Obstructive Sleep Apnoea

The Genesis Of Daytime Somnolence and Cognitive Impairment

- Arousals, Hypoxia and Circadian Rhythm

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A thesis submitted in fulfillment of the requirements for the degree of Doctor of Philosophy

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September 1997
STATEMENT

The work described in this thesis was carried out in the Department of Respiratory Medicine of the Royal North Shore Hospital, University of Sydney, under the supervision of Professor Norbert Berend. Unless otherwise stated, it is the original work of the author and has neither been presented nor is it currently being presented for any other degree.

David Joffe
ACKNOWLEDGEMENTS

I wish to thank Professor Norbert Berend for his enormous support in this undertaking. His dedication to providing constant help and advice has been exceptional. He has been a mentor, guardian and friend throughout the period of this research and for this I cannot thank him enough.

I would also like to thank my co-supervisors, Dr Geoffrey Herkes and Professor Bruce Robinson. Their overview and input to this thesis has been most gratefully received.

I would like to thank Mr Geoffrey Marshall, Clinical Neuropsychologist, for all the time and effort he contributed to this work. Without his sound advice and broad experience this work would not have been so readily accomplished.

I would like to thank Dr Michael Jones, Statistician (Instat Australia) for all his time and effort. His advice and assistance has been most gratefully received. Thank you to Dr David Kennaway (Department of Obstetrics and Gynaecology - Adelaide University) for all his assistance with the urinary sampling of the melatonin metabolite.

Finally, I would like to thank my wife Sara. Her constant support and love through the long process of this thesis have been never ending. It would not have been possible for this work to have reached fruition without her. This work remains as much part of her as of me, and is a reflection of her strength and dedication.

DEDICATION

I would like to dedicate this thesis to my darling wife Sara, and my two loving sons Adam and Benjamin. Thank you.
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ABBRVIATIONS AND DEFINITIONS

AI: arousal index (definition: page 77 reference 166)
CAL: chronic airflow limitation (definition: physiologically determined reduction in airflow)
EDS: excessive daytime sleepiness
MSLT: multiple sleep latency test (definition: average time to sleep onset determined over 5 naps at 2 hourly intervals according to the standard criteria for sleep scoring)
MWT: maintenance of wakefulness test (definition: measure of a subjects ability to resist sleep under neutral conditions)
NREM: non- rapid eye movement sleep (definition: page 77 reference 166)
OSA: obstructive sleep apnoea (definition: page 6)
PLM: periodic limb movement (definition: periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep)
RDI: respiratory disturbance index (definition: page 76)
REM: rapid eye movement sleep (definition: page 77 reference 166)
SDB: sleep disordered breathing
SWS: slow wave sleep (definition: page 77 reference 166)
STM: short term memory
S.C.: Steer Clear
SUMMARY

Obstructive Sleep Apnoea (OSA) is a disease characterised by repetitive upper airway obstructions which are manifest by desaturation and arousal from sleep. It has been known for many years that this interruption to the normal architecture of sleep may present to the clinician as excessive daytime somnolence often with a complaint of difficulties with concentration and short term memory. Previous work had demonstrated a relationship between variables of cognitive dysfunction in patients with obstructive sleep apnoea, however, little was known about which components of the syndrome contributed to this outcome and whether specific clinical thresholds of sleep disordered breathing could be defined for the development of cognitive dysfunction. In the context of this body of work cognitive dysfunction is defined as: a level of cognitive performance below normal derived values for a given cognitive test, when the subjects performance is controlled for age, sex, and level of education.

55 patients were randomly recruited from the Sleep Unit of the Royal North Shore Hospital. Routine polysomnography was performed. A carefully selected battery of neurocognitive tests were administered the following morning. Correlations between cognitive performance and variables of sleep disordered breathing (SDB) were then derived. The data demonstrated a significant relationship between increasing sleep fragmentation and both immediate and delayed short term memory decrement. This finding was demonstrated to be independent of other variables of SDB. Further analysis demonstrated a relationship between the respiratory disturbance index (RDI) in rapid eye movement (REM) sleep and a decline in information processing speed. Again, this finding was demonstrated to be independent of other sleep variables and indeed independent of the total time spent in REM sleep. A separate sub-analysis of the sleep arousals, defined by modified criteria, was performed against all cognitive outcomes. These analyses demonstrated a significant relationship between repetitive
shifts in sleep to a lesser stage, arousals to wakefulness and decrements in working memory. This was a novel and unexpected finding.

The intention of this body of work was to clarify the role of hypoxia and arousals in altering cognitive function in patients with sleep apnoea. This work also sought to examine the relationship between these variables and somnolence, a common feature in obstructive sleep apnoea (OSA) patients. Finally, clinically significant thresholds for developing a given degree of cognitive decline were derived. It is believed these may have implications for the intention to treat in this condition.

A separate, but integral body of work, examined whether hypoxia and arousals may alter the secretion of melatonin (a sleep inducing hormone) in individuals with OSA, to explore the possibility that this may be contributing to daytime somnolence.

40 patients were randomly recruited from the Sleep Unit of the Royal North Shore Hospital. Polysomnography was performed and consecutive 12 hour urine samples were collected for 6-sulphatoxymelatonin analysis. This stable metabolite of melatonin was measured to gauge the total production of the hormone for analysis against variables of SDB. Despite the physiological evidence to support the hypothesis that abnormal secretion of this hormone may be present in OSA, no such relationship was able to be demonstrated.
Hypotheses - Neurocognitive study

1. Arousal from sleep gives rise to measurable abnormalities of cognition as a result of sleep fragmentation and this relationship is independent of hypoxia.

2. Repetitive hypoxia resulting from OSA gives rise to measurable abnormalities of cognition. This relationship is independent of sleep fragmentation.

3. The effects of somnolence (impairment of vigilance) acts as a co-variable in the genesis of cognitive dysfunction in OSA.

4. Sleep fragmentation gives rise to excessive daytime sleepiness independent of the magnitude of other the variables of sleep disordered breathing.

5. Different aspects of cognition may be affected by sleep disordered breathing depending on the type of insult i.e. hypoxic or fragmentational.

6. Defineable risks for cognitive impairment can be derived from the magnitude of the hypoxic injury and the degree of sleep fragmentation.

Hypotheses - Melatonin study

1. Excessive sympathetic activity due to hypoxia and arousal in obstructive sleep apnoea gives rise to excessive secretion of melatonin.
This hypothetical construct is best represented by the diagram below. Each pathway will be later referenced in the Results Chapters as relevant findings are presented.

**PATHWAY 1:** Sleep fragmentation and cognitive impairment (hypothesis 1).

**PATHWAY 2:** Hypoxia and cognitive impairment (hypothesis 2).

**PATHWAY 3:** Somnolence and cognitive impairment (hypothesis 3).

**PATHWAY 4:** Sleep fragmentation and somnolence (hypothesis 4).
Aims - Neurocognitive study

1. To analyse the relationship between arousal, cognitive dysfunction and somnolence in patients with sleep disordered breathing (SDB).

2. To analyse the relationship between hypoxic events (ie. duration, number, and severity), cognitive impairment and somnolence in SDB.

3. To investigate the relationship between cognitive impairment and excessive daytime sleepiness (EDS).

Aims - Melatonin study

1. To examine whether total secretion of melatonin as measured by urinary excretion of the metabolite 6-sulphatoxymelatonin is abnormal in a group of moderate OSA patients compared to a matched group of non-apnoeic patients.

2. To correlate the total excretion of 6-sulphatoxymelatonin with measures of hypoxia and arousal from sleep to examine the relationship between apnoea severity and melatonin production.