldn't seem to experience any positive feeling at all	0	1	2	3
4.	I experienced breathing difficulty (e g, excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5.	I found it difficult to work up the initiative to do things	0	1	2	3
6.	I tended to over-react to situations	0	1	2	3
7.	I experienced trembling (e g, in the hands)	0	1	2	3
8.	I felt that I was using a lot of nervous energy	0	1	2	3
9.	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10.	I felt that I had nothing to look forward to	0	1	2	3
11.	I found myself getting agitated	0	1	2	3
12.	I found it difficult to relax	0	1	2	3
13.	I felt down-hearted and blue	0	1	2	3
14.	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15.	I felt I was close to panic	0	1	2	3
16.	I was unable to become enthusiastic about anything	0	1	2	3
17.	I felt I wasn't worth much as a person	0	1	2	3
18.	I felt that I was rather touchy	0	1	2	3
19.	I was aware of the action of my heart in the absence of physical exertion (e.g., sense of heart rate increase, heart missing a beat)	0	1	2	3
20.	I felt scared without any good reason	0	1	2	3
21.	I felt that life was meaningless	0	1	2	3
0	Did not apply to me at all	Never			
1	Applied to me to some degree or some of the time	Sometimes			
2	Applied to me to a considerable degree, or a good part of the time	Often			
3	Applied to me very much, or most of the time	Almost always			

**Table 5     Functional Outcome of Sleep Questionnaire (FOSQ)**

FOSQ Test	
<p><b>Note:</b> In this questionnaire, when the words “sleep” or “tired are used, it describes the feeling that you can’t keep your eyes open, your head is droopy, that you want to nod off or that you feel the urge to nap. These words do not refer to the tired or fatigued feeling you may have after you exercised.</p> <p>FOSQ questions are answered using numbers from 0 to 4 (see answer key below ):</p> <p><b>0= I don’t do this activity for other reasons</b> <b>1= Yes, extreme</b> <b>2= Yes, moderate</b> <b>3= Yes, a little,</b> <b>4=No</b></p> <hr style="border: 0.5px solid black; margin: 10px 0;"/>	
<b>Q1)</b>	<p>Do you generally have difficulty concentrating on things you do because you are sleepy or tired?</p> <p style="text-align: center;"><input type="radio"/> 0   <input type="radio"/> 1   <input type="radio"/> 2   <input type="radio"/> 3   <input type="radio"/> 4</p>
<b>Q2)</b>	<p>Do you generally have difficulty remembering things because you are sleepy or tired?</p> <p style="text-align: center;"><input type="radio"/> 0   <input type="radio"/> 1   <input type="radio"/> 2   <input type="radio"/> 3   <input type="radio"/> 4</p>
<b>Q3)</b>	<p>Do you have difficulty finishing a meal because you become sleepy or tired?</p> <p style="text-align: center;"><input type="radio"/> 0   <input type="radio"/> 1   <input type="radio"/> 2   <input type="radio"/> 3   <input type="radio"/> 4</p>
<b>Q4)</b>	<p>Do you have difficulty working on a hobby (for example: sewing, collecting, gardening) because you are sleepy or tired?</p> <p style="text-align: center;"><input type="radio"/> 0   <input type="radio"/> 1   <input type="radio"/> 2   <input type="radio"/> 3   <input type="radio"/> 4</p>

<b>Q5)</b>	Do you have difficulty doing work around the house (for example: cleaning house, doing laundry, taking out the trash, repair work) because you are sleep or tired?
<input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4	
<b>Q6)</b>	Do you have difficulty operating a motor vehicle for short distances (less than 100 miles) because you become sleepy or tired?
<input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4	
<b>Q7)</b>	Do you have difficulty operating a motor vehicle for long distances (greater than 100 miles) because you become sleepy or tired?
<input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4	
<b>Q8)</b>	Do you have difficulty getting things done because you are too sleepy or tired to drive or take public transportation?
<input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4	
<b>Q9)</b>	Do you have difficulty take care of financial affairs and doing paperwork (for example: writing checks, paying bills, keeping financial records, filling out tax forms, etc.) because you are sleepy or tired?
<input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4	
<b>Q10)</b>	Do you have difficulty performing employed or volunteer work because you are sleepy or tired?
<input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4	
<b>Q11)</b>	Do you have difficulty maintaining a telephone conversation because you become sleepy or tired?
<input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4	
<b>Q12)</b>	Do you have difficulty visiting with you family or friends in <b>your</b> home because you become sleepy or tired?
<input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4	
<b>Q13)</b>	Do you have difficulty visiting with your family or friends in <b>their</b> homes because you become sleepy or tired?
<input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4	

**Q14)** Do you have difficulty doing things for your family or friends because you become sleepy or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**(For Question 15, answer using only 1, 2, 3 or 4)**

**Q15)** Has your relationship with family, friends or work colleagues been affected because you are sleepy or tired?

☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q16)** Do you have difficulty exercising or participating in a sporting activity because you are too sleepy or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q17)** Do you have difficulty watching a movie or videotape because you become sleepy or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q18)** Do you have difficulty enjoying the theatre or a lecture because you become sleepy or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q19)** Do you have difficulty enjoying a concert because you become sleepy or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q20)** Do you have difficulty watching television because you are sleepy or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q21)** Do you have difficulty participating in religious services, meeting or a group club because you are sleepy or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q22)** Do you have difficulty being as active as you want to be in the evening because you are sleepy or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q23)** Do you have difficulty being as active as you want to be in the morning because you are sleepy or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q24)** Do you have difficulty being as active as you want to be in the afternoon because you are sleepy or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q25)** Do you have difficulty keeping a pace with others your own age because you are sleepy or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q26)** How would you rate yourself in your general level of activity?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q27)** Has your intimate or sexual relationship been affected because you are sleepy or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q28)** Has your desire for intimacy or sex been affected because you are sleepy or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q29)** Has your ability to become sexually aroused been affected because you are sleepy or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Q30)** Has your ability to have an orgasm been affected because you are sleep or tired?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

**Table 6 Correlations between DFA with performance test (manual and ICA)**

DFA	Eyes Open ICA	Eyes Open Manual	Eyes Closed ICA	Eyes Closed Manual
Finger tapping test	$r=0.41$ $p<0.01$	$r=0.41$ $p<0.01$	$r=0.27$ $p=0.08$	$r=0.29$ $p=0.14$
Four choice reaction time	$r=-0.26$ $p<0.05$	$r=-0.17$ $p=0.2$	$r=-0.26$ $p<0.05$	$r=-0.26$ $p<0.05$

**Table 7 Correlation between EEG slowing and AusEd driving simulation test**

EEG slowing	Steering deviation		Speed deviation outside the 60-80km/h zone	Mean reaction time (braking in response to trucks)	Standard deviation of reaction time	Median reaction time	Number of crashes
	Centre of the left lane	Median lane position					
Delta+theta/ alpha+betaEO	r=-0.14 p=0.2	r=-0.12 p=0.3					
Delta+theta/ alpha+betaEC	r=0.12 p=0.3	r=0.16 p=0.2	r=0.08 p=0.5	r=. 296 p=0.01	r=-0.06 p=0.6	r=. 302 p<0.01	r=0.08 p=0.5
Theta/alpha EO	r=-0.15 p=0.2	r=0.06 p=0.6	r=-0.1 p=0.4	r=-0.08 p=0.5	r=0.01 p=0.9	r=-0.11 p=0.4	r=0.12 p=0.3
Theta/alpha EC	r=-0.07 p=0.5	r=0.11 p=0.4	r=-0.17 p=0.2	r=0.14 p=0.2	r=-0.03 p=0.8	r=0.13 p=0.3	r=0.15 p=0.2
DFA SE EO	r=-0.13 p=0.3	r=0.02 p=0.9	r=-0.13 p=0.3	r=-0.12 p=0.3	r=-0.14 p=0.2	r=-0.13 p=0.3	r=0.22 p=0.1
DFA SE EC	r=0.02 p=0.9	r=0.04 p=0.7	r=-0.08 p=0.5	r=0.11 p=0.3	r=-0.03 p=0.8	r=0.10 p=0.4	r=0.08 p=0.5



**Table 8 Correlation between EEG slowing and sleep study data**

EEG slowing	Sleep efficiency	Arousal index	Proportion of time below 90%	NREM RDI	REM RDI	Total RDI	Minimum saturations
Delta+Theta/ Alpha+Beta) (EO)	r=0.05 p>0.05	r=-0.17 p>0.05	r=-0.17 p>0.05	r=-0.21 p>0.05	r=-0.23 p>0.05	r=-0.22 p>0.05	r=0.26 p>0.05
Delta+Theta/ Alpha+Beta) (EC)	r=0.08 p>0.05	r=0.3 p<0.01	r=0.09 p>0.05	r=0.27 p=0.01	r=0.18 p>0.05	r=0.26 p=0.01	r=-0.09 p>0.05
Theta/alpha (EO)	r=0.06 p>0.05	r=-0.29 p>0.05	r=-0.17 p>0.05	r=-0.33 p>0.05	r=-0.28 p>0.05	r=-0.34 p>0.05	r=0.19 p>0.05
That/alpha (EC)	r=0.02 p>0.05	r=-0.02 p>0.05	r=-0.004 p>0.05	r=0.03 p>0.05	r=-0.01 p>0.05	r=0.02 p>0.05	r=-0.005 p>0.05
DFA (EO)	r=0.08 p>0.05	r=-0.12 p>0.05	r=-0.08 p>0.05	r=-0.14 p>0.05	r=-.24 p>0.05	r=-0.15 p>0.05	r=0.09 p>0.05
DFA (EC)	r=0.04 p>0.05	r=0.14 p>0.05	r=0.08 p>0.05	r=0.18 p>0.05	r=0.05 p>0.05	r=0.17 p>0.05	r=-0.11 p>0.05

**Table 9 Correlation between measurements of EEG slowing and self-rated questionnaires on sleepiness**

Measurement for EEG slowing	ESS	KSS
Delta+theta/alpha+beta EO	r=-0.2 p=0.06	r=0.2 p=0.2
Delta+theta/alpha+beta EC	r=-0.2 p=0.07	r=-0.1 p=0.4
Theta/alpha manual EO	r=-0.1 p=0.5	r=0.1 p=0.4
Theta/alpha manual EC	r=-0.3 p=0.01	r=0.01 p=0.9
DFA scaling exponent EC	r=-0.1 p=0.3	r=-0.01 p=0.9
DFA scaling exponent EO	r=-0.2 p=0.1	r=0.1 p=0.3

**Table 10 Correlation between EEG slowing and depression and anxiety scale and functional assessment of sleep questionnaire**

	FOSQ vigilance	DASS score for depression	DASS score for anxiety	DASS score for stress
Delta+theta/ alpha+beta EO	r=-0.01 p=0.92	r=-0.04 p=0.72	r=-0.06 p=0.6	r=-0.03 p=0.78
Delta+theta/ alpha+beta EC	r=0.09 p=0.41	r=0.09 p=0.41	r=0.297 p<0.01	r=0.11 p=0.33
Theta/alpha EO	r=0.07 p=0.51	r=-0.14 p=0.2	r=-0.11 p=0.34	r=0.03 p=0.77
Theta/alpha EC	r=0.22 p=0.05	r=0.05 p=0.64	r=0.06 p=0.58	r=0.03 p=0.78
KDT SE EO	r=-0.05 p=0.68	r=0.04 p=0.72	r=0.01 p=0.91	r=0.04 p=0.75
KDT SE EC	r=-0.02 p=0.89	r=0.09 p=0.43	r=0.17 p=0.13	r=0.06 p=0.6

**Table 11 (Part 1: Tests for attention) Correlation between EEG slowing and tests for performance**

	Finger tapping dominant hand	Finger tapping non-dominant hand	4-choice reaction time	Switching attention trail marking part A	Sustained attention		Visual attention timing
					Longest sequence correctly completed	No of incorrect responses	
Delta+theta/alpha+beta EO	r=0.1 p=0.3	r=0.2 p=0.1	r=-0.1 p=0.5	r=0.12 p=0.4	r=-0.06 p=0.6	r=0.01 p=0.9	r=-0.15 p=0.56
Delta+theta/alpha+beta EC	r=0.03 p=0.8	r=0.1 p=0.5	r=-0.2 p=0.2	r=-0.03 p=0.8	r=-0.02 p=0.9	r=-0.03 p=0.8	r=-0.03 p=0.78
Theta/alpha EO	r=0.2 p=0.1	r=0.22 p=0.2	r=-0.1 p=0.5	r=0.08 p=0.6	r=-0.04 p=0.8	r=0.04 p=0.7	r=-0.04 p=0.7
Theta/alpha EC	r=0.06 p=0.6	r=0.13 p=0.4	r=-0.16 p=0.2	r=-0.2 p=0.3	r=-0.03 p=0.8	r=-0.02 p=0.9	r=-0.09 p=0.45
DFA EO	r=0.2 p=0.1	r=0.4 p=0.01	r=-0.17 p=0.2	r=-0.1 p=0.4	r=0.09 p=0.4	r=0.163 p=0.18	r=0.11 p=0.4
DFA EC	r=0.2 p=0.3	r=0.2 p=0.1	R-0.250 p<0.05	r=-0.2 p=0.1	r=0.08 p=0.5	r=-0.01 P-0.9	r=0.06 p=0.6

**Table 12 (Part 2: Tests for intelligence) Correlation between EEG slowing and tests for performance**

	Switching attention trail marking Part B	Stroop test		Tower of London		Maze test
		No. of words identified	No. of colours identified	No. of moves	Average time taken to complete the task	
Delta+theta/ alpha+beta EO	r=0.0 p=1.0	r=0.04 p=0.7	r=-0.02 p=0.9	r=0.02 p=0.8	r=-0.05 p=0.6	r=-0.03 p=0.8
Delta+theta/ alpha+beta EC	r=0.07 p=0.6	r=0.04 p=0.7	r=-0.06 p=0.6	r=0.08 p=0.5	r=-0.07 p=0.5	r=0.1 p=0.4
Theta/alpha EO	r=0.002 p=0.98	r=0.14 p=0.25	r=0.06 p=0.6	r=0.1 p=0.3	r=-0.01 p=0.4	r=0.05 p=0.69
Theta/alpha EC	r=-0.01 p=0.9	r=0.08 p=0.5	r=0.05 p=0.7	r=0.1 p=0.4	r=-0.2 p=0.2	r=0.02 p=0.9
DFA Scaling Exponent EO	r=0.03 p=0.8	r=0.27 p<0.05	r=0.1 p=0.3	r=0.1 p=0.4	r=-0.1 p=0.4	r=-0.02 p=0.8
DFA Scaling Exponent EC	r=0.0 p=1.0	r=0.2 p=0.11	r=0.11 p=0.4	r=0.08 p=0.5	r=-0.09 p=0.5	r=-0.01 p=0.94

**Table 13 (Part 3: Tests for memory and verbal fluency) Correlation between EEG slowing and tests for performance**

	Span of visual memory	Digit span	R-digit spans	Memory recall			Word generation		Spot the real word test
				Words correctly recognised as from the list	No of words recalled over trials 1-4	No of words recalled after 25 mins	FAS test	Animal test	
Delta+theta/ alpha+beta EO	r=-0.02 p=0.9	r=0.05 p=0.6	r=-0.05 p=0.7	r=-0.1 p=0.2	r=0.2 p<0.05	r=0.1 p=0.3	r=0.1 p=0.5	r=0.07 p=0.5	r=-0.04 p=0.7
Delta+theta/ alpha+beta EC	r=-0.09 p=0.45	r=-0.02 p=0.9	r=-0.2 p=0.1	r=-0.2 p=0.1	r=0.01 p=0.9	r=-0.2 p=0.1	r=-0.03 p=0.8	r=-0.03 p=0.7	r=-0.25 p<0.05
Theta/alpha EO	r=-0.02 p=0.9	r=0.06 p=0.6	r=-0.12 p=0.2	r=0.01 p=0.9	r=0.03 p=0.8	r=0.04 p=0.8	r=-0.04 p=0.7	r=-0.04 p=0.7	r=-0.02 p=0.8
Theta/alpha EC	r=-0.04 p=0.7	r=0.05 p=0.6	r=-0.09 p=0.4	r=-0.1 p=0.6	r=-0.04 p=0.73	r=0.04 p=0.8	r=-0.09 p=0.4	r=-0.09 p=0.4	r=-0.03 p=0.8
DFA EO	r=-0.01 p=0.94	r=0.1 p=0.4	r=-0.08 p=0.5	r=-0.08 p=0.5	r=0.08 p=0.5	r=0.02 p=0.9 -0.046	r=0.1 p=0.4	r=0.1 p=0.4	r=-0.1 p=0.4
DFA EC	r=-0.05 p=0.7	r=0.1 p=0.2	r=-0.07 p=0.5	r=-0.001 p=0.9	r=0.03 p=0.8	r=-0.05 p=0.7	r=0.1 p=0.6	r=0.06 p=0.5	r=-0.1 p=0.4

## Appendix 2: RPAH Zone Ethics Approval

ADDRESS FOR ALL CORRESPONDENCE  
RESEARCH DEVELOPMENT OFFICE  
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CAMPERDOWN NSW 2050



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Sydney  
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REFERENCE: X06-0299  
5.0/9.13/OCT12

6 September 2012

Professor R Grunstein  
Centre for Respiratory Failure  
and Sleep Disorders  
Building 11  
Royal Prince Alfred Hospital

Dear Professor Grunstein,

**Re: Protocol No X06-0299 - "Neurobiological effects of sleep apnea and sleepiness"**

Thank you, on behalf of the Ethics Review Committee, for your correspondence of 20 August 2012.

The inclusion of Dr S Herath and Mr C Miller as associate investigators in the above study is noted and approved. If either of them will have access to patients, it is recommended that they undergo criminal records checks if these were not done as a routine part of their appointments at the WIMR.

Yours sincerely,

A handwritten signature in black ink that reads 'Lesley Townsend' in a cursive, flowing script.

Lesley Townsend  
Executive Officer  
Ethics Review Committee (RPAH Zone)

HERC\EXECOR\12-10

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