Sleep Restriction Therapy: Experimental Studies

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Bachelor of Science (First Class Hons.) in Psychology

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in Psychological Medicine

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June 2014

Thesis Overview

Insomnia is a common disturbance of sleep which can be treated effectively with cognitive behavioural therapy; a multicomponent 'package' of cognitive and behavioural strategies. Sleep restriction therapy is thought to be one of the most potent behavioural components of cognitive behavioural therapy. Subjective measures of sleep and daytime functioning improve not only with cognitive behavioural therapy, but also during and following sleep restriction therapy. However, it is unknown when these changes occur or if there are associated objective changes. This thesis addresses these issues, and presents: 1. a review of the literature of therapy and original research; 2. evaluates the nature and timing of changes in self-reported daytime functioning during therapy; 3. profiles potential objective changes (in measurements of sleep, plasma and salivary cortisol concentrations & temperature); and 4. compares patients with different subtypes of insomnia and healthy good sleeping controls for possible differences within the brain that might serve as future targets for treatment. The final general discussion ties together the results of these data-based chapters.

The following section aims to provide a brief summary of the overall thesis. This Ph.D. was undertaken as Cotutelle Agreement between the Universities of Glasgow, United Kingdom and Sydney, Australia. Specific chapters relate to the data collection performed at these two sites. Consequently this thesis has been split into specific chapters from where the data were obtained. Chapters four and five consist of data acquired from Glasgow, United Kingdom whilst in chapters six and seven the data were acquired in Sydney, Australia.

Chapter 1: Introduction

The first chapter sets the scene and introduces insomnia disorder, the prevalence, costs, aetiology and theories (*3-P* model & hyperarousal specifically). Treatment is then introduced and the chapter ends with an introduction to sleep restriction therapy.

Chapter 2: The evidence base of sleep restriction therapy for treating insomnia disorder

The second chapter consists of a review of the literature concerning sleep restriction therapy for insomnia. This review looks to discover the contribution of standalone sleep restriction therapy for the treatment of insomnia. It appears from the literature review and meta-analysis that improvements can be found in self-report sleep diary and questionnaire data due to therapy compared to control conditions. A summary of the research highlights that it is unknown when these subjective measures change, if there are any side effects, and what may change objectively due to therapy. Chapter two has been accepted for publication in Sleep Medicine Reviews and is referred to as Miller et al. (2014).

Chapter 3: Methodology for the assessment of sleep

The third chapter is different from the other chapters as it is a methods chapter which provides a short overview of sleep, circadian regulation and the two-process model of sleep. It then explores measures of sleep (polysomnography & actigraphy), cortisol and cerebral metabolism. The chapter ends with an overview of sleep restriction therapy for insomnia, the recruitment procedures and statistical analyses used in the data chapters. Chapter three has been accepted for publication as a book chapter but has been modified to reflect the methods used specifically in this thesis.

Chapter 4: An ecological momentary assessment of sleep restriction therapy for insomnia

Chapter four is the first treatment study at Glasgow and attempts to build on the findings of the review by looking to profile the timing of improvements due to sleep restriction therapy. Mood and daytime functioning are examined as part of an ecological momentary assessment during therapy for insomnia. The study highlights initial impairments and subsequent improvements due to therapy. Results also suggest alterations in the sleep experience (especially around pre-sleep and on awakening for measures of sleepiness and alertness). Chapter four has been published in the Journal of Sleep Research and is referred to as Miller, Kyle, Marshall, and Espie (2013).

Chapter 5: An assessment of salivary cortisol in response to sleep restriction therapy for insomnia

Chapter five is the second sleep restriction treatment study and by building on Chapter four considers changes in objective salivary cortisol levels throughout therapy. Salivary cortisol was used as a non-invasive, inexpensive method at Glasgow to repeatedly sample cortisol before and through three weeks of therapy in the home environment at specified time points. Changes to cortisol levels due to therapy (especially around the pre-sleep and awakening periods) may offer insights into objective alterations due to therapy.

Chapter 6: Sleep restriction therapy for insomnia disorder: An exploratory assessment of sleep and physiological markers of arousal in response to treatment

Chapter six is the final treatment study and takes place in Sydney with access to night time blood sampling equipment for plasma cortisol. The study builds on the results of the two previous studies by looking to objectively define changes due to sleep restriction therapy in insomnia through a specific in-lab test of sleep, plasma cortisol and core body temperature measures after six weeks of therapy. This is used to elucidate the potential mechanisms of action of sleep restriction therapy.

Chapter 7: Magnetic resonance spectroscopy of cerebral metabolism in insomnia

Chapter seven is a final case control study that takes advantage of the facilities at Sydney to look for differences between those with psychophysiological insomnia and healthy good sleeping controls for brain metabolism. The chapter aims to explore further potential differences in brain neurochemistry (magnetic resonance spectroscopy) and consider implications for insomnia management.

Chapter 8: Summary

Chapter eight is an overall summary and finishes the thesis with a general discussion tying the results of the studies together and suggesting reasons for the findings of the studies. This chapter also summarises the strengths, weaknesses and recommendations of the thesis.

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Acknowledgements

Firstly, I would like to thank all of the participants who were involved in this research, without participant involvement and the donation of your time, energy, and blood this thesis would not have been possible and for this I thank you.

I would like to thank my excellent, professional and dedicated supervisory team for enabling this work and for all of your encouragement: from the northern hemisphere to the southern hemisphere, I am indebted to Professor Colin Espie, Dr Simon Kyle, Professor Ron Grunstein and Associate Professor Delwyn Bartlett - thank you all for the effort, time, and patience in helping me with this body of work, you have all individually been excellent mentors to me and I am uniquely privileged to have studied and learned from you all.

Thank you to my funders, the National Health and Medical Research Council (NHMRC, Australia) Centre of Integrated Research and Understanding of Sleep (CIRUS) and the Sackler Institute of Psychobiological Research (University of Glasgow Sleep Centre, Scotland, UK). Thank you to all of my colleagues at the Woolcock Institute of Medical Research, University of Sydney, Australia, the University of New South Wales and at the University of Glasgow, UK - especially to Dr Nathaniel Marshall, Dr Christopher Gordon, Associate Professor Brendon Yee, Dr Keith Wong, Professor Caroline Rae, Professor Stephany Biello and Dr Maria Gardani for your encouragement and support.

Above all, thank you to my fiancée Hannah and my close family for all of your love and support throughout this educational journey that has led us to Australia.

Author's Declaration

I declare that, except when explicit reference is made to the contribution of other, that this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Signature:

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List of Abbreviations

AASM	American Academy of Sleep Medicine
ACC	Anterior Cingulate Cortex
ACTH	Adrenocorticotropic Hormone
AHI	Apnea Hypopnea Index
APA	American Psychiatric Association
ASP	Aspartate
BZRA	Benzodiazepine Receptor Agonist
CBT	Cognitive Behavioural Therapy
CBT-I	Cognitive Behavioural Therapy for Insomnia
CPAP	Continuous Positive Airway Pressure
CRE	Creatine
CRH	Corticotropin-Releasing Hormone
DASS	Depression Anxiety and Stress Scale
DISS	Daytime Insomnia Symptom Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EEG	Electroencephalogram
EMA	Ecological Momentary Assessment
EMG	Electromyogram
EOG	Electrooculogram
ES	Effect Size (*d*)
ESS	Epworth Sleepiness Scale
FFS	Flinders Fatigue Scale
fMRI	functional Magnetic Resonance Imaging
FOSQ	Functional Outcomes of Sleep Questionnaire
GABA	*Gamma*-Aminobutyric acid

GLN	Glutamine
GLU	Glutamate
GPC	Glycerylphosphorylcholine
GS	Good Sleeper
GSES	Glasgow Sleep Effort Scale
GSH	Glutathione
HPA-axis	Hypothalamic-Pituitary-Adrenal-axis
HW	Hypnotic Wthdrawal
ID	Insomnia Disorder
ICSD	International Classification of Sleep Disorders
ISI	Insomnia Severity Index
ISQ	Insomnia Symptom Questionnaire
LAC	Lactate
LOCC	Left Occipital Cortex
LPFC	Left Prefrontal Cortex
MDD	Major Depressive Disorder
MEG	Magnetoencephalography
MEGA-PRESS	MEshcher–GArwood Point RESolved Spectroscopy
MINO	*myo*-inositol
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MSLT	Multiple Sleep Latency Test
N1	NREM sleep stage 1
N2	NREM sleep stage 2
N3	NREM sleep stage 3 or slow wave sleep
NAA	*N*-acetylaspartate
NOAW	Number of Awakenings
NRCT	Non-Randomized Controlled Trial

NREM	Non-Rapid Eye Movement sleep
NSRT	Nap modification Sleep Restriction Therapy
MOS-A	Medical Outcomes Study general Adherence scale
OSA	Obstructive Sleep Apnea
PC	Phosphocholine
PET	Positron Emission Tomography
PI	Primary Insomnia / Psychophysiological Insomnia
PLMS	Periodic Limb Movements of Sleep
PRESS	Point RESolved Spectroscopy
PSA	Power Spectral Analysis
PSG	Polysomnography
PTSD	Post-Traumatic Stress Disorder
PSQI	Pittsburgh Sleep Quality Index
PVT	Psychomotor Vigilance Task
RCT	Randomised Control Trial
RDC	Research Diagnostic Criteria for insomnia
REM	Rapid Eye Movement
RT	Relaxation Therapy
SC	Salivary Cortisol
SCN	Suprachiasmatic Nucleus
SCT	Stimulus Control Therapy
SD	Standard Deviation
SE	Sleep Efficiency (%)
SHE	Sleep Hygiene Education
SOL	Sleep Onset Latency
SPSS	Statistical Package for the Social Sciences
SQ	Sleep Quality
SRAS	Sleep Restriction Adherence Scale
SRT	Sleep Restriction Therapy

SSS	Stanford Sleepiness Scale
SWA	Slow Wave Activity
SWS	Slow Wave Sleep
T	Tesla
TC	Core-body Temperature
TST	Total Sleep Time
UCT	Uncontrolled Clinical Trial
VOI	Volumes of Interest
WASO	Wake-time After Sleep Onset

Presentations (Abstracts)

1. 'Profiling the side-effects of sleep restriction therapy for insomnia' Kyle, S.D, Crawford, M., Miller, C.B., Espie, C.A. World Association of Sleep Medicine & Canadian Sleep Society Congress, Quebec, Canada, September 2011, Oral.
2. 'Sleepiness and fatigue in sleep restriction therapy for chronic insomnia disorder' Miller, C. B., Kyle, S.D., Espie, C.A. Australasian Sleep Association, Sydney, Australia. October 2011, Poster.
3. 'An ecological momentary assessment of insomnia in response to brief sleep restriction therapy' Miller, C. B., Kyle, S.D., Espie, C.A. Associated Professional Sleep Societies, Boston, USA, June 2012, Poster.
4. 'Acute in-lab implementation of sleep restriction therapy for insomnia disorder: impact on objective and subjective sleep' Kyle, S.D., Miller, C.B., Salveta, C., Kane, J., Rogers, Z., Espie, C.A. Associated Professional Sleep Societies, Boston, USA, June 2012, Oral.
5. 'Sleepiness, fatigue and self-reported side-effects during sleep restriction therapy for insomnia disorder' Kyle, S.D., Crawford, M., Miller, C.B., Espie, C.A. Associated Professional Sleep Societies, Boston, USA, June 2012, Poster.
6. 'Salivary cortisol activity in response to brief sleep restriction therapy for insomnia disorder: An exploratory mechanistic study' Miller, C.B., Kyle, S.D, Marshall, N., Espie, C.A. Australasian Sleep Association, Darwin, Australia, October 2012, Oral.
7. 'An ecological momentary assessment of daytime symptoms in insomnia during brief sleep restriction therapy' Miller, C.B., Kyle, S.D, Marshall, Espie, C.A. European Sleep Research Society, Paris, France, September 2012, Oral.
8. 'Emotional blunting in psychophysiological insomnia: preliminary results from a facial expression paradigm' S.D. Kyle, L. Beattie, Miller, C.B., A. Clark, Z. Rogers, C. Espie European Sleep Research Society, Paris, France, September 2012, Poster.

9. ‘Thermoregulatory responses and sleep-onset in primary insomnia: preliminary results’ Miller, C.B., Gordon, C. J., Yee, B., Mullins, A. E., Kyle, S. D., Grunstein, R. R. Associated Professional Sleep Societies, Baltimore, USA, June 2013, Poster.
10. ‘Implementation of sleep restriction therapy for insomnia is associated with objectively-impaired vigilance’ Kyle, S.D., Crawford, M. R., Rogers, Z., Miller, C.B., MacMahon, K. M., Siriwardena, N., Espie, C. A. Associated Professional Sleep Societies, Baltimore, USA, June 2013, Oral.
11. ‘Cognitive behavioural therapy for insomnia disorder: an overview of the evidence base and state of the science’ Miller, C.B., Morin, C., Bartlett, D., Lack, L. Australasian Sleep Association, Brisbane, Australia, October 2013, Oral, Plenary speaker & co-chair.
12. ‘An Asymmetric PRESS investigation of the brain in primary Insomnia: preliminary findings’ Rae, C.L., Miller, C.B., Bartlett, D.J., Geng, J., Grunstein, R.R. Asia-Pacific NMR Symposium in Conjunction with ANZMAG, Brisbane, Australia, October 2013, Poster.

Manuscripts in Progress

1. Miller, C.B., Kyle, S.D., Marshall, N.S., & Espie C.A. (2013). Ecological momentary assessment of daytime symptoms during sleep restriction therapy for insomnia. *Journal of Sleep Research*, 22:266-72.
2. Kyle S.D., Miller C.B., Rogers Z., Siriwardena A.N., Mac Mahon K.M., Espie, C.A. (2014). Sleep restriction therapy for insomnia is associated with reduced objective total sleep time, increased daytime somnolence, and objectively impaired vigilance: implications for the clinical management of insomnia disorder. *Sleep*, 37:229-237.
3. Miller, C.B., Espie, C.A., Epstein, D.R., Friedman, L., Morin, C.M., Pigeon, W.R., Spielman, A.J., & Kyle, S.D. The evidence base and efficacy of Sleep Restriction Therapy for treating insomnia disorder. *Sleep Medicine Reviews,* accepted 03/02/2014.
4. Miller, C.B., Kyle S.D., Melehan, K.L., & Bartlett D.J. (In Press) Methodology for the assessment of sleep. In K.A. Babson & M.T. Feldner (Eds.), *Sleep and affect: Assessment, Theory, and Clinical Implications. San Diego: Elsevier Academic Press Inc.* accepted 23/04/2014.
5. Espie, C.A., Kyle, S.D., Miller, C.B., Ong, J.C., Hames, P., & Fleming, L. Attribution, cognition and psychopathology in persistent insomnia disorder: outcome and mediation analysis from a randomized placebo-controlled trial of online cognitive behavioral therapy, *Sleep Medicine*, accepted 03/03/2014.

Chapter 1: Introduction

Sleeping is no mean art: for its sake one must stay awake all day. ~ Friedrich Nietzsche

1.1 Insomnia disorder

Insomnia disorder (ID) is one of the most common health complaints with a serious socioeconomic burden to the world (Morin, Belanger, et al., 2009; Sivertsen, Lallukka, & Salo, 2011). It is also the most common sleep disorder with a prevalence of around 10% in the general population (Daley, Morin, LeBlanc, Gregoire, & Savard, 2009). Fifty percent of the population will experience symptoms of insomnia during their life and insomnia has risen over the last ten years (Pallesen, Sivertsen, Nordhus, & Bjorvatn, 2014). ID is also a complex, paradoxical and heterogeneous disorder that is difficult to define (Spielman & Glovinsky, 1991). The following sections will explore the specific diagnostic classifications of insomnia.

The two main classification systems have defined ID as both a disorder in its own right and a symptom of other conditions (see Table 1 & Table 2): the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM: APA (2000)) and the American Academy of Sleep Medicine's (AASM) International Classification of Sleep Disorders (ICSD-2, 2005). For research, specific criteria have also been developed to aid the categorisation of groups of patients with insomnia for specific research settings (Research Diagnostic Criteria: RDC; Edinger et al. (2004), see Table 3 & Table 4). Depending on the classification system employed, ID is generally difficulty with initiating sleep, maintaining sleep, early morning awakenings, or a combination of these complaints where individuals report significant daytime impairment and in the absence of any physical, mental, or substance-related cause. Co-morbid insomnia generally involves a physical, mental or substance-related complaint. Adding to the complexity of insomnia, symptoms can also change over the progression of the condition. Insomnia can exist as chronic condition or an acute experience - with time differentiating between transient or acute insomnia (1 month) and chronic insomnia (≥ than 3 months). The insomnia complaint may also be assigned to one of four specific subtypes: 1. sleep-onset insomnia (≥ than 30 minutes): where patients display increased time to initiate sleep; 2. maintenance insomnia: where the patient is unable to maintain sleep throughout the night and is forced to attempt to re-initiate the sleep process (≥ than 30 minutes). This can take

the form of repeated unsuccessful attempts to fall back to sleep during the night; 3. early morning insomnia: patients may complain of disruption to sleep by waking earlier than desired and being unable to return to sleep; 4. mixed insomnia: the patient may suffer from a combination of any of the previously mentioned complaints.

Until recently, the DSM-IV-TR (2000) distinguished between primary and secondary insomnia. Primary insomnia was defined as a complaint of initiating and/or maintaining sleep, early morning awakenings, and interrupted or non-restorative sleep. These symptoms were also accompanied by a significant impairment to daytime functioning, again with no identifiable cause beyond sleep disturbance (DSM-IV-TR, 2000). Due to this, the 4th edition of the DSM was criticised for not reflecting the complexity and heterogeneity of insomnia (Riemann, Baglioni, Feige, & Spiegelhalder, 2014). In response, the 5th edition of the DSM (APA, 2013) now attempts to simplify the diagnosis of insomnia by introducing a new overarching diagnosis of ID to include symptoms of primary and co-morbid insomnia. Thus, the DSM-V no longer refers to 'primary' and 'secondary' insomnia classification which was eliminated from the previous DSM-IV-TR (2000). This recognises the coding of insomnia where diagnostic criteria are met and treats insomnia as a disorder in its own right (APA, 2013; Espie, Kyle, Hames, Cyhlarova, & Benzeval, 2012). This change is useful when we consider conditions like depression whereby, chronic untreated insomnia is a risk factor in a bi-directional relationship between insomnia and depression (Baglioni et al., 2011; Sivertsen et al., 2012). One further change to the classification within DSM-V relates to the daytime component of insomnia. This has become more specific compared to the previous general statement of the DSM-IV of requiring a 'significant distress or impairment in social, occupational, or other important areas of functioning' (APA, 1994; pp. 557). The DSM-V now requires a more specific daytime sequel involving one of the following complaints including: fatigue, daytime sleepiness, cognitive impairment, mood disturbance, impaired work function, or impaired interpersonal functioning (APA, 2013). This is in line with recent research findings that suggest chronic ID is a 24-hour disorder impacting on daytime functioning (Espie, Kyle, Hames, et al., 2012).

DSM-V: Insomnia Disorder *(Verbatim from APA, 2013)*	**ICSD-2: General Insomnia Disorder** *(Verbatim from ICSD-2, 2005)*
A. A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms: 1. Difficulty initiating sleep. 2. Difficulty maintaining sleep, characterised by frequent awakenings or problems returning to sleep after awakenings. 3. Early-morning awakening with inability to return to sleep.	A. A complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early, or sleep that is chronically nonrestorative or poor in quality.
B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.	B. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.
C. The sleep difficulty occurs at least 3 nights per week.	C. At least one of the following forms of daytime impairment related to the night time sleep difficulty is reported by the patient: *1. Fatigue or malaise* *2. Attention, concentration or memory impairment* *3. Social or vocational dysfunction or poor school performance* *4. Mood disturbance or irritability* *5. Daytime sleepiness* *6. Motivation, energy, or initiative reduction* *7. Proneness for errors or accidents at work or while driving* *8. Tension, headaches or gastrointestinal symptoms in response to sleep loss* *9. Concerns or worries about sleep*
D. The sleep difficulty is present for at least 3 months.	
E. The sleep difficulty occurs despite adequate opportunity for sleep.	
F. The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g. narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia).	
G. The insomnia is not attributable to the physiological effects of a substance (e.g. a drug of abuse, a medication).	
H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.	

Table 1 The DSM-V and ICSD-2 classification systems

The move towards an overall ID is reflected in the categorisation of insomnia in the ICSD-2 (2005) and also in the RDC for insomnia (Edinger et al., 2004). The overall umbrella term of ID now spreads across three classification systems as a disorder in its own right and is therefore a more helpful description for both medical clinicians and researchers in relation to treatment interventions. However the varying insomnia subtypes across systems still require acknowledgement. The ICSD-2 (2005) offers both a comprehensive (see Table 1) and more specific criteria through detailed sub-categories of ID (see Table 2). Nine areas of dysfunction are described and the impairment must occur despite adequate sleep opportunity (see Table 1). When compared to the DSM-IV-TR (2000), this approach is useful as it does not exclude those with comorbid medical or psychiatric disorders compared with the previous distinction between primary/secondary insomnia (Schutte-Rodin, Broch, Buysse, Dorsey, & Sateia, 2008). This approach is also applied as part of RDC criteria (Edinger et al., 2004) and reflects the utility of the ICSD-2 approach to insomnia and specific sub-categories (see Table 3). For example, the ICSD-2 goes into greater detail specifically differentiating insomnia subtypes into those with difficulties such as paradoxical insomnia, idiopathic insomnia and classic psychophysiological insomnia or 'learned insomnia' (a chronic complaint of insufficient amount of sleep or not feeling rested after the habitual sleep episode) (see Table 2).

ICSD-2 Sleep Disorder: Insomnia Categories
(Verbatim from ICSD-2, 2005)

1. Adjustable (Acute) Insomnia
2. Behavioural Insomnia of Childhood
3. Psychophysiological Insomnia
4. Paradoxical Insomnia
5. Idiopathic Insomnia
6. Inadequate Sleep Hygiene
7. Insomnia Due to Mental Disorder
8. Insomnia Due to Medical Condition
9. Insomnia Due to Drug or Substance
10. Insomnia Not Due to Drug or Substance or Known
11. Physiological Condition, Unspecified
12. Physiological (Organic) Insomnia, Unspecified

Table 2 The International Classification of Sleep Disorders, 2nd edition (ICSD-2, 2005) specific sub categories for Insomnia Disorder.

Recently, a third edition of the ICSD has been released and is more consistent with the DSM-V approach. This edition helps to collapse the diagnosis of overall insomnia into one specific disorder. Further refinements to the ICSD criteria also include the removal of certain phenotypes of insomnia to focus on psychophysiological insomnia, paradoxical insomnia, idiopathic insomnia and inadequate sleep hygiene insomnia (ICSD-3, 2014) . This thesis used RDC to include participants with insomnia. Any comparisons made now will need to take this into account (see Table 3 & Table 4).

In using RDC classification criteria it is possible to obtain a reliable definition of insomnia and possible phenotypes within both clinical and research settings (Edinger et al., 2004). RDC criteria were developed in an attempt to bridge the previous DSM and ICSD nosologies and provide a common framework for defining insomnia for research settings. A work group was formed by the AASM leading to the development of standardised RDC for insomnia (see Table 3) and relevant subtypes (see Table 4). This criterion helps to standardise and improve the reliability of diagnosing insomnia for the selection of study participants (Edinger et al., 2004).

Research Diagnostic Criteria for Insomnia Disorder
(Verbatim from Edinger et al., 2004)

A. The individual reports one or more of the following sleep related complaints: *1.* Difficulty initiating sleep, *2*. Difficulty maintaining sleep, *3*. Waking up too early, or *4*. Sleep that is chronically nonrestorative or poor in quality.
B. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.
C. At least one of the following forms of daytime impairment related to the night time sleep difficulty is reported by the individual: *1*. Fatigue/malaise; *2*. Attention, concentration, or memory impairment; *3*. Social/vocational dysfunction or poor school performance; *4*. Mood disturbance/irritability; *5*. Daytime sleepiness; *6*. Motivation/energy/initiative reduction; *7*. Proneness for errors/accidents at work or while driving; *8*. Tension headaches, and/or GI symptoms in response to sleep loss; and *9*. Concerns or worries about sleep.

Table 3 Research diagnostic criteria for Insomnia Disorder.

Research Diagnostic Criteria for Psychophysiological Insomnia
(Verbatim from Edinger et al., 2004)

A. The individual meets the criteria for insomnia disorder.
B. The insomnia noted in A. has been present for at least one month
C. The patient has evidence of conditioned sleep difficulty and/or heightened arousal in bed as indicated by one or more of the following: *1*. Excessive focus on and heightened anxiety about sleep. *2*. An inability to fall asleep in bed at the desired bedtime or during planned naps but relative ease falling asleep during other relatively monotonous activities (e.g. watching TV, reading, etc.) when not intending to sleep. *3*. Being able to sleep better away from home than at home. *4*. Mental arousal in bed characterized either by intrusive thoughts or a perceived inability to volitionally cease sleep-preventing mental activity. *5*. Heightened somatic tension in bed reflected by a perceived inability to relax the body sufficiently to allow the onset of sleep.
D. One of the following two conditions applies: *1.* There is no current or past mental disorder. *2.* There is a current or past mental disorder, but the temporal course of the insomnia shows some independence from the temporal course of the mental disorder.
E. One of the following two conditions applies: *1.* There is no current or past sleep-disruptive medical condition. *2.* There is a current or past sleep-disruptive medical condition, but the temporal course of the insomnia shows some independence from the temporal course of the medical condition.
F. The insomnia cannot be attributed solely to another primary sleep disorder (e.g. sleep apnea, narcolepsy, or parasomnia) or to an unusual sleep/wake schedule or circadian rhythm disorder.
G. The insomnia cannot be attributed to a pattern of substance abuse or to use or withdrawal of psychoactive medications.

Table 4 Diagnostic criteria for psychophysiological insomnia.

Factors responsible for psychophysiological insomnia are: 1. a sleep-related hyperarousal response and 2. the presence of learned associations that are not compatible with sleep and maintained by perpetuating factors (behaviour, mood, thoughts & beliefs: see Figure 1). In comparison to other subtypes of insomnia, Psychophysiological insomnia is acquired and normally sleep disruption can be traced to an identifiable event (e.g. stress, divorce, grief) or precipitating factor. This is not explained by another sleep disorder or illness. In Idiopathic insomnia, no specific trigger can be identified and Idiopathic insomnia starts off at a lower level and only becomes a chronic condition when not addressed. Paradoxical insomnia is a specific sub type that is characterised by a noticeable mismatch between subjective and objective estimates of sleep duration. This subtype requires objective evidence about sleep duration in relation to subjective estimations for classification (e.g. differences between actigraphy and estimations of sleep time from sleep diaries over a number of nights). It is unknown if this finding may or may not be a unique insomnia sub type characteristic (Manber & Ong, 2010). Other categories of insomnia relate the condition to problems with sleep hygiene (poor sleep practices) including: an irregular sleep schedule, frequent daytime napping, engaging in activities at bedtime that are wake promoting (work) or consuming alcohol, nicotine or caffeine in amounts that are likely to disrupt sleep. Other subtypes relate the condition of insomnia to co-morbid sleep disorders or medical or psychiatric illnesses that prevent sleep (e.g. pain) (see Table 2 for an overview) (AASM, 2005).

1.2 Prevalence

Estimates of insomnia suggest that approximately one-third of adults report insomnia symptoms making insomnia the most prevalent sleep disorder (APA, 2013). Around 10-15% of the individuals will report daytime impairments due to poor sleep and will complain of insomnia in primary healthcare settings (APA, 2013; Ohayon & Hong, 2002). Approximately, 30% of Australians will be affected by insomnia symptoms, with 10% developing chronic insomnia (Bartlett, Marshall, Williams, & Grunstein, 2008). Similarly in the United Kingdom, the prevalence of insomnia has been found to be 37% of the general population with over two thirds of sufferers also reporting symptoms after one year (Morphy, Dunn, Lewis, Boardman, & Croft, 2007). For DSM-V criteria one recent large-scale cross-sectional study suggested a prevalence rate of 7.1% in the total population of Norway (8.6% in women, 5.5% in men) (Uhlig, Sand, Ødegård, & Hagen, 2014). Prevalence varies widely depending upon criteria employed and whether it is considered a symptom of another disorder or an independent disorder. Frequently, insomnia is documented as a comorbid condition linked to another medical or psychiatric condition. For example, around half of individuals presenting with insomnia symptoms will also present with another psychiatric disorder (APA, 2013). Insomnia is also more prevalent in females than males with a ratio of about 1.44:1 and in those with lower social economic status (Pallesen et al., 2014). However, further epidemiological research is now required in order to elucidate the prevalence and varying nature of insomnia through longitudinal population-based cohort studies. This will enable researchers to understand if insomnia can be prevented and associated morbidity reduced (Morin & Jarrin, 2013).

1.3 Costs

The overall cost to society of insomnia is significant (Leger & Bayon, 2010). One study estimated the direct treatment costs of insomnia in 1995, totalled at $1.97 billion (Walsh & Engelhardt, 1999) in the United States. Another study has suggested direct costs are approximately $1,143 greater for patients with insomnia (Ozminkowski, Wang, & Walsh, 2007). In 2010, national annual costs for insomnia in the USA have been placed within the range of $92 to $107 billion (USD) (Rosekind & Gregory, 2010). In Canada, untreated insomnia is estimated to cost $5,000 (CAN) per case (Daley, Morin, LeBlanc, Gregoire, & Savard, 2009). Overall in the United States, health care services totalled $11.96 billion making the total direct cost estimate for insomnia to be approximately $13.9 billion (Walsh & Engelhardt, 1999). Cost estimates are difficult to assess due to lack of data from different countries and the difficulty of applying findings from the limited number of studies to the rest of the world.

Other overall costs which are difficult to quantify include: work, health, quality of life, road traffic accidents, and absenteeism. In addition, untreated insomnia is also a risk factor for the development of physical problems (Vgontzas, Fernandez-Mendoza, Liao, & Bixler, 2013) and has mental health implications in a bi-directional relationship with depression (Baglioni et al., 2011; Sivertsen et al., 2012). Considered together, all these factors accentuate the complexity of estimating the total cost of insomnia. Nevertheless, the overall cost to society appears significantly high.

1.4 Pathophysiology of insomnia

The pathophysiology of insomnia is best demonstrated through a diathesis stress model commonly referred to as the '*3P*-model of insomnia'. This model aims to provide a framework for the development and maintenance of chronic insomnia through time (Buysse, Germain, Hall, Monk, & Nofzinger, 2011; Spielman & Glovinsky, 1991). Spielman and Glovinsky (1991) proposed the 3*P*-model which describes predisposing (behaviour & genetic predisposition); precipitating (significant & often traumatic life events that may act as a trigger for insomnia); and perpetuating (behaviour, mood, thoughts & beliefs) factors that may contribute to both the development and maintenance of insomnia across time. Spielman and Glovinsky (1991) suggest certain individuals may be more vulnerable to the development of insomnia, depending upon *predisposing* factors like a heritable susceptibility to stress. Prior to the onset of insomnia, sleep is not stressful but resilient and plastic to mild sleep disturbance. However, *precipitating* events can increase the likelihood of the development of insomnia in certain vulnerable or 'at-risk' individuals and families. This may set off a period of poor sleep or acute short-term (1-month) insomnia. Subsequently, insomnia can be maintained with *perpetuating* factors. These include, maladaptive behaviours (spending too much time in bed in an attempt to obtain sleep) and thoughts, attributions or beliefs about sleep (obtaining at least 8 hours of sleep or next day performance will suffer for example). Also, over the course of chronic insomnia patients may become further sensitised to sources of sleep disruption (e.g. noise, light or temperature).

Wake-promoting processes may also become conditioned at sleep initiation, preventing sleep onset, developing into psychophysiological insomnia (ICSD-2, 2005) . Attentional biases towards bedroom and sleep related stimuli have been described and are thought to provoke this conditioned response (Espie, Broomfield, MacMahon, Macphee, & Taylor, 2006). Figure 1 highlights the natural history of insomnia from conception (premorbid), development (acute/short-term) and maintenance (chronic) from the *3P*-model. Anxiety towards sleep may then form with patients

attempting to 'catch' enough sleep. If such anxiety develops, it may then also accompany increases to time in bed in an effort to control and obtain sleep (Spielman, Chien-Ming, & Glovinsky, 2010).

The *3P*-model is a useful conceptual framework for describing the development of insomnia. One limitation of this model is the underlying premise that the risk of insomnia is a stable trait across time but fails to adequately take into account within-subject variability. It is also highly likely the risk of insomnia development is a spectrum with some individuals at increased risk whilst others have a reduced risk which varies throughout the life cycle. This risk of insomnia development is not explained adequately by the current *3P*-model, which also fails to take account of circadian and homeostatic factors (Perlis, Shaw, Cano, & Espie, 2011).

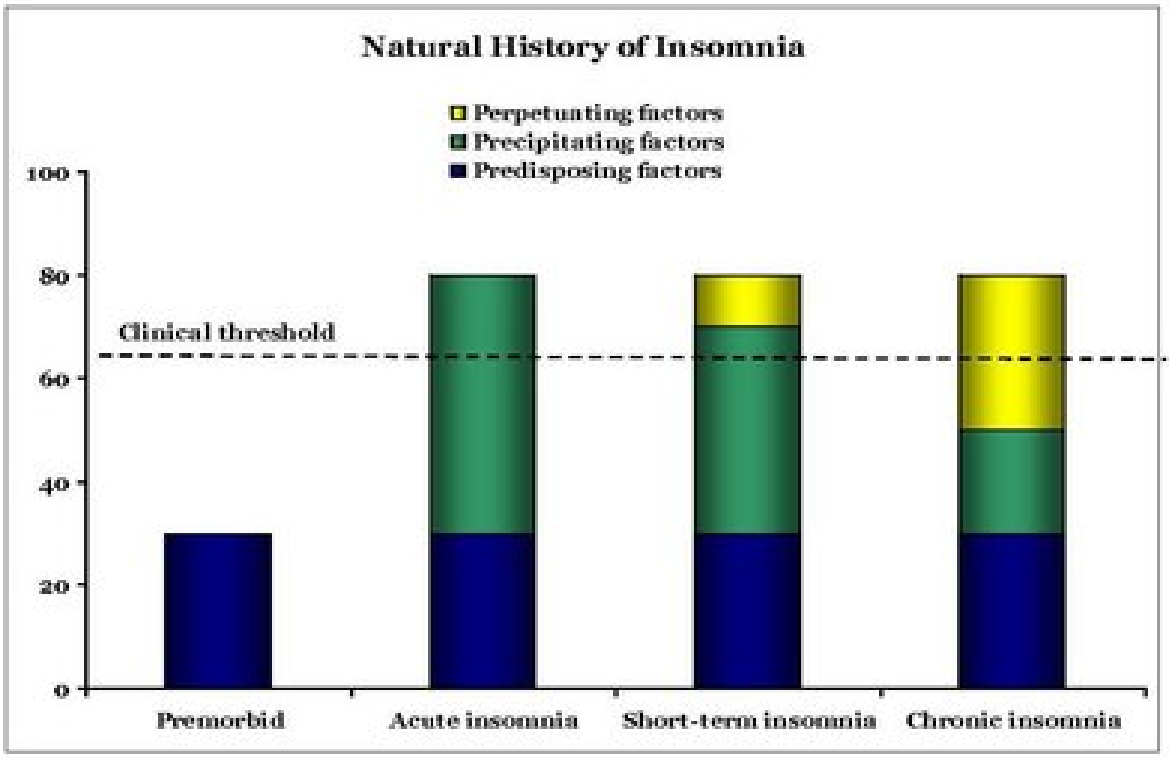


Figure 1 The natural history of insomnia. Displays the influence of the *3P*'s with predisposing (blue), precipitating (green) & perpetuating (yellow) factors in the development and maintenance of insomnia. Adapted from Spielman and Glovinsky (1991).

1.5 Models & theories of insomnia

In addition to the *3P*-model temporal development of insomnia (Spielman & Glovinsky, 1991), a number of models and theories of insomnia have been described to explain aspects in the development and maintenance of chronic insomnia. A number of the most prominent and current theories will now be discussed.

1.5.1 Stimulus control

In the development of insomnia conditioned cues normally associated with sleep (e.g. bed, bedroom, bedtime, increasing darkness etc.) become paired with wake activities or those that are not normally involved in sleep. Coping behaviours are often initiated in an attempt 'to control sleep' where the individual starts with spending more time in bed in order to catch-up on sleep. This strategy is generally counter-productive resulting in more time awake, often engaging in alerting activities and sleeping less. Stimulus control initially formulated by Bootzin (1973) describes how wake-promoting activities can be paired with the sleep environment which reinforces the insomnia symptoms. Stimulus control therapy (SCT) seeks to decondition the individual to the wakefulness of the environment (leaving the bed) and the wake promoting activities (television, radio, computers etc.) by removing these from the bedroom. SCT is one of the most widely used behavioural treatments for insomnia yet, it does not explain those who have an increased risk of developing and/or maintaining insomnia. This theory also does not take account of biological processes including the circadian rhythm or homeostatic sleep pressure. Interestingly however, it is these same factors which are positively manipulated through treatment with SCT (Perlis et al., 2011).

1.5.2 Cognitive & neurocognitive models

Cognitive models of insomnia posit that insomnia is maintained by dysfunctional cognitive processes including excessive worry, anxiety and catastrophising which negatively impact on sleep. Harvey (2002), suggests attention needs to be placed on daytime factors in insomnia which equally disrupt night time sleep, in line with anxiety literature. Both cognitive and neurocognitive models of

insomnia build on the initial behavioural perspective and recognise that insomnia is precipitated by stressful life events (Perlis, Giles, Mendelson, Bootzin, & Wyatt, 1997). Neurocognitive models argue that increased cortical arousal (measured through cerebral electroencephalographic: EEG rhythms) cause increased sensory/information processing and disrupt sleep initiation and maintenance (Perlis et al., 1997). This increased sensory/information processing appears to contribute to an attenuated mesograde amnesia of sleep in insomnia (Perlis et al., 1997; Perlis, Smith, Orff, Andrews, & Giles, 2001). Unlike other models, the main strength of the neurocognitive model is that it accepts for a developmental approach to cognitive arousal, leading to sleep inhibition. Increased arousal does not need to directly inhibit sleep, but only needs to reach an individual critical level to become wake promoting; in terms of neurocognitive processing. Once conditioned arousal has set in, it potentially perpetuates long term insomnia. However, this model neither specifically acknowledges the homeostatic drive for sleep nor the role of self-perpetuating insomnia from an initial conditioned response which are both key components in the onset of insomnia (Perlis et al., 2011).

1.5.3 Psychobiological-inhibition model & attention–intention–effort pathway

Espie (2002) critically reviewed models of insomnia suggesting a psychobiological-inhibition model where the individual begins in a normal state with regards to sleep but it is their premorbid/predisposing state that contributes to the development of psychophysiological insomnia (Espie et al., 2006). In a subsequent theoretical review, Espie extends this initial work by considering a model of an attention–intention–effort pathway in the development and maintenance of psychophysiologic insomnia (Espie et al., 2006). In this model, relatively normal and automatic processes (de-arousal and sleep engagement) are disturbed in insomnia which causes an increased focus on sleep preventing the automaticity of sleep. This focused attention or ‘sleep effort syndrome‘ (Espie, 2007) is maintained overtime and potentially becomes chronic resulting in maladaptive sleep attention, and an inability to inhibit wakefulness. The individual then embarks on a fruitless attempt to re-establish control on sleep which further contributes to the chronicity of insomnia. Such cognitive effort is measureable in attentional biases concerning bedroom and sleep

related stimuli. These biases in attention appear to set-off arousal activation when sleep is attempted and may be a target for treatment and act as a marker of treatment response (Woods, Scheepers, Ross, Espie, & Biello, 2013). Other factors of this paradigm include: dysfunctional beliefs about sleep and increased worry and rumination on the negative consequences of sleep loss characterised by a racing mind and intruding thoughts during the night (Espie et al., 2006). This attentional bias model is supported by a range of psychiatric disorders including disorders of anxiety (Dalgleish & Watts, 1990). Measures of attentional bias can also be used to objectively quantify cognitive processes used by individuals with insomnia which does not rely solely on self-report. An animal model of insomnia (described next) suggests a similar neurobiological mechanism where there is also a failure to inhibit wakefulness. However, this research remains to be replicated across differing subtypes of insomnia with objective measures of attention (Perlis et al., 2011).

1.5.4 An animal model of induced insomnia:

Sleep deprivation studies of animals have produced little insight into the function of the sleep-wake system in insomnia due to methodological problems of having to apply a continuous stressor to deprive the animal of sleep (Richardson, 2007). Often the stressor used is physical in nature, which interferes with the results of the experiment. However Cano, Mochizuki, and Saper (2008) describe a stress-induced model of insomnia in rats. A 'dirty cage exchange' procedure was used which takes advantage of psychological stressors. An animal is placed in another animal's cage and by being exposed to another animal's territory (droppings, food remnants and odour) becomes hypervigilant (safety concerns) resulting in acute difficulties in initiating and maintaining sleep (Cano et al., 2008). Sleep architecture was found to change and closely resemble the sleep characteristics that occur with human insomnia.

Initially, the cage-exchange 'stressor' induces a fight-or-flight response which is a component of the hypothalamic-pituitary-adrenal axis (HPA-axis) and autonomic nervous system activation (Cano et al., 2008; Perlis et al., 2011). After some time, homeostatic and circadian

pressure builds within the animal forcing sleep. The resulting sleep is of poor quality, is less than that of controls, hard to maintain, has decreased amounts of non-rapid eye movement (NREM) sleep, and is subjectively fragmented (Cano et al., 2008). Humans report similar sleep patterns when experiencing transient insomnia that is commonly induced by anxiety and stress (Bonnet & Webb, 1976; Cano et al., 2008). Brain circuitry was also examined by Fos expression which is a marker for neuronal activation. Increased activation was observed in the cerebral cortex, limbic system, the locus coeruleus and tuberomamillary nucleus and the autonomic system (Cano et al., 2008). Interestingly, simultaneous activation was uncovered in the ventrolateral preoptic area and the median preoptic nucleus. This co-activation is different from that observed during either normal sleep or wake and was associated with high frequency EEG activity (Cano et al., 2008; Perlis et al., 2011). Activation was also found to be modified with brain lesions or pharmacological interventions. The work by Cano et al. (2008), is a possible useful model of sleep disruption but future research is needed to further explore how this can be utilised in relation to the pathophysiology and treatment of insomnia in humans.

1.5.5 Psychobiological approaches to insomnia

Three main biological factors involved in the sleep-wake process are thought to underlie the occurrence and causation of chronic insomnia: hyperarousal, circadian dysrhythmia, and homeostatic dysregulation (Pigeon & Perlis, 2006). Homeostatic dysregulation has been postulated as a possible factor which underlies insomnia (Pigeon & Perlis, 2006). There is some evidence to support this perspective including the premise that slow wave sleep (SWS) may be deficient in insomnia compared to good sleeping controls (Baglioni et al., 2014). Suggesting, a reduction of EEG defined SWS due to an under primed sleep homeostat. However, this may also be due to irregular timing of sleep and a reduction in sleep pressure associated with increased time spent in bed attempting sleep and stress (Edinger & Means, 2005).

The hyperarousal concept suggests that those who focus their cognitive attention on their insomnia may develop conditioned arousal that inhibits sleep. This hypothesis posits that maladaptive behavioural and neurobiological processes lead to a state of conditioned autonomic arousal through learned associations (Bonnet & Arand, 1996; Hauri, 1983; Kales, Caldwell, Soldatos, Bixler, & Kales, 1983; Mendelson, James, Garnett, Sack, & Rosenthal, 1986; Merica, Blois, & Gaillard, 1998; Perlis et al., 1997; Riemann et al., 2010). These physiological phenomena expressed by autonomic activation are what appear to define 'psychophysiological insomnia' (Riemann et al., 2010). A number of physiological markers have been profiled between healthy good sleepers and those with insomnia including; cardiac, hormone (elevated cortisol levels), body temperature, metabolic measures and spectral EEG measures (Bonnet & Arand, 2010; Riemann et al., 2010; Roth, Roehrs, & Pies, 2007). Hyperarousal can generally be assumed to increase over the full 24 hour period in those with insomnia compared to controls. However, there may be more vulnerable times when these differences are more pronounced with hypersecretion of hormones including cortisol, before sleep and during the early night in insomnia (Vgontzas et al., 2001).

However, one of the biggest challenges for the hyperarousal hypothesis is specifying when the onset of hyperarousal takes place in the development of insomnia. Hyperarousal may exist prior to the development of insomnia, or it may develop as a result of a precipitating or perpetuating factors – in line with the pathophysiology of insomnia described through the *3P*-model. Speculatively, this pre-disposition to insomnia may take the form of the heritable serotonin short allele (5-HTTLPR) and requires a stressful environmental interaction (provided by a physical or psychological stressor) in order to create an epigenetic effect (Harvey, Gehrman, & Espie, 2014; Palagini, Biber, & Riemann, 2014). This initial vulnerability may produce acute sleep disruption that is maintained long-term through cognitive and inhibitory factors (see Figure 2). This overall interaction potentially may cause hyperarousal and insomnia at any point in time: either prior to, or as a result of the stressor, during the acute period or even after a number of months. Chronic changes to the sleep-wake and brain systems may adapt to such stress resulting in insomnia even after the initial

stressor has remitted (Meerlo, Sgoifo, & Suchecki, 2008). Well-designed long-term follow-up studies are needed to investigate when and what changes actually take place as insomnia develops. Only recently, have studies attempted to define changes in the development of acute to chronic insomnia. For example, Ellis, Perlis, Bastien, Gardani, and Espie (2014) recently attempted to evaluate this transition and found that differences in sleep architecture including slow wave sleep (SWS) and rapid eye movement (REM) sleep latency at baseline was able to differentiate between those who remitted and those who went on to develop chronic insomnia. Those who did not remit were found to be more depressed and this was thought to perhaps precede the development of depression (Ellis et al., 2014). A second important question is to explore the impact of successful insomnia treatments like cognitive behavioural therapy for insomnia (CBT-I) or pharmacotherapy and evaluate whether effective therapy specifically alters physiological hyperarousal.

Circadian dysrhythmia has also been suggested as a factor in the development and maintenance of chronic insomnia (Pigeon & Perlis, 2006). It is likely the combination of irregular sleep-wake schedules and increased time in bed (both behaviours used to achieve more sleep) disrupt the circadian rhythm. Spending excessive amounts of time in bed is the predominant perpetuating factor that prevents the individual from re-establishing normal sleep (Buysse, Germain, Moul, et al., 2011; Spielman et al., 2010; Spielman, Saskin, & Thorpy, 1987). Consistent rising times and amount of time spent in bed are predictive of better treatment outcomes (Riedel & Lichstein, 2001). Stability to the circadian cycle for both sleep and wakefulness is important to initiate and maintain successful sleep (Riedel & Lichstein, 2001). Further during constant 24-hour routine conditions in individuals with insomnia, increased performance difficulties were found on objective measures of vigilance and working memory and increased fatigue, sleepiness and mood disturbance were also reported in individuals with insomnia compared to healthy controls (Varkevisser & Kerkhof, 2005). Differing circadian periods have also been profiled in specific subtypes of insomnia. For those with early morning awakenings, core body temperature (a reliable marker of the human endogenous

circadian period) is advanced (Lack & Wright, 1993). A phase delay in core body temperature has also been profiled in those with sleep initiation insomnia (Pigeon & Perlis, 2006).

Linking these three main biological processes together (sleep homeostasis, the circadian period and hyperarousal) creates a picture of the potential disruptions to the sleep-wake system that may all or in part contribute to the development of insomnia (Roth, 2007a). Figure 2 can be used to highlight and explore the potential interactions between the circadian and homeostatic processes with the previously mentioned cognitive and behavioural factors that may all interact to produce insomnia.

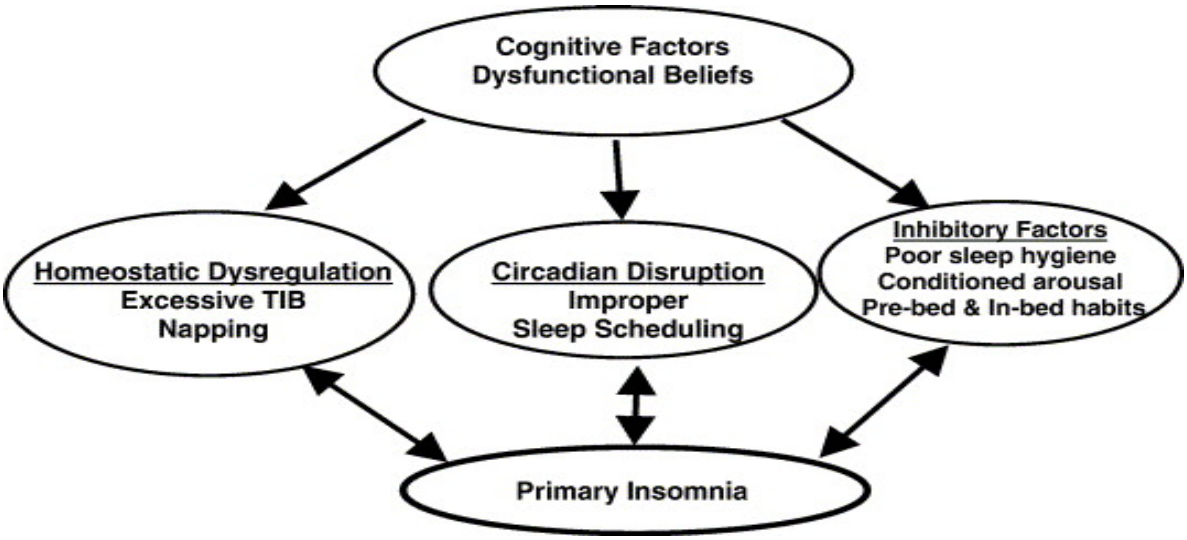


Figure 2 Interacting model of insomnia Highlights the potential interaction of sleep-disruptive pre-bed habits with biological sleep-wake processes (circadian and homeostatic) contributing to insomnia symptoms. Taken from Edinger and Means (2005).

1.5.6 Hyperarousal as a conditioned stress response in insomnia

Corticotropin-releasing hormone (CRH) is a peptide hormone and neurotramsmitter involved in the human stress response. CRH is produced within the hypothalamus and is carried to the pituitary gland (as part of the HPA-axis), stimulating adrenocorticotropic hormone (ACTH) (Lehnert, Schulz, & Dieterich, 1998). In turn, ACTH stimulates the synthesis of cortisol through the adrenal gland which causes stress related metabolic effects on the body (Hiller-Sturmhofel & Bartke, 1998). Cortisol is believed to possess anti-inflammatory properties by feeding back (at times) and inhibiting further ACTH and CRH secretion by acting on the hypothalamus and pituitary gland (see Figure 3) (Hueston & Deak, 2014). Richardson and Roth (2001) proposed a theory whereby increased activation of CRH appears to be involved in insomnia as higher levels of CRH may contribute to overall hyperarousal in insomnia with CRH thought to be involved in the regulation of spontaneous waking during sleep (Chang & Opp, 2001). Previous research reported a reduction in hypercortisolemia and HPA-axis activation with treatment in those with depression (Richardson & Roth, 2001; Roth, 2007b). Unfortunately this model has received little attention in the insomnia literature, regarding treatment of the HPA-axis and hypercortisolemia with either antiglucocorticoid agents or behaviour treatments for insomnia (Roth, 2007c).

Recently, increased measures of CRH and cortisol concentrations have been found in insomnia compared to healthy controls in one study that measured this in the morning (Xia, Chen, Li, Jiang, & Shen, 2013). The authors suggest that increased levels of CRH may indicate an objective blood test for insomnia although further measurement of CRH at different time points is required (Xia et al., 2013). In addition it is also unknown if CRH levels respond to treatment in insomnia (Roth et al., 2007). Of considerable interest is the abnormal CRH regulation which has been identified in the pathogenesis of depression (Liu et al., 2004; Roth, 2001). CRH regulation may also share a common pathophysiology with insomnia due the common overlap with depression and insomnia (Baglioni et al., 2011). Indeed, markers of HPA-axis hyperactivity like plasma cortisol concentrations have been known to normalise after successful therapy for depression (Arborelius, Owens, Plotsky,

& Nemeroff, 1999; Nemeroff, Bissette, Akil, & Fink, 1991). CRH and cortisol may be highly linked as they share a common pathway through the HPA-axis. Further research is required to substantiate if markers of HPA-activation and overall hyperarousal such as cortisol concentrations can be reduced through treatment for insomnia. Treatment for insomnia will be explored in the next section.

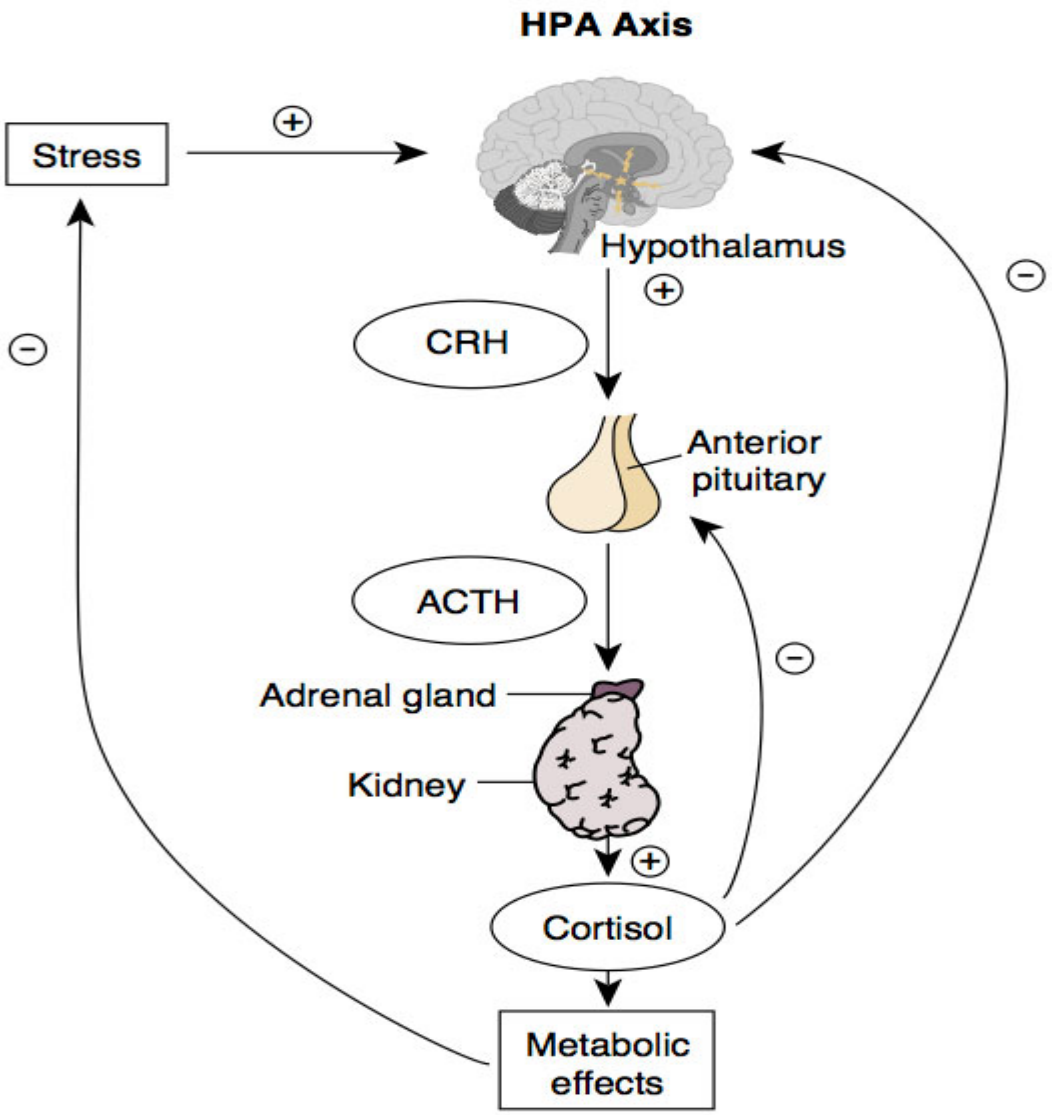


Figure 3 Regulation of the hypothalamic-pituitary-adrenal axis (HPA). ACTH: adrenocorticotropic hormone; CRH: corticotropin-releasing hormone; (+) stimulates; (-) inhibits. Taken from Hiller-Sturmhofel and Bartke (1998).

1.6 Treatment for insomnia disorder

There are a range of approaches available to treat insomnia. Most of the evidence-based treatment and management for insomnia can be distilled into two mainstay modalities: 1. pharmacotherapy or 2. CBT-I (Krystal, 2007). Newer 'third-wave' treatment approaches including Mindfulness and Acceptance-commitment therapy also appear to have benefits (Ong, Ulmer, & Manber, 2012) and can be combined with CBT-I. Prior to seeking treatment directly from a health care professional (many with insomnia do not seek treatment), individuals often report attempting alcohol, 'over the counter' (e.g. antihistamines) medications, or herbal/dietary interventions to alleviate symptoms (Morin, Bootzin, et al., 2006). In primary care settings, insomnia is predominately treated with prescription medications (e.g. benzodiazepines) despite a lack of evidence for long term effectiveness (more than 4 weeks) (Riemann & Perlis, 2009). Although in the short-term (first 4 weeks) pharmacotherapy is as clinically effective as CBT-I (Smith, Perlis, Park, et al., 2002). The main non-pharmacological treatment for insomnia is CBT-I, which is an evidence based intervention, usually delivered by a psychologist individually, in small groups, or through automated web-based programs (Espie, Hames, & McKinstry, 2013).

1.6.1 Cognitive behavioural therapy for insomnia

Cognitive behavioural therapy for insomnia (CBT-I) is a multi-component approach that seeks to manage insomnia by targeting maladaptive thoughts, behaviours and beliefs about sleep (Edinger & Means, 2005) (see Figure 2). CBT-I is a multiple component approach which aims to normalise sleep wake behaviour and when standardised appears to be efficacious for 70% of insomnia sufferers (Morin, Bootzin, et al., 2006). It has proven effectiveness in clinical trials over the last three decades (Espie, Kyle, Williams, et al., 2012; Morin & Benca, 2012; Morin et al., 1999; Morin, Vallieres, et al., 2009) and has lasting treatment effects over pharmacotherapy (Riemann & Perlis, 2009; Smith, Perlis, Park, et al., 2002). Therefore, CBT-I is considered the first line treatment for insomnia by the AASM (Morin, Bootzin, et al., 2006), the National Institutes of Health ("National Institutes of Health State-of-the-Science Conference Statement on manifestations and management

of chronic insomnia in adults," 2005) and by the British Association of Psychopharmacology (Wilson et al., 2010). The overall approach consists of five main treatment modalities including: cognitive therapy, relaxation therapies, SCT, sleep restriction therapy (SRT), and sleep hygiene education (Morin, Bootzin, et al., 2006; Morin et al., 1999). The following list is a description of the five main components that commonly combine to form overall CBT-I (adapted from Morin, Bootzin, et al. (2006)):

1. Cognitive therapy: A psychotherapeutic approach that looks to modify and dysfunctional thoughts, beliefs, attributions, expectations and cognitions regarding sleep and resulting daytime functioning. This also normally includes altering excessive worry and self-monitoring to improve cognition regarding the sleep-wake process.
2. Relaxation therapies: use of imagery rehearsal therapy and progressive muscle relaxation techniques in order to reduce the awareness of unwanted thoughts or worries when attempting to initiate sleep.
3. Stimulus control therapy: a set of behavioural instructions aimed at associating the bedroom environment cues with sleep and facilitating faster sleep onset.
4. Sleep restriction therapy: a curtailment of time in bed in order to match the total sleep need of individuals. Mild sleep deprivation may reduce in bed wakefulness by facilitating efficient sleep.
5. Sleep hygiene education: a set of information regarding lifestyle habits (alcohol, diet, exercise, caffeine, tobacco, drug use) and environmental factors (light, temperature, noise) that may be altered to improve sleep.

1.6.2 Sleep restriction therapy for insomnia

SRT is a primary component within CBT-I and uses mild sleep deprivation and correct sleep timing opportunities to address the excessive time spent in bed, along with worry and anxiety about 'getting to sleep' which is common in insomnia individuals (Spielman et al., 2010). Spielman et al. (1987) first utilised SRT in a sample of 35 patients with chronic insomnia to help reduce excessive time spent in bed. At the end of the eight week intervention compared to baseline, there was a significant improvement on the following self-report sleep diary variables including: total sleep time (TST), sleep onset latency (SOL), wake-time after sleep onset (WASO), and sleep efficiency (SE). Subjective perception of their insomnia disorder had also changed (measured by improvements in the Insomnia symptom questionnaire) and these improvements in sleep remained constant at nine months for the 23 subjects in the follow up assessment. SRT requires an in-depth examination as it may be one of the most potent components of CBT-I however studies into the mechanisms of action for SRT are limited (Miller et al., 2014). It should be noted that SRT is different compared to experimental sleep loss where participants are exposed to sleep deprivation conditions. Sleep loss experiments ask participants to reduce time in bed (TIB) along with parameters of specific studies (e.g. 4 hours in bed to assess neurocognitive performance). In sleep restriction therapy, TIB is restricted in order to match self-reported (perceived) sleep duration and this aims to improve the overall quality of their sleep.

SRT is normally implemented by prescribing a maximum amount of time allowed in bed initially by matching this to the participants self-reported average TST (from a one or two week sleep diary). If a participant reports sleeping for five hours on average (most report low amounts of TST prior to therapy of about 5-6 hours), then the maximum TIB would equal this for one week until subsequent titration with a therapist. Patients are not prescribed a TIB (sleep window) of less than five hours due to the negative consequences that can be associated with extreme sleepiness. However, the minimum TIB can vary and there is currently no open consensus yet. More vulnerable patients with co-morbid medical or psychiatric disorders are recommended not to have a sleep

window less than six hours (Spielman et al., 2010). After the total amount of 'allowed' TIB has been arranged, a standard rising time is then set in the morning for the individual for each day of the week (including weekends). The rising time is settled on and assigned in concordance with the daily obligations of the individual along with their circadian preference for rising early or later in the morning. The therapist will then work backwards around the clock to prescribe the new threshold bedtime. Individuals are told that they may only go to bed after the threshold time has been reached and when they are sleepy. If a patient reports a baseline average TST of five hours then a 06:00 rising time would result in a bedtime of 01:00. Naps or lying down are generally not permitted until the opportunity to sleep (except where mentioned in modified SRT). This new sleep-wake schedule must be maintained and adhered to everyday of the week until the next weekly meeting with the therapist where TIB is re-examined.

A sleep diary is kept throughout the intervention period and is used to examine changes in the sleep-wake pattern. Subjective self-report diary data is used to calculate the previous week's average SE. This is calculated during each week of treatment by using aspects of the sleep diary (TST / TIB multiplied by 100). Generally, the sleep window is modified in 15 minute increments over the weeks of the therapy with improved and consolidated sleep (higher SE) (Spielman et al., 2010). Changes in the sleep-wake schedule within SRT works on the following criteria: (a) when the mean %SE is more than or equal to 90%, then the time in bed can be increased by fifteen minutes; by either setting the retiring time earlier or rising time slightly later; (b) Time in bed is decreased when the mean SE is less than 85%; (c) If the mean SE is less than 90% and more than or equal to 85, then the time in bed is not altered (Spielman et al., 2010).

SRT produces improvements in both sleep and daytime functioning in those with insomnia (Kyle, Morgan, Spiegelhalder, & Espie, 2011). However, in 2006 the AASM did not find sufficient evidence to categorise SRT as a standard treatment intervention (Morin, Bootzin, et al., 2006). This is thought to be due to a neglect of examining SRT and is perhaps explained by researchers and

clinicians, willing to see an improvement insomnia symptoms by employing all components of CBT-I. Further, only a small number of studies have evaluated single component SRT without any further CBT-I components. The efficacy and evidence for SRT is explored in a systematic review and subsequent meta-analysis in Chapter 3 (Miller et al., 2014). Miller et al. (2014) suggest that therapy was effective for self-report sleep diary outcomes including: SOL, WASO, overall ratings of sleep quality and also TST. However, the true clinical effectiveness of SRT is yet to be examined thoroughly in adequate clinical-controlled trials and further research is required to ascertain the mechanisms of action.

SRT is thought to work by aligning circadian drives for sleep and wakefulness and by utilising mild sleep deprivation to help facilitate sleep but may be associated with difficulties with adherence (Miller et al., 2014). However, SRT does have a number of benefits: Firstly, it has a strong behavioural focus and can avoid some of the perceived stigma associated with other cognitive psychological interventions (Buysse, Germain, Moul, et al., 2011; Troxel, Germain, & Buysse, 2012) perhaps regarding the effectiveness of so-called 'talking therapies'. Further, the theory behind SRT is strongly linked to the two-process physiological model of sleep regulation by taking account of both circadian and homeostatic factors of sleep (Borbély & Achermann, 1999) and can be used as a means of prescribing/describing the intervention to a patient. It is also simple and easy to follow once prescribed. As a result, SRT can easily be prescribed in a stepped care approach to psychological services or in primary care settings (Espie, 2009). However, distinct problems exist with this treatment option: 1. there is a lack of robust evidence regarding the effectiveness/efficacy of this intervention on objective markers of sleep and insomnia severity; 2. side effects, adherence and compliance with this intervention have never been thoroughly examined and investigated as part of treatment response; 3. this procedure is believed to have a lasting impact on improvement of sleep variables yet the mechanisms of action are not fully understood; 4. issues regarding the titration and delivery of the therapy remain as most studies using SRT do not use standardised procedures as set out initially (Spielman et al., 1987); 5. with regards to impact of the intervention, it is unknown

whether or not certain types of insomnia disorders and/or individuals fair better or worse during therapy. Therefore, the main aim of this thesis is to begin to unravel these pivotal questions regarding SRT for treatment of insomnia by evaluating therapeutic changes due to SRT.

Chapter 2: The evidence base of sleep restriction therapy for treating insomnia disorder

The contents of this chapter have been accepted for publication as follows:

'The evidence base of sleep restriction therapy for treating insomnia disorder', Christopher B. Miller, Colin A. Espie, Danna R. Epstein, Leah Friedman, Charles M. Morin, Wilfred R. Pigeon, Arthur J. Spielman & Simon D. Kyle, *Sleep Med Rev, accepted* 03/02/2014.

2.1 Abstract

Sleep restriction therapy is routinely used within cognitive behavioural therapy to treat chronic insomnia. However, the efficacy for sleep restriction therapy as a standalone intervention has yet to be comprehensively reviewed. This review evaluates the evidence for the use of sleep restriction therapy in the treatment of chronic insomnia. The literature was searched using web-based databases, finding 1,344 studies. Twenty-one were accessed in full (1,323 were deemed irrelevant to this review). Nine were considered relevant and evaluated in relation to study design using a standardised study checklist and levels of evidence. Four trials met adequate methodological strength to examine the efficacy of therapy for chronic insomnia. Weighted effect sizes for self-reported sleep diary measures of sleep onset latency, wake time after sleep onset, and sleep efficiency were moderate-to-large after therapy. Total sleep time indicated a small improvement. Standalone sleep restriction therapy is efficacious for the treatment of chronic insomnia for sleep diary continuity variables. Studies are insufficient to evaluate the full impact on objective sleep variables. Measures of daytime functioning in response to therapy are lacking. Variability in the sleep restriction therapy implementation methods precludes any strong conclusions regarding the true impact of therapy. A future research agenda is outlined.

2.2 Introduction

Sleep restriction therapy (SRT) is a behavioural intervention that is used to treat chronic insomnia (Morin, Bootzin, et al., 2006; Spielman et al., 1987), either as single component therapy, or as part of cognitive behavioural therapy for insomnia (CBT-I) (Buysse, Germain, Moul, et al., 2011; Edinger, Wohlgemuth, Krystal, & Rice, 2005). Anecdotally, SRT is believed to be one of the most active elements of CBT-I. Indeed, Spielman et al. (2010) emphasise the importance of SRT in an overview of 12 CBT-I trials, where all trials incorporated SRT procedures. However, the first American Academy of Sleep Medicine (AASM) practice parameters for the nonpharmacologic treatment of chronic insomnia considered SRT to be an optional patient-care strategy whereby, "patient improvement was unclear due to combination therapy" (pp. 1,131) (Chesson Jr et al., 1999). The most recent update of the AASM practice parameters suggest that SRT should be considered a "guideline" intervention due to the addition of two randomised controlled trials (Morgenthaler et al., 2006). This is one step below that of a "standard" intervention such as stimulus control therapy (SCT), (Morgenthaler et al., 2006; Morin, Bootzin, et al., 2006) as assessed through study design levels of evidence adapted from Sackett criteria (Sackett, 1989). Nevertheless, the review group and the AASM committee did conclude that "sleep restriction is effective and a recommended therapy in the treatment of chronic insomnia" (pp. 1,417) (Morgenthaler et al., 2006).

Since the publication of the guidelines in 2006, behavioural interventions have shown further promise in controlled studies (Buysse, Germain, Moul, et al., 2011; Harris, Lack, Kemp, Wright, & Bootzin, 2012). Recently, and salient to this review, Epstein, Sidani, Bootzin, and Belyea (2012) conducted a dismantling study to compare multi component therapy (consisting of SRT and SCT with no structured cognitive therapy component), SRT, and SCT, to a waitlist control group. This study found SRT to be as effective as SCT and multi component therapy; suggesting SRT is a powerful standalone intervention. Earlier work also demonstrated that patient adherence to, and preference for SRT is more strongly associated with treatment outcome than other CBT-I components (Harvey, Inglis, & Espie, 2002; Vincent & Lionberg, 2001). As a field, Behavioural Sleep Medicine has

encouraged broad dissemination of brief behavioural therapies (Morin & Benca, 2012; Neylan, 2011; Troxel et al., 2012), potentially as a "low-intensity" intervention within affordable stepped-care health-frameworks (Espie, 2009; Espie et al., 2013; Espie, Kyle, Williams, et al., 2012; Vitiello, McCurry, & Rybarczyk, 2013).

The aim of this review is to evaluate the evidence for the use of SRT in the treatment of chronic insomnia. It should be noted that we are referring in this review only to the therapeutic use of sleep restriction. We acknowledge that the term "sleep restriction" is more widely used in sleep science; usually in studies where healthy participants are experimentally exposed to a predefined (restricted) period of time in bed, to investigate the effects of sleep loss upon cognitive and physiological functioning (Dinges et al., 1997; Van Dongen, Maislin, Mullington, & Dinges, 2003). Although not the focus of this review, closer reference to this experimental approach may be useful to aid understanding of both the acute effects and the therapeutic use of SRT for people with insomnia. Specifically, therapeutic SRT involves implementing a new prescribed sleep window (amount of total time allowed in bed) that initially matches the average total sleep time (from a one or two week sleep diary). Normally, for safety reasons, a minimum time in bed of no less than 4-5 hours is used to protect against excessive daytime sleepiness. The sleep window is then titrated on a weekly basis through the use of average sleep efficiency scores from a weekly sleep dairy (see Table 5 for an example of the treatment guidelines) (Spielman et al., 2010). This is opposite to sleep compression therapy which uses a progressive and systematic reduction of time in bed to closely match sleep time/sleep need.

Our aim was to evaluate the evidence for the use of SRT in the treatment of insomnia. To achieve this aim, a systematic review of the literature was implemented. Suitable studies were then evaluated against a standardised quality assessment criteria (Kmet, Lee, & S., 2004) and levels of evidence as per Sackett criteria (Sackett, 1989). Only studies that utilised SRT as a standalone intervention strategy for chronic insomnia, in accordance with SRT clinical guidelines (Schutte-Rodin et al., 2008) were included. Based on the evidence from the review, we conclude with a section regarding future directions to advance our understanding of SRT.

2.3 Methods

Criteria for inclusion of research articles

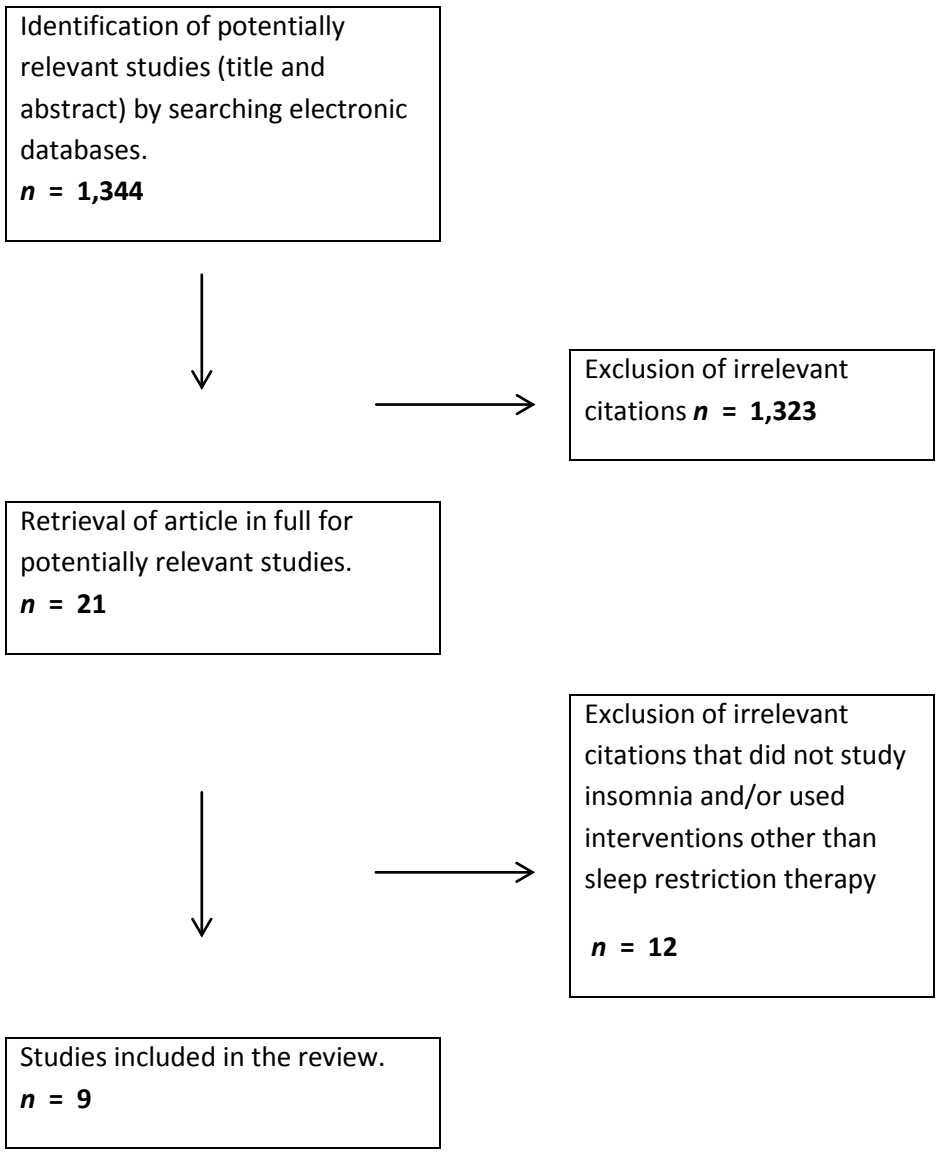
This review aimed to include studies that were similar to the treatment delivery approach first described by Spielman et al. (1987). This involves using the average total sleep time (from a one or two week sleep diary) to implement a new prescribed sleep window with the patient. More recently, a minimum time in bed of no less than 4-5 hours is used to protect against excessive daytime sleepiness (Edinger & Means, 2005; Edinger, Wohlgemuth, Radtke, Marsh, & Quillian, 2001; Spielman et al., 2010). The sleep window is then titrated on a weekly basis through the use of average sleep efficiency scores from a weekly sleep dairy (see Table 5).

Sleep efficiency scores (SE)		
SE < 85%	SE ≥ 85% or < 90%	SE ≥ 90%
Decrease TIB by 15 minutes	No Change	Increase TIB by 15 minutes

Table 5 Titration guidelines for sleep restriction therapy. Displays the recommended titration guidelines for sleep restriction therapy from Spielman et al. (1987). SE: sleep efficiency = (average total sleep time ÷ average time in bed from sleep diary) x 100; TIB: time in bed.

Online databases WEB OF KNOWLEDGE, PubMed, and SCOPUS were searched from 1986, one year before the publication of the SRT guidelines by Spielman et al. (1987), until the end of October 2012. The search was re-run in August 2013 to take account of subsequent studies available online. The review used a subject and text word strategy with “insomnia” and “sleep restriction” or “sleep compression” (which is a systematic reduction of time spent in bed to closely match total sleep time/sleep need) as the primary search terms. Sleep compression therapy was included so that we would not miss any potentially relevant studies that may have applied a form of SRT. If the titles were appropriate and included any of the following terms: “insomnia”, “behaviour/behavior”, “treatment” the online article was accessed and the abstract reviewed. Only full text articles were included and any published conference abstracts were omitted. If the abstracts were deemed suitable (for example, described a standalone intervention involving the curtailment of time in bed for the treatment of chronic insomnia), a full copy of the article was acquired and assessed for inclusion in this review (see Figure 4). Studies were then considered for inclusion if they: (a) implemented a standalone form of sleep restriction therapy; (b) examined response to sleep-wake outcome variables in a systematic manner (including uncontrolled clinical trials and case studies); (c) included adult populations (≥18 years old); (d) were published in the English language. Reviews, duplicates and studies that implemented sleep compression therapy or SRT as a treatment package (CBT-I), were excluded (see Figure 4). The reference sections of all retrieved articles were also searched to further identify suitable studies for inclusion.

Figure 4 Flowchart showing the process of selecting studies included in the review



Standardised quality assessment criteria (Kmet et al., 2004) (see Table 6) were applied to provide structure to the review process. The quality of a study is defined in terms of the extent that design, conduct, and analyses minimised errors and biases for both randomised controlled trials (RCT) and controlled trials. This yields a global score for each study, and so enabling comparisons to be made across trials. Thus, the overall quality score enables a consistent assessment of evidence and quality of available medical research studies (Kmet et al., 2004). This approach normally involves appraisal of 14 items (study; objective, design, method, subjects, intervention, blinding investigator and subject, outcome, sample size, analytic methods, variance, confounds, description and conclusion), on a three-point rating scale (yes = 2, partially = 1, and no = 0). However, one item (relating to blinding of the investigators to treatment) was removed as this was not applicable to the present review (see Table 6). The items are consistent with the recommendations from the Centre for Reviews and Dissemination for systematic reviews (Akers, Aguiar-Ibáñez, Baba-Akbari Sari, Beynon, & Booth, 2009) and in line with the previous study assessment approach by the AASM (Morin, Bootzin, et al., 2006). Item scores are summed and a percentage is given to each study (see Table 7). For each study, we report this overall score to gauge study quality (Kmet et al., 2004), the study design and evidence level (using the Sackett system (Sackett, 1989) as per the previous AASM practice parameters) (Chesson Jr et al., 1999; Morgenthaler et al., 2006; Morin, Bootzin, et al., 2006; Morin et al., 1999). The Sackett system (Sackett, 1989) grades evidence levels through the following criteria: randomised well designed trials with low alpha and beta error (grade I), randomised trials with high alpha and beta error (grade II), non-randomised concurrently controlled studies (grade III), non-randomised historically controlled studies (grade IV), case series (grade V). Single case studies were not assigned any evidence level. Only studies that met grade III evidence or above were examined further for SRT outcome data. This is considered the minimum level of evidence for the AASM to recommend psychological treatments for insomnia as either a “standard” or “guideline patient care option”. (Chesson Jr et al., 1999; Eddy, 1992; Morgenthaler et al., 2006).

Question	Criteria	Yes (2)	Partial (1)	No (0)	N/A
1	Question / objective sufficiently described?				
2	Study design evident and appropriate?				
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?				
4	Subject (and comparison group, if applicable) characteristics sufficiently described?				
5	If interventional and random allocation was possible, was it described?				
6	If interventional and blinding of investigators was possible, was it reported?				
7	If interventional and blinding of subjects was possible, was it reported?				
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? means of assessment reported?				
9	Sample size appropriate?				
10	Analytic methods described/justified and appropriate?				
11	Some estimate of variance is reported for the main results?				
12	Controlled for confounding?				
13	Results reported in sufficient detail?				
14	Conclusions supported by the results?				

Table 6 Checklist for assessing the quality of quantitative studies from (Kmet et al., 2004). Question number 6 was omitted from this review process as it was considered not applicable to this review process

The primary outcome data are based on sleep diary continuity variables: sleep onset latency (SOL), wake-time after sleep onset (WASO), sleep efficiency (SE: total sleep time ÷ time in bed × 100). Secondary variables reported include: total sleep time (TST), number of awakenings (NOAW), total time in bed (TIB), and subjective ratings of sleep quality (SQ) (see Table 8). This approach has been used previously to provide a common mode of assessment for different insomnia interventions (Riemann & Perlis, 2009). The primary outcome variables of the surviving studies were then analysed through the use of effect size (ES) scores. Effect size uses standard deviation units to provide a measure of change; these are defined as small (0.2), medium (0.5) and large (>0.8) (Cohen, 1988). The overall weighted effect size was calculated by the formula ($\sum[di*N]/\sum[N]$), where *di* is the effect size of the individual study (Smith, Perlis, Park, et al., 2002). The effect sizes were weighted to account for individual sample sizes. This methodology has been used to evaluate response to insomnia treatments (Riemann & Perlis, 2009; Smith, Perlis, Park, et al., 2002).

Table 7 Description of studies included in the review of sleep restriction therapy for insomnia . Displays an overview of each study included in the review process. CS: case study; ESS: Epworth sleepiness scale; GSES: Glasgow sleep effort scale; HW: hypnotic withdrawal; ISI: insomnia severity index; ISQ: insomnia symptom questionnaire; MSLT: multiple sleep latency test; NOAW: number of awakenings; non-randomised control trial; NRST: nap modification sleep restriction therapy; PSG: polysomnography; PSQI: Pittsburgh sleep quality index; PVT: psychomotor vigilance task; RCT: randomised control trial; RT: relaxation therapy; SE: sleep efficency; SHE: sleep hygiene education; SOL: sleep onset latency; SSS: Stanford sleepiness scale; SQ: sleep quality; SRT: sleep restriction therapy; TST: total sleep time; UCT: uncontrolled trial; WASO: wake time after sleep onset. * Only the sleep restriction therapy group was included in the meta analysis section of this review for this study.

Author(s) (year)	Design and level of evidence	Treatment type	Enrolled participants	Sleep outcome(s)	Summary of findings at post-treatment	Summary of findings at follow-up	Assessment quality score (%)
Bliwise, Friedman, Nekich, and Yesavage (1995) USA	**NRCT; III**	SRT vs. relaxation therapy	32 elderly adults (mean age = 68.7) with primary insomnia	Sleep diary data	SOL ↓ for SRT & RT ($p < .01$). No significant Δ in TST.	3mths: SOL maintained and TST ↑ ($p < .001$).	19 out of 26 (73.1%)
Epstein et al. (2012) USA	**RCT; I**	SRT vs. SCT vs. multi-component behavioral intervention vs. wait-list control	179 older adults (mean age = 68.9) with primary insomnia	Sleep diary data, actigraphy and the ISI.	Sleep diary compared to waitlist controls: SOL↓, WASO↓, TST↑, SE ↑, SQ↑ (all $p < .01$). Actigraphy: TST no Δ, SOL ↓, WASO ↓, SE ↑ (all $p < .01$). ISI ↓ ($p < .05$).	All gains maintained at 3mths and 12mths.	23 out of 26 (88.5%)
Fernando III, Arroll, and Falloon (2013) NZ	**RCT; II**	SRT vs. sleep hygiene instructions	45 adults (median age = 58) with primary insomnia	Telephone response regarding sleep quality.	The SRT group benefitted significantly better than the SHE group for sleep quality ($p < 0.05$).	N/A	23 out of 26 (88.5%)
Friedman et al. (2000) USA*	**RCT; II**	SRT & sleep hygiene instructions vs. NSRT & sleep hygiene instructions vs. sleep hygiene instructions	39 older adults (mean age = 64.2) with primary insomnia	Telephone sleep diary data, PSG and MSLT (sub-sample n = 19 at baseline, treatment end, and 3 month follow-up), actigraphy and the SSS.	Sleep diary: SE ↑ ($p < .05$). Actigraph: TST ↓ ($p < .05$). PSG and MSLT: means and standard deviations only reported due to small sample size.	3mths: sleep diary: SE maintained. No Δ in actigraphy. SSS for SRT & SHE ↓ ($p < .05$).	22 out of 26 (84.6%)

Kyle et al. (2011) UK	**UCT; V**	SRT only	18 adults (mean age = 42) with primary insomnia	Sleep diary data, Qualitative voice recordings, ISI, PSQI, GSES	SOL ↓, WASO ↓, SE↑, SQ↑, (all $p < .01$). No Δ in TST. ISI ↓, PSQI ↓, GSES ↓, (all $p < .001$).	3mths: All gains maintained and TST ↓ ($p < .01$).	16 out of 26 (61.5%)
Kyle et al. (2014) UK	**UCT; V**	SRT only	16 adults (mean age = 47.1) with primary insomnia	Sleep diary data, PSG, ISI, ESS, GSES, PVT	Sleep diary: SOL ↓, WASO ↓, SE↑ (all $p < .05$). No Δ in TST. PSG: TST ↓ ($p < .001$). ISI ↓ ($p < .001$). No Δ in ESS. PVT: attentional lapses ↑, reaction times ↑ (both $p < .05$).	3mths: sleep diary: All gains maintained and TST ↑ ($p < .05$).	19 out of 26 (73.1%)
Morin, Kowatch, and Oshanick (1990) USA	**CS**	SRT only	1 female (49 year-old) with comorbid insomnia	Sleep diary data and hourly hospital staff reports	27 days: TST ↑.	16 weeks: TST ↑.	8 out of 26 (30.8%)
Spielman et al. (1987) USA	**UCT; V**	SRT only	49 adults (mean age = 46) with chronic insomnia	Sleep diary data, PSG (screening only in a sub-sample of 31), 13 ISQ	Sleep diary: TIB ↓, SOL ↓, WASO ↓, TST ↑, SE ↑ (all $p < .05$), ISQ ↓.	9mths: Improvements maintained (n= 23, no ISQ follow-up).	16 out of 26 (61.5%)
Taylor, Schmidt-Nowara, Jessop, and Ahearn (2010) USA	**RCT; II**	SRT & hypnotic withdrawal vs. Sleep hygiene instructions	46 adults (mean age = 53.7) with chronic insomnia	Sleep diary data & reported use of hypnotics.	SRT + HW compared to SHE: SOL ↓ ($p < .05$), WASO ↓ ($p = .052$), SE ↑ ($p < .05$), No difference in TST. Hypnotic use ↓ ($p < .001$) compared to SHE: SOL ↓ ($p < .05$), WASO ↓ ($p = .05$), SE ↑ ($p < .05$), No difference in TST. Hypnotic use ↓ ($p < .001$) compared to SHE.	6mths (for SRT + HW only): All gains maintained and TST ↑ ($p < .001$). All gains at 6mths maintained at 12mths.	22 out of 26 (84.6%)

2.4 Results

2.4.1 Description of studies included in the review

The initial and updated electronic database search yielded 1,344 (WEB OF KNOWLEDGE = 664, PubMed = 445, SCOPUS = 235) potentially relevant studies combined; after reading titles and then abstracts of these studies, 21 were deemed adequate and a full version of the article was acquired. From these 21 studies, nine fulfilled the inclusion criteria (see Figure 4). Twelve studies were excluded for the following reasons: two did not study insomnia, (Hoch et al., 2001; Reynolds & Banks, 2010); four used sleep compression therapy, (Hoelscher & Edinger**,** 1988; Lichstein, 1988; Riedel & Lichstein, 2001; Riedel, Lichstein, & Dwyer, 1995); two used multi component therapy (Vincent, Lewycky, & Finnegan, 2008; Vincent & Lionberg, 2001); one implemented a form of sleep compression therapy (Riedel & Lichstein, 2001); and finally, three studies were preliminary reports of subsequently reported data and were not included in this review (Brooks, Friedman, Bliwise, & Yesavage, 1993; Friedman, Bliwise, Yesavage, & Salom, 1991; Miller et al., 2013). The following sub-sections report an overall audit of these initial studies (see Table 7).

2.4.2 Design / Randomisation / Controls

Of the nine studies found in the literature search, four implemented randomised controlled trials, (Epstein et al., 2012; Fernando III et al., 2013; Friedman et al., 2000; Taylor et al., 2010), one was a non-randomised controlled trial (NRCT) (Bliwise et al., 1995), three were uncontrolled clinical trials (UCT) (Kyle et al., 2014; Kyle et al., 2011; Spielman et al., 1987) and one was a case study (Morin et al., 1990). Out of the four RCT's, all used well-defined randomisation procedures (Epstein et al., 2012; Fernando III et al., 2013; Friedman et al., 2000; Taylor et al., 2010). Adequate control groups (waitlist controls, matched for therapist time and/or a comparison to another CBT-I intervention) were used in the majority of both the randomised and controlled trials (see Table 7).

2.4.3 Participants / Power / Sample

Of the nine included studies, seven treated participants with primary insomnia (Bliwise et al., 1995; Epstein et al., 2012; Fernando III et al., 2013; Friedman et al., 2000; Kyle et al., 2014; Kyle et al., 2011; Taylor et al., 2010) (this was either specified by research diagnostic criteria (Edinger et al., 2004) or was ascertained from the methods sections of the studies), and two treated those with co-morbid insomnia (Morin et al., 1990; Spielman et al., 1987). Three studies employed lab-based polysomnography (PSG) to exclude occult sleep disorders prior to testing (Friedman et al., 2000; Kyle et al., 2014; Spielman et al., 1987). The average participant age (and standard deviation) across the nine studies was found to be 55.3 years (10.2) (Table 7). Three studies sampled older adults only (60 years+) (Bliwise et al., 1995; Epstein et al., 2012; Friedman et al., 2000). One study had sufficient power (≥ 30 participants in each arm) to detect a medium-to-large treatment effect, as per previous power calculations (Epstein et al., 2012). The remaining nine studies may have high false-positive and/or high false-negative errors due to low statistical power.

2.4.4 Post treatment assessments

Post-treatment assessments were carried out at three (Bliwise et al., 1995; Epstein et al., 2012; Friedman et al., 2000; Kyle et al., 2014; Kyle et al., 2011), four (Morin et al., 1990), six (Taylor et al., 2010) and nine months post treatment (Spielman et al., 1987). Two studies also re-assessed gains at 12 months post-treatment (Epstein et al., 2012; Taylor et al., 2010).

Next, for comparison an evaluation criterion (see Table 6) was applied to all of the nine studies. Overall study quality scores varied considerably (mean: 18.7; range: 8 to 23, out of 26; see Table 7). All studies were assessed independently by two reviewers (CBM & another post-graduate level researcher). Inter-rater reliability was found to be fair (Cohen's kappa = 0.22). Discrepancies in assessment were discussed and re-assessed by each reviewer resulting in greater reliability (Cohen's kappa = 0.60) (Landis & Koch, 1977). Studies with grade III evidence and above (as per Sackett criteria) (Sackett, 1989) were deemed to be adequate to examine the impact of therapy. Out of the nine studies, four met this criterion (average age = 63.9 years, standard deviation = 7.1) (Bliwise et al., 1995; Epstein et al., 2012; Friedman et al., 2000; Taylor et al., 2010). The following results examine the efficacy of these studies. Primarily, studies were deficient for sample size, randomisation and for sufficient placebo controls. One RCT was not included as it did not report any primary sleep diary measures pre-to-post therapy (Fernando III et al., 2013).

2.4.5 Post treatment sleep diary outcome measures

Of the four studies with the minimum level of evidence (grade III and above), weighted ES scores were calculated to take account of individual sample sizes for sleep diary outcome variables (SOL, WASO, SE, TST, NOAW, TIB, & SQ). These were calculated between post-treatment and baseline for the active SRT arm and the control condition. For the SRT arm, it was found that SOL decreased in all studies (Bliwise et al., 1995; Epstein et al., 2012; Friedman et al., 2000; Taylor et al., 2010), the weighted ES for SOL was medium (0.64). Reductions for WASO were found in three of the four studies (Epstein et al., 2012; Friedman et al., 2000; Taylor et al., 2010) as one did not report this

(Bliwise et al., 1995); the weighted ES was large (1.36). Sleep efficiency increased in three studies (Epstein et al., 2012; Friedman et al., 2000; Taylor et al., 2010) one study failed to report this (Bliwise et al., 1995); the mean weighted ES for SE was also large (1.5). Secondary pre-to-post measures of sleep diary variables (TST, NOAW, TIB, and SQ) were also compared at post-treatment to baseline levels. This revealed a small increase in TST (ES = 0.3), NOAW was not reported in any of the four studies, whereas a large reduction in TIB was reported in two studies (weighted ES = 1.26), and finally SQ ratings were only reported in one study and were found to increase (ES = 0.3) (see Table 8) (Epstein et al., 2012). The control condition did not reveal significant improvements across the studies. Although SOL, WASO and TIB all decreased (ES = 0.06, 0.01 and 0.3 respectively) and SE, TST and SQ all increased (ES = 0.04, 0.01 and 0.03 respectively).

Subjective sleep outcome measure (sleep diary)	Pre-treatment value		Post treatment value		Pre-to-post treatment change		Number of studies	Number of participants	Weighted effect size*	
	Mean	SD	Mean	SD	Value	%			Mean	SD
Sleep latency (minutes)										
Sleep restriction therapy	42.15	37.50	22.81	19.65	-19.34	46	4	98	0.64	0.37
Control	41.32	29.43	37.68	24.14	-3.64	9		94	0.06	0.36
Wake time after sleep onset (minutes)										
Sleep restriction therapy	72.98	39.04	30.81	23.78	-42.17	58	3	82	1.36	0.42
Control	66.62	38.31	55.32	30.28	-11.30	17		78	0.01	0.55
Sleep efficiency (%)										
Sleep restriction therapy	66.60	13.02	82.88	8.78	16.28	24	3	82	1.50	0.35
Control	67.00	11.88	71.59	8.92	4.59	7		78	0.04	0.23
Total sleep time (minutes)										
Sleep restriction therapy	334.08	69.00	351.14	49.58	17.06	5	4	98	0.30	0.31
Control	335.80	68.60	341.93	55.56	6.13	2		94	0.01	0.40
Number of awakenings										
Sleep restriction therapy	.	.	.	.	.	.	0	.	.	.
Control	.	.	.	.	.	.		.	.	.
Total time in bed (minutes)										
Sleep restriction therapy	500.60	55.30	439.19	40.12	-61.41	12	2	60	1.26	0.40
Control	509.60	51.40	489.98	45.32	-19.62	4		61	0.38	0.01
Sleep quality ratings										
Sleep restriction therapy	2.77	0.50	2.90	0.38	-2.39	86	1	44	0.30	.
Control	2.57	0.42	2.58	0.37	0.01	0		50	0.03	.

Table 8 Effect size scores for the four studies with sufficient methodological strength at post-treatment compared to baseline. Control groups either consisted of wait-list controls, or were compared to another cognitive behavioural therapy intervention.*Overall weighted effect size scores were calculated by the formula (∑[*diN]/ ∑ [N]), where *di* is the effect size of the individual study.**

2.4.6 Post treatment objective sleep measures

For objective outcome measures, statistical differences in objectively-defined sleep variables were not tested in the one study that employed PSG pre-to-post SRT. This was due to the small number of participants who underwent PSG testing (*n*=6) (Friedman et al., 2000). The same study also used the multiple sleep latency test (MSLT) but again only in the same sub-group of participants (Friedman et al., 2000). Two studies evaluated actigraphy data as an outcome measure; one found a decrease in SOL, WASO, and an increase in SE compared to a waitlist control (Epstein et al., 2012), with no further changes at the three month and one year follow-ups. TST did not change (Epstein et al., 2012). The other study revealed a decrease in TST at post-treatment but was underpowered, based on a previous power calculation (Epstein et al., 2012) to test any interaction effects (Friedman et al., 2000).

2.4.7 Sleep related questionnaire outcome measures

Overall, from the nine studies profiled in this review, pre-to-post decreases on subjective questionnaire measures were observed (e.g. insomnia severity index (ISI)) (Epstein et al., 2012; Kyle et al., 2014; Kyle et al., 2011), insomnia symptom questionnaire (ISQ) (Spielman et al., 1987), Pittsburgh sleep quality index (PSQI) (Kyle et al., 2011), and the Glasgow sleep effort scale (GSES) (Kyle et al., 2011). Only one study with adequate methodological strength employed one of these instruments; a significant difference ($p<.01$) between the SRT and waitlist control condition was found with the ISI at post treatment (ES = 1.18) for the SRT group (Epstein et al., 2012). This study also quantified a treatment response rate using the ISI, whereby a response was defined as a change of six points from baseline to post-treatment and remission was considered if the post-treatment ISI score was <8 (no clinical insomnia) (Epstein et al., 2012; Morin, 1993). It was found that 50% of the SRT group (*n*=44) responded to treatment and the remission rate was 22.7% (Epstein et al., 2012).

2.4.8 Adverse effects of treatment and daytime functioning measures

Adverse effects were profiled in two studies out of nine included in this review. One used a mixed methods approach (involving post-treatment semi-structured interviews, qualitative audio-diaries) (Kyle et al., 2011). Daytime functioning and health related quality of life outcomes were also included in this study and involved the daytime functioning and sleep attribution scale, the Glasgow sleep impact scale, the occupational impact of sleep questionnaire and the short-form health-survey 36. All measures were found to improve significantly at both four weeks and three months post treatment compared to baseline scores (Kyle et al., 2011). Another study used PSG, the psychomotor vigilance task (PVT) and subjective markers of sleepiness pre, during and post SRT. SRT was initially found to be associated with substantially reduced objective TST, vigilance impairment on the PVT and increased daytime sleepiness through the Epworth sleepiness scale (ESS). Both the PVT and ESS were found to normalise at three months post treatment (Kyle et al., 2014). One further study also used the Stanford sleepiness scale (SSS) but this was underpowered to test for differences (Friedman et al., 2000). No other daytime functioning measures were reported in any of the trials.

2.4.9 Sleep restriction therapy instructions

As a result of the literature search, it is important to also highlight that all of the nine assessed studies used a range of therapeutic guidelines for the implementation of SRT in comparison to the initial SRT procedures (Spielman et al., 1987) (see Table 9) for an overview.

Spielman et al. (1987)	From a 2-week sleep diary, a sleep wake schedule was prescribed. The average subjective TST was used to calculate the initial TIB. The time for rising was established first and then the time for retiring at night was set to equal the new prescribed TIB (none were prescribed < 4.5 hours). Changes to TIB were made to the sleep window through therapy via the following criteria over the previous 5 days: (a) when the mean SE is ≥ 90%, then the TIB was increased by fifteen minutes - by setting the retiring time earlier. (b) When the mean SE is < 85% TIB is decreased to the mean sleep time of the previous 5 days. (c) If the mean SE is < 90% and ≥ 85%, then the time in bed is not altered.
Morin et al. (1990)	**Spielman et al. (1987)** + 4 hours minimum time in bed. Achievement of high SE increased TIB.
Bliwise et al. (1995)	**Spielman et al. (1987)** + flexibility to TIB.
Friedman et al. (2000)	Group 1: **Spielman et al. (1987)** + TIB at the start of treatment and was not set strictly at the mean TST from baseline and was not reduced for failure to reach criterion and sleep hygiene. Group 2: same as group 1 plus participants were encouraged to take a 30-minute daily afternoon nap between 13:00 and 15:00. Both groups were given weekly increments of TIB according to an algorithm (based on baseline diary data of TST and TIB) and also of subjective reported sleepiness. All subjects started with at least 5 hours TIB but by the end of the fourth week TIB was increased to 7 hours. Time in bed was only increased by going to bed earlier.
Taylor et al. (2010)	**Spielman et al. (1987)** + TIB = 10% above the average estimated TST reported for the previous week but no less than 5 hours. Once SE = 90%, hypnotics were withdrawn (50% of dose for per week).
Kyle et al. (2011)	**Spielman et al. (1987)** + 5 hours minimum TIB; if SE <85% then sleep window decreased by 15 minutes.
Epstein et al. (2012)	**Spielman et al. (1987)** + 5 hours minimum TIB.
Fernando III et al. (2013)	No specific details given apart from participants received personalised instructions on bedtime and wake time routines.
Kyle et al. (2014)	**Spielman et al. (1987)** + 5 hours minimum TIB; if SE <85% then sleep window decreased by 15 minutes.

Table 9 Description of sleep restriction therapy intervention types. Displays an overview of the sleep restriction therapy implementation methods for each study included in the review process. TIB: time in bed; TST: total sleep time; SE: sleep efficency.

2.5 Discussion

The primary objective of this review was to rigorously examine the evidence base for the use of single component sleep restriction therapy (SRT) in the treatment of insomnia. Nine studies met the initial inclusion criteria and were then assessed using standardised study assessment criteria (Kmet et al., 2004). Of these, four studies (three randomised controlled trials and one controlled trial) were considered eligible to evaluate the efficacy of SRT. The weighted effect size (ES) scores for sleep diary parameters (sleep latency; SOL, wake after sleep onset; WASO, and sleep efficiency; SE) were calculated. The majority of ES scores for sleep diary parameters were greater than 0.6, indicating medium-to-large treatment effects (Cohen, 1988). For total sleep time (TST), a small improvement was found by the end of treatment (weighted ES = 0.3), consistent with previous CBT-I studies (Irwin, Cole, & Nicassio, 2006; Montgomery & Dennis, 2003; Morin, Culbert, & Schwartz, 1994; Murtagh & Greenwood, 1995; Okajima, Komada, & Inoue, 2011). Ratings of sleep quality were found to improve in the only study that reported these (ES = 0.3) (Epstein et al., 2012). For comparison, the weighted ES for the control condition did not reveal significant improvements across studies. For example, the weighted ES was extremely small for the following variables: SOL = 0.06, WASO = 0.01, SE = 0.04, TST = 0.01 and SQ = 0.03 (see Table 8).

From the four studies with adequate methodological strength, the results suggest that single component SRT is an efficacious insomnia treatment with moderate-to-large effects on sleep diary variables at post-treatment. There are several caveats and limitations with respect to these findings.

First, the current review found only nine studies evaluating SRT for insomnia disorder and just four that met our inclusion criteria, limiting the strength of the overall findings. Nonetheless, it is also important to consider the most recent American Academy of Sleep Medicine (AASM) practice parameters in 2006 that considered SRT as a "guideline" intervention, one step below that of stimulus control therapy (SCT) which is a "standard" intervention (Morgenthaler et al., 2006). Since that time, five additional SRT studies have been published and included in this review (Epstein et al.,

2012; Fernando III et al., 2013; Kyle et al., 2014; Kyle et al., 2011; Taylor et al., 2010), including one with level I evidence (Epstein et al., 2012) and one with level II evidence (Taylor et al., 2010) (as per Sackett criteria and the AASM classification of evidence) (Chesson Jr et al., 1999; Morgenthaler et al., 2006; Sackett, 1989). Overall, with four RCT's and one NRCT, SRT now has sufficient evidence to be classified as an established "standard" treatment intervention as per the American Psychological Association Task Force Report and Recommendations: Criteria for Empirically validated treatments (Association, 1995). The American Psychological Association criteria have been used previously by the AASM to quantify the evidence for psychological treatments for insomnia (Chesson Jr et al., 1999; Morgenthaler et al., 2006; Morin, Bootzin, et al., 2006; Morin et al., 1999). The AASM may wish to re-consider the evidence base for SRT, in light of this systematic review, and determine whether an upgrade in line with other CBT-I components, such as SCT and relaxation training is deserved. It is important to note that SCT obtained its "standard" status through five RCT's with level II evidence (Chesson Jr et al., 1999; Morin et al., 1999). In the 2006 update, one further RCT (with level II evidence) was added to this (Morgenthaler et al., 2006; Morin, Bootzin, et al., 2006). When compared to SCT, SRT may not have been used as frequently as a standalone intervention, either because researchers and clinicians utilise multicomponent cognitive behavioural therapy (by way of both brief and full versions) (Buysse, Germain, Moul, et al., 2011; Edinger et al., 2001; Germain et al., 2006; Harvey & Tang, 2003; Troxel et al., 2012) or use SRT in combination with CBT-I or brief behaviour therapy. Until recently, the insomnia field has generally failed to dismantle individual components of CBT-I through RCT methodology (Epstein et al., 2012).

The results of this review are comparable to previously published meta-analytic data for CBT-I sleep diary treatment outcome variables (Irwin et al., 2006; Montgomery & Dennis, 2003; C. M. Morin et al., 1994; Murtagh & Greenwood, 1995; Okajima et al., 2011). In particular, the weighted ES of the sleep variables (SOL, WASO, SE, and TST) resemble or are greater than those of CBT-I at post-treatment compared to baseline (Irwin et al., 2006; Okajima et al., 2011; Smith et al., 2002). For example, Irwin et al. (2006) and Okajima et al. (2011) both found a medium mean ES

reduction for SOL, a medium-to-large mean ES reduction for WASO and large mean ES increase for SE. This is in line with findings from the present review (weighted ES; SOL = medium reduction, WASO = large reduction, SE = large increase, only one study reported SQ ratings and found a medium ES improvement). Total sleep time was also found to improve at post-treatment, although the weighted effect size was in the small range (ES = 0.3). It may be that studies are unable to detect large changes in TST, longer follow-up times are required to examine robust changes in TST, or that different implementation methods of SRT affect treatment outcome. However, the ES for TST was also comparable to previous CBT-I meta-analytic data whereby Irwin et al. (2006) discovered a 0.17 weighted ES increase for TST, Okajima et al. (2011) found a mean ES increase of 0.32, and also Smith, Perlis, Park, et al. (2002) found a mean ES increase of 0.46 at post-treatment compared to baseline.

Objective measures of sleep-wake parameters are lacking in trials of SRT. Only one of the four studies with sufficient methodological strength attempted to measure in-lab objective sleep variables but this was underpowered to test for differences (in both PSG and MSLT variables) (Friedman et al., 2000). Actigraphy has been used marginally more, in two of the four studies with sufficient methodological strength (Epstein et al., 2012; Friedman et al., 2000). One found a decrease in SOL, WASO, and an increase in SE compared to a waitlist control at post treatment only (Epstein et al., 2012). The other study found a decrease in TST at post treatment but was also underpowered to test for between group effects (Friedman et al., 2000). Actigraphy may be valuable in providing an objective marker of changes in sleep due to SRT and as a marker of adherence and implementation of therapy. Further objective (PVT) and subjective markers of sleepiness pre, during and post SRT were profiled in one uncontrolled study (Kyle et al., 2014) Participants also slept for three nights in the lab with PSG to profile sleep during therapy implementation (on days one, eight and 22). Sleep restriction therapy was initially found to be associated with substantially reduced objective TST, vigilance impairment (PVT) and increased daytime sleepiness (ESS). Both the PVT and ESS were found to normalise at three months post treatment. Healthy controls were employed to examine differences in vigilance performance data only. No baseline differences were found,

suggesting the impact of SRT was contributing to the vigilance performance deficits (Kyle et al., 2014).

For subjective questionnaire measures, studies found pre-to-post decreases in the ISI (Epstein et al., 2012; Kyle et al., 2014; Kyle et al., 2011), ISQ (Spielman et al., 1987), PSQI (Kyle et al., 2011) and GSES (Kyle et al., 2011). However, no average ES data were examined for these outcomes as three studies with sufficient methodological strength (Bliwise et al., 1995; Friedman et al., 2000; Taylor et al., 2010) collected data prior to the development and validation of the ISI (Bastien, Vallières, & Morin, 2001), GSES (Broomfield & Espie, 2005) and ISQ (Okun et al., 2009). One study out of this four used the ISI pre-to-post treatment. Interestingly, the post treatment ES difference between the SRT group and the waitlist control group for the ISI was 1.18, similar to the SCT group (ES = 1.22) and the multicomponent therapy group (ES = 1.24) (Epstein et al., 2012). No studies with sufficient methodological strength used the PSQI as an outcome measure, perhaps as this is not specifically designed to evaluate insomnia (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006). Global measures of sleep symptomology (ISI & PSQI) are recommended measures and likely to change due to a treatment response from SRT (Buysse et al., 2006). In particular, the ISI may be the most useful for standardising response and remission outcomes due to treatment (Epstein et al., 2012). One study removed from the review process as it was a preliminary report of a subsample of participants from Kyle et al. (2014), measured subjective changes in mood and daytime functioning before and throughout SRT in nine patients with psychophysiological insomnia (Miller et al., 2013). Changes in mood and cognition were profiled pre and during the first three weeks of SRT implementation using ecological momentary assessment, where the daytime insomnia symptom scale was completed at four defined points through the day (Buysse et al., 2007; Levitt et al., 2004). Interestingly, measures of sleepiness/fatigue increased overall at week one of SRT but, by week four, decreased below baseline levels. Alert cognition, displayed a significant week by time-point interaction, whereby a reduction in alertness at bedtime was observed at week three, while morning

rise-time alertness was improved. This data indicates that SRT moderates alertness and sleepiness in therapeutic ways (Miller et al., 2013).

With regards to study quality and methodological strength, it was found that only one of the nine studies (Epstein et al., 2012) had sufficient power (≥ 30 participants in each arm) to be classed as grade I evidence (Sackett, 1989). This suggests that most studies included in this review may suffer from statistical error (Type I and/or Type II). Therefore, the approach by Epstein et al. (2012) is an important contribution to the literature. Specifically, the authors were able to differentiate ES scores of SRT compared to multi-component therapy (consisting of SRT and SCT only), SCT and to a waitlist control. Importantly, the authors found no differences between single and multi-component therapy for sleep outcome measures (sleep diary and actigraphy). For example, medium-to-large ES improvements were found for SRT, SCT and multi-component therapy on sleep diary data (SOL, WASO, SE, TST and SQ). Therefore, this study suggests that SRT, SCT and multi-component therapy are comparable for efficacy on sleep diary and actigraphy outcomes. For participant screening, only three trials included overnight PSG screening in most subjects prior to enrollment to assess for other potential occult sleep disorders prior to therapy implementation (Friedman et al., 2000; Kyle et al., 2014; Spielman et al., 1987). Likewise for study follow-up times, only two studies re-examined outcomes after six months of SRT. These studies did find that initial gains in sleep diary variables (SOL, WASO, and TST) were maintained (Epstein et al., 2012; Taylor et al., 2010). The lack of long term follow-up data across all of the studies makes it difficult to evaluate long term outcomes of SRT and further trials are required with sufficient follow-up times. Large samples of participants are also required to achieve grade I evidence. Such adequately powered studies will help to avoid any type I or II statistical errors and will provide definitive evidence for SRT.

With respect to participant demographics, the mean participant age for the nine studies was found to be 55.3 years (Table 7), although three studies specifically sampled participants aged 60 years and above. However, from the four studies with adequate methodological strength the mean

age was found to be 63.9 years. This may be considered a limitation to the generalisability of the findings of this review and further SRT studies need to be conducted across different age groups in order to determine whether SRT may be more or less beneficial depending on patient age. It must be noted, however, that multicomponent CBT-I studies have not found age to be a predictor of treatment response (Morin, Bootzin, et al., 2006; Morin et al., 1999).

The delivery of SRT can also vary between studies making it difficult to compare SRT interventions directly. For example, one common variant of the SRT approach is the minimum time in bed which has changed as the literature has progressed (see Table 9). It is common to spend no less than five hours (six hours in vulnerable patients) time in bed as part of CBT-I procedures (Edinger & Means, 2005). This guideline has developed to guard against negative consequences associated with extreme sleepiness with a reduction of time in bed (Dinges et al., 1997). For example, in the initial SRT study, 14 out of the 49 enrolled participants dropped out after a mean period of 19 days (Spielman et al., 1987). Adherence to SRT guidelines is known to be extremely difficult and has previously been examined (Riedel & Lichstein, 2001). Naps or lying down are generally not permitted until prescribed bed-time has been reached (except where explicitly integrated into a modified SRT). Studies have so far looked to vary the SRT procedures to include naps in order to aid adherence to therapy but have so far failed to rigorously test naps as countermeasures. One study attempted to evaluate adherence by encouraging older adults to nap in one of the two SRT treatment arms (Friedman et al., 2000). However differences were not observed between the two conditions, perhaps limited by the small sample size in each group (SRT *n*=16, Nap SRT *n*=12) (Friedman et al., 2000). In addition, the newly prescribed sleep-wake schedule must be maintained and adhered to everyday of the week until the next weekly meeting with the therapist where it is then re-examined. This is often a form of negotiation with the participant but has received little attention in the literature. The reduction of time in bed has also been suggested in the literature Spielman et al. (2010) but this remains to be formally evaluated. Future comparative studies of treatment procedures are required to test the effectiveness of the guidelines set out by

Spielman et al. (2010) for optimal treatment delivery. Once this has been achieved then standardisation of therapy guidelines may take place.

Based on the results of our review we suggest the following research directions to advance clinical understanding of SRT

1) Study design and measures of sleep: future well-controlled studies are required with grade I evidence, like that of the recent Epstein et al. (2012) trial. Studies should also look to include objective assessments of sleep (actigraphy and PSG) in an effort to understand treatment effects further. This would enable the evaluation of acute and chronic changes in objective sleep parameters. For example, one recent meta-analysis of PSG-defined sleep parameters found evidence of objective sleep continuity disruption and reduced time spent in rapid eye movement (REM) and slow wave sleep (SWS), relative to controls (Baglioni et al., 2014). The extent to which these parameters normalise through SRT is worthy of future research attention. Changes in sleep electroencephalography (EEG) power densities remain relatively untested. Previously, one CBT-I treatment study found a more rapid decline of EEG delta power in insomnia participants after therapy compared to placebo controls (Krystal & Edinger, 2010). Sleep architecture has also been shown to change due to non-pharmacologic treatment of insomnia. For example, increased stage two, REM and SWS durations have been reported after effective CBT-I (Cervena et al., 2004). Future studies should test for specific SRT-related changes in the continuity and proportion of objectively defined sleep, as well as changes in the micro structure of sleep.

With respect to insomnia assessment, studies now need to adequately screen and measure insomnia before, during and at follow-up, in line with standard research guidelines for insomnia (Buysse et al., 2006; Edinger et al., 2004). It is also currently unknown if SRT is efficacious for co-morbid insomnia as this remains to be formally evaluated. For example, moderate-to-large treatment gains as a result of SRT in those with insomnia with medical and psychiatric comorbidities would be in line with previous CBT-I outcomes (Smith, Huang, & Manber, 2005).

2) Measures of daytime functioning: Examination of daytime functioning in SRT studies is severely lacking. Daytime impairment is an important aspect to consider given that the diagnosis of insomnia is dependent upon this complaint (Harvey & Tang, 2003; Kyle, Espie, & Morgan, 2010). Further, it is this impairment that drives help-seeking behaviour and makes insomnia a 24 hour (Kyle et al., 2010). An improvement in this area would be expected as part of any treatment response. Future studies should specifically test for improvements in measures of daytime functioning, using appropriate (Kyle et al., 2013) and recommended measures (Buysse et al., 2006; Kyle et al., 2010).

3) Adverse effects and contraindications of therapy: adverse effects were profiled in two studies that were assessed as part of this review process (Kyle et al., 2014; Kyle et al., 2011). One used a mixed methods approach involving: post-treatment semi-structured interviews, qualitative audio-diaries, and questionnaire assessments (Kyle et al., 2011). The other used objective (PVT) and subjective (ESS) measures of daytime sleepiness throughout therapy (Kyle et al., 2014). However, the majority of previous studies have thus far failed to adequately measure and profile any potential side effects or daytime impairment of SRT or CBT-I for that matter (Kyle et al., 2013). Further studies specifically testing initial daytime impairments and adverse effects of SRT are required, particularly during the acute period of therapy, where the effects of sleep restriction are likely to be most pronounced (Kyle et al., 2014; Miller et al., 2013). Such detailed profiling may help shed light on the relationship between adverse effects, treatment response and patient attrition. It is also important to consider that SRT may be contraindicated in specific sub-samples of patients, where restricted sleep opportunity may stimulate negative outcomes. For example, SRT may trigger mania in bipolar disorder, lower the seizure threshold in those with seizure disorders such as epilepsy or exacerbate patients with excessive daytime sleepiness (Smith, Perlis, Park, et al., 2002). SRT-“light” or fixed bed and rise times may be effective alternatives to SRT in these patients (Kaplan & Harvey, 2013).

Limitations of this review

A number of limitations of the review process should be highlighted. First, there are deviations from Cochrane and PRISMA guidelines with regards to the conduct and reporting of this review. For example, publication bias and the heterogeneity across studies were both not assessed. Second, the comparisons in the meta-analytic section of the review only evaluated studies before and after therapy and were therefore uncontrolled. The comparisons also did not involve any follow-up assessments and included subjective measures only. Third, there was poor reliability in the initial literature search and study evaluation between the scorers (Cohen's kappa of 0.22). Fourth, the literature search found and included low grade research evidence (below Grade III). Lastly, studies included participants with both co-morbid insomnia and psychophysiological insomnia subtypes. Despite these limitations it is worth to note that this was a clinical review based predominately on the AASM guidelines in order to evaluate the state of the literature for the use of standalone SRT for insomnia. Future reviews into SRT for insomnia should now implement standardised criteria to examine the clinical effectiveness of therapy.

2.6 Conclusions

The primary objective of this review was to evaluate the evidence for the use of single component SRT in the treatment of chronic insomnia. Out of the nine studies included in this review, four were deemed adequate to fully evaluate the impact of SRT. It can be concluded that SRT is an effective single behavioural intervention for the treatment of insomnia for sleep diary variables. Thus, in light of this review, the AASM may wish to re-consider the status of SRT, to determine whether a clinical guideline upgrade is required. Results may be limited due to studies using slightly different SRT implementation strategies. Further research is required to systematically examine the clinical effectiveness of SRT through well designed large scale randomised controlled trials. Attention should be placed on further measures of subjective daytime functioning and of objective sleep changes.

2.7 Practice points

1. Single component SRT for insomnia is efficacious for the treatment of insomnia for primary sleep diary measures (SOL, WASO, SE and TST). The AASM may wish to re-evaluate the status of SRT.
2. A number of studies utilised various and different methods in the delivery and titration of SRT. As a result, studies should look to test the SRT guideline recommendations by Spielman et al., (2010) for effectiveness. Standardisation of the SRT guidelines may then take place.
3. There is currently little evidence to suggest that single component SRT improves daytime functioning and quality of life in insomnia. Further data is required to evaluate if daytime functioning improves as a result of SRT.

2.8 Research agenda

1. To implement randomised controlled trials to establish the clinical effectiveness of the SRT guidelines by Spielman et al. (2010) in line with previous insomnia research recommendations.
2. To evaluate the initial minimum amount of time in bed required for a treatment response.
3. To further examine potential daytime consequences (impairments and/or improvements) of treatment through questionnaire measures in controlled experimental studies.
4. To profile changes in the proportions of PSG-defined sleep staging and the power spectral analysis of sleep in response to SRT.

2.9 Moving forward

The review highlights the effectiveness of SRT for primary sleep diary measures in insomnia but questions remain regarding the use and the impact of SRT on sleep and daytime functioning outcomes. Further testing is required to elucidate the effectiveness of this therapy in relation to subjective daytime and, objective measures of sleep as well as physiological functioning. The next chapter will describe the methodology for the assessment of sleep and set the scene for the subsequent experimental chapters.

In chapter four an ecological momentary assessment is used to evaluate subjective point-in-time alterations to daytime cognition in those with insomnia through SRT. This new approach hypothesises that daytime levels of cognition and mood will initially deteriorate (acute restriction of sleep) but will then improve beyond baseline levels through SRT. In chapter five, salivary cortisol concentrations are assessed throughout therapy to inform potential changes to hypothalamic-pituitary-adrenal-axis functioning with SRT. A further hypothesis relates to a reduction in salivary cortisol concentrations compared to baseline levels after effective SRT.

The results of these initial studies were used to substantiate the overall assessment of the data in chapter six. Chapter six evaluates the role of objective sleep, temperature and night time plasma cortisol concentrations in response to effective SRT. It was hypothesised that objectively defined sleep would improve, and measures of physiological arousal would reduce (cortisol & core body temperature). Chapter seven is a case control study which evaluates the differences in cerebral metabolism between those with insomnia and healthy good sleeping controls. This was undertaken to: 1. assess whether brain metabolites in individuals with insomnia are different from good sleeping controls and 2. to provide further objective potential markers of insomnia. It was hypothesised that concentrations of brain metabolites would display increased arousal across the brain in line with the hyperarousal theory of insomnia.

Chapter 3: Methodology for the assessment of sleep

The contents of this chapter have been accepted for publication as follows:

'Methodology for the assessment of sleep', Christopher B. Miller, Simon D. Kyle, Kerri L. Melehan & Delwyn J. Bartlett, *(In Press). In K.A. Babson & M.T. Feldner (Eds.), Sleep and affect: Assessment, Theory, and Clinical Implications. San Diego: Elsevier Academic Press Inc, accepted* 23/04/2014.

3.1 Abstract

This chapter provides an overview of the assessments and methodology applied in this thesis. The chapter initially focuses on the tools and techniques that are commonly used to diagnose insomnia and other sleep disorders. A number of methods will be covered in this chapter including: polysomnography, actigraphy, cortisol assessment, magnetic resonance spectroscopy, and subjective measures including self-report questionnaires and sleep diaries. The chapter ends with an overview of the procedures of sleep restriction therapy, participant recruitment and the statistical analysis employed in this thesis.

3.2 Introduction

As this chapter has been accepted for publication as an overview of the assessments used in sleep research, the format of this chapter is different to the rest of the thesis. Compared to the accepted version, the chapter has also been modified to provide a specific overview of the assessments and methods employed directly in this thesis. The chapter begins with an overview of sleep and the measurement of sleep (including polysomnography, actigraphy, clinical interviews & sleep diaries) and then moves on to address subjective assessments of sleepiness and insomnia. The chapter then covers objective measures of cortisol and cerebral metabolism and ends with an overview of sleep restriction therapy for insomnia, the recruitment procedures and statistical analyses used in the data chapters.

Sleep is a complex behaviour that has been described as: "a reversible state of perceptual disengagement and unresponsiveness from the environment" (Carskadon and Dement (2011), p. 16). In addition to perceptual disengagement, normal sleep also consists of closed eyes, postural recumbency, and relative stillness (Carskadon & Dement, 2011; Hirshkowitz, 2004). Although the primary function for sleep is currently unknown many theories exist. Sleep is thought to be necessary for repair of bodily 'wear and tear', memory encoding, and learning processes (Colrain, 2011). However, measuring sleep is difficult. The aim and focus of this chapter is to provide an overview of the measures and techniques used in this thesis (see Table 10 for an overview).

Two main processes interact to regulate sleep and wakefulness. The first is the homeostatic drive for sleep, which is commonly referred to as sleep propensity or 'sleep need/debt' (Borbély, 1982). Sleep homeostasis is dependent upon the amount of time spent awake and can be quantified physiologically by the main objective measure of sleep, electroencephalography (EEG) (Achermann, Dijk, Brunner, & Borbely, 1993). Cognitive performance and specifically alertness is known to be sensitive to accumulating sleep pressure during the day (Van Dongen & Dinges, 2005). Homeostatic sleep pressure can only be reset through sleep. Secondly, sleep is also governed by the circadian

rhythm. Internal biological rhythms have evolved to revolve around the Earth's solar period of roughly 24 hours (Hirshkowitz, 2004). Such rhythms are endogenously produced and therefore can operate without external time cues (Czeisler et al., 1999). Photic and non-photic cues are used by the body to synchronise the internal clock to the light-dark environment (Czeisler et al., 1999). Internal circadian timing is known to be controlled by the suprachiasmatic nucleus (SCN). The SCN is the master clock and is located in the hypothalamus, directly above the optic chiasm (Dibner, Schibler, & Albrecht, 2010). Exposure to light synchronises the SCN with the external light dark cycle and serves as the primary circadian time giver for mammals (Czeisler et al., 1999; Stephan & Nunez, 1977).

3.3 Electroencephalography & Polysomnography

Sleep and wake states are measured by EEG whereby electrical brain activity is recorded through electrodes placed on the scalp (Rechtschaffen & Kales, 1968). Electrical brain activity is the gold standard objective measurement of sleep (Kushida et al., 2005) and electrodes are placed according to standardised international criteria called the 10-20 placement system (Jasper, 1958) which aims to ensure reproducibility of EEG studies. In the 10-20 system, each electrode site is mapped with letters and numbers. The letters F, T, C, P and O refer to scalp location and stand for frontal, temporal, central, parietal and occipital areas. Even numbers denote the right hemisphere and odd numbers denote the left. "Z" means zero and stands for the midline of the head (Oostenveld & Praamstra, 2001).

A diagnostic sleep study is used to diagnose sleep disorders including: sleep related breathing disorders, parasomnias, sleep related seizure disorders and periodic limb movement disorders (Kushida et al., 2005). The diagnostic sleep study is extensive and provides a significant amount of useful information but is expensive, difficult to obtain access to, and often uncomfortable for the patient (Ancoli-Israel et al., 2003). The recording of brain activity by EEG is only one aspect of the overall diagnostic sleep study. Other information about the body during sleep can also be

gathered from overall polysomnography (PSG), which simply means 'many sleep recordings'. In addition to EEG, the following measures also determine sleep including: eye movements through the electrooculogram (EOG) and muscle tone through the electromyogram (EMG) on the chin. Any sleep disturbance due to sleep disorders like obstructive sleep apnea (OSA), periodic limb movement disorder or parasomnias can be detected as part of the overall PSG assessment. Such disorders can be distinguished from a number of measures including: respiratory effort and airflow, snoring, body position, heart rate, oxygen saturation levels, and limb and jaw movements over the course of the night.

The behaviour of sleep can be scored according to standardised PSG criteria (Iber, 2007), which involves an evaluation of electrical wave forms produced by the brain, eye movements, and muscle activity. Primarily, a Sleep Scientist will evaluate brain electrical wave form patterns for amplitude and frequency, as well as bursts of brain activity. Including K-complexes (a single large amplitude wave-form < 2Hz in frequency with a brief positive electrical peak followed by a slower negative component; Loomis, Harvey, and Hobart (1938)) and sleep spindles (a short burst of oscillatory electrical activity of sigma frequency waves at 12–16 Hz that may follow from a K-complex (Loomis et al., 1938)); to categorise sleep stages (see Figure 5). Sleep is normally scored by a trained and certified sleep polysomnograpic technician into distinct sleep stages which are summarised and reported on by a specialised Sleep Physician. A hypnogram is used to give an overview of the staging of sleep for the entire night (see Figure 6 for an example). In adults, sleep consists of two main phases: 1. Non-rapid eye movement (NREM) sleep and 2. Rapid eye movement (REM) sleep. In healthy sleepers, the brain transitions through these stages of sleep in approximately 90 minute cycles. On average, an individual will experience 4-5 sleep cycles across the night. NREM sleep is comprised of three distinct sleep stages. At sleep onset, an initial short period (5-10 minutes) of stage 1 sleep (N1) occurs, characterised by theta (4-7Hz) waves and an absence of alpha waves (8-12 Hz) on the EEG recording, followed by a longer (approximately 20 minute) period of stage 2 sleep (N2) characterised by a mixed frequency background featuring sleep spindles and K-complexes.

Stage 3 sleep (N3), otherwise known as slow wave sleep (SWS) is characterised by delta frequency (0.5-4.5 Hz) wave formations of at least 75µV amplitude, which lasts for approximately 30-40 minutes (Iber, 2007).

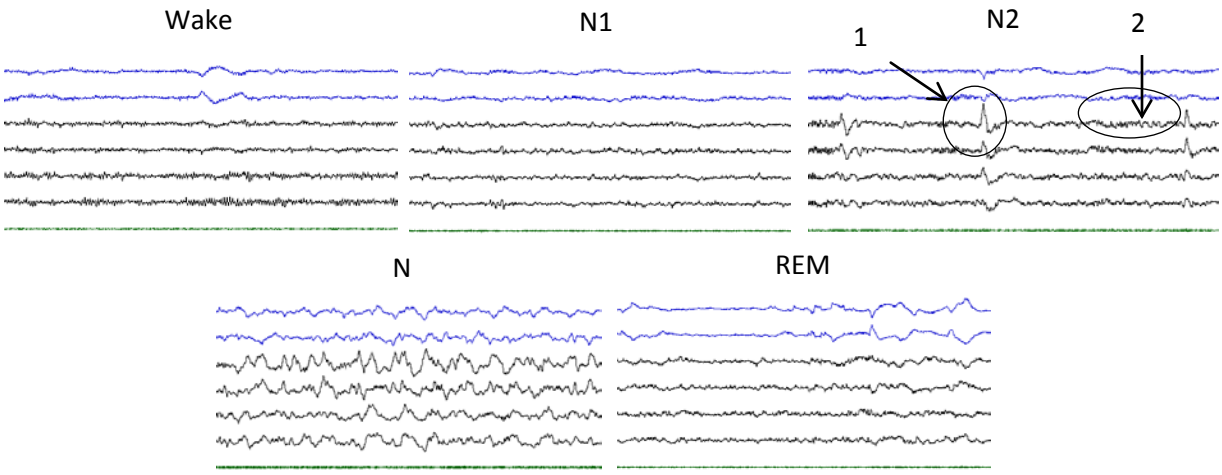


Figure 5 Stages of sleep and scoring information. Figure displays examples of objectively defined wake and sleep through electroencephalography (EEG) from one healthy 22 year-old male as part of an overnight sleep study. Each example presents 30 seconds of data from the following 7 electrodes (top to bottom): left eye, right eye (EOG: electrooculogram); C3-A2, C4-A1, O2-A1, O1-A1; and a single channel of chin EMG (electromyogram). The top left hand image displays wake, the second (middle) top image displays Stage 1 sleep (N1) and the top right hand side image displays Stage 2 sleep (N2). The bottom left hand image displays Stage 3 (N3 or SWS). Rapid Eye Movement (REM) sleep is displayed in the bottom right hand image. 1. Denotes a K-complex and 2. Denotes a sleep spindle.

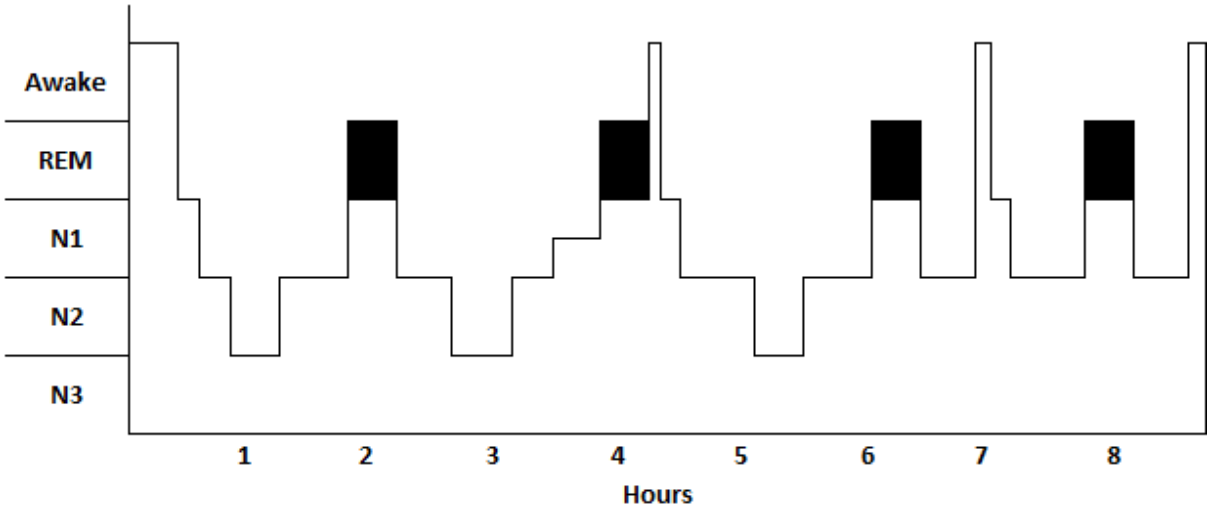


Figure 6 Hypnogram of scored human sleep staging. Figure displays an example of a normal hypnogram used to provide an overview of the progression of sleep stages during the night for an individual's sleep. The hypnogram is a continuous recording of EEG (electroencephalogram), EOG (electrooculogram), and EMG (electromyogram) measures to score sleep. The *y-axis* represents sleep stages (evaluated in 30-second epochs) including: REM (Rapid Eye Movement); Stage 1 (N1); Stage 2 (N2); Stage 3 (N3 or SWS). The *x-axis* represents time during the night in hours.

REM sleep is distinct and contains mixed frequency theta and beta EEG activity, with characteristic sawtooth shaped waves, rapid eye movements and muscle atonia. REM sleep usually occurs for the first time at the end of each sleep cycle and the first period is generally short, lasting 5-10 minutes or less. REM sleep episodes become increasingly longer throughout the sleep period (Aserinsky & Kleitman, 1953; Dement & Kleitman, 1957). The sleep cycles tend to alter their alignment as the sleep period progresses with SWS dominant in the first third of the night and REM sleep more dominant towards the end of the sleep period (Carskadon & Dement, 2011). The proportion relative to total sleep time (TST) is as follows for the following sleep stages: N1 approximately 2-5%, N2 is 45-55%, N3 (SWS) is 20%, and REM sleep 20-25% of TST (Williams, Agnew Jr, & Webb, 1964).

Overall, SWS is associated with homeostatic sleep pressure or the 'amount of time spent awake' and can be quantified physiologically through EEG derived slow-wave activity (SWA; spectral power in the 0.75-4.5 Hz bandwidth) (Achermann et al., 1993). It is important to note that not only is the majority of SWS obtained during the first third of the night but SWS is normally preserved by the brain under sleep restricted schedules (Spiegel, Leproult, & Van Cauter, 1999). In addition, there is also a fast onset of 'deep' SWS sleep (normally after about 20 minutes of lighter stages N1 and N2 sleep) in healthy individuals indicating the importance of this stage of sleep. Studies disrupting SWS have shown impairment in next day performance and endocrine secretion in healthy individuals (Spiegel et al., 1999). One of the primary functions of SWS may be to restore and repair both the brain and the body. On the other hand, REM sleep is more adaptable around SWS sleep needs. REM sleep (named after the discovery of rapid eye movements during this sleep phase; (Aserinsky & Kleitman, 1953) appears important for the consolidation of memory traces through increases in synaptic plasticity in the cortex of the brain (Diekelmann & Born, 2010). REM sleep is related to dream content with people who awake during REM more likely to report being in a dream relative to other stages of sleep (Foulkes, 1962). Crucially, muscle paralysis or atonia takes place during REM sleep and prevents dream enactment. REM behaviour disorder on the other hand is characterised by a lack of muscle atonia and leads to patients acting out their dreams (Schenck, Hurwitz, & Mahowald, 1993). REM behaviour disorder may also be a marker for the subsequent development of a neurodegenerative disorder such as Parkinson's disease (Schenck, Bundlie, & Mahowald, 1996).

2.3.5 Actigraphy.

Sleep can also be profiled through the use of actigraphy which allows patterns of light, sleep, and wake behaviour to be assessed over days or weeks. Actigraphy is cost effective, more convenient than a full PSG (Ancoli-Israel et al., 2003) and can be used repeatedly across many nights to build an ecologically valid assessment of sleep without a first night effect of PSG (Ancoli-Israel et al., 2003). A first night effect is common with a PSG evaluation and is known to impair sleep in healthy good sleepers (Agnew, Webb, & Williams, 1966). Wrist monitors are typically watch-like devices worn on the non-dominant hand and use an accelerometer to record movement over a given threshold (see Figure 7). An event marker can also be used by the wearer to denote time in bed and awakenings during the night. Collected data is downloaded to a computer to observe rest and activity patterns across both night and day. Through analysis software, validated algorithms are used for movement thresholds (Ancoli-Israel et al., 2003). These data can be used to estimate wake and sleep parameters (see Figure 8).

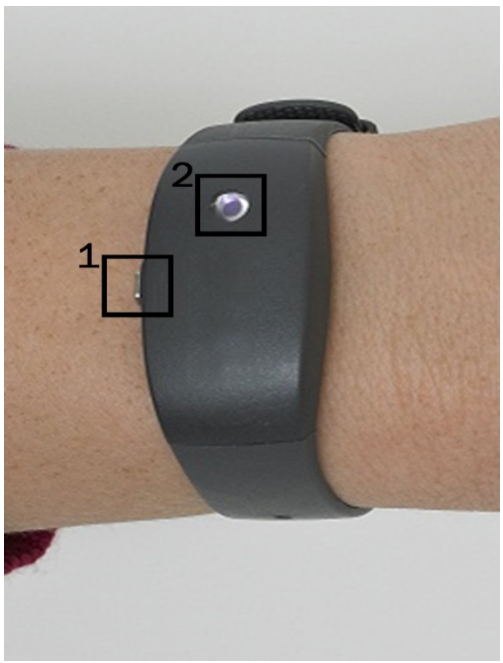


Figure 7 Picture of an actigraph worn on the wrist of the non-dominant hand.1. Denotes the event marker button. 2. Denotes the light sensor.

Figure 8 Actogram of human rest-wake activity from an individual figure displays an example of a scored actogram of human rest-wake activity and light levels from a 42 year-old female patient with insomnia undergoing bed restriction therapy. The *x-axis* represents time across the 24-hour period (12:00pm until 12:00pm). The *y-axis* represents the day of the week (Friday until Thursday). Black lines represent activity levels. Red lines underneath indicate wakefulness. Lighter yellow lines above the black activity levels represent light levels. Light blue in the middle indicates a rest period. The dark blue triangles represent event markers for time in bed by the patient.

The very first analogue wrist monitors were developed and used in the 1970's for an overview see Sadeh and Acebo (2002). They initially underwent reliability testing for the assessment of sleep by Kripke, Mullaney, Messin, and Wyborney (1978). Digital wrist monitors are now used today and have sufficient memory storage for long term use. The sampling rate (epoch) is normally standardised to once every minute although this can be changed by the user through computer software (Sadeh & Acebo, 2002). A longer sampling rate can increase the battery length although this not generally used for research purposes as may compromise data validity if greater than one minute. Previously, actigraphy has been found to have high agreement rates with PSG data for TST and sleep efficiency (SE) variables in healthy subjects (Kushida et al., 2001). However, these variables have been found to have lower agreement rates in patients with OSA and insomnia. Therefore, practice guidelines for the use of actigraphy suggest it should be used in combination with a sleep diary (Ancoli-Israel et al., 2003).

Actigraphy can be used as an inexpensive way to follow-up with patients with varying sleep disorders. It is very useful for patients with insomnia symptomology and treatment (see Figure 8) and also in the diagnosis of circadian rhythm disorders where there is a discrepancy between the patient's internal circadian timing and the external environment (Morgenthaler et al., 2007). In advanced or delayed sleep phase disorder the internal circadian clock of the patient may be ticking either too fast (advanced) or too slow (delayed). The strength of actigraphy is that it provides a non-invasive and long-term measure of activity and sleep. However, unlike PSG, actigraphy does not provide an assessment of sleep architecture and cannot provide a specific diagnosis of a sleep disorder (like OSA).

3.4 Subjective measures of sleep

3.4.1 Clinical interview

An overview of the sleep of a patient can be acquired initially through a common unstructured clinical interview (Buysse et al., 2006). Such clinical interviews are extremely useful for providing a baseline screening assessment and patient history prior to the start of treatment or research study. In terms of taking a patient's history, a clinician would normally ask questions to probe the following areas including: family history, physical health history, previous medication and alcohol use, history of mental illness as well as specific questions regarding the timing and onset of sleep (Schramm et al., 1993). Observations of sleep-wake behaviour during the night from the partner of the patient, family, caregivers or travelling companions can also add useful information to clinical history. For example, reports of parasomnias including acting out of dreams and nightmares can be described by the patient or others and documented in sleep logs/diaries (Blagrove, Farmer, & Williams, 2004).

However, a lack of common standardisation reduces the reliability of these clinical assessments (Buysse et al., 2006). As a result, specifically designed structured interviews for sleep disorders have been used to probe symptoms of insomnia, idiopathic hypersomnia, sleep-wake schedule disorders, sleep-induced respiratory impairment, narcolepsy, restless legs syndrome and periodic movement disorders for example (Ohayon, Guilleminault, Zulley, Palombini, & Raab, 1999; Schramm et al., 1993). One structured interview was initially developed and tested for reliability and validity according to DSM-III-R and DSM-IV criteria (Schramm et al., 1993). The interview can be used to evaluate sleep-wake disorders. The average time for administration is approximately 20-30 minutes. The interview consists of the following: 1. A brief semi-structured overview of physical and mental health and questions regarding OSA and narcolepsy; 2. A specific and structured inquiry of sleep disorder symptoms; and 3. A summary score sheet is filled in at the end of the interview. The interviewer may omit irrelevant sections depending on the response of the patient (Schramm et al., 1993). The interview can be given by physicians or health care professionals with no prior knowledge

of sleep disorders. In this thesis, all participants with insomnia underwent at least a 30-minute semi-structured interview prior to study enrollment.

3.4.2 Sleep diary measures

Sleep can be profiled through daily self-report measures of sleep. Sleep diaries are widely used in sleep science and fundamental to understanding the subjective complaint of patients. Self-monitoring of sleep through a sleep diary enables nightly perceived metrics to be identified and normally includes the following estimated measures: sleep onset latency (SOL), wake-time after initial sleep onset (WASO), TST, total time spent in bed (TIB), SE (percentage of time spent asleep relative to the amount of time spent in bed) and a numerical estimation of overall sleep quality. Normally, patients are asked to complete the diary before they commence their day and refer back to the previous night's sleep with 'approximations' to the nearest five minutes. Some patients may complete this daily in the morning or at both the morning and evening time points. The morning assessment time point is both sufficient and preferred (Carney et al., 2012). Patients (especially those with insomnia) are advised to avoid filling in the sleep diary during the night time, as this may further disrupt their sleep. Likewise, the use of a clock during the night to quantify periods of wakefulness should also be avoided. Estimations of time are therefore necessarily generalised to the nearest five minutes. When compared to gold standard PSG and actigraphy, healthy participants tend to overestimate their TST whereas patients with insomnia underestimate their sleep time (Lichstein et al., 2006; Maes et al., 2014).

Nevertheless, the sleep diary is the gold standard subjective assessment of sleep and an extremely important assessment of insomnia (Carney et al., 2012). The subjective complaint is considered primary and treatment through cognitive behavioural therapy for insomnia (CBT-I) is typically quantified through change and potentially, improvement in primary sleep diary outcomes metrics (SOL, TST, WASO and SE). However, a lack of sleep diary standardisation has hampered research methodologies in measuring sleep, resulting in inconsistent results between studies and a

difficulty in translating in lab findings into clinical practice. To address this, the American Academy of Sleep Medicine set-up an expert consensus of sleep medicine experts in order to standardise a self-report sleep diary. The proposed consensus sleep diary is currently a live document that can be used; however it requires validation, testing, and refinement (Carney et al., 2012). In this thesis, daily measures of sleep diaries (similar to Morin & Espie, 2003) were implemented for two weeks before and for the initial 4-5 weeks of therapy as a primary outcome variable to map response to sleep restriction therapy (SRT) for insomnia. Sleep diaries were also implemented in chapter seven to profile differences between those with insomnia and healthy controls.

3.4.3 Questionnaire assessments of sleep and insomnia

Sleep can be profiled subjectively through self-report questionnaire measures. There are many questionnaires available for patients to report on sleep, quality of life, affect, health related quality of life and also daytime functioning (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). This section will focus on measures of sleepiness, insomnia symptomology and daytime cognition in those with insomnia.

The Epworth sleepiness scale (ESS) is used to profile subjective estimations of excessive daytime sleepiness (Johns, 1992). The overall total score (out of 24) comprises a single factor, the propensity to fall asleep over the previous two weeks. The scale asks people to rate how likely they would be able to doze or fall asleep in eight different settings (sitting and reading for example). Patients are asked to rate on a 0-3 scale (0 = *"would never doze"*, 3 = *"high chance"*) their chance of dozing within those situations. Scores above 16 are regarded as evidence of extreme sleepiness, indicated in patients with idiopathic hypersomnolence or narcolepsy (Johns, 1992). In patients with moderate-to-severe OSA the ESS is sensitive to change with continuous positive airway pressure (CPAP) treatment (Antic et al., 2011); can be used to profile individuals with restricted sleep opportunities or who undertake shift work (Garbarino et al., 2002; Van Dongen, Baynard, Maislin, &

Dinges, 2004). Generally, patients with insomnia will score low but anecdotally if a score >8 is identified it is useful to look for another sleep disorder or depression.

The Insomnia severity index (ISI; Morin (1993)) is a short seven item questionnaire that attempts to define the severity of both the night time and daytime impact of insomnia over the past two weeks (Morin, 1993). It has previously been validated as a clinically useful diagnostic tool and as a treatment outcome (Bastien et al., 2001). The items of the questionnaire evaluate the following: duration of sleep onset, sleep maintenance, early morning awakening, sleep dissatisfaction, daytime functioning, noticeability of sleep problems by others, and the distress caused by the sleep problem. Each item uses a 5-point Likert scale to capture a rating (0 = *"no problem"*; 4 = *"very severe problem"*). Each item score is summed and yields a total score from 0 (no insomnia) to 28 (severe clinical insomnia). The total score is interpreted as follows: no insomnia (0-7); subthreshold insomnia (8-14); moderate clinical insomnia (15-21); and severe clinical insomnia (22-28). The questionnaire has also been used in population based studies to quantify and evaluate insomnia symptomology in community samples. High internal consistency has been found for both clinical and community based samples (Cronbach $\alpha \geq 0.90$).

The daytime Insomnia symptom scale (DISS; Levitt et al. (2004)) has been used previously to probe differences in sleep, rhythms and affect in groups of patients with insomnia compared to healthy good sleeping controls (Buysse et al., 2007; Levitt et al., 2004). The DISS will be used in the next chapter to map changes during the acute phase (first 3 weeks) of a successful behavioural intervention for insomnia (Miller et al., 2013). Specifically, the DISS uses 20 visual analogue scales (ranging from 0 to 10 on a 10cm line) and asks the participant to mark where they believe to agree or disagree with each of the statements at the specified moment in time. For example, question one asks; *"How alert do you feel"* with *"Very little"* at the extreme left of the 10cm line and *"Very much"* at the far right. These items form four factors (alert cognition, sleepiness/fatigue, and positive and negative mood).

Previously, participants have been asked to complete the DISS at four assessment time points per day as part of an ecological momentary assessment (EMA: at awakening, noon, early evening and bedtime) for at least one week (Buysse et al., 2007; Levitt et al., 2004). We used EMA in contrast to the more sophisticated sampling technique of event sampling monitoring which to our knowledge has not been used in sleep research. EMA is a component of event sampling monitoring where a stimulus is randomly given to a participant during the day and they are asked about an aspect of behaviour or mood (Shiffman, Stone, & Hufford, 2008).

EMA is advantageous as it allows the reporting of ecologically valid symptoms within the context of the individuals own environment and has been validated in insomnia research (Buysse et al., 2007). EMA can profile the daytime impact, potential mechanisms of action, and adverse effects during treatment of insomnia on a day-by-day basis and through the course of treatment. Insomnia is a highly variable condition that can alter in severity across time and EMA is well suited for characterising these changes in symptomology. EMA can detect specific micro point-in-time alterations in mood and cognition during the day compared to more global retrospective assessments of insomnia (e.g. ISI).

3.5 Cortisol

Hormones are used by the endocrine system to signal changes related to sleep-wake timing and sleep stages. Many hormones can be measured as part of sleep research and this section will specifically highlight cortisol as a measure of increased arousal in those with insomnia (Bonnet & Arand, 2010). The following section focuses on cortisol as a primary outcome measure in this thesis.

The alerting/stress hormone cortisol is known to be affected by sleep and has a strong circadian rhythm. Cortisol is the output from the hypothalamic-pituitary-adrenal axis, which is an endocrine system malleable to both bodily and external influence (Elder, Wetherell, Barclay, & Ellis, 2014). Cortisol secretion can be measured in saliva, blood, urine or hair. Specifically, it has a 24 hour circadian rhythm with secretion increasing after awakening and peaking in the first 30 minutes of wakefulness. Cortisol then gradually declines over the course of the day and reaches its lowest point at around midnight. Levels remain low and begin to rise again in time for awakening (Follenius, Brandenberger, Bandesapt, Libert, & Ehrhart, 1992). Therefore cortisol must be analysed for expected circadian rhythmicity when measuring as an outcome. During sleep, diminished cortisol secretion has been found to be associated with SWS, suggesting cortisol may be involved in regulating sleep (Follenius et al., 1992). The first sample on awakening and the resulting morning peak in cortisol (referred to as the cortisol awakening response) have both been studied extensively in sleep research (Elder et al., 2014). Plasma and urinary cortisol concentrations are increased in patients with insomnia compared to healthy good sleeping controls (Rodenbeck, Huether, Ruther, & Hajak, 2002; Vgontzas et al., 2001; Vgontzas et al., 1998). Chapters five and six evaluate change in salivary and plasma cortisol concentrations during and after SRT for insomnia. Although more stressful to the participant and more difficult to obtain, plasma cortisol is considered a more robust measure of cortisol compared to salivary cortisol due to variability that can occur in sampling with saliva. For example, brushing teeth, cigarette smoking or drinking orange juice may cause erroneous results in saliva collection (Clow, Thorn, Evans, & Hucklebridge, 2004).

3.6 Neuroimaging & magnetic resonance spectroscopy

Neuroimaging can be used to investigate changes and differences in the brain in those with sleep disorders. Specifically, magnetic resonance spectroscopy (MRS) can evaluate *in vivo* brain metabolism. Within insomnia, MRS has been used to document differences in brain metabolism compared to healthy good sleeping controls (Spiegelhalder, Regen, Baglioni, Riemann, & Winkelman, 2013). However, the use of MRS in insomnia sleep research and sleep pathology is still in its infancy and one of the aims of this thesis is to provide novel data on potential differences between those with insomnia and healthy controls. The following section provides a brief overview of MRS and the metabolites that can be measured with this technique.

3.6.1 Magnetic resonance spectroscopy

Brain metabolism can be measured through *in vivo* proton MRS which is useful for understanding subtle changes due to disease and/or response to treatment. A number of metabolites are examined through this technique including: *N*-acetylaspartate (2.05 relative units parts per million: ppm); creatine (3.02ppm), choline (3.22 ppm), glutamate (2.35 ppm), glucose (3.43 ppm), *myo*-inositol (3.56 ppm) and lactate (1.33 ppm) among other measures (Rae, 2014). The sleeping brain and the consequences of sleep disorders have also been studied using MRS. Moderate oxygen desaturation can affect brain bioenergetic status during sleep (Rae et al., 2009). Brain neurochemistry is known to be altered in those with OSA compared to healthy individuals (Bartlett et al., 2004; Kamba et al., 2001) with reduced creatine levels in the left hippocampal area correlating with increased OSA severity and deteriorating cognitive performance. The following section provides an overview of the metabolites that can be obtained from MRS.

3.6.2 Metabolites from magnetic resonance spectroscopy

Gamma-Aminobutyric acid (GABA) is found at 3.0ppm and is the primary inhibitory neurotransmitter in the central nervous system (Gottesmann, 2002). GABA is closely linked to and metabolised from glutamate (GLU) (Stagg et al., 2011). GABA is also linked to brain function (Puts & Edden, 2012) and higher GABA levels have been associated with increased concentration and decision making speed (Sumner, Edden, Bompas, Evans, & Singh, 2010). Lower levels of GABA are thought to contribute to symptoms of depression, anxiety (Kalueff & Nutt, 2007) and also insomnia (Winkelman et al., 2008). Also, GABAergic interneuron inhibition is thought to impact a number of processes concerning the regulation of sleep, anxiety, motor control and pain (Möhler, 2006). In psychiatric disorders like schizophrenia, deficits in GABAergic inhibition may have implications for symptomology (Lewis, Hashimoto, & Volk, 2005). Thus agents are used that increase GABAergic activation (Kalueff & Nutt, 2007).

Creatine (CRE) protons resonate at 3.02ppm and this peak is made from protons consisting of free CRE and phosphocreatine which are in almost equilibrium exchange (Chen, Zhu, Adriany, & Uğurbil, 1997). Creatine is the central energy marker of both neurons and astrocytes and plays an important role in maintaining energy homeostasis within the brain (Lin, Ross, Harris, & Wong, 2005). Higher levels may provide protection from hypoxia with a supplement potentially reducing neurological and atherosclerotic disease risk (Wyss & Schulze, 2002) and improved cognitive performance (Rae, Digney, McEwan, & Bates, 2003). CRE should not be assumed to be stable in the brain, but studies do use metabolite ratios with CRE as the denominator and has questionable significance (Rae, 2014). This practice is potentially misleading with increased variability found with this method when compared to reporting individual metabolite components (Li, Wang, & Gonen, 2003).

GLU and Glutamine (GLN) are a mixture of closely related amino acids, amines and derivatives involved in neurotransmission (excitatory and inhibitory) and lie between 2.05 and

2.5ppm. At times, GLU and GLN can be collectively referred to as GLX due to overlapping spectral resonances at 1.5 Tesla (T). At 3T this is also the case and a GLU resonance may contain GABA and GLN. Although an asymmetric point-resolved surface coil spectroscopy (PRESS) sequence can be used to further uncover GLU (Snyder & Wilman, 2010). However, by increasing the power of the magnet to approximately 7T it is possible to decisively separate out these resonances. It is not currently clear if higher field strengths have adverse effects but 7T has been found to be tolerated by humans (Theysohn et al., 2008).

GLU is found at 2.35ppm and is the highest concentrated amino acid and major excitatory neurotransmitter in the brain (Bennett & Balcar, 1999; Fonnum, 1984). GLU has the potential to be neurotoxic but protective mechanisms are able to inhibit those excitatory and neurotoxic effects (Choi, 1988). GLU levels have been shown to be linked to increased metabolic activation (Sibson et al., 1998). In alcoholics, increased levels of GLU have been found and may be due to a combination of increased metabolic activation and poor excretion/removal processes from the brain (Kalivas, 2009; Koga et al., 2011).

GLN is found at 2.45ppm in high concentrations across the brain and is synthesised from GLU. GLN is an astrocyte marker, aids synthesis of GABA, is a by-product of GLU neurotransmission (Rae, 2014), is increased during hypoxic-ischemic events (Mountford, Stanwell, Lin, Ramadan, & Ross, 2010) and is decreased in Alzheimer's disease and in those with major depressive disorder (Walter et al., 2009). Currently little data are available on the role of GLN and brain function.

Glutathione (GSH) is found at 2.95ppm and is a major antioxidant and tripeptide found in high concentrations across the brain but difficult to detect due to overlap with other resonances (Rae, 2014). GSH is pivotal to life and plays important roles in protein synthesis and degradation as well as forming precursors to deoxyribonucleic acid (Rae, 2014). Increased GSH levels may be a marker for drug resistance as GSH is associated with removal of electrophilic compounds from cells (Leslie, Deeley, & Cole, 2001). Reductions in GSH levels indicate degeneration of neurons in specific

areas of the brain (e.g. Parkinson's disease) (Han, Cheng, Yang, & Dryhurst, 1999). Increased GSH levels appear protective against toxic oxidative stress in the central nervous system (Dringen, Gutterer, & Hirrlinger, 2000; Satoh & Yoshioka, 2006). GSH levels are also known to decline with age (Rae, 2014).

Myo-inositol (MINO) is a sugar found at 3.56ppm and is considered a glial marker (Castillo, Kwock, Scatliff, & Mukherji, 1998). Increases in MINO denote change in glial size and proliferation associated with inflammation and the breakdown of myelin (Rosen & Lenkinski, 2007). MINO has been reported to be increased after stroke, head injury, Alzheimer's disease, gliosis and astrocytosis (Rae, 2014; Soares & Law, 2009).

N-acetylaspartate (NAA) is found at 2.02ppm (Soares & Law, 2009) and displays one of the largest resonance peaks. It is also one of the most highly concentrated free amino acids in the brain (Rae, 2014). NAA is synthesized from acetyl coenzyme-A and aspartate (ASP) and contains components from *N*-acetyl methyl groups. Breakdown of *N*-acetyl-aspartylglutamate releases both NAA and GLU. NAA is increased only in Canavan disease and reduced NAA can be a marker of insult to the brain (Castillo et al., 1998). NAA is thought to be a marker of neuronal viability, functioning and density although the exact role for NAA is unknown (Castillo, Kwock, & Mukherji, 1996). NAA may be reduced in those with OSA (Kamba et al., 2001). However, the brain may be able to compensate in alternate ways if NAA is reduced (Rae, 2014).

3.6.3 Voxels of interest

For the measurement of brain metabolism voxels of interest must be located be chosen *a-priori* to the beginning of a MRS study. Voxels refer to the volume of the area of the brain (volume of interest: VOI) that is to be sampled. Generally in MRS, the volume is between 2 and 8cm^3 (Castillo et al., 1996). Larger voxels have larger volumes of tissue and therefore have a decreased signal-to-noise ratio which will consist of more background noise and artifacts making interpretation of the spectra difficult (Mountford et al., 2010).

3.7 Sleep restriction therapy

For the treatment intervention in chapters four, five and six a standardised SRT intervention was developed as part of this thesis and used across both sites at Glasgow and Sydney. Therapy comprised one, 40 minute face-to-face session, using previous instructions (Spielman et al., 2010). In line with previous SRT impairment findings, a minimum time in bed (sleep window) was set to no less than five hours (Kyle et al., 2014) see Appendix A: Sleep restriction therapy method for an example. The sleep window was firstly anchored with a morning wake-up time that considered the participants normal daytime commitments. From this, the therapist (CBM) worked back around the clock to establish the initial go to bed 'threshold time'. Participants were instructed not to go to bed until after the threshold time and to only go to bed if they felt 'sleepy tired'. The intervention was standardised and supported by a brief set of digital slides (eight in total see Appendix B: Sleep restriction therapy presentation slides) and an information manual (11 pages, in plain English: see Appendix C: Sleep restriction therapy information manual). For chapters four and five, two further in-person sessions and two telephone calls (each 5-10 minutes) were provided to review SE and titrate the sleep window each week, therapy ceased after 4 weeks. For chapter six only, up to five weekly telephone calls only (each 5-10 minutes) were provided to review SE and titrate the sleep window. For titration, TIB was modified on a weekly basis. Changes were made to TIB incrementally, depending upon the achievement of "good sleep efficiency"; 85-89% no change, ≥ 90% increase by 15 minutes, less than 85% decrease by 15 minutes (Spielman et al., 2010). Time out of bed was rarely changed. In nearly all cases time to bed was modified in line with previous instructions by Spielman et al. (2010) (see Table 5). No other CBT-I components were addressed.

Home adherence to SRT was monitored through subjective sleep diary (throughout therapy), and also through a specific sleep restriction adherence scale (SRAS; Kyle & Crawford, unpublished), completed on a week-by-week basis. The SRAS is loosely based on the Medical Outcomes Study general adherence scale (MOS-A; Kravitz et al. (1993)), but is modified to probe adherence to different aspects of SRT, through five specific questions (e.g. Item 4: "I got up at my calculated 'rising time' on weekdays..." / response selection: 1= ' None of the time'; 2= 'A little of the time'; 3= 'Some of the time'; 4= 'A good bit of the time'; 5= 'Most of the time'; 6= 'All of the time'). Possible total SRAS scores range from 5-30, with higher scores being indicative of greater levels of adherence. Preliminary (unpublished) psychometric evaluation of the SRAS, with 42 insomnia patients undergoing SRT, reveals high levels of internal consistency (Cronbach's α = .92; range of item-deletion α = .89-.93, mean α = .91).

3.8 Recruitment & participants

All participants with insomnia recruited in this thesis went through a similar recruitment process at both Glasgow and Sydney. Patients were recruited through responses to advertisements in clinic, online and in the local community. Potential participants were initially interviewed by telephone through the use of a screening assessment based on Morin and Espie (2003) and asked to refer into a sleep clinic by their general practitioner. All participants were seen by a Sleep Physician for an initial 30 minute sleep and medical evaluation to determine insomnia disorder and evaluate subtype through research diagnostic criteria (RDC) for insomnia (Edinger et al., 2004). Only those with psychophysiological insomnia (PI) were included. PI was determined from the following inclusion/exclusion criteria: the primary complaint of insomnia, a subjective sleep disturbance of three nights per week for at least three months of SOL and/or WASO >30 minutes and a specific daytime impairment attributed to disturbed sleep (Edinger et al., 2004). Current or unstable medical, co-morbid sleep or psychiatric conditions were exclusionary. If suitable, all participants were asked to initially complete sleep diaries and wear actigaphs for at least one week to provide a baseline assessment of sleep and screen for circadian rhythm disturbances. Participants were then screened for evidence of sleep disorders through a full PSG sleep assessment prior to enrolment. Mean apnea hypopnea index (AHI) scores of >10, periodic limb movements of sleep (PLMS) arousal index scores of <10 or minimum oxygen saturations of <90% during the night were all deemed exclusionary. Participants were also excluded if they reported chronic hypnotic use (>3 times per week). Those with occasional hypnotic use (1-3 times per week) were included in this thesis but were asked to refrain from any hypnotic medication for two weeks prior to the initial screening overnight PSG assessment and then refrain from any further use of hypnotics during the entire course of study. ISI (Morin, 1993) scores were used to define insomnia severity.

3.9 Statistical analysis

For within subjects repeated measures data, all outcome variables were evaluated with boxplots and histograms to check data for normality and outliers. Paired samples *t*-tests were employed to profile the effect of therapy and effect size scores were calculated as previously described (Cohen, 1988): Cohen's $d = M_1 - M_2 / SD_{pooled}$, where $SD_{pooled} = \sqrt{[(SD_1^2 + SD_2^2) / 2]}$ (Dunlap, Cortina, Vaslow, & Burke, 1996). Due to potential problems with the small sample size and potential lack of statistical power data were also graphed and visually examined to evaluate individual changes due to therapy.

For primary dependent repeated measures outcome variables in chapters four, five and six a linear mixed model analysis using Statistical Package for the Social Sciences (SPSS) software (IBM v 19.0.0; IBM, Amonk, NY, USA) was implemented for each outcome variable. Fixed effects included: time (before, during or after) of the intervention, and for time of day or night. Random effects were run to account for between-subject variation. Only random effects were included for the intercepts. Uncorrected Pairwise comparisons based on estimated marginal means were implemented to investigate the primary outcomes. In chapter seven, boxplots and histograms were checked for outliers and independent samples *t*-tests were implemented to profile differences between those with insomnia and healthy good sleeping controls.

Methods used for the assessment of sleep

Method	Description	Pros	Cons
Polysomnography (PSG)	Objective measure of sleep and disorders of sleep	1.Gold standard measure of sleep and the disorders of sleep	1. Expensive 2. Difficult to access 3. Discomfort 4. First night effect 5. Requires analysis & interpretation
Actigraphy	Objective measure of movement used to infer sleep-wake behavior	1. Correlates with PSG 2. Can be used long-term 3. Ecologically valid 4. Target for treatment	1. Limited by battery length 2. Requires analysis & interpretation
Clinical interview	Objective measure of movement used to infer sleep-wake behavior	1. Accessible 2. Clinically valid 3. Useful prior to treatment or research	1. Lack of standardization 2. Limited without further measures of sleep
Sleep diary	Subjective measure of sleep-wake behaviour	1. Accessible 2. Target for treatment 3. Easy to use & inexpensive	1. Poor correlation with PSG 2. Must remember to fill in 3. Subjective measure of sleep 4. Requires analysis & interpretation
Questionnaires	Subjective measures of sleep, wake, health & cognition	1. Accessible 2. Target for treatment 3. Easy to use & inexpensive	1. Open to bias 2. Requires analysis & interpretation
Magnetic Resonance Spectroscopy (MRS)	Objective measure of metabolites of the brain	1. Non-invasive method to investigate brain metabolism 2. Can be used during sleep	1. Expensive 2. Difficult to access 4. Lack of validity 5. Requires analysis & interpretation
Cortisol assessment	Hormone used to infer stress & increased arousal in insomnia	1. Objective measure 2. Closely linked to the sleep cycle	1. Requires analysis 2. Difficult to access 3. Test requires further validation

Table 10 Overview of the methods used for the assessment of sleep. Displays the pros and cons of a range of the most commonly used measures to research and diagnose sleep and its disorders.

Chapter 4: An ecological momentary assessment of sleep restriction therapy for insomnia

The contents of this chapter have been published as follows:

'Ecological momentary assessment of daytime symptoms during Sleep Restriction Therapy for Insomnia' Miller, C.B., Kyle, S.D., Marshall, N.S., & Espie C.A. (2013). *Journal of Sleep Research,* 22, 266-72.

4.1 Abstract

This study profiles changes in self-reported daytime functioning during sleep restriction therapy (SRT) for insomnia. Ecological momentary assessment captured point-in-time symptomatology to map the time course of symptoms. We hypothesised a deterioration (week 1) followed by improvements at week three of therapy relative to baseline. Nine patients with psychophysiological insomnia completed the daytime insomnia symptom scale (DISS) at risetime, 12:00hr, 18:00hr, and bedtime, for one week before and three weeks during SRT. Four validated factors from the DISS were analysed (alert cognition, positive mood, negative mood, and sleepiness /fatigue) across 28 days yielding 17,170 data points. Factors evaluated week (baseline v. weeks 1 and 3) and time of day symptomatology. Insomnia severity index scores decreased significantly pre-to-post treatment (mean = 18 v. 7). Reflecting acute effects of SRT, significant differences were found for all factors, except negative mood, between baseline and week one of SRT, suggesting adverse effects. By week three, sleepiness/fatigue and negative mood decreased significantly compared to baseline, and positive mood showed a trend towards improvement (p=.06). Sleepiness/fatigue displayed a significant week x time of day interaction, explained by a reduction in sleepiness/fatigue at every daytime assessment point (except bedtime, which remained high). A significant interaction for alert cognition was associated with reduction in alertness at bedtime by week three, and an increase in alertness at risetime; suggesting, SRT not only improves sleep, but moderates alertness and sleepiness in therapeutic ways. Initial SRT is associated with an increase in sleepiness/fatigue and a decrease in alert cognition.

4.2 Introduction

Insomnia is a highly prevalent and costly disorder (Daley, Morin, LeBlanc, Gregoire, & Savard, 2009). It is associated with workplace deficits, increased health risks and health care utilisation (Siebern & Manber, 2010). Further, health-related quality of life has been found to be impaired and it is thought that this drives treatment seeking behaviour (Kyle et al., 2010).

One of the main effective treatments for insomnia is cognitive behavioural therapy (CBT-I) (Morin, Bootzin, et al., 2006; Smith, Perlis, Park, et al., 2002). Sleep restriction therapy (SRT) has been widely utilised within CBT-I Indeed, it is nearly always included in single or brief interventions to treat insomnia (Buysse, Germain, Moul, et al., 2011; Edinger & Means, 2005). Anecdotally, it is believed to be one of the most active components within CBT-I. Despite this, our current understanding of how and why this potent and difficult behavioural intervention may work is poorly understood (Morgenthaler et al., 2006). Further, adherence and the perceived benefits of this therapy have previously been linked to a positive treatment response (Harvey et al., 2002). Yet, it may also cause some adverse effects (Kyle et al., 2014; Kyle et al., 2011). In order to further understand the daytime impact, mechanisms, and adverse effects of this brief behavioural therapy, novel measurement approaches must be implemented. Ecological momentary assessment (EMA) was used to profile the daytime impact, potential mechanisms of action, and adverse effects of standalone SRT on a day-by-day basis through the course of treatment (see section 3.4 Subjective measures of sleep for an overview).

The aim of this study was to profile self-report daytime functioning over the course of three weeks of SRT for insomnia. We hypothesised that daytime levels of alert cognition, sleepiness/fatigue, positive and negative mood, from the daytime insomnia symptom scale (DISS; Buysse et al. (2007) would initially deteriorate in line with an acute restriction of sleep opportunity, but then improve beyond baseline levels through SRT in line with a treatment response.

4.3 Methods

Nine participants who responded to advertisements were recruited from the general population and were screened for psychophysiological insomnia (Edinger et al., 2004) see chapter 3.8 Recruitment & participants. Participants slept for two nights in the University of Glasgow Sleep Centre, Scotland, prior to study enrolment as part of a concurrent insomnia trial (grant # R01MH077901).

Two nights of polysomnography (PSG) were used to exclude sleep-related co-morbidities and to acquire a baseline assessment of sleep. A standard PSG montage was used, involving Electroencephalographic (EEG: Fp1 (neutral), C3, P3 (reference), O1, Fpz, Fz, Cz, Pz, Oz, F4, C4), electrooculographic (EOG: horizontal and vertical) and electromyographic (EMG) submental recordings. On night one, all participants were screened for sleep-disordered breathing and periodic limb movements through monitoring of abdominal and thoracic effort, nasal airflow, oximetry, and bilateral tibialis anterior EMG. Sleep was recorded on a lifelines trackit ambulatory recorder and scored visually by two experienced scorers (>90% inter-scorer reliability) according to criteria by Rechtschaffen and Kales (1968). For study inclusion, patients were required to have an apnea hypopnoea index (AHI) and periodic limb movements of sleep (PLMS) index < 10. This study was reviewed and approved by the West of Scotland NHS research ethics committee (protocol #10/SO701/85: see Appendix D: Ethical approval for Chapters 4 & 5).

Therapy was delivered and adherence was measured as described previously in chapter 3.7 Sleep restriction therapy. The insomnia severity index (ISI) (Morin, 1993) was completed before and after therapy to monitor more global effects of treatment. Pairwise comparisons were used to evaluate differences.

Participants completed paper-based versions of the DISS at four assessment points per day (risetime, 12:00hr, 18:00hr, and bedtime) for one week before the SRT intervention (baseline) and for three weeks during the intervention (weeks: 1, 2, and 3), representing the acute treatment phase (See Figure 9). The DISS consists of 20 visual analogue scales (ranging from 0 to 10 on a 10 cm line). The participant is asked to mark along the line where they believe to agree or disagree with each of the twenty statements at the specified moment in time. For example, question one asks; "How alert do you feel" with "Very little" at the extreme left of the 10 cm line and "Very much" at the right.

Eighteen of the 20 items were utilised, forming four previously validated factors; sleepiness/fatigue (containing adjectives; sleepy, fatigued, and exhausted), negative mood (anxious, stressed, tense, sad, & irritable), positive mood (relaxed, energetic, calm, happy, & efficient), and alert cognition (forgetful, clear-headed, concentrate, effort, & alert) (Buysse et al., 2007). In order to improve adherence to this procedure, participants were offered short messaging service text reminders to their mobile phone. Two participants opted to receive these at the 12:00hr and 18:00hr time points only.

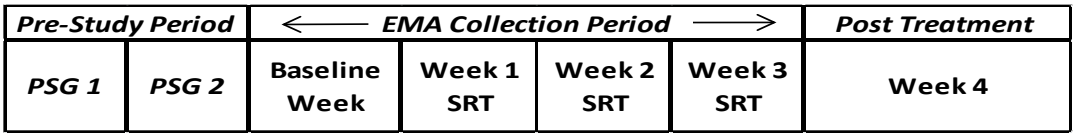


Figure 9 Ecological momentary assessment data collection through brief SRT for insomnia: Participants were sampled from a concurrent insomnia study and underwent two nights of polysomnography (PSG 1 & 2), prior to study enrolment. This was followed by a 4 week ecological momentary assessment (EMA) first through an initial baseline data collection week and then with 3 weeks of sleep restriction therapy (SRT). SRT post treatment outcome measures were assessed at week 4.

A linear mixed model was implemented for each factor (see chapter 3.9 Statistical analysis). Fixed effects included: week (B, 1, 2, 3) of the intervention, and for time of day of DISS completion (risetime, 12:00hr, 18:00hr, and bedtime). Random effects were run to account for between-subject variation. Only random effects were included for the intercepts. Uncorrected Pairwise comparisons based on estimated marginal means were implemented to investigate the primary outcomes.

4.4 Results

In total, 9 patients (6 females; mean age = 46.4yr, range = 34-58) thoroughly screened for psychophysiological insomnia (Edinger et al., 2004) completed this study. No participants were taking prescribed sleep promoting hypnotics during the course of this study.

Confirming the expected therapeutic benefits of SRT, sleep diary data reveals significant and robust improvements, baseline to week four, in both sleep efficiency (73% v. 93%; $p<.01$) and sleep quality ratings (1.8 v. 2.3; $p<.01$). Significant pre-to-post reductions ($p<.001$) were found for; sleep onset latency (33.7 v. 10.7 minutes), time awake after sleep onset (58.7 v. 15), number of awakenings during the night (2.5 v. 1.6), and total time spent in bed (489 v. 367). Total sleep time marginally reduced (357 v. 340); this was not significant ($p>.05$). A significant reduction was found for both total sleep time (357 v. 284; $p <.001$) and time in bed (489 v. 355; $p<.001$) between baseline and week 1 of SRT (see Table 11). ISI scores decreased significantly at post treatment (M=18 (5) v. 7 (5), $p<.05$). The SRT self-report adherence mean scores remained high across the weeks of therapy (week; 1 = 26.1 (3.5), 2 = 24.0 (3.8), 3 = 25.1 (1.3), 4 = 23.1 (6.1); with a range of 10-30.

Turning to the primary purpose of the study, the completion rate for the DISS questionnaire throughout the four weeks of data collection was highly satisfactory at 94.6% (ranging from 76% to 100%), yielding 19,075 data points out of a possible 20,160. Each participant was asked to complete the 20 item DISS at four times per day every day for 4 weeks (B, 1, 2, 3). For the primary analysis 18 questions evaluated four dimensions of interest; sleepiness/fatigue, alert cognition, positive and negative mood. This resulted in 17,170 data points (out of a possible 18,144). The following sections report findings.

In order to firstly evaluate differences for time of questionnaire completion, we looked to evaluate potential daytime patterns to each of the four factors by analysing the main effect of time of day. Significant differences were found across the four daytime assessment points for three factors; sleepiness/fatigue, alert cognition, positive mood [F (3, 930), sleepiness/fatigue = 63.97,

alert cognition = 82.93, positive mood = 42.28]; (all p<.001). Negative mood displayed no diurnal change [F (3, 930) = 0.48]; (p=.699).

To test the initial hypothesis for a deterioration in symptoms at week one of SRT, main effects were analysed for week, yielding significant results for all four factors [F (3, 930), sleepiness/fatigue = 14.30, alert cognition = 6.54, negative mood = 7.75, positive mood = 6.81]; (all p<.001). We then compared baseline to week one of SRT for all factors. Pairwise comparisons revealed a significant increase for sleepiness/fatigue (p<.01), a significant decrease for alert cognition (p<.001), and positive mood (p <.05), and no change for negative mood. This deterioration in symptoms at week one was in line with our initial hypothesis regarding early adverse effects due to acute sleep restriction as part of therapy. To test the second part of our hypothesis (that daytime insomnia symptoms would reduce through SRT) we evaluated differences between baseline and week three. Consistent with expectation, a significant decrease (p≤.001) was found for sleepiness/fatigue and negative mood, with a trend for improvement in positive mood (p=.06). Alert cognition, however, was not significantly different (see Table 11).

	Mean and Standard Deviations			*Mean and 95% Confidence Intervals*			
	Prescribed Time in bed (apart from baseline)	***Total Sleep Time***	***SRAS***	***Alert Cognition***	***Sleepiness / Fatigue***	***Negative Mood***	***Positive Mood***
Baseline Week	489 (49.4)	357 (35.8)		53.0 [45.3, 60.8]	54.5 [44.8, 64.2]	26.1 [15.8, 36.4]	55.0 [48.0, 61.9]
Week 1	355 (24.5)	285 (33.1)	26.1 (3.5)	47.7 [39.9, 55.6]	59.2 [49.5, 68.9]	27.4 [17.1, 37.7]	52.0 [45.1, 58.9]
Week 2	350 (21.2)	311 (27.3)	24.0 (3.8)	51.8 [42.2, 61.7]	52.0 [42.2, 61.7]	25.9 [15.6, 36.2]	54.5 [47.6, 61.4]
Week 3	362 (20.5)	323 (27.4)	25.1 (1.3)	53.0 [45.2, 60.8]	48.4 [38.7, 58.1]	22.5 [12.2, 32.8]	57.1 [50.2, 64.1]
Week 4	367 (21.3)	340 (24.8)	23.1 (6.1)				
Paired Differences Testing							
	Mean and Standard Errors			*Mean Difference and 95% Confidence Intervals*			
Baseline v. Week 1	489 (16.5) v. 355 (8.7)***	357 (11.9) v. 285 (11.0)***		5.2 [2.5, 8.0]***	4.7 [-8.1, -1.4] **	1.3 [-3.4, 0.8]	3.0 [0.7, 5.2] *
Baseline (Week 1 for SRAS) v. Week 3 (Week 4 for TIB, TST & SRAS)	489 (16.5) v. 367 (7.5)***	357 (11.9) v. 340 (9.4)	26.1 (1.2) v. 23.1 (2.2)	0.0 [-2.8, 2.7]	6.2 [2.8, 9.6] *	3.6 [1.5, 5.7] **	2.2 [-4.5, 0.94]

Table 11 Sleep restriction therapy for insomnia (SRT): mean sleep diary data, sleep restriction adherence scale (SRAS), and daytime insomnia symptom scale factor scores. The top half of the table describes the mean sleep diary data with range and standard deviations (minutes) for total sleep time (TST) and prescribed time in bed (TIB) for weeks 1-4 of SRT, the mean, range and standard deviations of SRAS scores (for weeks 1-4 of SRT), and the mean (with 95% CI) for the 4 daytime symptoms variables over the 4 weeks of observation. The bottom half of the table tests for differences in TST, TIB and SRAS results. This also tests our specific hypotheses about a transient worsening of mood in response to SRT at week 1 followed by an overall improvement over the course of treatment by week 3 (*p<.05, **p<.01, ***p≤.001).

Next, a time of day x week interaction was used to examine potential diurnal changes in the daytime assessment of symptoms through SRT between baseline and week three. Sleepiness/fatigue [F (9, 930) = 2.54]; (p<.01), and alert cognition [F (9, 930) = 2.42]; (p<.05), displayed significant interactions. This was non-significant for positive [F (9, 930) = 1.24]; (p=.27) and negative mood [F (9, 930) = 0.36]; (p=.96). Specifically, pairwise comparisons revealed a decrease at week three compared to baseline for sleepiness/fatigue at the risetime (61.9, 95% CI [51.6, 72.2] v. 52.2, 95% CI [42.0, 62.5]; p<.01), 12:00hr (47.9, 95% CI [37.6, 58.2] v. 37. 0, 95% CI [26.7, 47.3]; p<.01), and 18:00hr (48.3, CI [38.1, 58.6] v. 39.6, CI [29.3, 49.9]; p<.05), time points. The bedtime time point increased but not significantly (p=.17). For alert cognition, comparisons revealed a significant increase for risetime (42.2, CI [33.8, 50.5] v. 48.5, CI [40.2, 56.7]; p<.05) and a significant decrease at the bedtime assessment point (49.4, CI [41.1, 57.712] v. 40.3, CI [32.0, 48.6]; p<.01) at week three of SRT. With no significant differences for the 12:00hr and 18:00hr time points (see Figure 10).

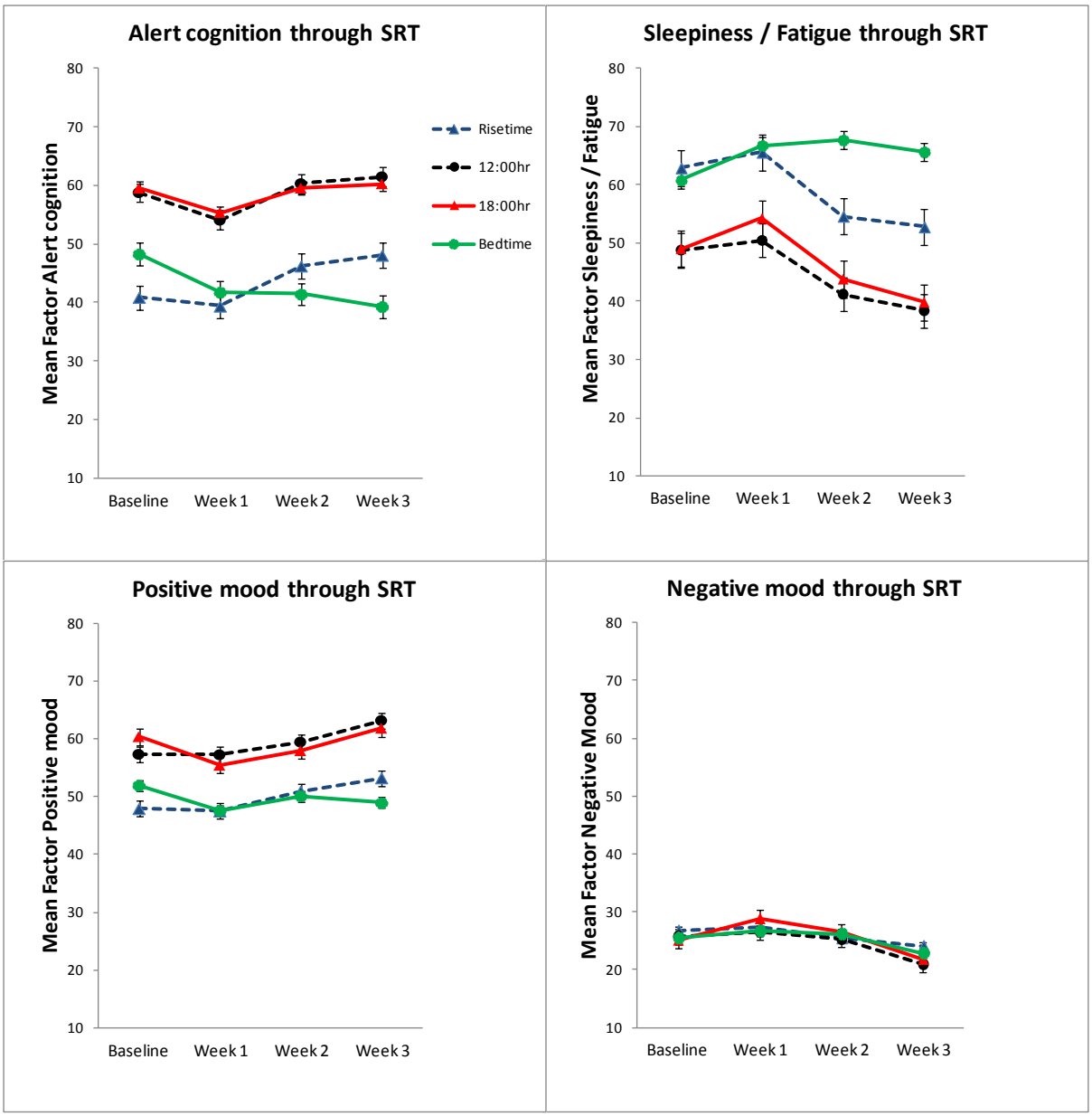


Figure 10 Time course of daytime symptoms through baseline and 3 weeks of sleep restriction therapy. Graphs of each of the 4 factors of the daytime insomnia symptom scale (DISS); Sleepiness/fatigue, alert cognition, negative mood, and positive mood for all (*n*=9) participants through the 4 weeks of ecological momentary assessment. Mean visual analogue scores (0-100mm) are represented on the *y*-axis. Week of data collection (baseline - week 3) is represented along the *x*-axis. Each line represents a daytime assessment time point; Risetime (blue), noon (green), 18:00 (black), and bedtime (red), for the specific factor through baseline and weeks 1-3 of therapy. Error bars represent one standard error of the mean.

4.5 Discussion

As a prelude to discussing the impact of SRT on daytime variables, it is important to first note the following about this exploratory treatment study; participants adhered to the SRT instructions (as evaluated by the SRT adherence scale), SRT was effective in improving sleep through a reduction in insomnia severity, and the completion rate for the DISS questionnaire was high.

Our primary aim was to examine self-report daytime functioning during the acute course of SRT and to evaluate any initial impairment compared to baseline. Initial implementation of SRT led to significant elevations in sleepiness/fatigue and significant reductions in alert cognition and positive mood (week 1 compared to baseline), suggesting a general deterioration in symptoms in line with previously found adverse effect data (Kyle et al., 2011). Negative mood remained unchanged. Our data suggest a reduction of symptoms by week three of SRT compared to baseline, with sleepiness/fatigue and Negative mood both reducing significantly. Specifically, sleepiness/fatigue reduced at risetime, 12:00hr, and 18:00hr, but the bedtime assessment increased (but not significantly). Alert cognition did not change overall but instead evidenced changes at specific time-points; increasing at risetime and decreasing at bedtime (both significantly), suggesting improvements due to SRT (see Figure 10).

Modification in daytime 'alert cognition' may suggest a potential mechanism by which SRT exerts its therapeutic effect. That is, SRT may help re-structure cognitive arousal, inhibiting it at sleep-onset (to permit sleep) and restoring it at risetime (to permit optimum daytime functioning). This is perhaps an important finding as cognitive arousal is a hallmark of psychophysiological insomnia prior to sleep. Patients who implement SRT should spend less time in bed awake, have a higher sleep drive and be less likely to have a 'racing mind' due to increased sleepiness and less time to think in bed prior to sleep onset. Re-structuring may therefore allow a normalisation of cognitive arousal which reflects a treatment response. Interestingly, baseline alert cognition scores resemble those previously found in insomnia, by week three of treatment, however, these scores resemble

that of the good sleeping controls (Buysse et al., 2007). Specific testing of this normalisation of alert cognition at risetime and bedtime may help uncover the role of cognitive arousal in insomnia in response to effective behavioural treatment. Further trials are required with untreated waitlist controls in order to fully understand if these changes are related to SRT.

Further, the increase in the factor sleepiness/fatigue at bedtime at week three of SRT is indicative of heightened sleep pressure at bedtime (reflected, also, in reduced sleep latencies). This may help to overcome cognitive arousal (as previously described in the reduction in alert cognition), suggesting a validation of alterations to the sleep experience and cognitive arousal facilitating the initiation of sleep. This has previously been postulated as a mechanism of action within SRT (Pigeon & Perlis, 2006; Spielman et al., 1987). Future studies, with larger samples and in the context of a more controlled design, should assess whether changes in sleepiness/fatigue relate to changes in cognitive arousal. As for the two affect factors; positive mood increased overall through SRT (but not significantly), with a slight trend for higher scores at risetime. Negative mood displayed no daytime differences (unlike the other 3 factors). This may be attributable to these factors all assessing the same fundamental construct, a lack of power to test this hypothesis, or no dysphoric symptoms within the subject group. Although negative mood did reduce significantly at week three compared to baseline (the mean difference was only 3.6; see Figure 10). It should be noted that results now need to be replicated in larger scale studies not only to validate findings but to provide context and the meaningfulness of the changes in daytime cognition. Overall, sleepiness/fatigue decreased by approximately 6 points, negative mood by 3 and positive mood by only 2 (alert cognition did not change). It remains to be seen if these relatively small changes in scores reflect improvements that are meaningful and detectable to patients as they improve with therapy.

This is the first study to map changes in daytime functioning, using an EMA micro approach as opposed to a macro between subjects approach through brief SRT for psychophysiological insomnia. Previously, researchers have focused on differences between groups of insomniacs and

good sleepers in order to profile differences in daytime functioning (Buysse et al., 2007; Levitt et al., 2004). Two studies have validated the use of the DISS through EMA methods in insomnia and healthy good sleepers, but not through treatment. It is, however, difficult to compare the present study findings with that of previous studies as these initially used a non-validated version of the DISS (Levitt et al., 2004) and also solely reported factor scores for the groups of insomniacs and good sleeping controls (Buysse et al., 2007). One other previous study has attempted to compare the differences between good sleeping control participants and insomniacs through ambulatory assessment (Varkevisser, Van Dongen, Van Amsterdam, & Kerkhof, 2007). In this study, the authors attempted to probe differences in performance and well-being (concentration, fatigue, mood, and sleepiness). No differences were found on the performance measures but they did discover that subjective wellbeing was compromised in insomniacs compared to controls. Further trials using EMA methods are now required to evaluate the role of daytime symptoms in response to other single components of CBT for insomnia.

Further, it is also important to note that although the term 'sleep restriction' (SR) is more widely used in sleep science, this is usually in studies where healthy participants are systematically denied a predefined period of sleep to investigate the effects of sleep loss upon cognitive and physiological functioning (Dinges et al., 1997; Van Dongen et al., 2003). However, the context between those studies and ours where SRT is used therapeutically do differ greatly. Nevertheless, some of the effects of SR in these carefully conducted laboratory studies are what have prompted our taking a careful look at the potential adverse effects of SRT insomnia patients. Results suggest that TST reduced significantly between baseline and week one, but not between baseline and week four of SRT. Therefore the changes that we see at week one in the three factors (alert cognition, sleepiness/fatigue & positive mood) may be attributable to changes in perceived sleep time. It is possible that participants adapted over time to the initial effects of this type of sleep restriction by week three (Belenky et al., 2003). Yet, this does not fully explain the significant reduction in sleepiness/fatigue and negative mood at week three compared to baseline levels. Further controlled

studies are required to evaluate acute sleep restriction in patients with insomnia compared to healthy good-sleeping controls.

A number of limitations regarding this study must be addressed. A regression to the mean may explain the reduction in daytime impairments in alert cognition and sleepiness/fatigue. However, an initial decrease in alert cognition and an elevation in sleepiness/fatigue at week one and the subsequent reversal of this at week three suggests a contrary conclusion. The experimenter (CBM) also acted as therapist in this study. Therefore, it is difficult to rule out experimenter, performance, and demand effects. It could be argued that a lack of participants in this study represents low statistical power and increases the probability of obtaining a Type-II statistical error. Also, the precision of estimating unknown parameters may be compromised by the lack of statistical power. Participants were asked to repeatedly respond to items on a visual analogue scale, a fine-grained continuous outcome measure with increased statistical power compared to more standard ordinal measures. Further, we were not able to determine objective adherence to EMA questionnaire completion previously, hand-held computers with time-stamped recordings have been used to determine exactly when a participant completes a questionnaire (Buysse et al., 2007). Use of such devices may be more reliable but they do also bring about difficulties such as battery life and learning how to use them.

In summary, results demonstrate that the DISS, completed through EMA, can profile changes in self-report daytime functioning through SRT for psychophysiological insomnia. Changes at risetime and bedtime for alert cognition and sleepiness/fatigue seem like candidates for further study as mechanisms of action in treatment response; potentially reflecting changes to the input and output of the sleep homeostat and cognitive arousal. Further objective assessments of insomnia treatment through repeated-measures are required in order to elucidate the role of sleep and arousal in response to SRT for insomnia. Results may help uncover mechanisms of action within single components of CBT-I. Those delivering SRT as part of CBT-I should be mindful of an initial

deterioration in symptoms at week one (Kyle et al., 2011). It may be necessary to tailor SRT to suit the needs of the patient in order to reassure and overcome the initial symptoms of therapy. Such understanding may help to safely disseminate this treatment option.

Chapter 5: An assessment of salivary cortisol in response to sleep restriction therapy for insomnia

5.1 Abstract

Physiological hyperarousal has been proposed to be expressed by increased secretion of cortisol concentrations in patients with insomnia compared to healthy sleeping controls. This study aims to profile salivary cortisol concentrations during sleep restriction therapy (SRT) for the treatment of insomnia. A reduction in salivary cortisol concentrations compared to baseline levels after effective SRT for insomnia was hypothesised. In particular, pre-sleep levels were postulated to be lower whilst morning awakening levels remained unchanged. Eight participants with psychophysiological insomnia self-collected salivary cortisol samples at two hours before bedtime, bedtime, and on awakening for 12 stipulated nights during SRT for the following four phases of treatment: baseline (days 1 & 2 of sample collection); early (days 3, 4, & 8); late (days 9, 10 & 11); and follow-up (days 22-25). Insomnia severity index scores decreased significantly pre-to-post therapy (mean (SD) 17.8 (2.7) vs. 8.0 (3.2). No significant differences were found pre-to-post therapy for salivary cortisol concentrations. The lack of a significant difference may be due to the underpowered nature of the study. However, an exploratory analysis revealed a significant difference in the timing of cortisol prior to sleep after therapy. This study may therefore be considered a preliminary range finding investigation in order to determine future protocol for further research into the effects of SRT and salivary cortisol concentrations. Effective SRT for insomnia may reduce cortisol concentrations over a longer timeframe (6 weeks +). Further studies are required to evaluate cortisol in response to treatment for insomnia.

5.2 Introduction

The hyperarousal theory of insomnia suggests an elevated state of activity/reactivity of the central nervous system through cognitive, emotional, or physiological systems may both cause and maintain insomnia (Bonnet & Arand, 1997, 2010). Hyperarousal may cause the hypothalamic-pituitary-adrenal axis (HPA axis) to be elevated in insomnia, increasing the secretion of the stress hormone cortisol when compared to healthy good sleeping controls (Bonnet & Arand, 2010; Riemann et al., 2010).

Previously, higher urinary and plasma cortisol concentrations have been found in insomnia patients compared to controls (Backhaus, Junghanns, & Hohagen, 2004; Rodenbeck et al., 2002; Shaver, Johnston, Lentz, & Landis, 2002; Vgontzas et al., 2001; Vgontzas et al., 1998). For salivary cortisol (SC) concentrations, three studies have profiled differences between insomnia patients and controls. One found significantly lower SC concentrations on awakening compared to controls, which was found to correlate with higher numbers of nightly awakenings and poor subjective sleep quality. The authors speculated that low morning SC concentrations may be due to increased levels of SC during the night and suggested support for the hyperarousal theory of insomnia (Backhaus et al., 2004). Testing of night time measures of SC would have aided the interpretation of this finding. A second study looked at evening cortisol measures prior to sleep compared to controls (Varkevisser et al., 2007), although no between group differences were found. This may have been due to a lack of sensitivity in the assessment of SC concentrations and the timing of sample collection (8pm, 1.5 hours before bed and 15 minutes before bed). Recently, Seelig et al. (2013) found significantly higher SC concentrations during the night in females with primary insomnia (n=13) compared to healthy good sleeping control females matched for age (n=12), suggesting that night time levels of SC concentrations are increased in those with insomnia compared to controls.

With treatment for insomnia, plasma cortisol concentrations appear to be alterable. Rodenbeck et al. (2003) found a significant reduction in night time plasma cortisol secretion after

three weeks of Doxepin compared to placebo in a crossover study with 10 insomnia patients. One recent study described reduced salivary cortisol levels during sleep restriction therapy (SRT) for insomnia. Although, this study lacked any formal statistical testing of cortisol due to a low number of participants (*n*=5) (Vallieres, Ceklic, Bastien, & Espie, 2013). Overall, there are few studies evaluating change in cortisol concentrations through effective treatment for insomnia. This may have occurred due to limited resources. Case control studies are easier to implement, with fewer salivary samples required. Studies have so far failed to adequately evaluate within-subject changes through repeated sampling of SC concentrations over the course of the night and throughout treatment for insomnia. Other measures like heart rate may also have been used to evaluate arousal but again it is difficult to monitor this remotely at multiple time points throughout treatment and in the home environment. Therefore, SC concentrations appear a useful measure as they are less invasive to measure repeatedly, display a distinct circadian period like plasma cortisol concentrations (Elder et al., 2014) and react to stressors that correlate with serum and plasma cortisol concentrations (Kirschbaum & Hellhammer, 1994).

The aim of this study was to profile changes in SC concentrations before, during and after effective single component SRT for chronic psychophysiological insomnia (PI). It was hypothesised that SC concentrations would significantly reduce overall by the end of the acute treatment phase (week 4) of effective SRT compared to baseline levels and that there would be distinct alterations in the individual sampling time points through treatment. Specifically, cortisol would reduce at sampling prior to sleep and increase on awakening in the morning, in line with previous findings (Backhaus et al., 2004; Rodenbeck et al., 2003; Seelig et al., 2013; Vallieres et al., 2013).

5.3 Methods

5.3.1 Participants, therapy & adherence

Due to cost restrictions, 8 out of the 9 participants were invited to complete the following study and were recruited as described previously in chapter 3.7 Sleep restriction therapy. Similar to the previous chapter, participants slept for two nights in the University of Glasgow Sleep Centre, Scotland, prior to study enrolment as part of a concurrent insomnia trial (grant # R01MH077901). The end point for sleep restriction therapy was at the end of 4 weeks of treatment. Polysomnography (PSG) was used to exclude occult sleep-related co-morbidities and to acquire a baseline assessment of sleep (Kyle et al., 2014). The study was reviewed and approved by the West of Scotland NHS research ethics committee (protocol #10/SO701/85) see Appendix D: Ethical approval for Chapters 4 & 5.

5.3.2 Salivary cortisol

Standard procedures for sampling SC concentrations were implemented in this study (Eller, Netterstrom, & Hansen, 2006; Lowson, Middleton, Arber, & Skene, 2013; Schulz, Kirschbaum, Prussner, & Hellhammer, 1998). Participants sampled their own saliva through a collection kit with salivettes (supplied by Salimetrics Europe Ltd, Suffolk, UK). Salivettes are cotton dental rolls and participants were instructed to place these in the back of the mouth for two-three minutes (or until saturation) at three time points per day; two hours before bed, bedtime, and on awakening, for two days before the SRT intervention (baseline: days 1-2 of SC sample collection), for three specified days during the early (first week) and late phases (second week) of SRT, and for four days at treatment end (week four) of SRT totaling to 36 samples for each participant (see Figure 11). Salivettes were stored in two tightly capped sterile plastic tubes. All samples were on weekdays only. (See Appendix E: Participant sampling instructions for salivary cortisol concentrations).

<table>
<tr><td rowspan="2">PSG 1</td><td rowspan="2">PSG 2</td><td colspan="4">Saliva Collection Period</td></tr>
<tr><td>Baseline Phase
(Days 1 & 2)</td><td>Early Phase
(Days 3, 4 & 8)</td><td>Late Phase
(Days 9, 10 & 11)</td><td>Follow-up
(Days 22-25)</td></tr>
<tr><td colspan="2">Pre-Study Period</td><td colspan="4">Sleep Restriction Therapy</td></tr>
</table>

Figure 11 Mean salivary cortisol concentrations through sleep restriction therapy (SRT) for insomnia: Participants (*n*=8) were sampled from a concurrent insomnia study and underwent 2 nights of polysomnography (PSG 1 & 2), prior to study enrolment. This was followed by a saliva collection period, first through an initial baseline collection consisting of 2 days and then followed by 3 further phases during SRT (Early: days 3, 4, & 8; Late: days 9, 10 & 11; Follow-up: days 22-25). Post treatment outcome measures were assessed after 4 weeks.

Participants were instructed to: sample at their specified times according to an individualised timetable (in line with their prescribed sleep schedule), to mark on this timetable the time of the sample collection, to rinse their mouth with water five minutes before sample collection (Clow et al., 2004) to be in the bedroom and in bed for the bedtime sample, before they brushed their teeth as teeth brushing may contaminate the sample with blood (Kivlighan et al., 2004). Participants were also instructed to implement the awakening sample as soon as possible in the morning (the sample kit was instructed to be stored beside the participant's bed prior to sleep) and prior to anything else (no longer than 15 minutes). Participants were asked to then store the samples immediately after collection at -20^{o}C (in their home freezer see Appendix E: Participant sampling instructions for salivary cortisol concentrations).

Samples were collected from participants at treatment end and were transported to the laboratory by the participant. Samples were then stored in the laboratory at -20^{o}C until all were ready for batch analysis by Salimetrics, UK. Tubes were thawed and then centrifuged for 15 minutes at 3000 RPM (1500 x g) at room temperature for separation of supernatant. All samples were assayed for mean SC concentrations (nmol/L). The analysis of SC was performed in duplicate using a commercially available high sensitivity SC enzyme immunoassay (Salimetrics, UK). The assay uses 25 microliters of saliva per determination, has a lower limit of detection of 0.003 nmo/L, standard curve range from 0.012 to 3.0 µg/dL, and average intra- and inter-assay coefficients of variation of 3.5 and 5.1 %, respectively. This approach has been used previously (Eller et al., 2006; Lowson et al., 2013; Schulz et al., 1998).

5.3.3 Data analysis

A linear mixed model analysis was implemented as described previously (see chapter 3.9 Statistical analysis). Fixed effects included phase of SC collection (baseline, early, late, & follow-up), and for time of sample collection (two hours before bed, bedtime, and on awakening). Random effects were run to account for between-subject variation. Only random effects were included for the intercepts. Uncorrected Pairwise comparisons based on estimated marginal means were implemented to investigate primary outcomes.

5.4 Results

Eight participants (5 females; mean age = 46.4yr, range = 34-58) thoroughly screened for PI (Edinger et al., 2004) completed this study. No participants were taking prescribed sleep promoting hypnotics. Participants adhered to therapy as the SRT self-report adherence mean scores remained high (> 20) across the weeks of SRT (week; 1 =26.0 (3.7), 2 = 25 (2.5), 3 = 25.4 (1.1), 4 = 22.9 (6.5); ranging from 10-30. Statistical analysis for treatment data were implemented as described previously in 3.9 Statistical analysis. Confirming the expected therapeutic benefits of SRT mean insomnia severity index (ISI) and sleep diary outcome scores including: wake-time after sleep onset (WASO), number of awakenings (NOAW) and ratings of sleep quality (SQ) improved significantly pre-to-post treatment (baseline to week 4: see Table 12).

5.4.1 Subjective measures of sleep

Outcome measure	Time point (Mean and SD)		Paired differences testing		
	Baseline	Week 4	Baseline versus week 4 (Mean and SE)	*p*-value	Effect size (*d*)
ISI	18 (2.7)	8.0 (3.2)	10 (1.8)	<.01*	3.3
SE (%)	72.1 (6.7)	91.5 (3.7)	19.4 (3.6)	<.01*	1.7
SQ	1.6 (0.6)	2.2 (0.4)	0.6 (0.2)	.06	1.2
SOL	33.7 (28.3)	10.2 (6.0)	23.5 (11.3)	.92	1.2
WASO	53.9 (33.1)	16.3 (11.6)	37.6 (10.6)	.02*	1.5
NOAW	2.9 (1.4)	1.7 (1.3)	1.3 (0.9)*	.02*	0.9
TIB	486.0 (54.1)	378.5 (20.8)	107.5 (19.3)	<.01*	2.6
TST	350.8 (43.6)	345.5 (33.1)	5.3 (15.8)	.75	0.1

Table 12 Baseline to week four difference testing for mean Insomnia Severity Index and Sleep Diary outcome scores at baseline and at week 4 of therapy: The left hand side of the table describes the mean and standard deviation (SD) Insomnia Severity Index (ISI); Sleep Diary: Sleep Efficiency (SE), Sleep Quality (SQ), Sleep Onset Latency (SOL), Wake-Time After Sleep Onset (WASO), Number of Awakenings (NOAW), Time In Bed (TIB), and Total Sleep Time (TST) scores at Baseline and Week 4 of Sleep Restriction Therapy (*n*=8). The right hand side of the table tests for differences between Baseline (week 1 for the SRAS) and Week 4 for all of the scores and displays the mean difference and standard error (SE), *p*-value, and effect size. (*) = *p*<.05.

5.4.2 Salivary cortisol

The average time for sample donation was profiled as an indicator to compliance with sampling procedures (see Table 13). Linear mixed effects models revealed no significant differences between baseline and any of the 3 treatment phases for any of the specific daytime collection time points.

Time-point	Time of Day	Average time of sample donation (SD)
Baseline	2 Hours Before Bed	10:56 PM (4:19)
	Bedtime	12:18 AM (3:11)
	Awakening	07:11 AM (0:51)
Early phase	2 Hours Before Bed	10:44 PM (4:47)
	Bedtime	12:43 AM (0:48)
	Awakening	06:48 AM (0:33)
Late phase	2 Hours Before Bed	12:21 AM (5:45)
	Bedtime	12:44 AM (0:45)
	Awakening	06:44 AM (0:35)
Follow-up	2 Hours Before Bed	10:30 PM (0:49)
	Bedtime	11:44 PM (2:59)
	Awakening	06:32 AM (0:41)

Table 13 Mean (SD) times for saliva sample donation before and during Sleep Restriction Therapy (*n*=8) for Baseline (Days 1 & 2), the early phase (Days 3, 4 & 8), the late phase (Days 9, 10 & 11) and Follow-up (Days 22-25). Each collection day consisted of 3 saliva samples (2 hours before bed, bedtime & awakening).

Turning to the primary analysis of cortisol for this study regarding a reduction in SC cortisol levels between baseline and follow-up (4 weeks of therapy), the adherence rate for the sampling procedure was high at 98.96% (285 samples collected out of a possible 288). From this, 12 samples were unable to be analysed (9 samples had insufficient saliva and 3 were contaminated with blood). Therefore, 273 samples were assayed for cortisol out of a possible 288 (94.8%). Only biologically relevant samples (<60 nmol/L) were included in the analysis (Lowson et al., 2013). This resulted in the removal of seven samples. Thus, 266 (92.4%) samples formed the following analysis (see Table 14).

Participant	Time of sample	Treatment Phase			
		Baseline	Early Phase	Late Phase	Follow-up
1	2 hours before bed	1.0 (0.3)	1.2 (0.5)	0.9 (0.3)	1.5 (0.7)
	Bed time	1.1 (0.5)	3.1 (1.8)	2.0 (0.1)	2.6 (1.7)
	Awakening	5.4 (0.5)	12.3 (3.2)	9.9 (4.9)	13.2(6.2)
2	2 hours before bed	0.8 (0.1)	1.1 (0.1)	3.5 (3.4)	1.9 (1.5)
	Bed time	1.2 (0.5)	2.0 (0.5)	10.4 (7.3)	3.2 (1.8)
	Awakening	15.2 (.)	12.2 (3.8)	10.6 (0.8)	10.8 (2.5)
3	2 hours before bed	2.9 (1.6)	1.4 (0.4)	1.4 (0.3)	1.1 (0.1)
	Bed time	2.8 (0.8)	1.4 (0.1)	2.3 (1.1)	1.8 (0.4)
	Awakening	.	9.5 (2.1)	9.5 (0.3)	7.8 (1.9)
4	2 hours before bed	6.9 (6.0)	2.3 (1.7)	1.1 (0.1)	1.0 (0.4)
	Bed time	2.1 (0.4)	5.5 (4.7)	1.6 (0.7)	1.4 (0.8)
	Awakening	12.6 (0.3)	13.5 (7.2)	11.1 (2.8)	8.7 (3.4)
5	2 hours before bed	0.8 (0.2)	1.1 (<.1)	1.0 (0.5)	1.0 (0.2)
	Bed time	0.9 (<.1)	1.1 (0.3)	1.1 (0.5)	3.5 (4.7)
	Awakening	6.5 (1.0)	4.4 (0.7)	4.4 (0.5)	4.7 (2.4)
6	2 hours before bed	1.0 (0.2)	4.3 (6.6)	0.8 (0.5)	0.7 (0.3)
	Bed time	1.1 (<.1)	4.8 (7.4)	0.6 (0.4)	6.2 (6.4)
	Awakening	11.4 (3.3)	6.8 (5.3)	9.6 (0.7)	9.4 (2.4)
7	2 hours before bed	1.1 (<.1)	1.3 (0.7)	1.2 (0.7)	0.8 (0.3)
	Bed time	0.8 (0.7)	1.4 (0.2)	1.7 (0.7)	1.0 (0.3)
	Awakening	4.3 (1.0)	4.4 (0.9)	4.4(1.0)	3.5 (1.7)
8	2 hours before bed	34.1 (0.4)	5.2 (4.9)	20.9 (11.6)	0.8 (0.3)
	Bed time	21.1 (.)	9.9 (12.0)	32.8 (0.6)	1.2 (14.4)
	Awakening	25.2 (.)	23.2 (17.0)	20.0 (14.0)	7.7 (2.1)

Table 14 Mean (SD) cortisol concentrations (nmol/L) for each participant before and during Sleep Restriction Therapy for insomnia for each participant (*n*=8) and the following saliva collection time points: Baseline (Days 1 & 2), the early phase (Days 3, 4 & 8), the late phase (Days 9, 10 & 11) and Follow-up (Days 22-25). Each collection day consisted of 3 saliva samples (2 hours before bed, bedtime & awakening).

Boxplots and scatter graphs were checked for outliers and one participant was found to display extreme values. This participant demonstrated a large treatment response that was not in line with the rest of the sample and may not have been biologically possible. As a result, this participant (number 8) was therefore removed completely from the analysis (see Table 14, Figure 12 & Figure 13). This may have been caused by the ecological nature of the sampling. For example, such high values may be due to teeth brushing, cigarettes, alcohol or orange juice near the sample collection time-point (Clow et al., 2004).

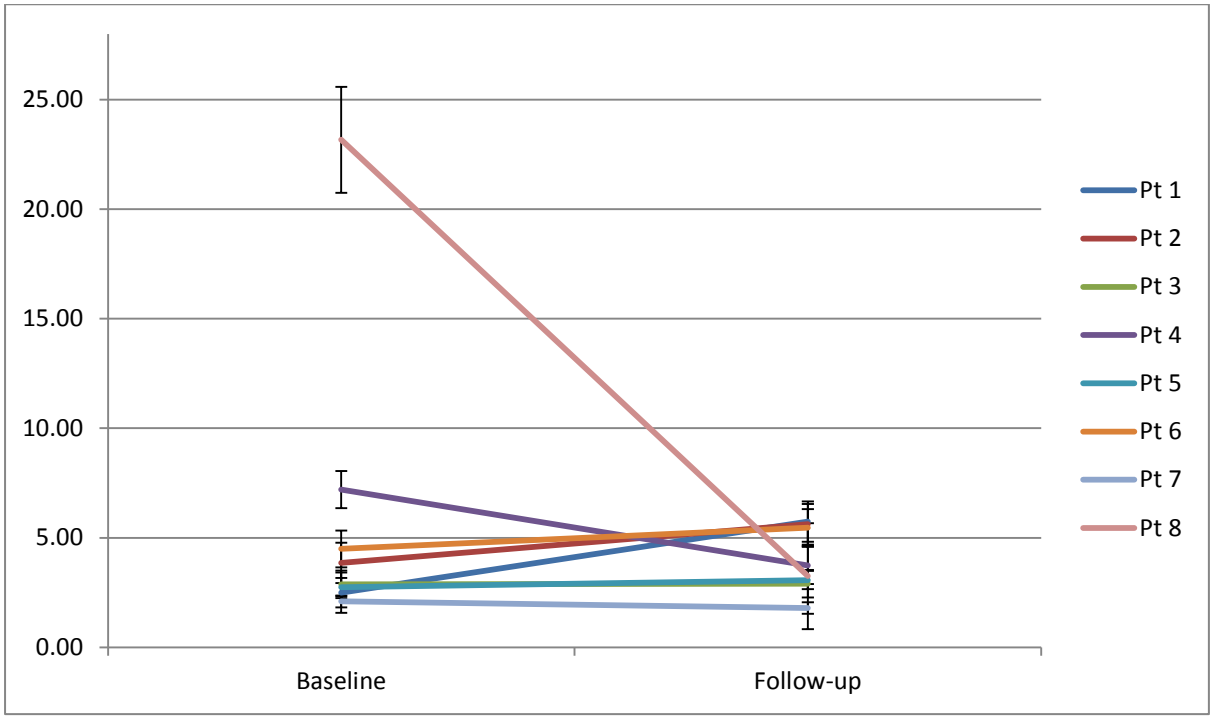


Figure 12 Mean salivary cortisol concentrations (nmol/L) pre-to-post SRT with all 8 participants . Mean cortisol concentrations pre-to-post SRT for insomnia for each participant (*n*=8) and the collection days for Baseline (Days 1 & 2) and Follow-up (Days 22-25). Each collection day consisted of 3 saliva samples (2 hours before bed, bedtime & awakening). Error bars represent one standard error of the mean.

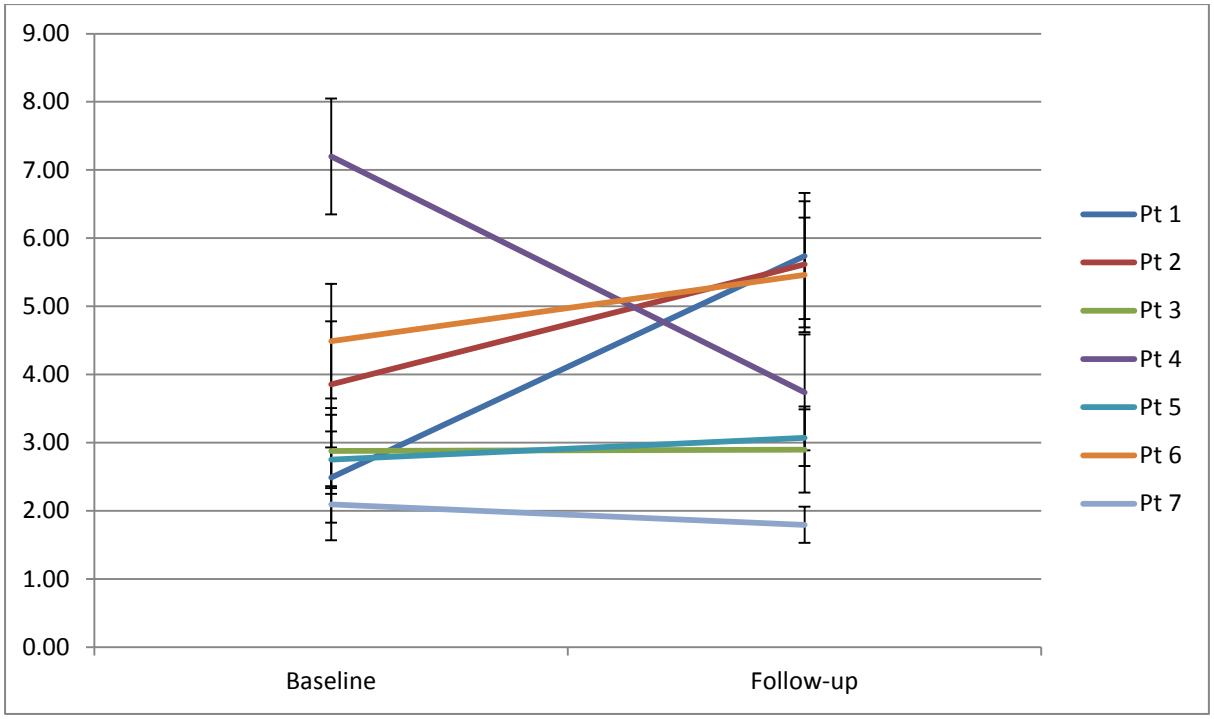


Figure 13 Mean salivary cortisol concentrations (nmol/L) pre-to-post SRT for insomnia for each participant (*n*=7) and the collection days for Baseline (Days 1 & 2) and Follow-up (Days 22-25). Each collection day consisted of 3 saliva samples (2 hours before bed, bedtime & awakening). Participant 8 was removed. Error bars represent one standard error of the mean.

Prior to the exploration of the primary hypothesis, samples were checked for circadian rhythmicity and expected diurnal pattern to SC concentrations (see chapter 3.9 Statistical analysis for an overview). A circadian period was evident in line with the circadian rhythm for SC concentrations (see Table 15). Results suggest that the samples were a valid measure of SC concentrations prior to and after sleep (see Figure 14).

Time of Day	Mean & 95% CI's
2 hours before bed	1.63 [0.91, 2.35]
Bedtime	2.46 [1.75, 3.18]
Awakening	8.64 [7.87, 9.41]

Table 15 Displays mean (95% CI's) salivary cortisol concentrations over the course of the three time-points for saliva collection before and after sleep for participants with insomnia (*n*=7).

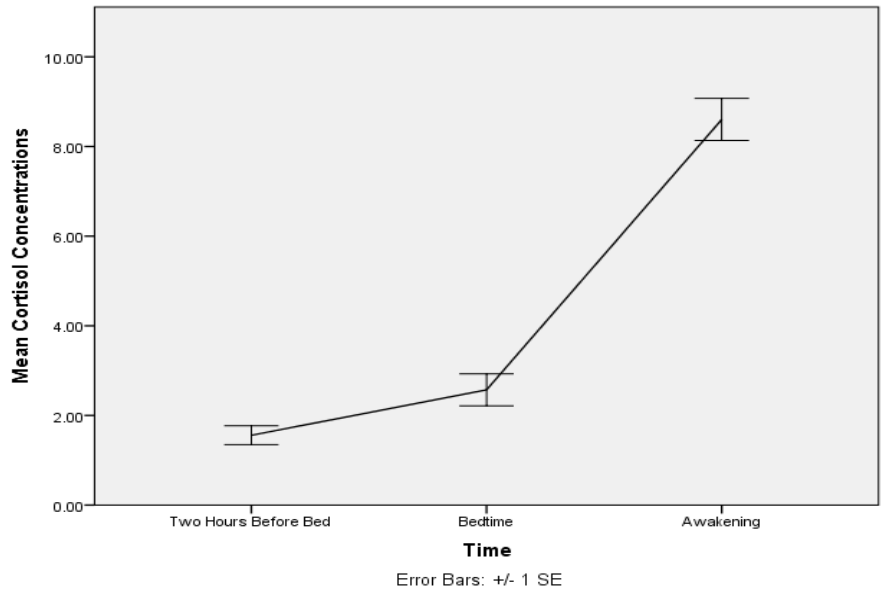


Figure 14 Time-course of salivary cortisol concentrations through the 3 collection time-points before and after sleep for participants with insomnia (*n*=7). Mean salivary cortisol concentrations (nmol/L) are represented on the *y*-axis. The *x*-axis indicates the sample collection time over the course of the evening (two hours before bed and bedtime) and the subsequent awakening measure in the morning after sleep. Error bars represent one standard error of the mean.

In order to test the hypothesis that SC concentrations would decrease through SRT, main effects were analyzed for collection phase between baseline and the early, late and follow-up phases. Results revealed no significant effect for phase of treatment [F (3, 218.2) = 0.25]; (p =.87). Simple main effects revealed no significant difference between the baseline and follow-up phases; (Mean & 95% CI's: 4.07, CI [3.06, 5.01] vs. 4.10, CI [3.40, 4.81]); (p=.96) (see Figure 15 & Table 16).

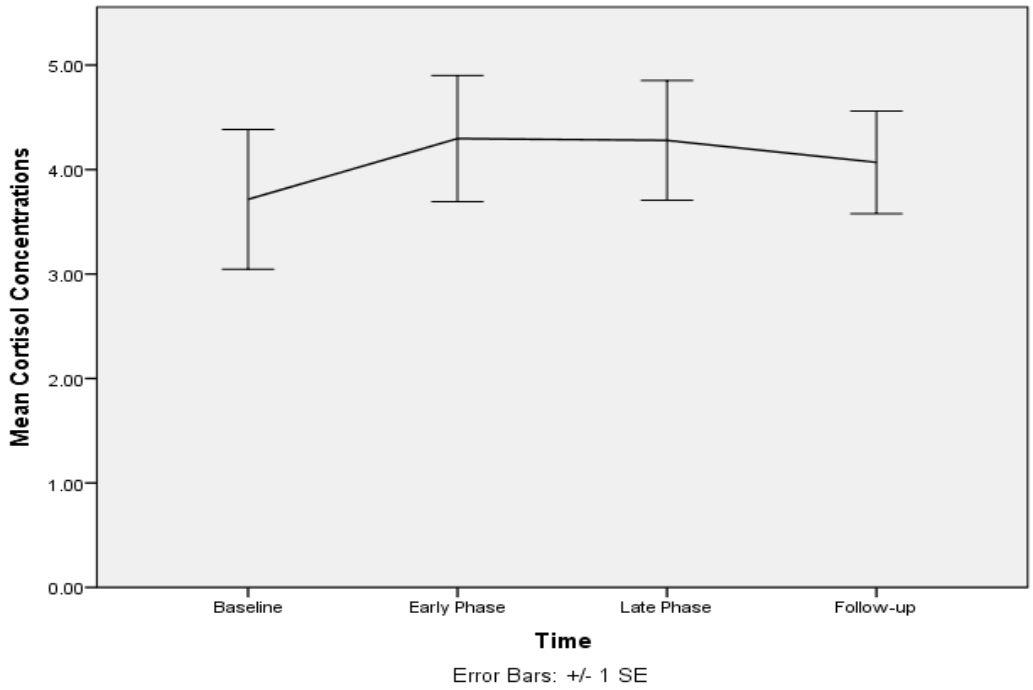


Figure 15 Time-course of salivary cortisol concentrations through the 4 phases of collection for participants with insomnia (n=7). Mean salivary cortisol concentrations (nmol/L) are represented on the y-axis. Phase of cortisol collection is represented along the x-axis (Baseline: days 1-2; Early: days 3, 4, & 8; Late: days 9, 10 & 11; Follow-up: days 22-25). Error bars represent one standard error of the mean.

Mean & 95% CI		Paired differences testing		
Baseline	4.07 [3.06, 5.01]	*Mean Difference & 95% CI*		*P-value*
Early Phase	4.50 [3.65, 5.30]	Baseline vs. Early Phase	0.40 [-1.71, 0.90]	.54
Late Phase	4.33 [3.50, 5.16]	Baseline vs. Late Phase	0.26 [-1.57, 1.05]	.70
Follow-up	4.10 [3.40, 4.81]	Baseline vs. Follow-up	0.03 [-1.31, 1.21]	.96

Table 16 Mean salivary cortisol concentrations during Sleep Restriction Therapy for insomnia from linear mixed model analysis output. The left hand side of the table describes the mean (95% CI's) for the 4 assessment for cortisol (nmol/L) collection (Baseline: days 1-2; Early: days 3, 4, & 8; Late: days 9, 10 & 11; Follow-up: days 22-25) for participants (*n*=7) with insomnia. The right hand side of the table tests the specific hypothesis regarding changes in SC concentrations in response to SRT.

Next and to examine the second aspect of our hypothesis, a time of day x phase of treatment interaction was used to examine potential diurnal changes in the assessment of SC concentrations throughout sleep restriction therapy compared to baseline (see Figure 16 & Table 17). This was found to be non-significant [F (6, 224.0) = 0.48]; (*p*=.82); suggesting no differences pre-to-post SRT for any of the three specific assessment time-points (see Figure 16 & Table 17).

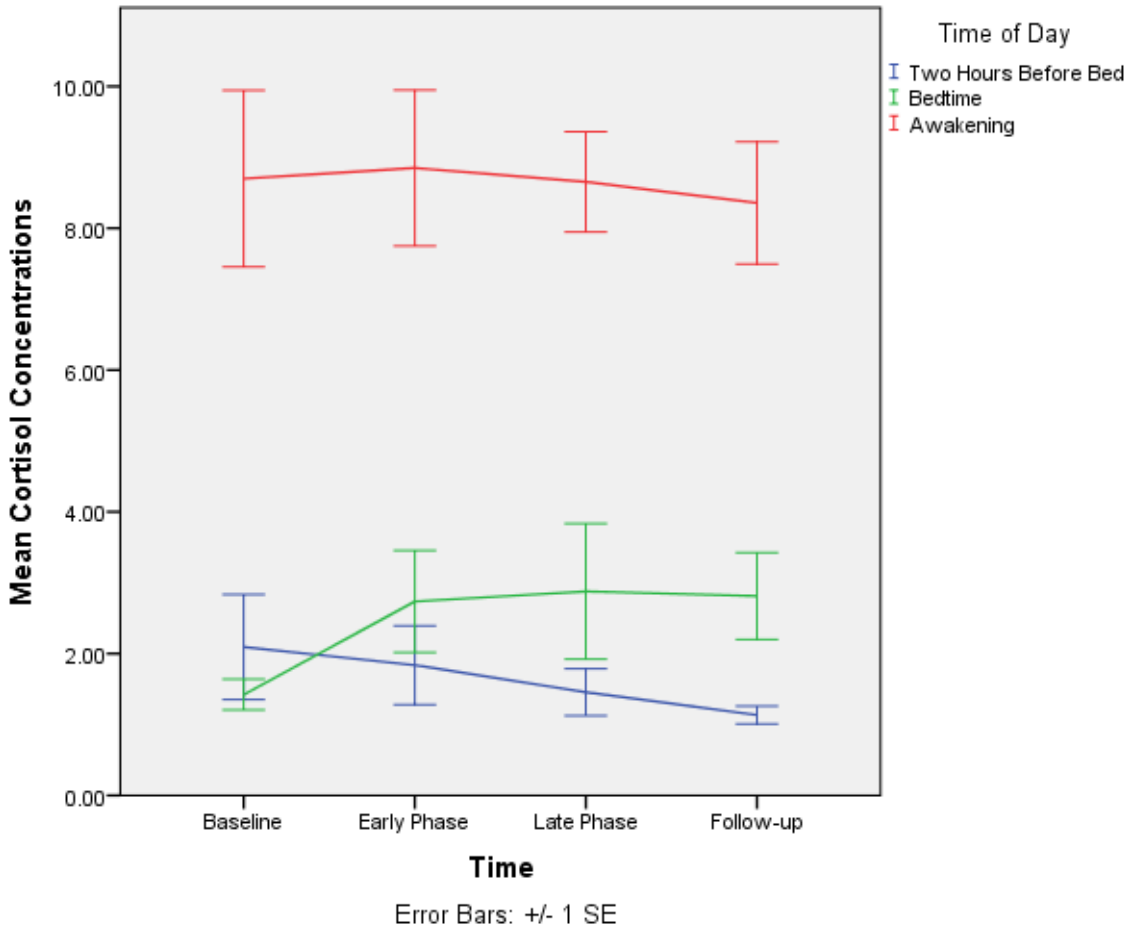


Figure 16 Mean salivary cortisol concentrations through sleep restriction therapy. Through the 4 phases of collection for participants (*n*=7) with insomnia. Mean salivary cortisol concentrations (nmol/L) are represented on the *y*-axis. Phase of cortisol collection is represented along the *x*-axis (baseline: days 1-2; early: days 3, 4, & 8; late: days 9, 10 & 11; follow-up: days 22-25). Each line represents an assessment time-point: two hours before bed (blue), bedtime (green) and awakening (red). Error bars represent one standard error of the mean.

Time of Sample	Time Point	Mean & 95% CI	Paired Differences Testing		
2 hours before bed	Baseline	2.09 [0.41, 3.78]	*Mean Difference & 95% CI for 2 hours before bed*		*P-value*
	Early Phase	1.84 [0.43, 3.25]	Baseline vs. Early Phase	0.26 [-1.94, 2.50]	.82
	Late Phase	1.46 [0.05, 2.86]	Baseline vs. Late Phase	0.64 [-1.56, 2.83]	.57
	Follow-up	1.13 [0.10,2.37]	Baseline vs. Follow-up	1.0 [-1.13, 3.05]	.37
Bedtime	Baseline	1.42 [0.26, 4.11]	*Mean Difference & 95% CI for Bedtime*		*P-value*
	Early Phase	2.74 [1.36, 4.11]	Baseline vs. Early Phase	1.31 [-3.50, 0.86]	.23
	Late Phase	2.88 [1.43, 4.32]	Baseline vs. Late Phase	1.5 [-3.45, 0.67]	.20
	Follow-up	2.81 [1.62, 4.00]	Baseline vs. Follow-up	1.39 [-3.45, 0.70]	.19
Awakening	Baseline	8.7 [6.80, 3.78]	*Mean Difference & 95% CI for Awakening*		*P-value*
	Early Phase	8.85 [7.37, 10.33]	Baseline vs. Early Phase	0.15 [-2.56, 2.26]	.90
	Late Phase	8.65 [7.21, 10.10]	Baseline vs. Late Phase	0.05 [-2.34, 2.43]	.97
	Follow-up	8.36 [7.12, 9.59]	Baseline vs. Follow-up	0.34 [-1.92, 2.61]	.77

Table 17 Mean salivary cortisol concentrations during Sleep Restriction Therapy for insomnia from the linear mixed model analysis output. The left hand side of the table describes the mean (and 95% CI) for the 3 sampling times for salivary cortisol collection (nmol/L) prior to sleep and in the morning (2 hours before bed, bedtime, and awakening) before and during sleep restriction therapy (Baseline: days 1-2; Early: days 3, 4, & 8; Late: days 9, 10 & 11; Follow-up: days 22-25) for participants (*n*=7) with insomnia. The right hand side of the table tests our specific hypothesis regarding changes in SC concentrations in response to SRT.

After reviewing Figure 16 and due to the exploratory nature of this study, it was thought that the saliva samples may be altering over the course of the day pre-to-post therapy, especially for the two hours before bed and the bedtime samples at baseline compared to the follow-up time point. Therefore, the mixed model analysis was updated to also compare for differences in the time of sampling (2 hours before bed vs. bedtime) at each of the four assessment phase time points. At baseline, no differences were found between the two evening samples (mean difference & 95% CI's: 0.67 [-1.53, 2.87], (p=.55). At follow-up however, a significant difference was found between the two evening assessment points (mean difference & 95% CI's: 1.63 [-3.21, -0.04], (p=.04) (see Figure 17).

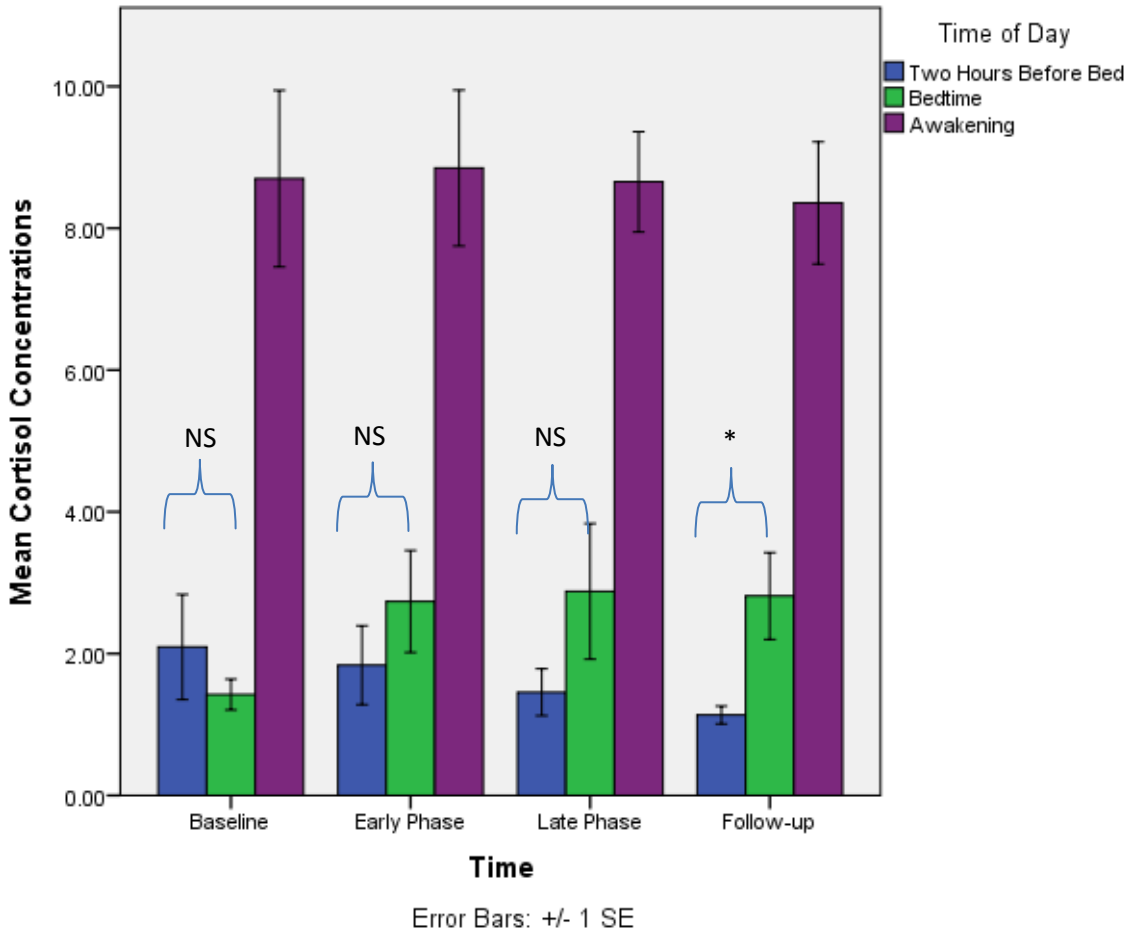


Figure 17 Mean salivary cortisol concentrations through sleep restriction therapy. Time-course of salivary cortisol concentrations through the 4 phases of collection for participants (*n*=7) with insomnia. Mean salivary cortisol concentrations (nmol/L) are represented on the *y*-axis. Phase of cortisol collection is represented along the *x*-axis (Baseline: days 1-2; Early: days 3, 4, & 8; Late: days 9, 10 & 11; Follow-up: days 22-25). Each colour represents an assessment time-point: two hours before bed (blue), bedtime (green) and awakening (purple). Differences are displayed between the evening assessment time points only *= *p*<.05. Error bars represent one standard error of the mean.

5.5 Discussion

The aim of this exploratory treatment study was to examine if salivary cortisol (SC) concentrations decrease during effective sleep restriction therapy (SRT) for psychophysiological insomnia. Overall, results suggest that SC concentrations do not change during the initial stages of therapy (first 4 weeks: see Figure 15). Further, there were no significant diurnal changes in the time of sample collection (see Table 16) or differences in the time for sample donation (see Table 13) through SRT. However and as expected, a distinct diurnal pattern in SC concentrations was found for the pre-sleep and awakening samples, aligned with the circadian rhythm for cortisol secretion, similar to normal healthy participants with increased SC concentrations in the early morning 06:00 am (Elder et al., 2014) (see Figure 14). The following sections discuss these results.

Previously, only two treatment studies have attempted to profile differences in cortisol concentrations as a result of treatment for insomnia. Vallieres et al. (2013) looked to measure SC concentrations daily (before bed and on awakening) prior to, during and after SRT in five participants. However, due to low numbers of participants this study lacked formal statistical testing of SC. The study therefore merely described a general reduction in SC concentrations for those who responded to SRT. Rodenbeck et al. (2003) report a significant reduction in night time plasma cortisol secretion after three weeks compared to placebo in a crossover study with 10 insomnia patients. Suggesting, plasma cortisol concentrations may be reduced with Doxepin for insomnia, in line with the hyperarousal theory of insomnia. This decline in cortisol secretion was attributed by the authors as a reduction in hypothalamic-pituitary-adrenal axis activiation (Rodenbeck et al., 2003).

Although, SC concentrations were not found to change overall during the initial stages of therapy, the intervention was found to be effective as improvements were found for self-report measures including the insomnia severity index (ISI) and sleep efficiency from sleep diary data (see Table 12). Participants subjectively reported adherence to the intervention as evaluated through the high scores on the SRAS (>20). Scores however generally reduced throughout the weeks of therapy

(see Table 11), indicating a reduction in adherence as the weeks of therapy progressed. This trend of a reduction in adherence towards the end of the sampling period may have impacted the results and prevented any significant changes to SC concentrations. However, a significant reduction in the amount of time spent in bed from the sleep diary data between baseline and week four of therapy was found (see Table 12) and this suggests adherence to therapy. Differences in the assessment of adherence may be to blame for these inconsistencies. Further, difficulties with adhering to the saliva sampling procedures may have also affected the results of this study, particularly between the early and the follow-up phases of treatment as the mean bedtime assessment time is earlier (see Table 13).

The lack of a significant finding was perhaps due to a low number of participants (n=8 overall; n=7 for the primary cortisol analysis). This was due to limited resources. A post hoc power calculation revealed that the study was indeed underpowered in order to detect any statistically significant effect in SC concentrations through therapy (d=0.03, α=0.05, and n=7). The low statistical power (0.03) increased the likelihood of a Type II statistical error. No corrections for multiple comparisons were employed and therefore findings should be considered exploratory. This study may be considered a preliminary range finding assessment to determine future protocol and participant numbers, in order for future studies to detect an effect in SC concentrations in response to treatment for insomnia. For example, a longer sampling time-frame (after >4 weeks into therapy) and a larger number of participants (>10) would have improved the design of the study. It is however reassuring that SRT did not increase SC concentrations significantly during treatment (see Figure 15). This may have been possible due to the introduction of sleep loss as a result of therapy with restricted time in bed (Dinges et al., 1997; Kyle et al., 2014). Indeed, time in bed reduced significantly (p<.01) from a baseline average of 486.0 minutes to 378.5 minutes during week four (see Table 12) although the lack of an effect may again be due to low statistical power.

Further and in line with the preliminary nature of this study, an exploratory analysis suggested pre-sleep SC concentrations at two hours before bed and at bedtime were found to significantly differ only at the follow-up assessment time point but not at baseline (see Figure 16). Perhaps suggesting, a modification in the timing of SC secretion prior to sleep at follow-up compared to pre-therapy levels. SRT is thought to work by utilising mild sleep deprivation to help facilitate sleep and by aligning circadian drives with the correct time for sleep and wakefulness (Spielman et al., 2010). A modification to the circadian timing of sleep and wake may be reflected by these pre-sleep changes to SC concentrations. At follow-up (week 3), SC concentrations were found to be significantly higher at bedtime compared to two hours before bedtime, no difference was found between these samples at baseline. For the two hours before bed assessment, a reduction in SC concentrations may reflect reduced stress and worry for the ensuing sleep period. For the bedtime assessment, the increase in SC concentrations may reflect modification to the circadian period of SC secretion during therapy and reflect later bedtimes as a result of the implementation of SRT. This has previously been found in healthy volunteers exposed to circadian misalignment (Gonnissen et al., 2012; Scheer, Hilton, Mantzoros, & Shea, 2009).

Varkevisser et al. (2007) found no group differences between those with insomnia and healthy controls for SC prior to sleep or in the evening (8pm, 1.5 hours before bedtime or 15 minutes before bedtime). This lack of a difference was thought to be due to a lack of sensitivity in the assessment of SC concentrations to detect the influence of hyperarousal (Varkevisser et al., 2007). However, the timing of the sample collection may have been responsible for a lack of a difference. Seelig et al. (2013) found increased levels of SC concentrations during the night time in females with insomnia compared to controls (11:30pm; mean (SD): 1.5 (1.4) vs. 0.7 (0.4), (p=.02)), but not no difference for the morning sample (06:00am; 10.3 (6.3) vs. 7.3 (3.5), (p= .18). As a comparison, the mean baseline bedtime sample from the present study compared with the 11:30pm sample from the Seelig et al. (2013) study was found to be elevated when compared to the control participants (1.42 (2.6) vs. 0.7 (0.4)) and also similar to the participants with insomnia (1.42 (2.6) vs.

1.4 (1.4). Comparing the bedtime sample at follow-up to the participants with insomnia, a clear difference can be seen between the means (2.81 (1.6) vs. 1.4 (1.4). This is also much larger than controls (2.81 (1.6) vs. 0.7 (0.4)). This elevation may due to the mismatch in the timing of the samples as it is very difficult to compare across studies. For the awakening samples from the present study, the baseline SC concentrations were found to be greater than the 6am control participants in the Seelig et al. (2013) study (8.7 (2.0) vs. 7.3 (3.5)). However for the participants with insomnia, the mean SC concentrations from the Seelig et al. (2013) study were larger than the present study (8.7 (2.0) vs. 10.3 (6.3)). This may be due to the standardisation of the sampling procedure to 6am compared to the present study (where participants were instructed to capture the sample on awakening). Sampling SC around a specific time does not take into consideration individual differences due to the circadian rhythm of SC secretion and may produce large variability. This is because the amount of time since wake by 6am will be different between participants and across days of the week. The cortisol awakening response changes quickly from awakening onwards (Elder et al., 2014) and will alter the SC sample. Therefore, it is best to standardise morning SC samples from awakening onwards.

Further, case-control studies have found mixed results between patients with insomnia and healthy good sleeping controls. For example, SC concentrations on awakening were significantly decreased and correlated negatively to waking times during the night (r= -0.50). Patients with insomnia were also found to display decreased morning SC concentrations compared to controls (Backhaus et al., 2004). The authors suggested that low morning SC concentrations may be due to increased activation of SC during the night, supporting the hyperarousal theory of insomnia (Bonnet & Arand, 2010; Riemann et al., 2010), reflecting a nocturnal increase in hypothalamic-pituitary-adrenal-axis (HPA-axis) activity in response to insomnia. Further evidence for this was found from the previously mentioned Seelig et al. (2013) study, and also in serum cortisol concentrations during the latter half of the night which were elevated in a group of 16 patients with insomnia compared to 13 healthy controls (Backhaus et al., 2006).

Salivary cortisol concentrations are thought to serve as a reliable marker of HPA-axis activity (Kunz-Ebrecht, Kirschbaum, Marmot, & Steptoe, 2004; Tsigos & Chrousos, 2002) and a marker for change in response to stress through this system (Tsigos & Chrousos, 2002). Awakening SC concentrations that form the morning awakening response have been linked to change in response to the sleep-wake flip-flop switch (Clow et al., 2004). It is believed that hyperarousal (an elevated state of activity/reactivity of the central nervous system through cognitive, emotional, or physiological systems) may be a potential pathophysiologic mechanism for elevated cortisol in insomnia (Riemann et al., 2010). Cortisol and other neuroendocrine variables are also important in healthy human sleep (Buckley & Schatzberg, 2005). For example, morning measures of plasma and SC concentrations have been found to correlate with night time arousals during sleep (Ekstedt, Akerstedt, & Soderstrom, 2004). Sleep restriction (4 hrs time in bed: TIB for 6 nights) is known to elevate evening cortisol concentrations in healthy males (Spiegel et al., 1999). In sleep restricted (3 hrs TIB) healthy females, morning SC concentrations decreased and evening concentrations increased compared to a 10 hour sleep opportunity (Omisade, Buxton, & Rusak, 2010). Further, a two-hour nap after a night of sleep loss was able to reduce plasma cortisol concentrations (Vgontzas et al., 2007). Therefore suggesting that the implementation of the SRT schedule and resulting sleep loss may have masked any initial (first 4 weeks) improvement (decrease) in SC concentrations. However, only severe sleep restriction or sleep deprivation paradigms appear to increase cortisol secretion in healthy individuals, suggesting that cortisol is sensitive to stress and not sleep loss (Pejovic et al., 2013). Therefore sleep restriction may not be able to modify changes in SC concentrations. Perhaps then to observe a reduction in SC concentrations repeated measures of SC with longer follow-up times are required once hyperarousal has abated in insomnia. For example, it may be possible to see effects due to treatment after six weeks (when subjective sleep may improve). Follow-up times should also be included at three, six and 12 months once the sleep-wake schedule has stabilised after the acute implementation of SRT.

Overall, differences between studies may be due to the time of sample collection and type of cortisol collected (saliva vs. plasma; although SC concentrations have also known to correlate with levels found in plasma (Hellhammer, Wust, & Kudielka, 2009)). SC concentrations may also be variable over time and researchers should now look to standardise sampling techniques in order to reduce inconsistencies between studies (Elder et al., 2014). Therefore, the evidence concerning the role of SC concentrations in insomnia is mixed. With regards to limitations a number of factors should be considered. First, the number of participants was not large enough to measure an effect of treatment. Second, adherence and compliance to SRT and SC sampling procedures are difficult to initiate and confirm. Participants were asked to supply 36 samples of SC over the whole course of this study. Participants may have failed to comply with the sampling instructions at the correct time-point and other factors such as brushing teeth, cigarette smoking or drinking orange juice may cause erroneous results (Clow et al., 2004). Third, the study implemented a within-subjects repeated measures design. No control group was used in this study, it is therefore unknown if patients would have improved their sleep through a placebo or non-specific response. Fourth, the experimenter acted as a therapist in this study and it is difficult to rule out experimenter, performance, and demand effects. More rigorous studies are now required to evaluate the role of cortisol in insomnia and its response to treatment and may help to uncover the potential mechanisms of action for the successful treatment of insomnia. Future studies could measure other markers of sleep (e.g. actigraphy) and arousal (e.g. heart rate) with testing occurring over a longer time frame (after 6 weeks of therapy) using plasma cortisol concentrations. In-lab experimental testing with plasma cortisol may be less variable and will be evaluated in the subsequent chapter.

5.6 Conclusion

The primary aim of this study was to examine SC concentrations during the acute phase of SRT for chronic psychophysiological insomnia. Therapy improved insomnia symptomology and self-reported sleep but SC concentrations did not change during the acute phase (first 4 weeks). An exploratory analysis suggested changes to SC concentrations prior to bed at follow-up (week 3) with SC concentrations significantly higher at bedtime compared to two hours before bedtime, no difference was found between these samples at baseline. Further research is warranted regarding profiling the response of plasma cortisol concentrations after effective treatment for insomnia (6 weeks).

Chapter 6: Sleep restriction therapy for insomnia disorder: An exploratory assessment of sleep and physiological markers of arousal in response to treatment.

6.1 Abstract

Higher arousal levels have been found in those with insomnia compared to controls. This study aimed to profile objective changes in sleep and physiological arousal pre-to-post effective sleep restriction therapy (SRT) for insomnia. Eleven participants were sampled as part of this repeated measures treatment study. Objectively-defined sleep, plasma cortisol concentrations and core body temperature were assessed before and after 6-weeks of SRT. It was hypothesised that sleep would improve, and measures of physiological arousal would reduce (cortisol & core body temperature). Confirming the benefits of therapy, insomnia severity index scores decreased significantly (mean (SD) 18.2 (2.8) vs. 8.4 (4.8)). Improvements were found for sleep diary measures and objectively defined total sleep time (TST: 313.7 (54.2) vs. 353.6 (40.9)). Plasma cortisol concentrations (µg/dL) did not reduce pre-to-post therapy but displayed higher levels in the morning at post-treatment compared to baseline (mean (95% CI): 7.0 (5.9, 8.2) vs. 9.7 (8.5, 10.9). Core body temperature levels (°C) were found to reduce significantly (36.54 (36.3, 36.8) vs. 36.45 (36.2, 36.7)). SRT appears to increase objectively defined TST, early morning cortisol concentrations and decrease core body temperature. This study suggests that SRT may improve sleep and physiological functioning through modifications in arousal. Further studies are required to evaluate potential changes in a larger number of participants over the course of 24 hours under constant routine conditions.

6.2 Introduction

Insomnia may be characterised through a number of physiological factors including: circadian dysrhythmia, homeostatic dysregulation and hyperarousal (Pigeon and Perlis (2006); see Chapter 1: Introduction for an overview). Hyperarousal is the most prominent theory of insomnia and postulates that neurobiologic and maladaptive behavioural processes lead to a state of conditioned autonomic arousal that inhibits sleep (Bonnet & Arand, 1997, 2010; Riemann et al., 2010). A number of assessment markers have been found to be higher in those with insomnia compared to healthy good sleeping controls including: temperature, hormones, cardiac, metabolic, and electroencephalographic (EEG) spectral measures (Bonnet & Arand, 2010; Riemann et al., 2010). In addition to the effects of sleep loss, insomnia and hyperarousal can be viewed in a causal inference from a psychobiological perspective (Riemann et al., 2010; Spiegelhalder & Riemann, 2013). Arousal appears to contribute to the long term medical co-morbidities with additional health risks and health care utilisation (Daley, Morin, LeBlanc, Gregoire, & Savard, 2009; Daley, Morin, LeBlanc, Gregoire, Savard, et al., 2009; Taylor et al., 2007; Vgontzas et al., 2013).

A number of physiological arousal markers have been found to be higher in those with insomnia compared to controls including core body temperature, cortisol secretion, skin resistance, power in EEG fast frequencies, metabolic rate and heart rate (Bonnet & Arand, 2010; Riemann et al., 2010). These markers are linked to the self-reported description of a racing mind during sleep initiation which is one of the hallmarks of insomnia symptomology (Harvey, 2001). Bedtime alertness is reduced with sleep restriction therapy (SRT) in insomnia (Miller et al., 2013). However, it is unclear if SRT or overall cognitive behavioural therapy for insomnia (CBT-I) reduces physiological markers of arousal. Reductions in overnight cortisol concentrations have been found with Doxepin, possibly due to a reduction in arousal through reduced activation of the hypothalamic–pituitary–adrenal axis (HPA-axis) (Rodenbeck et al., 2003). Measuring objective changes in insomnia is important as there is currently a lack of robust measures of sleep and arousal pre-to-post treatment for insomnia. Indeed,

insomnia research is currently hampered by a lack of an objective diagnostic test for insomnia severity (Buysse et al., 2006; Zee et al., 2014).

Measures of increased arousal may be malleable with successful CBT-I. Irwin et al. (in press) report a decrease in C-reactive protein levels, a marker of physiological arousal, after CBT-I and treatment remission. A reduction in inflammatory markers may reduce the likelihood of the development of further co-morbid medical disorders associated with chronic insomnia. Other CBT-I studies have only focused on cerebral EEG based measures of cognitive arousal after CBT-I (Bonnet & Arand, 2010). Previously, decreases in high EEG frequencies after successful CBT-I have been found, suggesting preliminary evidence for a reduction in central nervous system arousal with CBT-I (Cervena et al., 2004). Studies are now required to evaluate change in arousal pre-to-post CBT-I by not only measuring objective sleep EEG, but by also considering changes in physiological measures of arousal which potentially normalise with successful treatment.

SRT is routinely used to treat chronic insomnia either as single component therapy, or as part of CBT-I. Anecdotally, SRT is believed to be one of the most active elements of CBT-I (Spielman et al., 2010). Indeed, a review of the literature (Miller et al., 2014) suggests that SRT is effective for self-report sleep diary variables (see Chapter 2: The evidence base of sleep restriction therapy for treating insomnia disorder). However, little is known regarding the physiological mechanisms of action of SRT for insomnia (Morgenthaler et al., 2006) and whether SRT is effective at improving objective measures of sleep and arousal. Previous studies have measured change in mood, daytime functioning (Kyle et al., 2011; Miller et al., 2013) and objective side effects of sleep loss due to SRT (Kyle et al., 2014). It now seems timely to evaluate the physiological process(es) by which SRT may yield beneficial effects in addition to self-reported sleep.

There are a number of theories regarding the mechanisms of action for SRT. First, SRT may work by aligning circadian drives to promote the correct timing for sleep and wakefulness (Spielman et al., 2010). Second, sleep homeostasis may be disrupted in primary insomnia (Pigeon & Perlis, 2006), SRT may prime sleep homeostasis to reduce sleep onset latency (SOL) and wake-time after sleep onset (WASO). This may explain the medium-to-large effect sizes found previously for these variables (Miller et al., 2014). Third, SRT may reduce the worry and anxiety of "getting to sleep" which is common in insomnia symptomology (Harvey, 2001; Kyle et al., 2011). Such worry is typically expressed in attempting to control sleep by spending excessive amounts of time in bed (TIB) to ensure some sleep opportunity (Spielman et al., 2010). SRT may address this excessive time spent in bed by acting as a behavioral counter-measure leading to worry and anxiety about sleep (Spielman et al., 2010) which is deemed a counterproductive safety behaviour (Harvey, 2002) and can cause circadian misalignment to the sleep period (Lack & Wright, 2007). Fourth, physiological HPA-axis over-activation may result in increased conditioned arousal that perturbs sleep initiation and maintenance. SRT may help to reduce overall arousal by promoting an efficient and consolidated sleep period.

In the preceding chapter, response to measures of salivary cortisol concentrations before and during the acute phase of therapy for insomnia was examined. This current chapter aims to evaluate plasma cortisol concentrations after six weeks of therapy to provide a less variable and more robust in-lab measure of cortisol during the night. Cortisol levels are reported to be higher in those with insomnia compared to healthy good sleeping controls. Four studies found elevations in plasma and urinary cortisol compared to controls (Rodenbeck & Hajak, 2001; Rodenbeck et al., 2002; Vgontzas et al., 2001; Vgontzas et al., 1998). Vgontzas et al. (2001) measured plasma cortisol concentrations over a 24-hour period with half hourly sampling in 11 patients with insomnia. Significant increased cortisol concentrations were identified in the evening and the first half of the night in those with insomnia (see Figure 18). This outcome was found in an otherwise normal

circadian pattern and was attributed to arousal in the central nervous system and not attributed to sleep loss (Vgontzas et al., 2001).

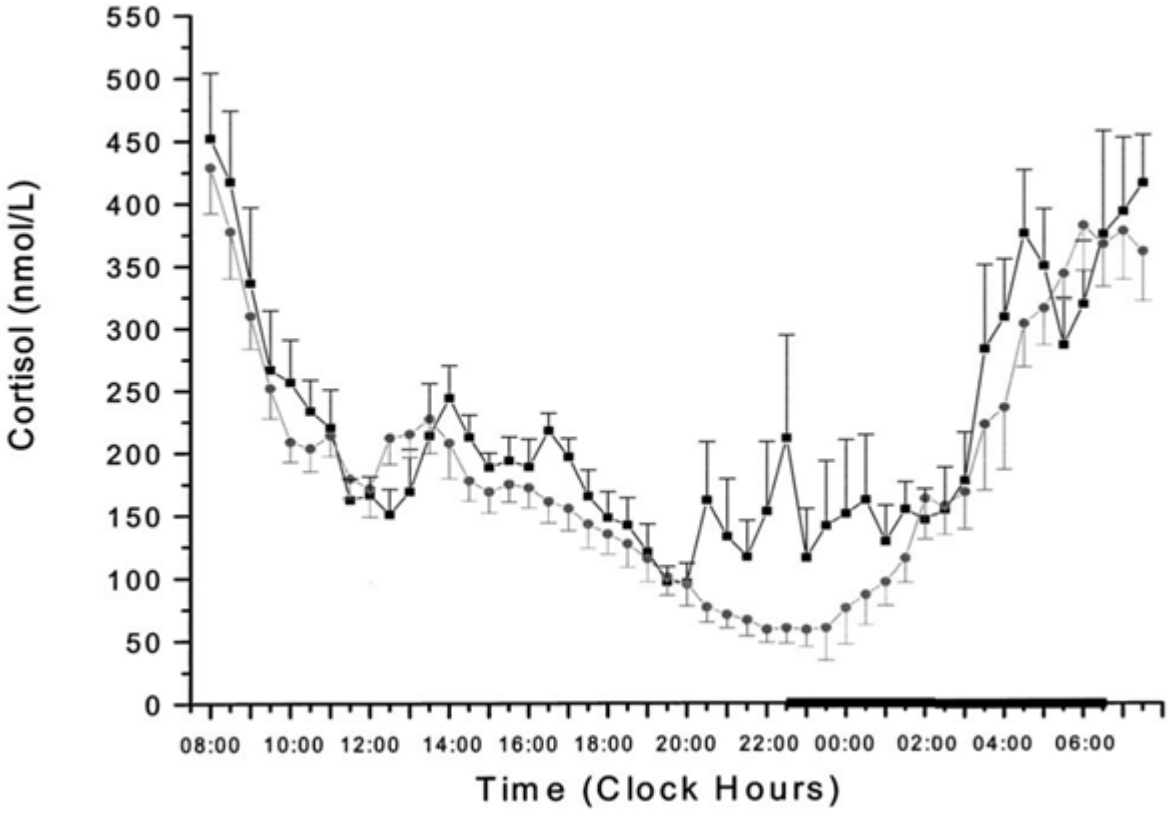


Figure 18 Plasma cortisol secretion in participants with insomnia compared to healthy volunteers. Displays serial 24-h cortisol values those with insomnia (■) and controls (●). Thick white, black lines on the abscissa indicate the night time sleep recording period (taken from Vgontzas et al. (2001), P. 3790). Error bars represent one standard error of the mean.

In healthy volunteers Pejovic et al. (2013) examined the influence of one week of mild sleep restriction on plasma cortisol concentrations throughout a 24 hour period in 30 healthy young males and females. In the sleep laboratory participants were studied over 13 nights with four baseline nights (TIB = 8 hours per night), six sleep restriction nights (TIB = 6 hours) and three recovery nights (TIB = 10 hours per night). Blood was sampled for cortisol concentrations during the last 24 hours of each phase of the experiment. During sleep restriction, cortisol concentrations did not change compared to baseline but values were significantly lower during the recovery sleep (Pejovic et al.,

2013). Findings suggest that cortisol concentrations may modify with changes to TIB in normal healthy volunteers (see Figure 19).

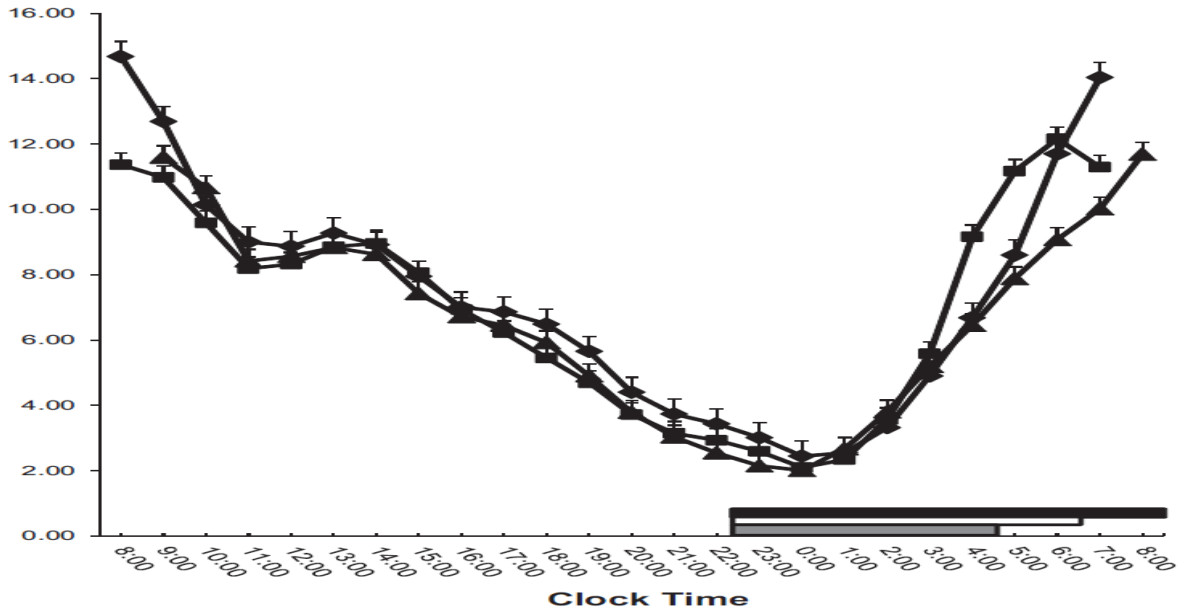


Figure 19 Plasma Cortisol secretion in healthy volunteers. Displays serial 24-h cortisol values in healthy volunteers at baseline (◆), restriction (■), and recovery (▲) Thick white, gray, and black lines on the abscissa indicate the night time sleep recording period at baseline, restriction, and recovery, respectively. Taken from Pejovic et al. (2013), P. E893.

Studies have also found higher core body temperature levels in insomnia, suggesting a marker of increased arousal compared to healthy good sleeping controls (Bonnet & Arand, 2010). Gradisar, Lack, Wright, Harris, and Brooks (2006) found significantly higher core body temperature levels in those with insomnia by approximately 0.2°C compared to controls (see Figure 20). Lushington, Dawson, and Lack (2000) also found increased core body temperature levels by approximatley 0.3°C compared to controls (see Figure 21).

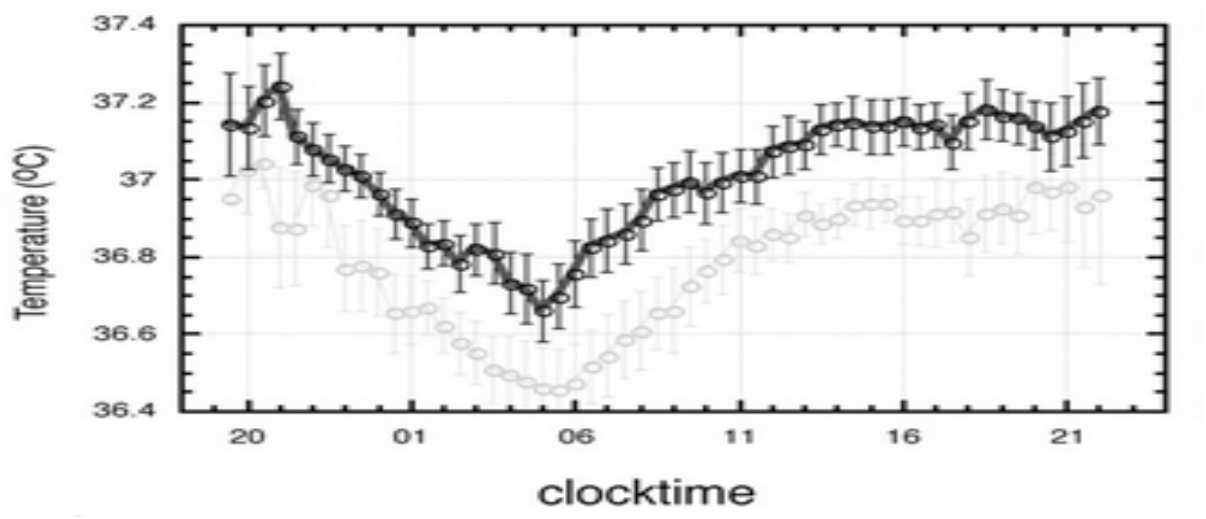


Figure 20 Twenty-four hour rectal temperature in insomnia compared to controls. Displays serial 24-h rectal temperature for those with insomnia *n*=11 (O) and controls (O) *n*=8 with fitted temperature curves. Error bars represent one standard error of the mean. Taken from Gradisar et al. (2006), P. R1118.

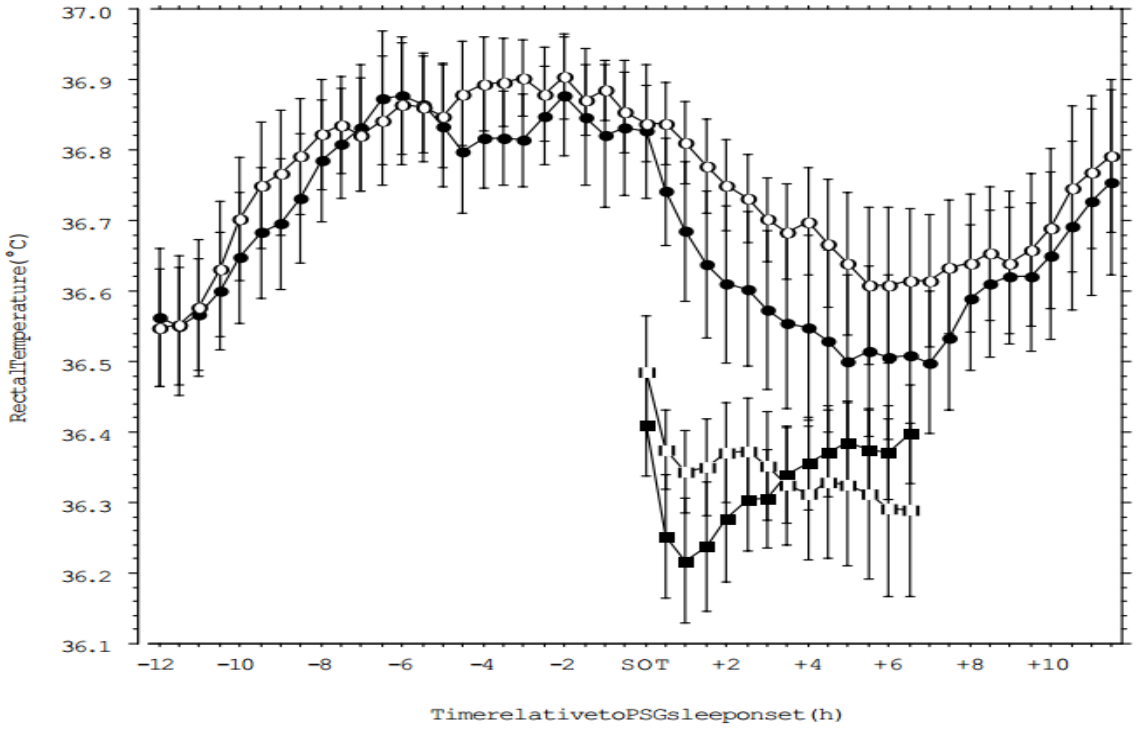


Figure 21 Twenty-four hour temperature in insomnia compared to controls. Displays serial 24-h rectal temperature for those with insomnia (O) and controls (●). Temperature curves are aligned to the period for sleep onset plus six and a half hours under ad lib sleep conditions. Error bars represent one standard error of the mean. Taken from Lushington et al. (2000), P.4.

A review of the literature by Lack, Gradisar, Van Someren, Wright, and Lushington (2008) of studies conducted under constant routine conditions concluded that core body temperature is increased in insomnia patients compared to controls, during the subjective night only. In induced stress studies an increase in core body temperature levels was found in normal healthy participants (Vinkers et al., 2008). Given the role of stress and arousal in insomnia, it is feasible that SRT may reduce both core body temperature and resulting physiological arousal.

Therefore, this study evaluated the role of potential changes in objectively defined sleep and physiological arousal through plasma cortisol concentrations and core body temperature pre-to-post SRT for insomnia. We hypothesised the following: 1. Effective SRT will improve the efficiency, duration and consolidation of both subjective and objective sleep parameters; and 2. SRT will reduce overall physiological arousal from measures of plasma cortisol concentrations and core body temperature.

6.3 Methods

6.3.1 Participants, therapy & adherence

Eleven participants were recruited through responses to advertisements in clinic, online and in the local community see Chapter 3.8 Recruitment & participants. Potential participants were recruited as previously described in Chapter 3: Methodology for the assessment of sleep. Insomnia severity index (ISI; Morin, 1993) scores were used to define insomnia severity. Only those with an ISI score ≥ 15 (the cut off for clinical insomnia; (Morin, 1993)) and a predominant complaint of initiating and/or maintaining sleep were included in the study (see Figure 22 for an overview of the study procedures).

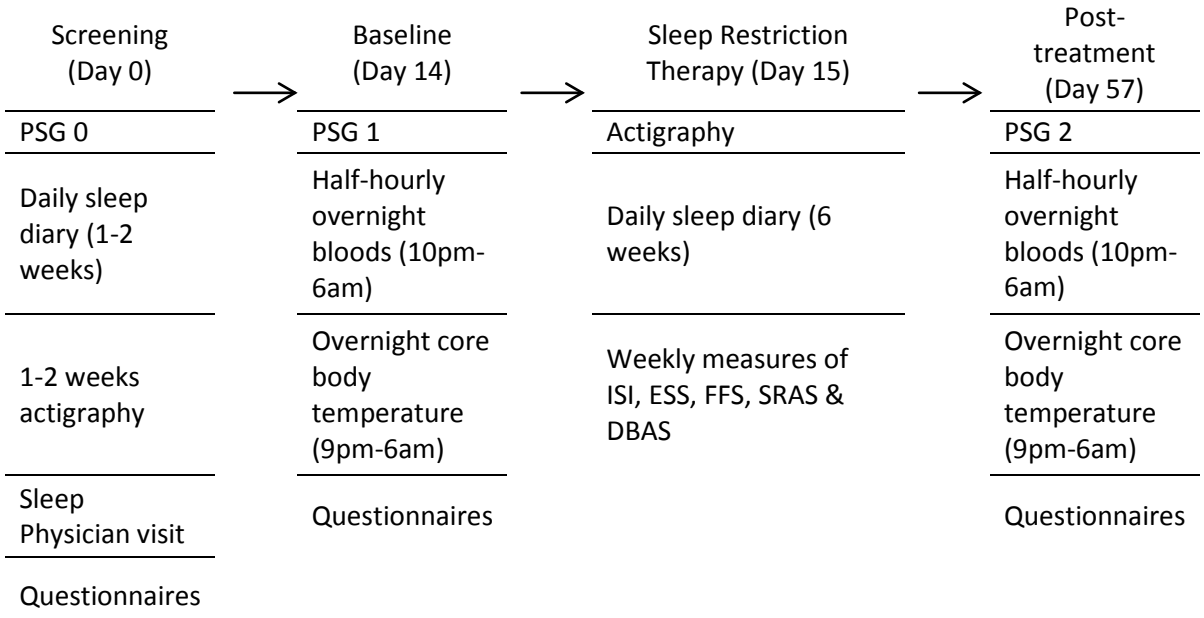


Figure 22 Displays the time course of the study. Prior to study enrolment, participants were examined for sleep disorders through 1 night of polysomnography (PSG) evaluation, sleep diary and actigraphic data. Prior to therapy, a baseline assessment of sleep with half hourly blood and minutely core body temperature measures was implemented. Sleep Restriction Therapy was initiated over the course of 6 weeks with daily sleep diaries, actigraphic recordings and weekly questionnaire assessments including: the insomnia severity index: ISI; the Epworth sleepiness scale: ESS; Flinders fatigue scale: FFS; sleep restriction adherence scale: SRAS. After 6 weeks, participants returned for a post-treatment overnight study again with overnight measures of blood & temperature.

SRT was implemented as described previously in Chapter 3.7 Sleep restriction therapy. Home adherence to SRT was monitored with self-report sleep diaries, actigraphy and the sleep restriction adherence scale (SRAS; Kyle & Crawford, unpublished) throughout therapy. The SRAS was completed on a week-by-week basis and asks participants to rate on a 1-6 scale (with 1 = none of the time and 6 = all of the time) their adherence to SRT through five specific questions. Higher scores are indicative of greater adherence as described previously (see Chapter 3.7 Sleep restriction therapy).

Home adherence to the sleep schedule was also monitored through secondary measures including a daily subjective sleep diary and objective actigraphy (throughout therapy continuously for 6 weeks). The sampling time on the actigraph was set at two minutes (normally this is every minute). As actigraphy was used as an objective measure of adherence of therapy, the battery life of the watch was extended to six weeks to limit the number of patient visits and capture TIB to confirm the sleep window. The limited number of wrist monitors also made it difficult to guarantee the availability of another watch every two weeks with a minutely sampling rate. Actigraphy (Philips Respironics, Bend, Oregon, USA) was visually inspected for TIB and missing data (sustained period with a lack of activity) concurrently by two experienced scorers in line with previous practice parameters (Morgenthaler et al., 2007). Outcome variables were processed and scored by an automated computer program (Actiware V6.0, Philips Respironics Bend, Oregon, USA). The ISI (Morin, 1993) was completed before and after therapy to monitor global effects of treatment. This study was reviewed and approved by the Royal Prince Alfred Hospital Ethics Review Committee, Sydney, Australia (see Appendix F: Ethical approval for Chapter 6). All participants gave written consent to take part in the study.

6.3.4 Polysomnography

Polysomnography (PSG) was used to uncover any potential occult sleep disorders at screening prior to the start of the study. PSG was also used at baseline and after six weeks of SRT to define objective sleep architecture and continuity variables before and after SRT. For all three PSG assessments, a research montage was used involving electroencephalographic [EEG: Fpz (neutral), F3, Fz, F4, C3, Cz, C4, Cz-Pz (Reference), Pz, O1, Oz, O2], electrooculographic (EOG: horizontal and vertical), electrocardiographic (ECG) and electromyographic (EMG: submental) recordings. Data were recorded on an Embla Titanium ambulatory recorder (Mortara, Milwaukee, USA) and scored visually by two experienced sleep scorers concurrently according to AASM criteria (Iber, 2007).

6.3.5 Overnight cortisol and core body temperature data collection

Overnight blood and core body temperature collection was performed before and after therapy as part of a normal overnight PSG sleep assessment. To standardise blood and temperature data collection, all participants were set-up and in bed from 9pm on both nights of data collection. Participants remained awake in bed until they felt sleepy tired and ready to initiate sleep. Therefore, participants were allowed to decide on when to turn off the lights to initiate sleep. This was done primarily to enable and standardise the first blood sample of cortisol at 10pm. Cortisol is a primary outcome measure and difficulties with catheter insertion are common which potentially would disrupt the timing of sample collection. Therefore participants were set-up with PSG prior to the insertion of the catheter at 9pm.

Blood collection was achieved half-hourly from 10pm until the last sample at 6am (17 samples in total). Samples were collected by a qualified nurse in another room from the bedroom with the 'hole in the wall technique'. An intravenous catheter was inserted within the cubital fossa vein for all sampling (Vgontzas et al., 2001). If not already awake (6 were asleep at baseline, 2 were asleep at post treatment) participants were awoken after the final 6am sample. Samples were placed on ice for five minutes and then centrifuged at 5,000 RPM for 10 minutes at 3°C. Samples

were stored at -80°C until analysis by enzyme immunoassay (Cayman Chemical Company, Ann Arbor, Michigan; limit of detection: 80% B/B_0: 35 pg/ml, Sensitivity: 50% B/B_0: 180 pg/ml). Cortisol was analysed on site at the Woolcock Institute of Medical Research (Sydney, Australia) as described previously (Vgontzas et al., 2001; Yanovski, Cutler, Chrousos, & Nieman, 1993). Core body temperature was collected minutely from 10pm onwards until 6am the next morning. Core body temperature was measured through the use of a previously validated (O'Brien, Hoyt, Buller, Castellani, & Young, 1998) ingestible core body temperature pill (Phillips Respironics, Bend, Oregon, USA).

6.3.6 Sleep diary and questionnaire data

Participants were asked to complete daily measures of sleep through sleep diaries for at least one week prior to therapy and six weeks during treatment. The daytime insomnia symptom scale (DISS: Levitt et al. (2004)) was completed in bed prior to sleep initiation and in the morning after each overnight sleep study pre-to-post therapy only. The DISS was implemented to profile point-in-time changes in four factors (including: alert cognition; negative mood; positive mood and sleepiness/fatigue) after six weeks of therapy at the bedtime and awakening sampling time points as part of the overnight sleep study. Similar to previous studies, four factors were evaluated for potential evening and morning changes due to SRT (Buysse et al., 2007; Miller et al., 2013). Along with the ISI, sleep diary data were used as the primary outcome measures to define a response to treatment.

6.3.7 Statistical analysis

For outcome variables (including: sleep architecture and continuity, sleep diary and questionnaire data), boxplots and histograms were used to check data for normality and outliers in line with the approach described in Chapter 3.9 Statistical analysis. For cortisol and core body temperature, linear mixed model analysis was implemented to take account of fixed effects including time (pre-to-post therapy) and sample collection over the course of the night (22:00-06:00). Random effects were included to account for between-subject variation. Only random effects were included for the intercepts. Uncorrected pairwise comparisons based on estimated marginal means were implemented to investigate primary outcomes. The DISS was also analysed with linear mixed model analysis as described previously in Chapter 4: An ecological momentary assessment of sleep restriction therapy for insomnia (Miller et al., 2013).

6.4 Results

In total, 11 participants were initially enrolled into the study. However, three with baseline data collected left the study prior to completion. Reasons for drop out included: side effects of therapy during week two (stress of initial sleep loss), another due to the diagnosis of an unrelated medical condition, and one due to a motor vehicle accident (deemed unrelated to treatment since attributed to a drunk driver hitting the participants car). Eight participants (2 male: mean age 46.4 years, range 28-61) completed the study and data are reported. Full pre-to-post blood and core body temperature data are reported for six out of the eight participants. Baseline blood (due to problems inserting the intravenous catheter) and temperature collection (due to battery malfunction) failed in another subject. At post-treatment, there was a similar problem with catheter insertion. One participant was unable to ingest the core body temperature pill due to previous abdominal surgery.

6.4.1 Adherence

The mean SRAS scores supported adherence to therapy over the first five weeks remained above 20 for the eight participants (see Figure 23).

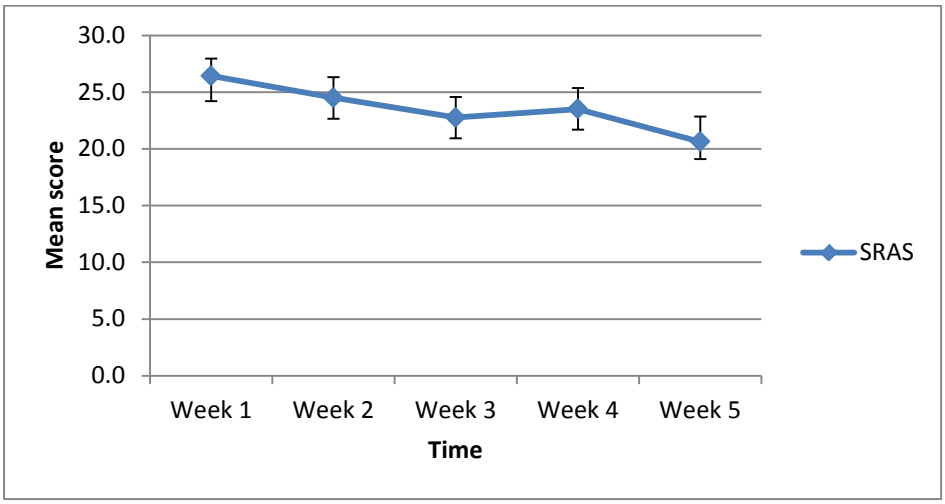


Figure 23 Mean sleep restriction adherence scales scores (SRAS) during five weeks of therapy (*n*=8). Error bars indicate one standard error of the mean.

Sleep diary and actigraphic data were analysed to evaluate adherence to therapy through TIB and total sleep time (TST). Figure 24 displays mean self-reports of TIB and TST before (2 weeks) and during SRT (weeks 1-6). Figure 25 profiles actigraphic data of TIB and TST before (2 weeks) and during SRT (weeks 1-6). Mean assigned TIB is included in both figures to provide a comparison to actual TIB and TST.

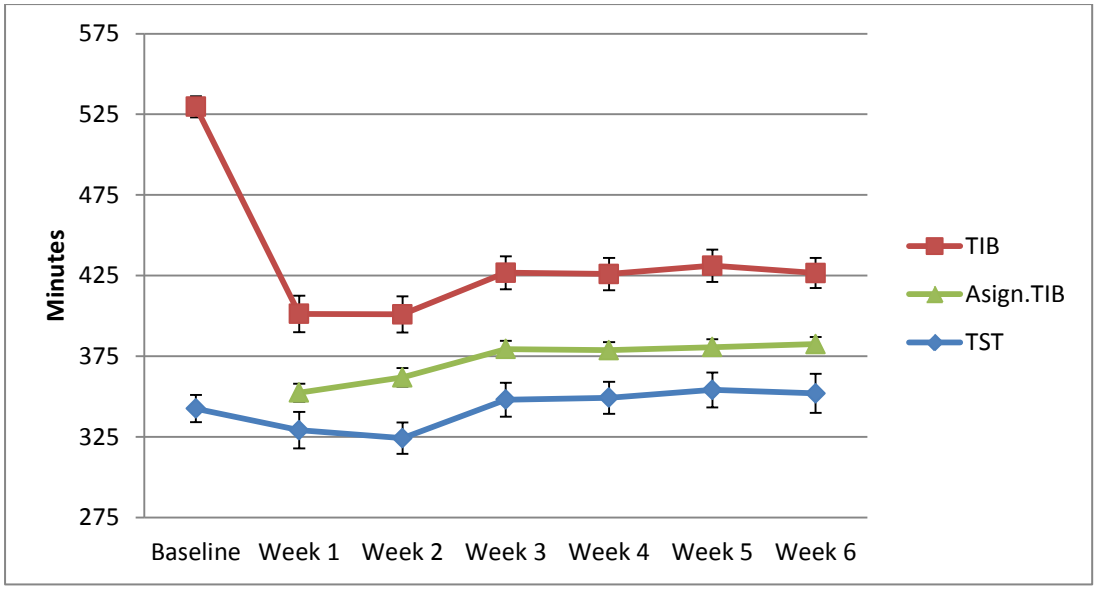


Figure 24 Mean sleep diary results prior to and during therapy. Displays values in minutes for total sleep time (TST) in blue, time in bed (TIB) in red and assigned time in bed (Asign. TIB) in green, prior to (baseline: 2 weeks) and during sleep restriction therapy for insomnia (weeks 1-6) (*n*=8). Error bars indicate one standard error of the mean.

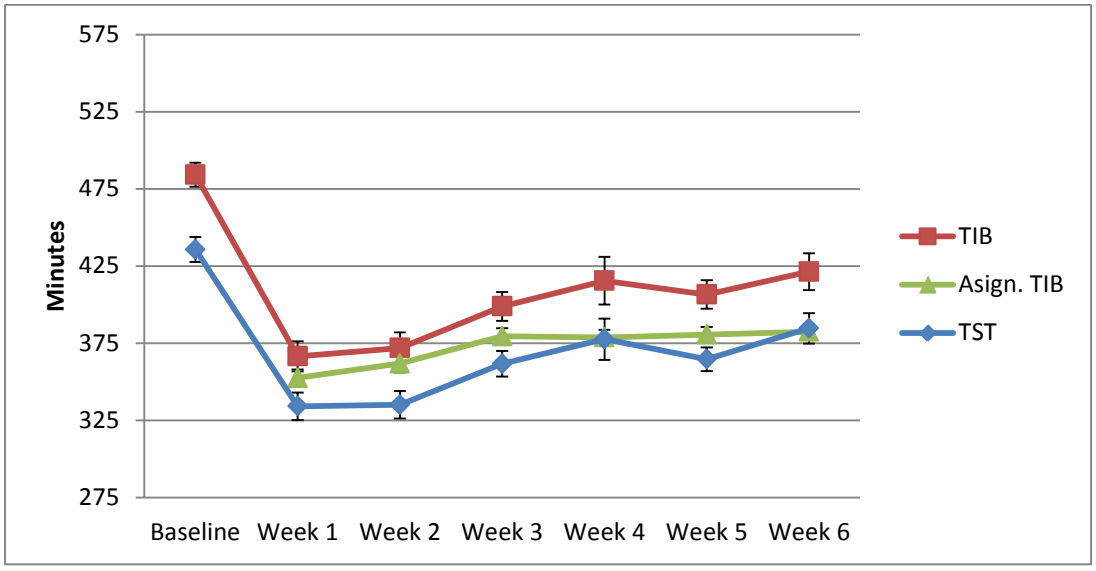


Figure 25 Mean actigraphy results prior to and during therapy. Displays values in minutes for total sleep time (TST) in blue, time in bed (TIB) in red and assigned time in bed (Asign. TIB) in green, prior to (baseline: 2 weeks) and during sleep restriction therapy for insomnia (weeks 1-6) (*n*=7). Error bars indicate one standard error of the mean.

6.4.2 Sleep

Pairwise comparisons and effect size scores (*d*) evaluated change in questionnaires after six weeks of SRT compared to baseline. Mean ISI scores decreased significantly pre-to-post therapy with a large effect size (mean (SD) 18.2 (2.8) vs. 8.4 (4.8), $p<.01$, $d=2.5$). For the first hypothesis, that SRT improves the efficiency, duration and consolidation of sleep, primary sleep diary variables were analysed (see Table 18 & Appendix G: Individual data for Chapter 6). SOL displayed a trend, suggesting a reduction (the effect size was medium: $d=0.6$). Both WASO and the number of awakenings (NOAW) decreased significantly with a large effect. Sleep efficiency (SE) and ratings of sleep quality (SQ) both increased significantly with a large effect and TST did not significantly increase (mean (SD): 335.9 (53.2) vs. 353.4 (72.8), $p=.27$, $d=0.3$).

Sleep Diary Variables (minutes)	**Time point (Mean and SD)**		**Paired differences testing**		
	Baseline	**Week 6**	**Baseline versus week 6 (Mean and SE)**	***p*-value**	**Effect size (*d*)**
SOL	51.6 (58.9)	23.0 (22.0)	-28.7 (14.7)	.10	0.6
WASO	73.9 (54.7)	11.2 (9.8)	-62.7 (59.1)*	<.05	1.6
NOAW	2.1 (1.4)	1.0 (0.9)	-1.1 (0.28)*	<.05	0.9
TST	335.9 (53.2)	353.4 (72.8)	17.5 (38.1)	.27	0.3
TIB	526.0 (36.1)	427.5 (57.2)	-98.6 (66.5)*	<.05	2.1
SE (%)	64.7 (12.3)	82.7 (12.5)	10.6 (4.0)*	<.01	1.5
SQ	0.6 (0.3)	1.24 (0.4)	0.66 (0.1)*	<.01	1.8

Table 18 Self Report sleep diary variables pre-to-post sleep restriction therapy for insomnia. The left hand side of the table displays mean self-report sleep diary data at baseline and after 6 weeks of Sleep Restriction Therapy (*n*=8). The right hand side of the table examines within subject differences between baseline and week 6. SOL: Sleep Onset Latency; WASO: Wake-time After Sleep Onset; NOAW: Number of Awakenings; TST: Total Sleep Time; TIB: Time in Bed; SE: Sleep Efficiency; SQ: Sleep Quality. (*) = *p*<.05.

Next, and to further evaluate the first hypothesis, the following objectively defined sleep parameters were examined: SOL; TST; WASO; SE; REM latency; NREM (mins); REM (mins); Stage 1 (mins); Stage 2 (mins) and SWS (mins). Sleep parameters did not change pre-to-post therapy (see Table 19). Upon inspection of boxplots, time spent in SWS was found to have an outlier at baseline. With the removal of this participant, SWS increased pre-to-post therapy (63.6 (13.6) vs. 78.5 (25.2), p=.05, d=0.7).

PSG Defined Variables (minutes)	Time point (Mean and SD)			Paired differences testing		
	Screening	Baseline	Week 6	Baseline versus week 6 (Mean and SE)	*p*-value	Effect size (*d*)
SOL	29.2 (13.4)	29.2 (24.7)	18.9 (32.7)	-10.3 (11.2)	.39	0.4
WASO	94.5 (37.6)	102.7 (52.5)	86.6 (42.5)	-16.1 (16.3)	.36	0.3
TST	333.2 (61.4)	313.7 (54.2)	353.6 (40.9)	39.9 (20.7)	.10	0.8
SE (%)	72.3 (10.4)	70.5 (11.8)	77.3 (10.7)	6.88 (4.6)	.18	0.6
REM	65.7 (29.1)	56.7 (30.4)	67.8 (25.8)	11.1 (9.0)	.82	0.4
REM Latency	168.1 (71.0)	156.2 (51.0)	152.9 (64.5)	3.29 (29.0)	.91	0.1
N1	9.5 (5.3)	23.2 (8.4)	20.1 (7.0)	-3.13 (2.9)	.32	0.4
N2	183.3 (22.0)	160.7 (38.7)	183.1 (31.3)	22.38 (16.7)	.22	0.6
SWS	74.6 (32.7)	73.1 (29.8)	82.7 (26.1)	9.5 (7.1)	.23	0.3
SWS[ǂ]	-	63.6 (13.6)	78.5 (25.2)	15.0 (5.7)*	.04	0.7
NREM	267.4 (36.9)	257.0 (44.0)	285.8 (22.4)	28.78 (15.6)	.11	0.8

Table 19 Objectively defined sleep variables pre-to-post sleep restriction therapy for insomnia. The left hand side of the table displays mean objectively defined sleep staging data at screening, baseline and after 6 weeks of Sleep Restriction Therapy (n=8). The right hand side of the table examines within subject differences between baseline and week 6. PSG: polysomnography; SOL: Sleep Onset Latency; WASO: Wake-time After Sleep Onset; TST: Total Sleep Time; SE: Sleep Efficiency; REM: Rapid Eye Movement sleep; N1: Stage 1 of sleep; N2: Stage 2 of sleep; SWS: Slow Wave Sleep; NREM: Non-Rapid Eye Movement sleep. [ǂ]SWS: Slow Wave Sleep with 1 patient removed who displayed very high amount of baseline SWS. (*) = p<.05.

To further test the initial hypothesis to evaluate the efficiency, duration and consolidation of sleep pre-to-post therapy, Figure 26 is used to display a graphical representation of the temporal pattern of individual objectively defined sleep (black) and wake (white) during the overnight sleep assessment (21:30-06:00) at baseline (A) and after 6 weeks of SRT (B). Grey shading on the left hand side denotes time in bed prior to lights out. Each line represents one individual. Visually, from the figure, it seems that sleep is more consolidated, faster to initiate and with participants more likely to be awake at the 06:00 time at post treatment (6/8 participants awake) compared to baseline (2/8 participants).

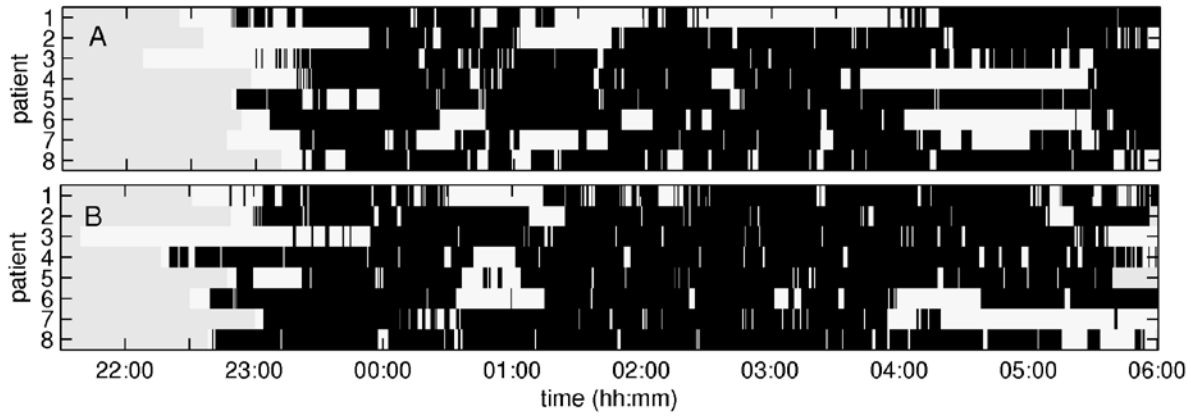


Figure 26 Temporal pattern of objectively defined sleep before and after therapy. Displays a graphical representation of estimated objectively defined sleep for each participant (*n*=8) before (A) and after (B) 6 weeks of sleep restriction therapy. Each individual row represents one participant during the course of a sleep study (21:30-06:00). Sleep is represented in black, time in bed prior to lights out is in grey and wakefulness (during lights out) is in white. Blood sampling occurred every half hour from 22:00 until 06:00. Lights on occurred after the last blood sample was obtained at 06:00.

6.4.3 Cortisol

In the second part of the hypothesis, SRT was expected to decrease overall arousal, mean plasma cortisol concentrations (for each half hour sample during the night: 22:00-06:00), were firstly examined for nocturnal secretion (µg/dL) by analysing for the main effect of time of sample collection for the 17 samples (see chapter 3.9 Statistical analysis). A significant effect for time of sample was found (F (16, 163.061) = 14.86; p<.001) indicating nocturnal variation, in line with the circadian rhythmicity of cortisol secretion (see Figure 27). Next, samples were evaluated for overall pre-to-post differences in cortisol concentrations for all participants with sufficient blood data (n=6). No overall differences were found pre-to-post therapy (mean and 95% confidence intervals: 3.58 [2.6, 4.5] vs. 3.89 [2.9, 4.9], (F (1, 163.028) = .570; p=.45).

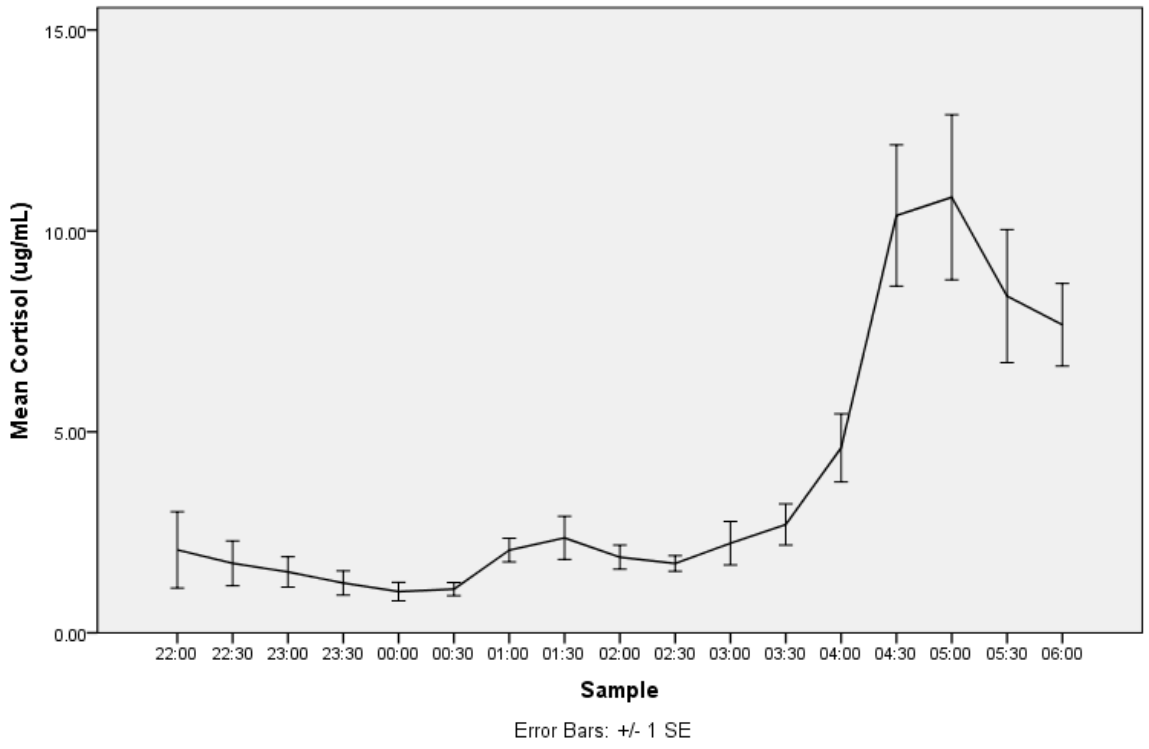


Figure 27 Mean nocturnal plasma cortisol concentrations across the night. Displays mean nocturnal cortisol secretion (n=6) for both sample collection time points (pre and post therapy) over the course the night (22:00-06:00). Error bars indicate one standard error of the mean. Cortisol (µg/dL).

Next, a sample (for each half hour sample during the night: 22:00-06:00) x time (pre-to-post) phase interaction was used to examine potential nocturnal differences after SRT [F (16, 163.064) = 1.68; *p*=.06]. Simple main effects were analysed and revealed a significant increase at the following sample time-points pre-to-post therapy: 05:00 (mean and 95% confidence intervals: 9.1 [6.6, 11.5], vs. 12.6 [10.2, 15.1], (F (1, 163.028) = 4.305; *p*=.04); 05:30 (5.5 [3.0, 8.0], vs. 11.3 [8.8, 13.7], (F (1, 163.028) = 11.34; *p*=.001); 06:00 (5.3 [2.8, 7.7], vs. 10.1 [7.6, 12.6], (F (1, 163.028) = 7.9; *p*=.01) (see Figure 28 & Table 20).

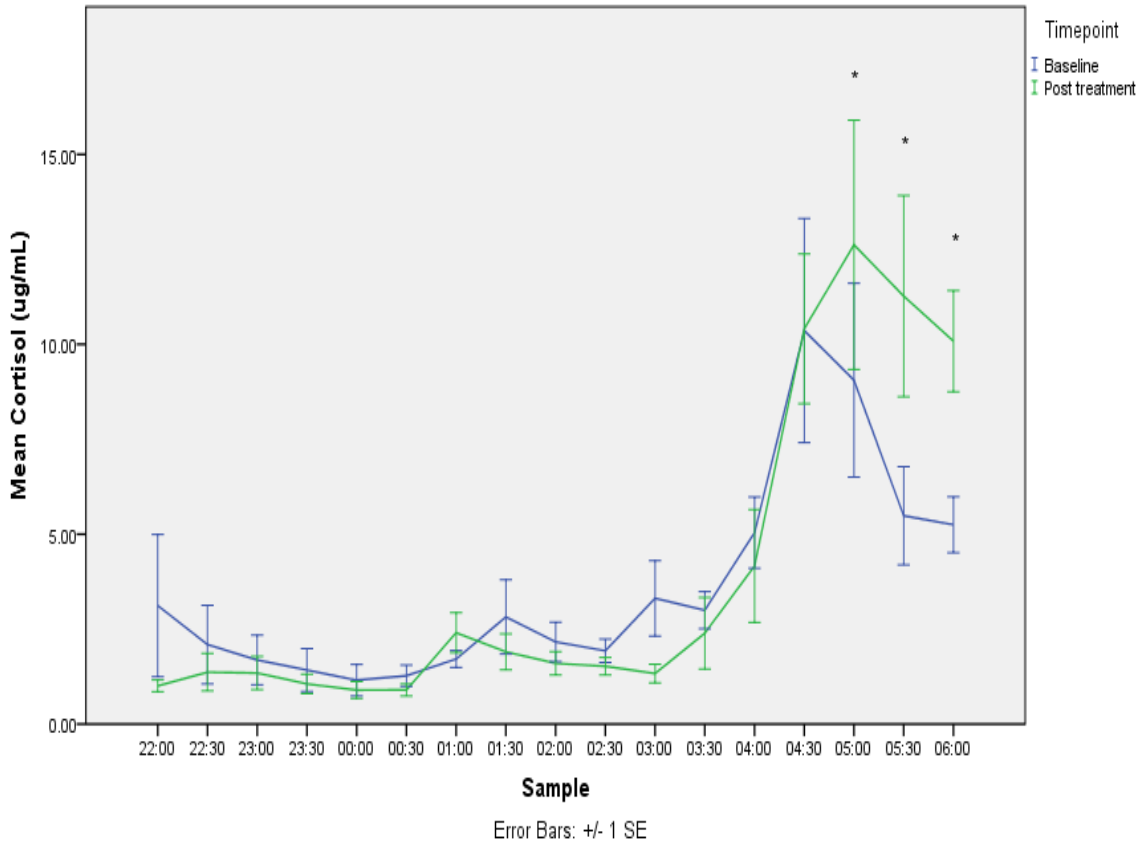


Figure 28 Mean nocturnal plasma cortisol concentrations pre-to-post sleep restriction therapy. Displays mean nocturnal cortisol secretion (*n*=6) for each sample collection time point at baseline (blue) and post treatment (green) over the course the night (22:00-06:00). Error bars indicate one standard error of the mean. Cortisol (µg/dL).(*) *p*<.05.

Time of sample	Baseline		Post-treatment		Difference Testing and 95% CI's			
	Mean (µg/dL)	95% CI	Mean (µg/dL)	95% CI	Mean Difference	*p*-value	Lower Bound	Upper Bound
22:00	3.1	0.7, 5.6	1.0	2.0, 3.5	2.1	.22	-1.28	5.51
22:30	2.1	0.4, 4.6	1.4	1.1, 3.8	0.7	.67	-2.66	4.12
23:00	1.7	0.8, 4.2	1.3	1.1, 3.8	0.3	.84	-3.05	3.74
23:30	1.4	1.1, 3.9	1.1	1.4, 3.5	0.4	.83	-3.03	3.76
00:00	1.2	1.3, 3.6	0.9	1.6, 3.4	0.3	.88	-3.13	3.65
00:30	1.2	1.2, 3.8	0.9	1.6, 3.4	0.4	.83	-3.02	3.76
01:00	1.7	0.7, 4.2	2.4	0.7, 4.9	-0.7	.69	-4.09	2.70
01:30	2.8	0.3, 5.3	1.9	0.6, 4.4	0.9	.59	-2.47	4.31
02:00	2.2	0.3, 4.6	1.6	0.9, 4.1	0.6	.74	-2.83	3.96
02:30	1.9	0.6, 4.4	1.5	1.0, 4.0	0.4	.81	-2.98	3.80
03:00	3.3	0.6, 6.0	1.3	1.1, 3.8	1.9	.29	-1.64	5.48
03:30	3.0	0.5, 5.5	2.4	0.1, 4.9	0.6	.73	-2.79	4.00
04:00	5.0	2.6, 7.5	4.2	1.7, 6.6	0.9	.61	-2.51	4.27
04:30	10.4	7.9, 12.8	10.4	7.7, 13.1	0.0	.99	-3.55	3.58
05:00*	9.1	6.6, 11.5	12.6	10.2, 15.1	-3.565*	.04	-6.96	-0.17
05:30*	5.5	3.0, 8.0	11.3	8.8, 13.7	-5.784*	<.01	-9.18	-2.39
06:00*	5.3	2.8, 7.7	10.1	7.6, 12.6	-4.832*	<.01	-8.22	-1.44

Table 20 Plasma cortisol concentrations pre-to-post sleep restriction therapy. The left hand side of the table displays mean plasma cortisol concentrations at baseline and after 6 weeks of sleep restriction therapy (*n*=6). The right hand side of the table examines within subject differences between baseline and week 6. Cortisol (µg/dL); (*) *p*<.05.

Due to the variability of samples and low numbers of participants, plasma cortisol concentration values were collapsed across the night into the following three groups; early: 22:00-00:30; middle: 00:31-03:30; and late: 03:31-06:00. Linear mixed models were implemented (intercept F (1, 196) = 309.5; p<.001). A nocturnal secretion pattern was found for cortisol (µg/dL) after analysing for the main effect of time of sample collection for each sampling period (early: 22:00-00:30, middle: 00:31-03:30, late: 03:31-06:00) (F (2, 196) = 88.2; p<.001). Overall, cortisol concentrations (µg/dL) did not change pre-to-post therapy (n=6: means and 95% CI's = 3.8 [3.1, 4.4] vs. 4.2 [3.6, 4.9]; F (1, 196) = 309.5; p=.33). However, a second time of sample x treatment phase interaction was used and was significant (F (2, 196) = 5.515; p=.005). Simple main effects revealed a significant difference for the late (03:01-06:00) sampling period only pre-to-post SRT (means and 95% confidence intervals: 7.0 [5.9, 8.2] vs. 9.7 [8.5, 10.9] (see Figure 29). Suggesting, plasma cortisol concentrations increase towards the end of the sleep period after SRT for insomnia (see Table 21).

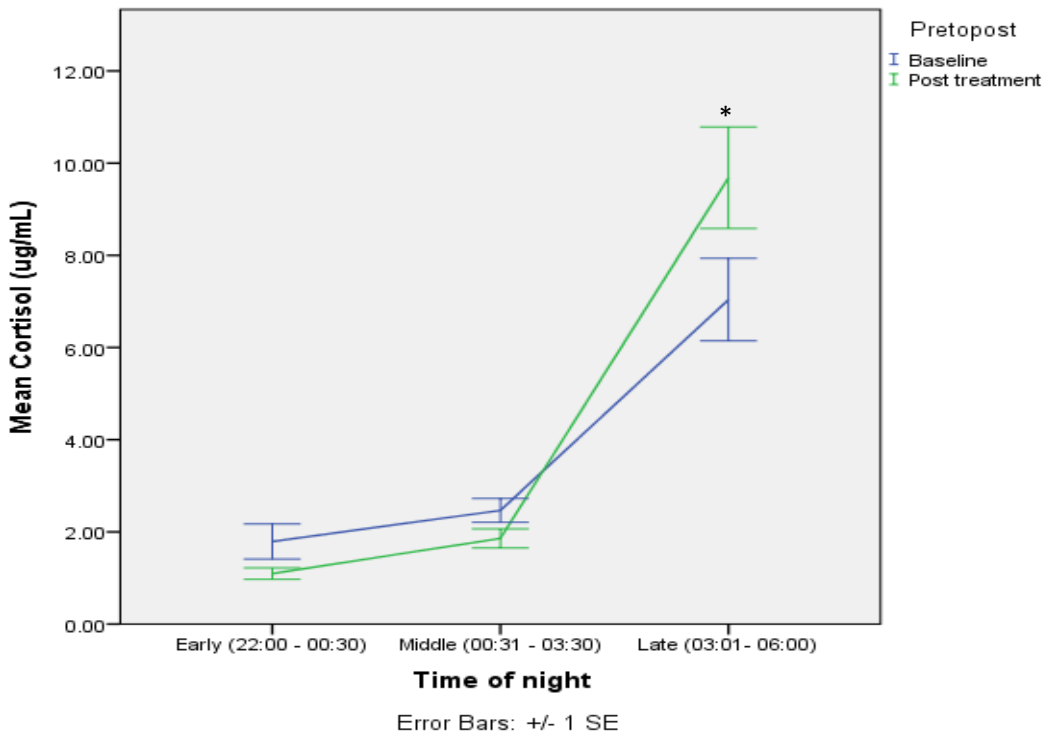


Figure 29 *Collapsed* mean nocturnal plasma cortisol concentrations across the night pre-to-post sleep restriction therapy (*n*=6). Displays mean nocturnal cortisol for time of night (early: 22:00-00:30; middle: 00:31-03:30; and late: 03:01-06:00) baseline (blue) & post treatment (green). Error bars indicate one standard error of the mean. Cortisol (ug/mL); **p*< .05.

Time of sample	Baseline		Post-treatment		Difference Testing and 95% CI's			
	Mean	95% CI	Mean	95% CI	Mean Difference	*p*-value	Lower Bound	Upper Bound
22:00-00:30	1.8	0.7, 2.8	1.1	0.0, 2.2	0.7	.35	-0.761	2.155
00:31-03:30	2.5	1.4, 3.5	1.9	0.8, 2.9	0.6	.42	-0.87	2.067
03:31-06:00*	7	5.9, 8.2	9.7	8.5, 10.9	-2.6*	<.01	-4.246	-1.023

Table 21 *Collapsed* plasma cortisol concentrations pre-to-post sleep restriction therapy. The left hand side of the table displays mean plasma cortisol concentrations at baseline and after 6 weeks of sleep restriction therapy (*n*=6). The right hand side of the table examines within subject differences between baseline and week 6. Cortisol (ug/mL); (*) *p*<.05.

6.4.4 Core body temperature

Next, core body temperature was evaluated to further test the second part of the hypothesis. Initially, nocturnal variation to core body temperature was analysed (*n*=6) for the main effect of time of sample collection (every 30 minutes from 22:00-06:00). Differences were found across the night in line with the circadian period of core body temperature F (15, 145.017) = 1.938; *p*=.024) (see Figure 30).

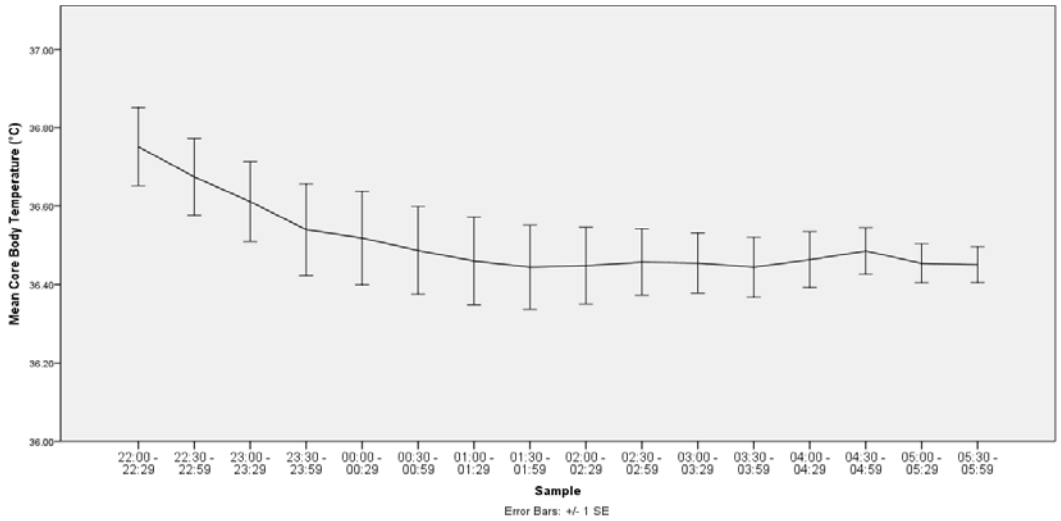


Figure 30 Mean core body temperature across the night. Displays mean core body temperature in degrees Celsius (°C) (*n*=6) across both sample collection time points (pre and post therapy) over the course the night (22:00-06:00). Error bars indicate one standard error of the mean.

Next, pre-to-post changes in core body temperature were evaluated and displayed a significant decrease after therapy (mean and 95% confidence intervals: 36.54 [36.3, 36.8] vs. 36.45 [36.2, 36.7], (F (1, 145.071) = 9.69; *p*=.002). Lastly, to examine specific differences in core body temperature across the night pre-to-post SRT a time of sample x treatment phase interaction was employed. Although this was not significant (F (15, 145.017) = 1.063; *p*=.396) (see Figure 31).

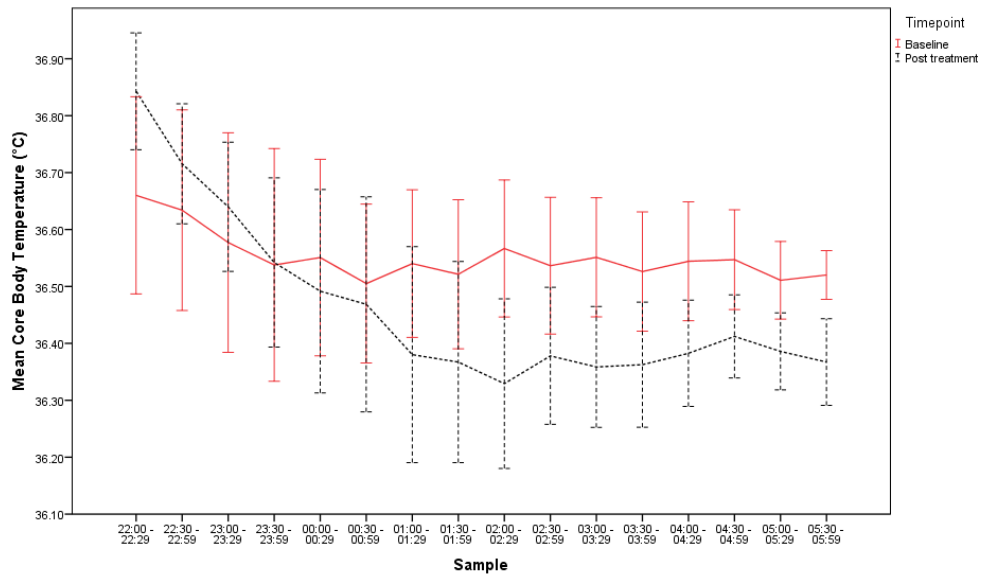


Figure 31 Mean core body temperature across the night pre-to-post sleep restriction therapy. Displays mean core body temperature degrees Celsius (°C) (*n*=6) for baseline (red) and post treatment (black) over the course the night (22:00-06:00). Error bars indicate one standard error of the mean; * *p*<.05.

In light of this, the rate of change of core body temperature over the first two hours of sleep initiation was profiled. Successful sleep initiation is most likely to occur during core body temperature decline at the start of the sleep period (Campbell & Broughton, 1994). Each minutely temperature sample was analysed with the following formula: (Tc final - Tc start) ÷ t (hour) = x°C × hour^{-1}, where Tc = core body temperature. Visually, the rate of change for core body temperature was greater in the post treatment condition although this was not significantly different (mean and 95% confidence intervals: before = -0.005 (0.103), after -0.155 (0.214), *p*=.25, *d*=0.8, see Figure 32).

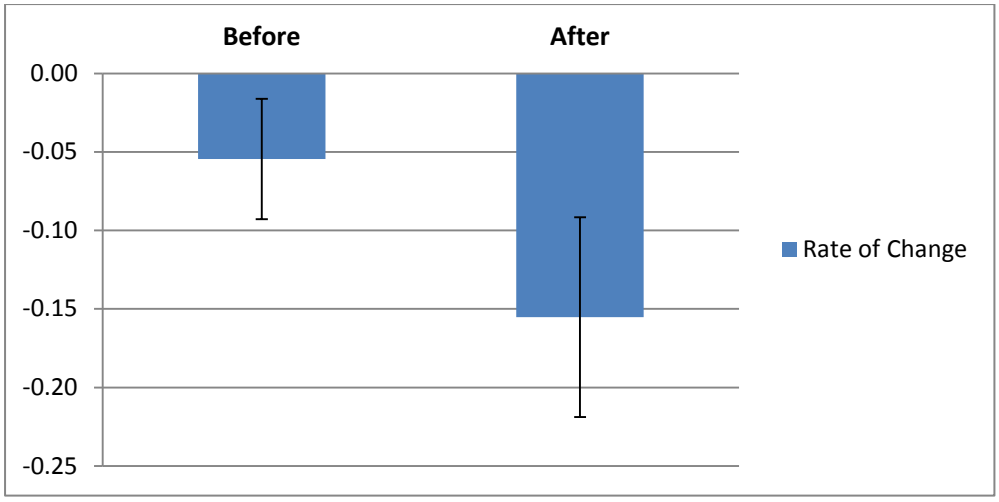


Figure 32 Rate of change for core body temperature. Displays the rate of change (*x*°C × hour^{-1}) across the first two hours of recording before and after Sleep Restriction Therapy for insomnia (*n=6*). Error bars indicate one standard error of the mean.

To determine if a difference in circadian timing was responsible for the improvement in insomnia symptomology, best fitting sinusoidal curves were fitted to temperature data to judge whether there was evidence of a phase delay or phase advance pre-to-post therapy. Curves were fit (see Figure 33) according to the following formula: $a+b*\sin(c*x+d)$, where *a* is the offset, *b* is the amplitude, *c* is close to *pi*/12 to achieve ca. 24hr periodicity and *d* is the phase (Conroy, Spielman, & Scott, 2005). All parameters are chosen to achieve the best fit (R-squared). From this, visual inspection of the core body temperature nadir was achieved before and after therapy to suggest either a phase delay or a phase advance.

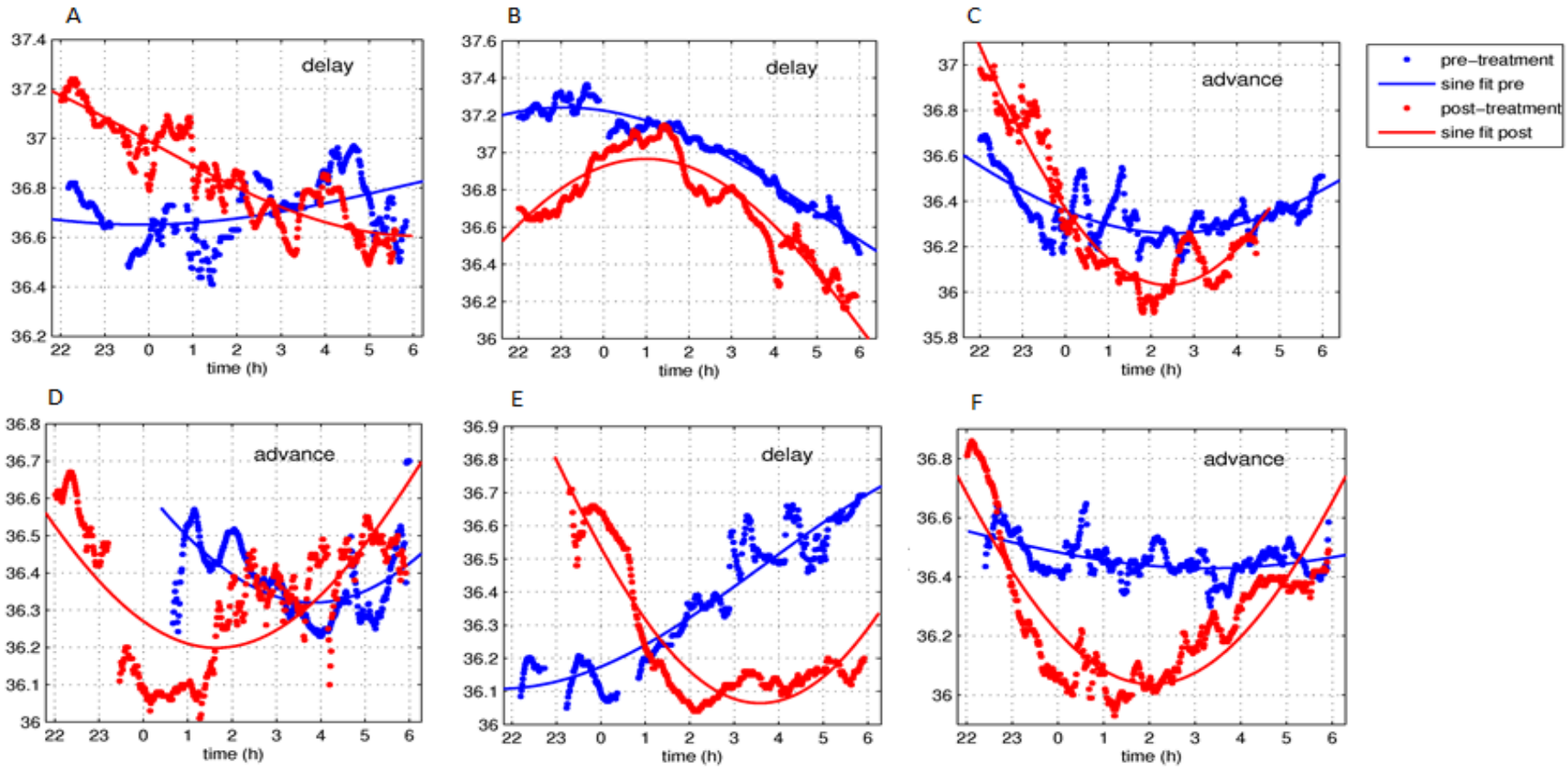


Figure 33 Displays core body temperature across the night before (blue) and after (red) 6 weeks of sleep restriction therapy for insomnia in degrees Celsius (°C) for each participant (*n*=6: A-F). Curves were fit according to the following formula: *a*+*b*sin*(*c***x*+*d*), where *a* is the offset, *b* is the amplitude, *c* is close to *pi*/12 to achieve ca. 24hr periodicity and *d* is the phase. All parameters are chosen to achieve the best fit (*R*-squared). The phase advance and delays were determined visually by identifying differences in the nadir.**

6.4.5 Daytime insomnia symptom scale

The DISS was analysed for main effects for time (pre-to-post) yielding significant improvements for morning measures of alert cognition (F (1, 21) = 3.745; M = 45.0 [36.2, 53.7] vs. 55.5 [46.7, 64.3], p<.05) (see Figure 34). Negative mood displayed a trend towards improvement (F (1, 21) = 5.7, M = 36.3 [21.4, 51.1] vs. 28.0 [13.2, 42.9], p=.07. Positive mood and sleepiness/fatigue did not change.

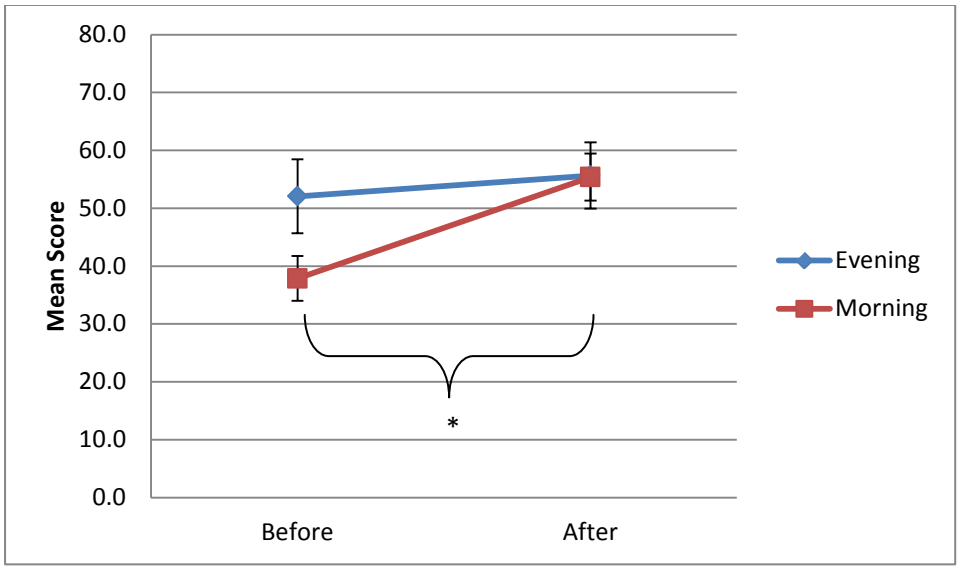


Figure 34 Alert cognition from the daytime insomnia symptom scale pre-to-post sleep restriction therapy at bedtime (blue) and on awakening (red) before and after sleep restriction therapy for insomnia. Error bars are of one standard error of the mean. (*) = p<.05

6.5 Discussion

The primary aim of this study was to investigate changes in objectively defined sleep and measures of physiological arousal (plasma cortisol concentrations & core body temperature) pre-to-post sleep restriction therapy (SRT) for insomnia. We hypothesised that: 1. Effective SRT improves the efficiency, duration and consolidation of both subjective and objective sleep parameters; and 2. SRT reduces overall increased arousal in measures of plasma cortisol concentrations and core body temperature.

As a prelude to this discussion, it is important to note that adherence to therapy was measured through weekly reports of questionnaires, daily sleep diary and actigraphic data. Participants adhered to the instructions of therapy as average sleep restriction adherence scale (SRAS) scores were found to be high over the course of the first five weeks of therapy (>20: see Figure 23). Further, sleep diary measures of time in bed (TIB) and prescribed TIB as used previously (Kyle et al., 2014), were suggestive of adhering to therapy. Objectively measured adherence through actigraphy closely matched the assigned amount of TIB (see Figure 24). Overall, suggesting therapy was adhered to.

6.5.1 Sleep restriction therapy

With regards to the first hypothesis, effective SRT improves sleep parameters, this study found significant pre-to-post improvements in primary sleep diary measures of wake-time after sleep onset (WASO), number of awakenings (NOAW), sleep efficiency (SE), and ratings of sleep quality (SQ). All were found to improve with a large effect ($d \geq 0.8$). Although non-significant, sleep onset latency (SOL) and total sleep time (TST) suggested a trend for improvement with a large (d=0.6) and small (d=0.3) effect size respectively (see Table 18 & Appendix G: Individual data for Chapter 6). These findings are in line with previous data regarding the efficacy of therapy on self-report diary measures (Miller et al., 2014).

In addition to these improvements, questionnaire measures of global insomnia severity (insomnia severity index: ISI) and fatigue (Flinders fatigue scale: FFS) reduced significantly pre-to-post therapy. Daytime functioning (daytime insomnia symptom scale: DISS) measured at bedtime and in the morning of both overnight assessments pre-to-post treatment, was found to significantly improve at the morning assessment time point for alert cognition only (see Figure 34). The increase in alertness in the morning after therapy provides further evidence for positive alterations to the sleep-wake experience (Miller et al., 2013). A reduction in alert cognition prior to sleep was not documented. This may have been due to a lack of data or the nature of the overnight test including the thought and stress of blood sampling and lack of ecological validity. Overall, self-report improvements are in line with previous research findings of measures of sleep and daytime functioning after effective SRT (Kyle et al., 2014; Kyle et al., 2011; Miller et al., 2013).

6.5.2 Sleep

Objectively defined TST improved (but not significantly, perhaps due to low statistical power) by a mean of 39.9 minutes (*d*=0.8) after six weeks of therapy compared to baseline and by 20.4 minutes compared to screening (see Table 19 & Appendix G: Individual data for Chapter 6). In a recent uncontrolled study, polysomnography (PSG) was used to profile sleep during therapy implementation (on days 1, 8 and 22) (Kyle et al., 2014). A significant decrease in TST was found (reducing by a mean of 75 minutes between baseline and day 22 of therapy). From these results, it would seem that improvements in TST may not be evident until well after 22 days of therapy.

There were no other significant improvements in objective sleep parameters (see Table 19). On inspection of boxplots, an outlier was found at baseline for slow wave sleep (SWS: 140 minutes). Once this participant was removed, SWS improved significantly pre-to-post SRT (see Table 19). In a meta-analysis (Baglioni et al., 2014) SWS was reduced and may be a future target for treatment response in insomnia research. In comparison to other previous studies of SRT, Kyle et al. (2014) did not report any objective sleep variables apart from TST. Only one other study by Friedman et al. (2000) attempted to measure objective improvements in therapy with PSG. This study and previous research was underpowered to test for between group differences (Friedman et al., 2000; Miller et al., 2014).

6.5.3 Effects on physiological measures of arousal

Arousal is thought to be both a precipitant and perpetuating factor in the development and maintenance of chronic insomnia (Spielman & Glovinsky, 1991). The hyperarousal hypothesis posits increased cortical and physiological arousal in those with insomnia compared to healthy good sleeping controls (Bonnet & Arand, 2010; Riemann et al., 2010). Markers of arousal may reduce with effective therapy for insomnia (Bonnet & Arand, 2010; Espie, 2002; Roth, 2007c). Following cognitive behavioural therapy for insomnia (CBT-I), a more rapid decline of EEG delta power (a marker of cognitive hyperarousal) was identified in insomnia participants compared to placebo controls

(Krystal & Edinger, 2010). Unfortunately changes in other physiological markers of arousal in CBT-I remain untested (Bonnet & Arand, 2010; Roth, 2007c). In this study, two markers of physiological arousal were profiled after effective therapy, plasma cortisol concentrations and core body temperature, the following sections discuss findings.

6.5.4 Cortisol concentrations

The results from the present study suggest that SRT increases morning levels of plasma cortisol concentrations after six weeks of therapy compared to baseline (see Figure 28 & Figure 29). This was mirrored by an increase in subjective morning levels of alertness after therapy that was first profiled previously in chapter four (Miller et al., 2013). From Figure 26, it appears that six out of the eight subjects were awake in the morning prior to the 6am sample at post treatment. At pre-treatment six out of the eight subjects were asleep (apart from one participant who was awake from around 04:00am at post treatment and on inspection this was due to problems re-siting a faulty cannula for blood collection). This is perhaps unexpected as the hypothesis assumed cortisol concentrations would decline. But this may be a plausible outcome after effective treatment for insomnia and suggests SRT increases subjective morning alertness and plasma cortisol concentrations.

Increased morning cortisol concentrations after therapy may in part be due to a normalisation of the circadian sleep-wake cycle. Previously in healthy males, sleep restriction (4hrs TIB for 2 nights) and resulting sleep loss was found to dampen the amplitude of the circadian rhythm of plasma cortisol concentrations (Guyon et al., in press). An increase in morning cortisol secretion after therapy may indicate a restoration to the circadian rhythm which may protect against adverse health effects where a dampening or misalignment of the circadian period occurs (e.g. increased risk of type 2 diabetes) (Guyon et al., in press). In one previous study individuals with insomnia showed significantly decreased salivary cortisol concentrations on awakening compared to healthy good sleeping controls (Backhaus et al., 2004). The authors postulated these findings supported the

hyperarousal theory of insomnia (as cortisol concentrations may have been higher during the course of the night in the insomnia participants prior to wake). However, this was not directly measured as part of their study (Backhaus et al., 2004). SRT appears to modify wake concentrations of cortisol by restoring a natural circadian amplitude reflected in improvements in sleep and daytime functioning measures.

Increases in objective TST and SWS may also be responsible for changes in cortisol concentrations. In normal healthy participants, temporal associations are found between SWS and cortisol with lower cortisol concentrations during SWS (Balbo, Leproult, & Van Cauter, 2010; Follenius et al., 1992) and higher cortisol levels appear to inhibit SWS (Krieger & Glick, 1974; Weibel, Follenius, Spiegel, Ehrhart, & Brandenberger, 1995). Significant positive correlations between increased cortisol activation and disturbed sleep have been identified (Backhaus et al., 2004; Rodenbeck et al., 2002; Vgontzas et al., 2001), an overall increase in TST after therapy of approximately 40 minutes appeared to contribute to increased morning cortisol concentrations. It is likely increased time spent in N2 (22.4 minutes) or REM (11.1 minutes) sleep contributed to this morning increase. Alternatively, an increase in cortisol may be due to the end of the sleep period and the beginning of the cortisol awakening response and possibly reflects an increase in circadian amplitude and not a phase advance (see Figure 33).

In healthy volunteers, Vgontzas et al. (2004) found a lower peak in cortisol secretion after sleep restriction (6 hours for 6 nights) compared to baseline. Comparing the graphs between studies, it appears that the post therapy condition in the current study resembles the healthy sleeping participants in the baseline condition of the previous study (Vgontzas et al., 2004). Pejovic et al. (2013) implemented mild sleep restriction on healthy volunteers (6 hours for 6 nights) and found no change in overall cortisol levels during sleep restriction but a slightly earlier and *dampened* cortisol awakening response. This is in contrast to the current study where the amplitude of cortisol was found to be significantly increased in the early morning at post treatment, suggesting that sleep

restriction may not be responsible for the changes to cortisol concentrations found in this study. This is a consistent finding across the literature in healthy volunteers where mild sleep restriction does not change or even reduces cortisol concentrations (Omisade et al., 2010; Pejovic et al., 2013; Schmid et al., 2011; Vgontzas et al., 2007; Vgontzas et al., 2004; Wu et al., 2008). Only severe sleep deprivation paradigms appear to increase cortisol secretion in healthy individuals (Pejovic et al., 2013). Mild sleep restriction may therefore not account for the findings of the current study and perhaps changes in the both the timing and amplitude of HPA-axis functioning are responsible for the observed changes in cortisol concentrations. These results suggest that sleep restriction may not increase morning levels of cortisol concentrations. Alternatively, our results may be a product of an as yet untested long term (6 weeks) outcome of SRT for insomnia.

Vgontzas et al. (2001) reported higher cortisol concentrations at the beginning the night in those with insomnia compared to controls whereas in the current findings there was no significant decrease in cortisol secretion pre-to-post therapy. Visually, cortisol concentrations appear to be lower for the first two thirds of the night (22:00-00:30 & 00:31-03:30) at post-treatment compared to baseline levels (see Figure 18). One concern is that significant reductions in cortisol values may have been missed as they occurred prior to the beginning of the blood sampling routine (before 22:00: see Figure 18). An optimal protocol is half hourly measures of plasma cortisol concentrations under constant routine conditions over the 24 hour period before and after therapy.

The only other study (*n*=10) examining the role of cortisol concentrations before and after treatment was one primarily using Doxepin over a three week period and found reduced plasma cortisol concentrations (Rodenbeck et al., 2003). Vallieres et al., (2013) investigated five participants with insomnia through an SRT protocol and evaluated the role of salivary cortisol concentrations. Unfortunately this study was inadequately powered to test for statistical differences and no other study has attempted to profile changes. There is also a need to acknowledge the effect of the HPA-axis (antiglucocorticoid agents) when implementing treatment for insomnia in line with the

hyperarousal theory of insomnia, but there have been no pre-to-post treatment studies (Roth, 2007c). Future studies should now look to profile potential changes to not only plasma cortisol but also adrenocorticotropic and corticotropin-releasing hormone concentrations before and after treatment for insomnia.

Following SRT treatment the cortisol profile mirrored the controls in the Vgontzas et al. (2001) study (see Figure 27 & Figure 28) with reduced cortisol at the start of the night which is an encouraging trend given the short intervention span. Vgontzas et al. (2001) did not find any between group differences in the morning cortisol concentrations whereas morning cortisol was increased after therapy. It could be argued that this outcome resulted from the use of a 24 hour routine condition and a sleep period. The present study reports sleep period data only making comparisons between the two studies difficult. Individuals with insomnia tend to report extreme difficulties with morning energy or not feeling refreshed. A rise in morning cortisol following treatment may be a positive outcome such as significant elevations found in the last three time points indicate improvements in alertness which was substantiated by subjective questionnaire data (see Figure 34).

Rodenbeck et al. (2002) found a delay in plasma cortisol concentrations in insomnia patients compared to healthy controls which was similar to the current results at post treatment where the onset of objective sleep advanced and participants were awake earlier in the morning (see Figure 26). A phase advance in cortisol secretion and cortisol awakening response would explain the increase in morning cortisol concentrations after therapy. Yet, it is still unclear whether a phase advance in circadian timing is reflected in the cortisol (Figure 28) and temperature data (Figure 31). Evaluation of changes in the circadian period after successful therapy for insomnia seems a necessary assessment.

6.5.5 Core body temperature

The significant mean decrease in core body temperature found after therapy in this study suggests a reduction in physiological arousal with SRT for insomnia. Previous research found similar outcomes in comparison with controls (Bonnet & Arand, 1997, 2010), ranging from 0.2°C (Gradisar et al. (2006): see Figure 20), to 0.29°C in sleep laboratory conditions (Lushington et al. (2000) (see Figure 21). A review by Lack et al. (2008) concluded core body temperature is increased under 24 constant routine conditions.

No previous studies have evaluated core body temperature after treatment for insomnia under the umbrella of CBT-I. Benzodiazepines alone appear to decrease oral temperature in healthy participants (Longbottom & Pleuvry, 1984) assuming a decrease in the sleep or arousal systems (Bonnet & Arand, 2010). Core body temperature levels in healthy individuals undergoing one night of sleep deprivation did not change (Romeijn et al., 2012) and was stable over five 24-hour constant routine schedules in healthy controls (Van Dongen, Kerkhof, & Souverijn, 1998). It is therefore likely that the reduction in core body temperature results from physiological arousal decreases and not from sleep restriction.

A bi-directional relationship exists between insomnia and depression (Baglioni et al., 2011; Sivertsen et al., 2012) and treatment interventions may modify circadian timing of temperature in both groups. In depression research, an increase in circadian amplitude and a decrease in core body temperature was found after effective electroconvulsive therapy and was interpreted as a restoration to a disrupted circadian system (Szuba, Guze, & Baxter Jr, 1997). However, insomnia symptoms were not measured. In seasonal affective disorder, the amplitude of core body temperature rhythm increases with phototherapy (Rosenthal et al., 1990). An increase in circadian amplitude at post treatment (see Figure 31 & Figure 33) compared to baseline may be due to entrainment of the master circadian pacemaker (Kräuchi, 2007) through increased activity, light exposure in the morning and reduced TIB with SRT. Mild sleep deprivation (5.7hrs for 1 week) in

healthy participants reduces the amplitude of circadian rhythm gene expression (Möller-Levet et al., 2013). In the current study, only a change in circadian amplitude was found and not a phase shift in the internal circadian rhythm, in line with Rosenthal et al. (1990) as no obvious and consistent phase alterations where found across patients from the temperature data pre-to-post therapy (see Figure 33).

The nadir of core body temperature from the current study was difficult to identify because of a lack of circadian amplitude at baseline (see Figure 33) but was more easily defined after therapy. Effective treatment for insomnia may moderate an initial arousal imbalance by consolidating sleep through an increase in circadian amplitude (see Figure 32 & Figure 33). A faster decline in core body temperature was visually apparent during the first two hours of sleep initiation at post treatment compared to baseline. This faster non-significant decline in temperature appears suggestive of change in circadian amplitude after therapy promoting sleep by providing a more relaxed state prior to sleep initiation (Kräuchi, 2007). Without 24-hour data under constant routine conditions, conclusions are speculative.

6.6 Limitations

A major limitation is the lack of a control group and patients may have improved through a placebo or non-specific response as the experimenter also acted as the therapist. Demand characteristics of the study and the researcher may result in improvements to subjective variables. Habituation to the overnight testing procedures may also have influenced objective sleep variables including blood sampling across the night.

The sample size was small and conclusions require caution due to the lack of statistical power and increased risk of a Type-II statistical error. No corrections for multiple comparisons were employed and therefore findings should be considered exploratory in nature and require further validation. Future studies with larger numbers will enable a clearer understanding of the effects of SRT on objectively PSG-defined sleep and physiological variables before and after therapy. 24-hour constant routine conditions would allow a further and more robust examination of both cortisol and temperature. Although adherence to sleep restriction therapy was difficult to gauge during the six weeks of therapy, participants were evaluated on self-report (sleep diary & SRAS) and objective (actigraphic) measures of adherence. A six month follow-up assessment would determine whether treatment is maintained over time.

6.7 Conclusion

This is the first study to specially profile physiological parameters relating to arousal after a behavioural intervention for the treatment of insomnia. Effective SRT reduced core body temperature and increased morning alertness and plasma cortisol concentrations in the later third of the night. Changes in increased circadian amplitude characterised by a faster rate of decline of temperature during sleep initiation is supportive. This SRT protocol enabled positive changes in arousal, however this can only be substantiated using larger numbers of participants under 24 hour constant routine conditions.

Chapter 7: Magnetic resonance spectroscopy of cerebral metabolism in insomnia

7.1 Abstract

Brain metabolism has been found to be altered in patients with insomnia compared to healthy good sleeping controls across the occipital and anterior cingulate cortices. So far studies have only looked at a limited number of metabolites and have failed to adequately quantify metabolites across the brain including the prefrontal cortex. A between-subjects study was used to evaluate differences in individual brain metabolites *in vivo* in patients with insomnia (*n*=15) compared to healthy good sleeping controls (*n*=14). Magnetic resonance spectroscopy (MRS) was used to quantify a range of metabolites including: aspartate (ASP); creatine (CRE); glutamate (GLU); glutamine (GLN); glutathione (GSH); glycerylphosphorylcholine (GPC); *myo*-inositol (MINO); and *N*-acetylaspartate (NAA) across the left occipital (LOCC), anterior cingulate (ACC) and left prefrontal cortices (LPFC) referenced to water. Findings suggest no differences in brain metabolites detectable at 3Tesla in those with insomnia across the three volumes of interest profiled in this study. In those with insomnia, objectively defined total sleep time correlated significantly with CRE levels in the LPFC (R^2=.48), suggesting possible links between objective sleep and brain metabolism in insomnia. Insomnia duration was found to significantly correlate with levels of GLU in LPFC (R^2=.42). No significant correlations were found for insomnia severity scores.

7.2 Introduction

A number of different brain imaging techniques have been used in insomnia and sleep research. With single-photon emission computed tomography, hypoperfusion has been identified across the frontal medial, occipital, parietal cortices and in the basal ganglia (Smith, Perlis, Chengazi, et al., 2002) in those with insomnia. Hypoactivation of the medial inferior prefrontal cortices was also found in insomnia compared to controls using functional magnetic resonance imaging (fMRI) (Altena et al., 2008), whilst smaller grey matter volumes correlated negatively with insomnia severity (Altena, Vrenken, Van Der Werf, van den Heuvel, & Van Someren, 2010) and micro structural changes in the orbitofrontal cortex have been found (Joo et al., 2013). The medial frontal areas are involved in the regulation of sleep (Koenigs, Holliday, Solomon, & Grafman, 2010), where increased insomnia symptoms were prevalent with left dorsomedial frontal damage in individuals with focal brain lesions (Koenigs et al., 2010). Using magnetoencephalography (MEG) increases in cerebral activity were identified during slow wave (SWS) and rapid eye movement (REM) sleep in the left dorsomedial prefrontal cortex (Ioannides, Kostopoulos, Liu, & Fenwick, 2009). As slow waves predominantly originate from the left frontoinsular area and cingulate gyrus during sleep (Murphy et al., 2009), the left medial prefrontal cortex appears critical for sleep initiation/maintenance requiring investigation in insomnia research.

Positron emission tomography (PET) has been used to document increased glucose metabolism in insomnia across the anterior cingulate cortex (ACC), prefrontal cortex, hypothalamus, amygdala and hippocampus (Nofzinger et al., 2004). Glucose metabolism also positively correlated with wake-time after sleep onset (WASO) during non-rapid eye movement (NREM) sleep (Nofzinger et al., 2006). Insomnia research also suggests that the ACC is chronically overactive (Winkelman et al., 2013), and is supported by the finding of a 21% reduction in *gamma*-Aminobutyric acid (GABA)/creatine(CRE) ratio in the ACC (Plante, Jensen, Schoerning, & Winkelman, 2012). Reductions in ACC volumes have also been observed in major depressive disorder (MDD) (Bora, Fornito, Pantelis, & Yücel, 2012; Koolschijn et al., 2009), along with reduced concentrations of glutamate

(GLU) and GABA (Auer et al., 2000; Bhagwagar et al., 2008; Hasler et al., 2007; Price et al., 2009). These findings appear to reinforce the bi-directional relationship between insomnia and depression (Baglioni et al., 2011; Sivertsen et al., 2012).

7.2.1 Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is used to measure chemical metabolite concentrations across selected regions of interest within the living brain (Govindaraju, Young, & Maudsley, 2000). MRS is different from conventional brain imaging as it consists of graphs producing information regarding the molecular structure of tissue within the brain giving a 'virtual biopsy' (Mountford et al., 2010). Approximately 35 metabolites can be measured with MRS in the human brain either *in vitro* or *in vivo* (Govindaraju et al., 2000; Mountford et al., 2010). The following metabolites can be detected using MRS: aspartate (ASP), CRE, GLU, glutamine (GLN), GABA, glutathione (GSH), glycerylphosphorylcholine (GPC) *myo*-inositol (MINO), *N*-acetylaspartate (NAA) (Rae et al., 2014: see Figure 35 and chapter 3.6.1 Magnetic resonance spectroscopy for an overview).

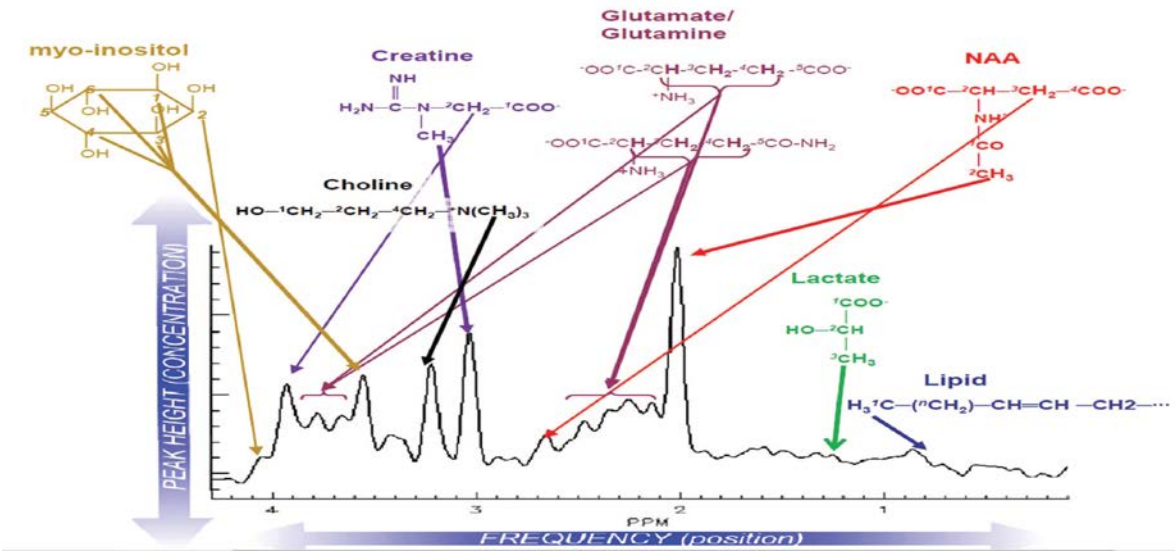


Figure 35 Representation of a typical spectrum of a healthy human brain in vivo from magnetic resonance spectroscopy. The peaks are labelled with the molecule and structure. Lactate and lipid concentrations are not observed in the healthy brain and therefore their absorptions are not visible. Taken from Mountford et al. (2010), P.3063.

7.2.2 Insomnia & brain metabolism

MRS has been used in a small number of insomnia studies that have mainly profiled differences in GABA/CRE concentrations. Winkelman et al. (2008) found evidence of a global reduction in GABA (by almost 30%) in 16 patients with insomnia compared to 16 healthy good sleeping controls. Lower GABA suggests an imbalance of the central nervous system in line with the hyperarousal theory of insomnia (Plante, Jensen, & Winkelman, 2012; Spiegelhalder, Regen, Baglioni, Riemann, et al., 2013; Winkelman et al., 2008). No other significant alterations were found between groups for levels of ASP, choline/phosphocholine (PC), GLU/GLN, glycine, MINO, NAA, and taurine (Winkelman et al., 2008). However, metabolites were averaged globally across the basal ganglia, thalamus, temporal, parietal, and occipital white-matter and cortices and were normalised to CRE, not water (a standard reference), making it unclear whether alterations in GABA or CRE levels were responsible for insomnia (Winkelman et al., 2008).

In a subsequent small study from the same group, Plante, Jensen, Schoerning, et al. (2012) found specific decreases in the GABA/CRE ratio in insomnia patients compared to healthy controls. The most significant differences were found in the middle occipital cortex (OCC) (33% reduction), and middle ACC (21% reduction) but not in the thalamus (Plante, Jensen, Schoerning, et al., 2012). No other differences in metabolite ratios were found (NAA/CRE, CHO/CRE, & GLU/CRE). Conversely in another study, the GABA/CRE ratio was increased by 12% in the middle of the OCC with no significant differences found for any other metabolites measured (Morgan et al., 2012). An explanation for these inconsistent results cited differences in methodologies (2 nights of ambulatory polysomnography: PSG vs. actigraphy) and sampling of participants (Plante, Jensen, & Winkelman, 2012). As insomnia is a heterogeneous disorder that is difficult to quantify, lack of PSG evaluation reinforces methodological differences in diagnoses. In the study by Plante, Jensen, Schoerning, et al. (2012), actigraphy was undertaken but this does not exclude other sleep disorders and does not quantify sleep staging.

A range of metabolites have been studied in those with insomnia compared to controls including: ASP, CHO, CRE, GLU, GLN, Glycine, NAA, MINO, scylloinositol and taurine (Morgan et al., 2012; Winkelman et al., 2008). However, no differences were found across the brain specifically in the OCC (Morgan et al., 2012) and also in the basal ganglia, thalamus, and smaller parts of the temporal, parietal, and occipital lobes (Winkelman et al., 2008). The frontal areas of the brain remain to be explored for any measure of brain metabolism in insomnia.

To indirectly evaluate GABAergic and glutamatergic activation in insomnia, Salas et al. (2013) used transcranial magnetic stimulation to profile intracortical motor excitability. Insomnia patients had alterations in glutamatergic mechanisms and not GABAergic neurotransmission dysregulation compared with controls. The authors urged for a more direct evaluation of glutamatergic activation in insomnia (Salas et al., 2013). Increases in GLU/GLN (referred to as GLX due to overlapping spectral resonances) has also been identified in patients with restless legs syndrome (Allen, Barker, Horská, & Earley, 2013) and positively correlated with WASO and total sleep time (TST). It appears the increased GLX/CRE levels are due to either sleep loss or both conditions share a generic sleep disorder nosology (Allen et al., 2013).

In post-traumatic stress disorder (PTSD) GABA and NAA levels were reduced in those compared to trauma exposed controls (Meyerhoff, Mon, Metzler, & Neylan, 2014). GABA concentrations correlated negatively with insomnia severity index scores (ISI) whilst GLU concentrations were increased in PTSD in the medial frontal cortex. Hyperarousal may be a factor in this altered brain metabolism in those with PTSD possibly linking to other stress related disorders such as insomnia. Profiling measures of brain metabolism the frontal regions of the brain in insomnia seems the next logical step.

To measure GABA and in order to provide a suitable signal-to-noise ratio to confidently detect GABA at 3Tesla (T), a specific MEshcher–GArwood Point RESolved Spectroscopy (MEGA-PRESS) programme patch is required along with an asymmetric point resolved spectroscopy patch

(Mescher, Merkle, Kirsch, Garwood, & Gruetter, 1998; Rae, 2014). In the current study and due to the scanning time restrictions to load a MEGA-PRESS patch to obtain GABA and other metabolites, a novel approach was undertaken in insomnia research as it was decided to not obtain GABA from the spectra. The following brain metabolites were selected to further evaluate brain metabolism in insomnia including: ASP, CRE, GLN, GLU, GSH, GPC, MINO, & NAA (for an overview please refer to chapter 3.6.2 Metabolites from magnetic resonance spectroscopy) across a number of areas across the brain including: the frontal, anterior cingulate and also occipital cortices. Therefore, it was hypothesised that these concentrations of brain metabolites would display increased arousal across the brain in those with insomnia compared to healthy good sleeping controls, in line with the hyperarousal theory of insomnia (Riemann et al., 2010; Spiegelhalder & Riemann, 2013). Secondly, it was also hypothesised that objective TST, subjective insomnia severity and insomnia duration (years) were associated with brain metabolism in those with insomnia, in line with previous research findings.

7.3 Methods

7.3.1 Participant sample

In the present study, 16 patients with chronic insomnia disorder and 14 healthy good sleeping controls (GS) took part. Participant's (<55 years of age) responded to local and online advertisements. Both groups were interviewed by telephone through the use of a screening assessment (Morin & Espie, 2003). Participants with insomnia were enrolled into the study if they met the inclusion/exclusion criteria as described previously in 3.8 Recruitment & participants. Control participants were matched to the insomnia patients by gender, age (within 3 years) and also for body mass index. Matched controls were defined through the same telephone interview to examine inclusion/exclusion criteria including the absence of a sleep complaint, psychiatric or medical disorder (unstable). Controls endorsed good sleep quality that was restorative and stable across the night (22:00-08:00) and reported a normal sleep onset latency (SOL: <15 minutes), wake-time after sleep onset (<15 minutes) with a total sleep time of >six hours, a high sleep efficiency (>85%) and low amount of night time awakenings (≤2). Any medication known to impact sleep was completely exclusionary for control participants. This study was approved by the Royal Prince Alfred Hospital Ethics Review Committee, Sydney, Australia (see Appendix H: Ethical approval for Chapter 7). All participants gave written consent to take part.

7.3.2 Assessment of sleep, mood and daytime functioning

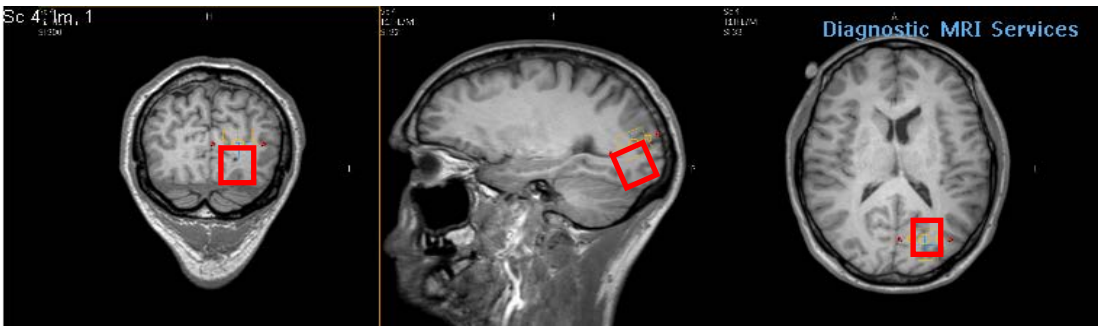
All participants kept a two week sleep diary (similar to Morin & Espie, 2003) to examine sleep quantity and quality. Participants wore wrist monitors during this period to exclude circadian rhythm disturbance. Actigraphy (Philips Respironics, Bend, Oregon, USA) was visually inspected for time in bed and missing data (sustained period with a lack of activity) concurrently by two experienced scorers in line with previous practice parameters (Chesson Jr et al., 1999). Outcome variables were processed and scored by an automated computer program (Actiware V6.0, Philips Respironics Bend, Oregon, USA). All participants also completed the following questionnaires to examine sleep and mood including: the ISI (Morin, 1993), the Epworth sleepiness scale (ESS) (Johns, 1992), and the 21-item version of the depression anxiety and stress scale (DASS) (Henry & Crawford, 2005). The DASS was used to quantify potential differences between those with insomnia and controls for measures of depression, anxiety and stress. One insomnia participant was excluded from the analysis as their scan was used to test the scan protocol. The final sample consisted of 15 patients with PI and 14 GS.

7.3.3 Magnetic resonance spectroscopy assessment

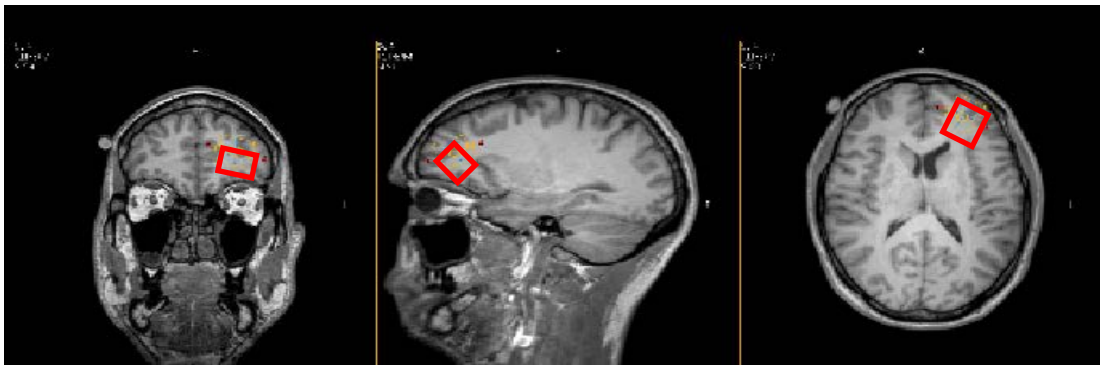
Proton 1H-MRS was used as an *in vivo* measure of intracerebral concentrations of metabolites. To measure metabolites, an asymmetric point resolved spectroscopy sequence (PRESS) was implemented with two echo times (TE: TE1 = 25ms, TE2 = 85ms) and a repetition time of 2,000ms. All spectra were acquired at 3T (Achieva TX, Philips, Best, The Netherlands) using a 32 channel head coil. In line with previous findings discussed in the introduction, three volumes of interest (VOI) were selected *a-priori* to the start of the study. Each measured (2x2x2cm) and was fitted to the following brain areas including: the left prefrontal cortex (LPFC), middle ACC and left occipital cortex (LOCC) (see Figure 36). The same axial slice was used for voxel placement. jMRUI (v4, build 162) was used to quantify metabolites in the time domain by fitting damped sinusoids to the fine reduction decay (equivalent to Lorentzian line shapes in the frequency domain). A QUEST algorithm was used and relied on a basis-set, generated using NMRSCOPE with published chemical shift and coupling constant information (Govindaraju et al., 2000). The following metabolites were obtained from each of these VOI's: ASP, CRE, GLU, GLN, GSH, GPC, MINO and NAA, see chapter 3.6.2 Metabolites from magnetic resonance spectroscopy for an overview. The area under the damped sinusoid gave a relative measure of the concentration of protons at each VOI. All signals were referenced to water. Total imaging time was ≈50 minutes for each subject. All scans were standardised to the afternoon-early evening only (12 noon to 7pm).

Figure 36 Highlights the 3 volumes of interest (VOI) across each of the 3-dimensions in space (x, y, & z) at the following locations within the brain: 1. Left occipital cortex; 2. Left medial prefrontal cortex and 3. Middle anterior cingulate cortex.

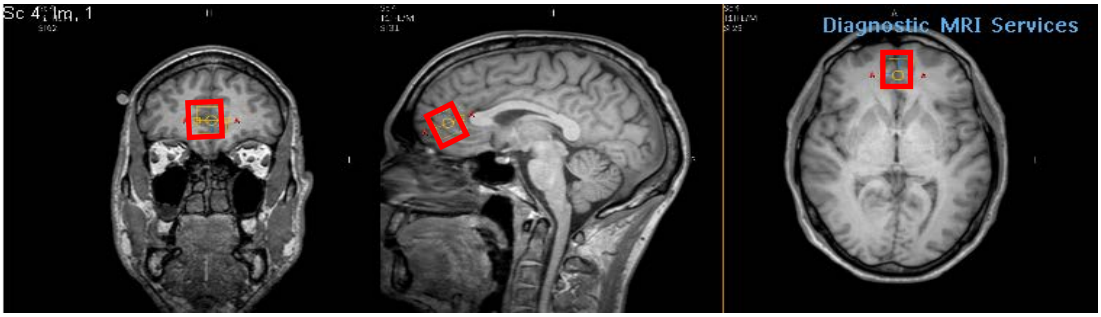
1. Left occipital cortex



2. Left medial prefrontal cortex



3. Middle anterior cingulate cortex



7.3.5 Analysis

Between group differences in demographic study characteristics were examined through independent *t*-tests (gender distributions were examined with Fisher's exact test) and nonparametric equivalents as described previously in chapter 3.9 Statistical analysis. All comparisons were two-sided, with $p<.05$ indicating statistical significance. Boxplots and histograms were used to check data for outliers. Outliers may have been due to movement during the scan and were conservatively labelled "outside" and removed from the analysis if they displayed values below Q1 – k (Q3 – Q1) or above Q3 + k (Q3 – Q1) where k = 2.2, Q1 = 25th and Q3 = 75th percentiles of the interquartile range of the data (Hoaglin & Iglewicz, 1987). This resulted in the removal of < 1.5% of the data (15 data points). Dependent variables were then examined for normality with kolmogorov-smirnov tests. All were found to be normally distributed. Independent *t*-tests examined differences between groups across the three VOI's (LPFC, ACC & LOCC) for the eight metabolites of interest including: ASP, CRE, GLU, GLN, GSH, GPC, MINO and NAA. Pearson's correlations were also run for potential associations between brain metabolites and objectively defined TST, subjective insomnia severity (ISI) and duration of insomnia symptoms (years) in patients with insomnia only. Correlations with $p\leq.01$ were considered robust and presented visually as graphs.

7.4 Results

7.4.1 Sample characteristics

Mean demographic participant study characteristics are displayed in Table 22. Groups were not different for age (PI: Mean = 38.33, 24-51 yrs; GS: M = 36.71, 24-53 yrs), gender, sex, body mass index (PI: M = 26.13, 16-39; GS: M = 22.5, 19-27), or for Epworth sleepiness levels. As expected, patients with insomnia had significantly higher ISI and DASS depression, anxiety and stress scale scores than GS. Although significantly increased in those with insomnia, the DASS depression and anxiety scores were still in the normal-to-mild range. The average duration of insomnia was 11.9 (range 1-20) years. PSG screening data are presented in Table 23 for the insomnia patients only. Actigraphic and sleep diary between group differences are presented in Table 24. For actigraphy, groups only differed significantly for the number of awakenings (increased in insomnia). TST, WASO and SOL were not significantly different between groups. However, data are only reported from 11 PI's and 11 GS due to corrupted data attributed to a fault with the actigraph computer program.

Between groups demographic information

	PI (*n*=15)	**GS (*n*=14)**	***P*-value**
Sex% (F:M)	60/40	64.3/35.7	1.00
Age (SD)	38.3 (9.6)	36.7 (8.9)	0.64
BMI (kg/m2)	26.1 (5.2)	22.5 (2.0)	0.23
Insm duration	11.9 (11.8) yrs	-	
ISI	19 (4.3)	1.9 (1.6)	<.01*
ESS	4.5 (2.6)	4.2 (2.6)	0.80
DASS - D	4.0 (13)	2.0 (4)	<.01*
DASS - A	5.0 (6)	0.0 (2)	<.01*
DASS - S	16.6 (8.5)	4.9 (1.1)	<.01*

Table 22 Mean (SD) demographic information for patients with insomnia (*n*=15) and healthy good sleeping controls (*n*=14). ISI: insomnia severity index; ESS: Epworth sleepiness scale; DASS: depression (D), anxiety (A), and stress (S) scale. **p*<.05. Note: median scores (interquartile range) are presented for DASS depression & anxiety scale scores.

Polysomnography Screening (PI only: *n*=15)	
SOL (min)	32.4 (21.5)
WASO (min)	77.8 (54.3)
TST (min)	324.82 (48.0)
SE (%)	81.0 (12.5)
NREM sleep (min)	261.2 (35.0)
REM sleep (min)	57.4 (21.6)
REM latency (min)	171.5 (63.8)
N1 (min)	11.0 (6.4)
N2 (min)	186.3 (37.5)
SWS (min)	69.6 (22.5)
AHI (/hr)	2.6 (1.7)
PLMS (/hr)	0.03 (0.1)

Table 23 Mean (SD) overnight polysomnograpic sleep study information for patients with insomnia (*n*=15) SOL: sleep onset latency; WASO: wake-time after sleep onset; TST: total sleep time; SE: sleep efficiency; NREM: non-rapid eye movement; REM: rapid eye movement; N1: stage 1 of sleep; N2: stage 2 of sleep; SWS: slow wave sleep; AHI: Apnea Hypopnea Index; PLMS: periodic limb movements.

Between groups sleep diary information			
	PI (*n*=15)	**GS (*n*=14)**	***P*-value**
SOL (min)	43.0 (31.4)	11.0 (5.3)	<.01**
WASO (min)	54.4 (53.2)	5.7 (7.7)	<.01**
NOAW	1.7 (1.5)	0.6 (0.6)	<.01**
TST (min)	320.5 (85.9)	446.7 (30.2)	<.01**
SE (%)	63.0 (14.7)	89.0 (5.1)	<.01**
SQ (0-2)	0.9 (0.5)	1.5 (0.4)	<.01**
Between groups actigraphy information^			
SOL (min)	13.1 (6.6)	8.2 (8.2)	0.14
WASO (min)	47.4 (15.8)	40.3 (10.4)	0.23
NOA	1.5 (0.6)	1.0 (0.3)	<.05*
TST (min)	443.5 (38.3)	434.7 (39.4)	0.30
SE (%)	86.1 (3.8)	88.7 (3.8)	1.10

Table 24 Mean (SD) demographic information for patients with insomnia (*n*=15) and healthy good sleeping controls (*n*=14). SOL: sleep onset latency; WASO: wake-time after sleep onset; NOAW: Number of awakenings; TST: total sleep time; SE: sleep efficiency; SQ sleep quality. ^Due to corrupted data comparison included 11 patients with insomnia vs. 11 controls.*p<.05 ** p<.01

7.4.2 Magnetic resonance spectroscopy

No statistically significant differences were found for any of the metabolites profiled using independent *t*-tests including: ASP; CRE; GLU; GLN; GSH; GPC; MINO; NAA; between patients with insomnia and good sleeping controls for the three VOI's: LPFC [F (1, 26-27) = 0.07-2.16, *p*=.15-.79]; LOCC [F (1, 25-27) = 0.00-1.16, *p*=.31-.94; ACC [F (1, 22-27) = 0.01-0.83, *p*=.37-.94]. See Figure 37, Figure 38, Figure 39, Table 25, Table 26 & Table 27.

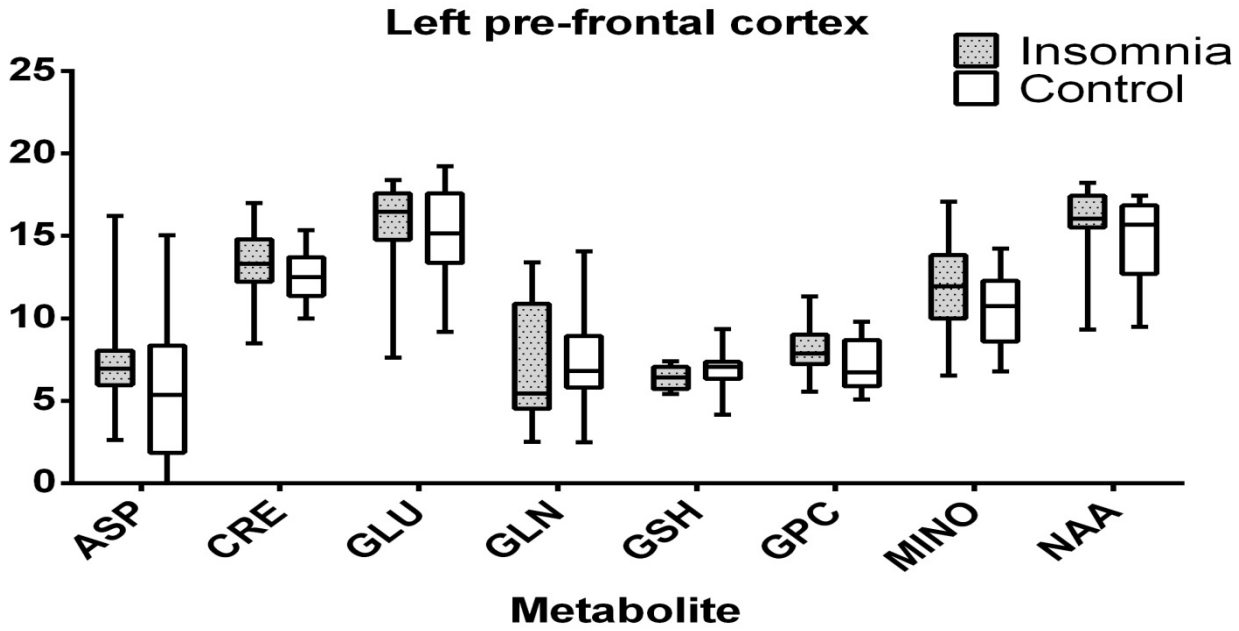


Figure 37 Left prefrontal cortex concentrations between patients with insomnia (*n*=15) and healthy good sleeping controls (*n*=14) for metabolites including: aspartate (ASP); creatine (CRE); glutamate (GLU); glutamine (GLN); glutathione (GSH); glycerylphosphorylcholine (GPC); *myo*-inositol (MINO); & *N*-acetylaspartate (NAA). Error bars indicate 95% confidence intervals.

Left prefrontal cortex									
Metabolite	**Group**	***N***	**Mean**	**SD**	**Difference testing and 95% CI**				
					***p*-value**	**ES**	**Mean Diff.**	**Lower**	**Upper**
ASP	Insomnia	15	7.68	3.24	.15	0.55	2.14	-0.85	5.13
	Control	14	5.54	4.54					
CRE	Insomnia	15	13.32	2.16	.28	0.42	0.78	-0.67	2.23
	Control	14	12.54	1.58					
GLU	Insomnia	15	15.72	2.69	.45	0.29	0.81	-1.34	3.00
	Control	14	14.91	2.97					
GLN	Insomnia	15	7.12	3.63	.79	-0.01	-0.34	-2.93	2.25
	Control	14	7.46	3.12					
GSH	Insomnia	12	6.40	0.69	.34	-0.40	-0.39	-1.24	0.44
	Control	13	6.78	1.21					
GPC	Insomnia	15	8.06	1.44	.22	0.47	0.70	-0.44	1.84
	Control	14	7.36	1.56					
MINO	Insomnia	15	11.93	2.67	.18	0.51	1.27	-0.63	3.17
	Control	14	10.66	2.28					
NAA	Insomnia	15	15.77	2.26	.22	0.47	1.12	-0.69	2.93
	Control	14	14.65	2.49					

Table 25 Metabolites in the left prefrontal cortex for mean, SD, *p*-value and effect size (ES: *d*) between insomnia and controls including: aspartate (ASP); creatine (CRE); glutamate (GLU); glutamine (GLN); glutathione (GSH); glycerylphosphorylcholine (GPC); *myo*-inositol (MINO); & *N*-acetylaspartate (NAA).

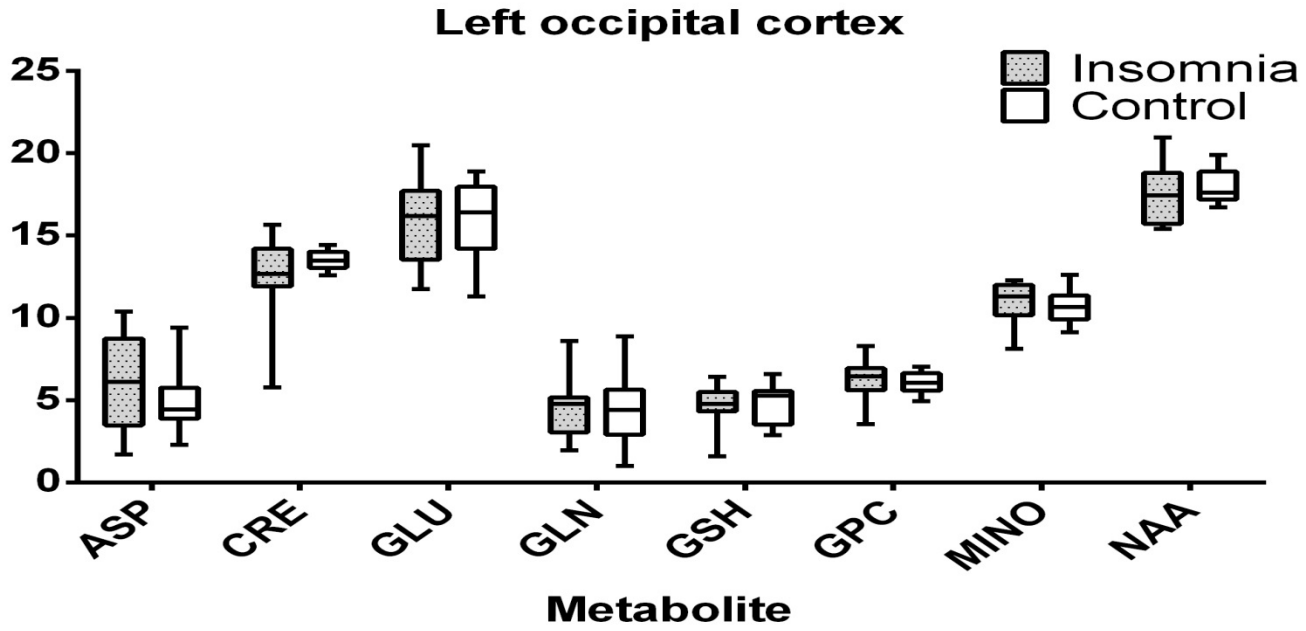


Figure 38 Left occipital cortex concentrations between patients with insomnia (*n*=15) and healthy good sleeping controls (*n*=14) for metabolites including: aspartate (ASP); creatine (CRE); glutamate (GLU); glutamine (GLN); glutathione (GSH); glycerylphosphorylcholine (GPC); *myo*-inositol (MINO); & *N*-acetylaspartate (NAA). Error bars indicate 95% confidence intervals.

Left occipital cortex									
Metabolite	Group	*N*	Mean	SD	Difference testing and 95% CI				
					p-value	ES	Mean Diff.	Lower	Upper
ASP	Insomnia	15	6.02	2.86	.31	0.39	1.00	-0.95	2.93
	Control	14	5.03	2.15					
CRE	Insomnia	15	12.80	2.31	.29	-0.48	-0.69	-2.00	0.62
	Control	14	13.48	0.55					
GLU	Insomnia	15	15.49	2.60	.57	-0.22	-0.53	-2.42	1.36
	Control	14	16.02	2.33					
GLN	Insomnia	14	4.41	1.70	.99	0.01	0.01	-1.43	1.46
	Control	14	4.40	2.01					
GSH	Insomnia	15	4.65	1.16	.69	-0.15	-0.17	-1.07	0.72
	Control	14	4.82	1.19					
GPC	Insomnia	15	6.26	1.13	.66	0.17	0.15	-0.56	0.86
	Control	14	6.11	0.65					
MINO	Insomnia	13	10.97	1.21	.56	0.23	0.26	-0.65	1.17
	Control	14	10.71	1.08					
NAA	Insomnia	14	17.53	1.79	.50	-0.27	-0.37	-1.50	0.75
	Control	14	17.91	0.99					

Table 26 Metabolites in the left occipital cortex for mean, SD, *p*-value and effect size (ES: *d*) between insomnia and controls including: aspartate (ASP); creatine (CRE); glutamate (GLU); glutamine (GLN); glutathione (GSH); glycerylphosphorylcholine (GPC); *myo*-inositol (MINO); & *N*-acetylaspartate (NAA).

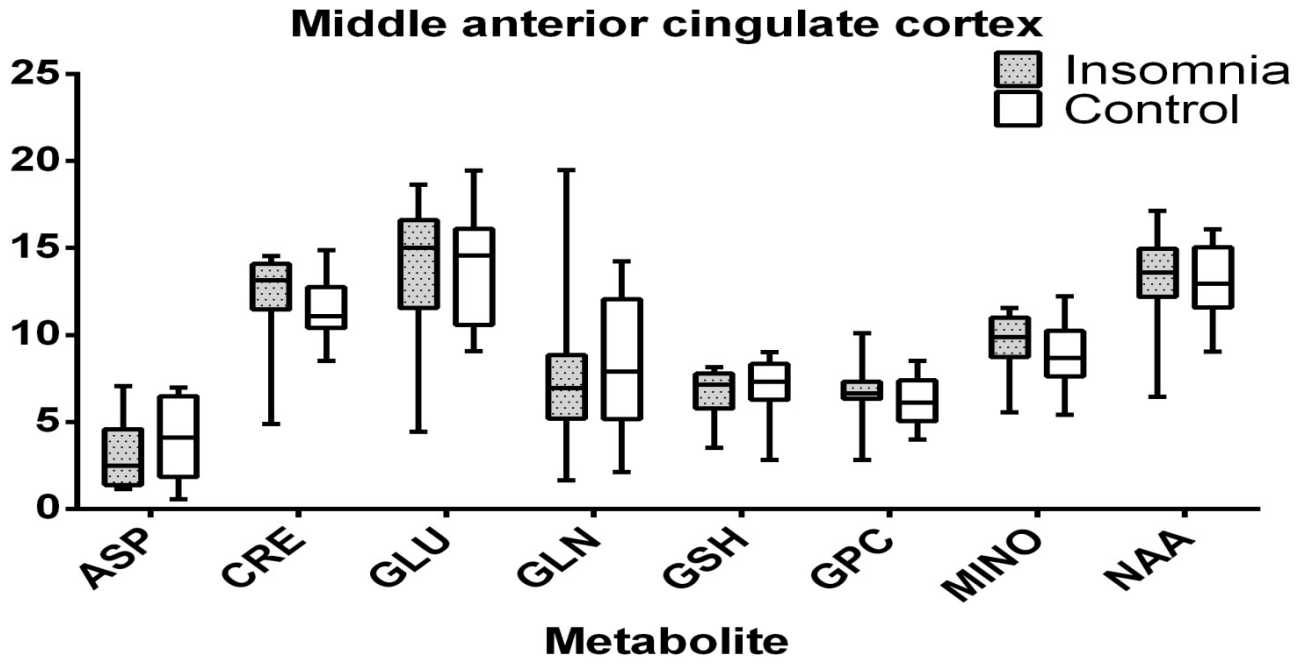


Figure 39 Middle anterior cingulate cortex concentrations between patients with insomnia (*n*=15) and healthy good sleeping controls (*n*=14) for metabolites including: aspartate (ASP); creatine (CRE); glutamate (GLU); glutamine (GLN); Glutathione (GSH); glycerylphosphorylcholine (GPC); *myo*-inositol (MINO); & *N*-acetylaspartate (NAA). Error bars indicate 95% confidence intervals.

Anterior cingulate cortex									
Metabolite	Group	*N*	Mean	SD	Difference testing and 95% CI				
					p-value	ES	Mean Diff.	Lower	Upper
ASP	Insomnia	12	3.11	1.90	.28	-0.14	-0.30	-2.23	1.63
	Control	10	3.42	2.61					
CRE	Insomnia	15	12.07	2.67	.44	0.30	0.67	-1.07	2.40
	Control	14	11.40	1.75					
GLU	Insomnia	15	14.35	3.65	.73	0.13	1.33	-2.27	3.19
	Control	14	13.89	3.49					
GLN	Insomnia	15	7.79	4.21	.73	-0.13	-0.52	-3.60	2.56
	Control	14	8.31	3.85					
GSH	Insomnia	15	6.72	1.27	.43	-0.30	-0.42	-1.51	0.67
	Control	14	7.14	1.58					
GPC	Insomnia	15	6.73	1.65	.37	0.34	0.53	-0.66	1.72
	Control	14	6.20	1.46					
MINO	Insomnia	14	9.62	1.81	.36	0.36	0.07	-1.77	1.91
	Control	14	8.97	1.84					
NAA	Insomnia	15	13.11	2.61	.85	0.07	0.17	-1.67	2.02
	Control	14	12.94	2.20					

Table 27 Metabolites in the middle anterior cingulate cortex for mean, SD, *p*-value and effect size (ES: *d*) between insomnia and controls including: aspartate (ASP); creatine (CRE); glutamate (GLU); glutamine (GLN); glutathione (GSH); glycerylphosphorylcholine (GPC); *myo*-inositol (MINO); & *N*-acetylaspartate (NAA).

7.4.3 Correlations with objective sleep time, insomnia severity and duration

In line with previous research findings, Pearson correlations were run between objective TST and measures of brain metabolism in patients with insomnia (*n*=15) at each VOI. For the LPFC: significant correlations were found for TST (with CRE, GPC & MINO). Only CRE levels were found to be significantly correlated at the $p \leq .01$ level ($R^2(13) = .48$, $p = .01$:see Figure 40). Correlations were also run for subjective insomnia severity (ISI) and insomnia duration (years). No significant correlations were found for insomnia severity scores. Insomnia duration was found to be negatively correlated with LPFC levels of GLU ($R^2(13) = -.30$, $p = .03$) only on inspection of scatter graphs one participant was found to be an outlier with 49 years of insomnia symptomology. With this participant removed LPFC levels of GLU correlated positively with years of insomnia symptoms ($R^2(13) = .42$, $p = .01$: see Figure 41).

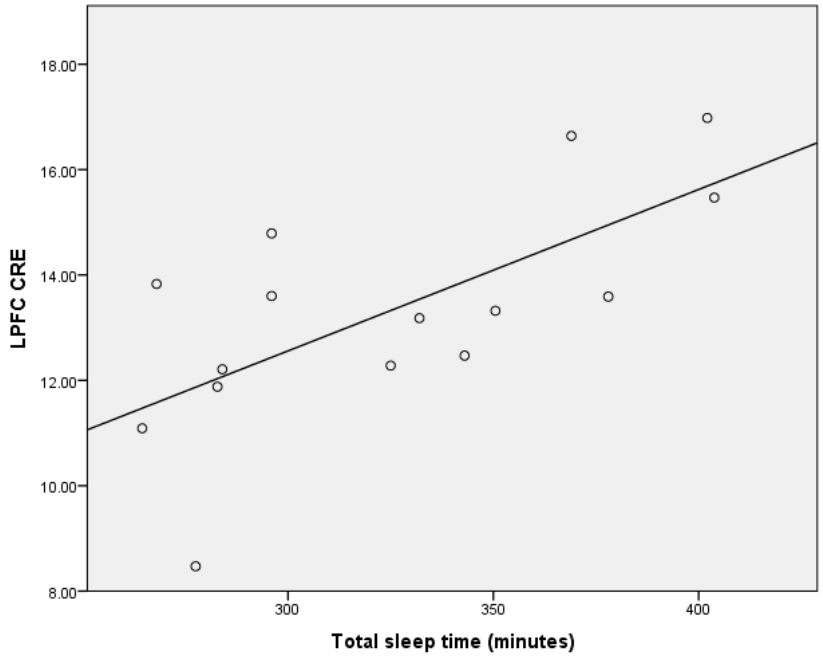


Figure 40 Scatterplot of relationship between left prefrontal cortex (LPFC) values of creatine (CRE) and objective total sleep time (minutes) from polysomnography (R^2= .48).

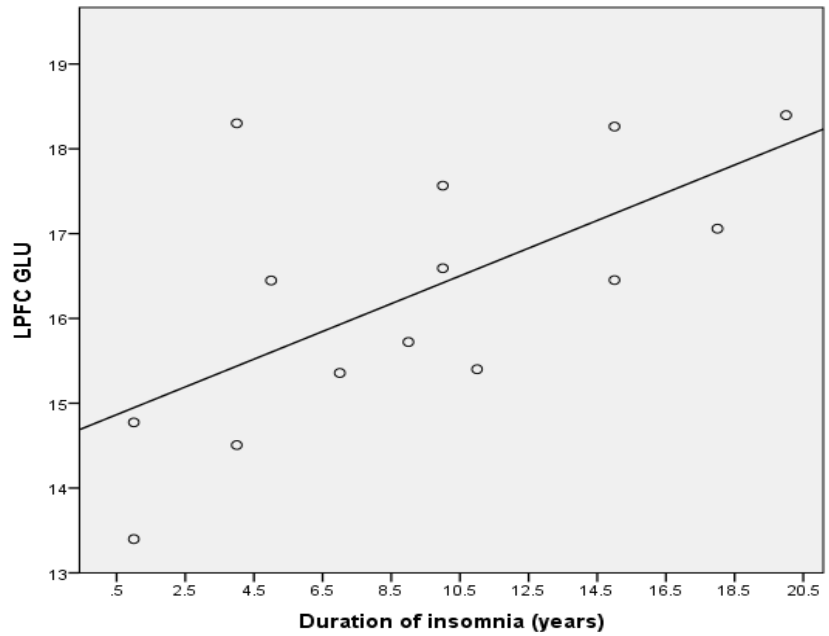


Figure 41 Scatterplot of relationship between left prefrontal cortex (LPFC) values of glutamate (GLU) and duration of insomnia (years) (R^2= .42).

7.5 Discussion

In this study no differences in brain metabolites were detected in those with insomnia and healthy controls including: aspartate (ASP), creatine (CRE), glutamate (GLU), glutamine (GLN), glutathione (GSH), glycerylphosphorylcholine (GPC) *myo*-inositol (MINO) and *N*-acetylaspartate (NAA) across the three volumes-of-interest (VOI) that were identified *a-priori.* The areas assessed were the left prefrontal cortex (LPFC), the anterior cingulate cortex (ACC) and the left occipital cortex (LOCC). Insomnia may not affect the acquired brain metabolites in the regions of the brain sampled in this research study. The following sections discuss implications.

Other metabolites have been explored in insomnia compared to controls including: ASP, CHO, CRE, GLU, GLN, *gamma*-Aminobutyric acid (GABA) Glycine, NAA, MINO, scylloinositol and taurine (Morgan et al., 2012; Winkelman et al., 2008). Again, no differences were found across the brain specifically in the occipital cortex (Morgan et al., 2012) and also in the basal ganglia, thalamus, and smaller parts of the temporal, parietal, and occipital lobes (Winkelman et al., 2008). The current study profiled a larger number of metabolites and is the only study in insomnia referenced to water (a standard reference) and not CRE, across more areas of the brain including the frontal, anterior cingulate and also occipital cortices of the brain. Specifically, Insomnia was not found to affect CRE levels in the brain suggesting, as in previous studies, that only GABA may be altered due to insomnia.

In the largest brain imaging study in insomnia, no differences were found in cerebral white matter volumes across the brain between those with insomnia (*n*=28) and controls (*n*=38) (Spiegelhalder, Regen, Baglioni, Klöppel, et al., 2013). From this research, the authors stated that insomnia appears unlikely to be responsible for major alterations in the structure of the brain; however subtle differences may exist at smaller morphometric levels. Previous positron emission

tomography (PET) studies have found increased glucose metabolism in the hypothalamus suggesting an increased arousal response in patients with insomnia compared to controls (Nofzinger et al., 2004; Nofzinger et al., 2006). It is unclear whether this increased arousal is a development from insomnia symptomology or is a stable trait predisposing an individual to insomnia. In the current study, differences may be present in other regions that are deeper within the brain such as the hypothalamus.

The most significant differences in brain metabolites have been in ratios of GABA/CRE in insomnia. GABA is the primary inhibitory neurotransmitter in the central nervous system (Gottesmann, 2002) and is closely linked to brain function (Puts & Edden, 2012); with higher GABA levels associated with increased concentration and speed of decision making (Sumner et al., 2010); lower GABA was associated with symptoms of depression, anxiety (Kalueff & Nutt, 2007) and insomnia (Winkelman et al., 2008). Agents that increase GABAergic activation, of which GABA is a primary component, are used in pharmacotherapy for insomnia (Kalueff & Nutt, 2007). Benzodiazepine receptor agonists (BZRAs) act on GABA receptor uptake (Gottesmann, 2002). The vast majority of GABA is metabolised from GLU and it is hard to separate GLU and GLN as they both contain similar amino acids, amines and derivatives involved in neurotransmission (excitatory and inhibitory) (Stagg et al., 2011). No differences were found for either GLU or GLN in this study, specifically suggesting that only GABA may be altered in those with insomnia.

When GABA was profiled previously, studies have found mixed results in those with insomnia compared to controls. A global reduction in the GABA/CRE ratio in 16 patients with insomnia has been discovered (Winkelman et al., 2008). However there was limited anatomical specificity as GABA/CRE levels were averaged ‘globally’ across the basal ganglia, thalamus, temporal,

parietal, and occipital white-matter and cortex. Metabolites were normalised to CRE not water suggesting either GABA or CRE may be responsible for this finding. Plante, Jensen, Schoerning, et al. (2012) found decreases in GABA/CRE ratio in insomnia in the occipital (33% reduction), and anterior cingulate cortices (21% reduction) but no differences were found in the thalamus (Plante, Jensen, Schoerning, et al., 2012). It is important to be cognisant in using ratios as it is difficult to assay the direct contribution of each metabolite. Increased GABA levels do not necessarily mean that there is increased inhibition but merely increased GABAergic activation and vice versa (Rae, 2014). For example, in the previous insomnia studies, it is impossible to specify the direct contributions of metabolites in the GABA/CRE ratio as GABA or CRE may be responsible for the differences in insomnia compared to controls found previously. This study measured CRE and found no differences were found, therefore suggesting that only GABA may be different with insomnia.

Phosphorus magnetic resonance spectroscopy (31P MRS) has also been used to explore and understand the energetic components of the brain in insomnia. Lower phosphocreatine in cerebral grey matter and a reduction in phosphocholine (PC) in white matter has been found in those with insomnia compared to healthy controls (Harper et al., 2013). A negative trend was found between polysomnograpic (PSG) defined wake-time after sleep onset (WASO) and grey matter beta-nucleoside triphosphate and white matter PC in those with primary insomnia (Harper et al., 2013). Winkelman et al. (2008) profiled a significant negative correlation with GABA levels and WASO in those with insomnia. An interpretation of this could link to cognitive hyperarousal commonly reported in those with insomnia (Harvey, 2001). With this information, correlations were run between TST, insomnia duration and subjective insomnia severity scores with brain metabolites. TST positively correlated with LPFC levels of ASP, CRE, and GPC, suggesting increased brain metabolism may relate to greater amounts of objectively defined TST. At the ≤.01 level, CRE correlated with TST

perhaps due to the important role CRE plays in maintaining brain energy homeostasis (Lin et al., 2005). However, correlations are difficult to interpret as the controls in the current study did not undergo PSG evaluation and it remains to be seen if this is specific to insomnia.

No significant correlations were found for subjective insomnia severity (ISI) in patients with insomnia. No other previous studies have found a significant positive correlation between brain metabolism and subjective insomnia severity. However, in post-traumatic stress disorder (PTSD), lower hippocampal volumes were found to be mediated by insomnia severity (as measured through the ISI). Higher ISI scores were associated with reduced levels of hippocampal CA3/Dentate Gyrus volumes (Neylan et al., 2010). Also in patients with PTSD, Meyerhoff et al. (2014) found metabolite concentrations in the parieto-occipital cortex to mediate ISI scores (higher ISI scores correlated with lower GABA and higher GLU levels) and suggested that this was in line with hyperarousal found in insomnia. The lack of an association between insomnia severity in this and previous studies suggest differences in brain metabolism in those with insomnia and those with PTSD.

In the current study however, a significant and strong positive correlation was found for insomnia duration (years) and LPFC GLU levels (R^2=.42), possibly suggesting a relationship between the duration of insomnia symptoms and LPFC GLU levels. This is the first time that insomnia duration has been found to be associated with brain metabolism and is in line with previous findings that used transcranial magnetic stimulation to detect increased glutamatergic activation in those with insomnia compared to controls (Salas et al., 2013). This finding is interesting as GLU is the major excitatory neurotransmitter in the brain (Bennett & Balcar, 1999; Fonnum, 1984) and has the potential to be neurotoxic (Choi, 1988). Although no significant differences were seen between insomnia patients and controls in the LPFC for GLU in this study. Further studies with larger numbers

of participants should now look to profile GLU across the frontal regions of the brain to elucidate the role of GLU in insomnia.

A number of limitations require consideration. Insomnia is a highly heterogeneous disorder and quantifying differences with a single measure of MRS may not be possible in this group. The largest effect size was 0.51, with a probability level of .05 and a sample size of 29, the observed power (2-tail) was 0.25. It is arguable that small sample size is responsible for non-significant findings. However, the heterogeneous nature of insomnia and methodological issues in previous research in this area cannot be discounted. A number of statistical tests were deployed without correction therefore significant results should be interrupted with caution and deemed exploratory. Although no differences were found in a number of metabolites across the brain, measuring GABA referenced to water in larger studies with a higher magnetic resonance would strengthen future research in insomnia. GABA was not measured as part of this study due to the time required for data collection. In a novel approach to insomnia research, it was decided to quantify other metabolites across the brain including the pre-frontal regions. Time of testing may have affected the results of the protocol but this study was standardised to the afternoon-early evening (12:00pm-19:00pm) and previously brain metabolism has been found to be stable across the day (Evans, McGonigle, & Edden, 2010). Individual chronotype was not measured as part of this study and this may have influenced the results of the study. Lastly, as control participants did not undergo an overnight sleep assessment other sleep disorders cannot be discounted.

7.6 Conclusion

This study investigated the role of brain *in vivo* cerebral metabolism in those with insomnia compared to healthy good sleeping controls. Objective TST correlated significantly with levels of CRE in the LPFC of the brain, suggesting a link between brain metabolism and sleep in insomnia. Insomnia duration was also significantly correlated with levels of GLU in the LPFC. Subjective insomnia severity scores did not correlate with brain metabolism. No significant differences were found across the following regions of the brain: LOCC, ACC and LPFC for any of the metabolites of interest: ASP, CRE, GLU, GLN, GSH, GPC, MINO and NAA. As this was the first study to profile a number of metabolites and reference them to water, the next logical step would be to explore GABA in the frontal regions to gain further understanding of what happens to brain metabolism in insomnia.

Chapter 8: Summary

8.1 Overall findings

This thesis brought together a number of novel methodologies to examine treatment response to sleep restriction therapy (SRT) and to address the current poor measurement of subjective and objective markers of insomnia. Previously the focus was predominately on subjective sleep report measures pre-to-post therapy, which in terms of physiological assessment resulted in a number of unanswered questions regarding treatment. A further aim of this thesis was to profile potential markers of insomnia within the brain which in the future could be matched to subjective reports. Key findings are listed below (see Table 28).

Chapter	Key findings
2	Review of sleep restriction therapy for the treatment of insomnia disorder. Discovered subjective improvements in sleep diary outcome variables. Further objective and subjective measures are required in well-designed controlled trials to evaluate the true impact of therapy.
4	First use of an ecological momentary assessment technique to profile changes in cognition throughout sleep restriction therapy for insomnia. Modifications to alertness and sleepiness/fatigue were found to increase at week 1 but reduce below baseline levels at week 3 suggesting these may be targets for therapy in insomnia.
5	Assessment of salivary cortisol concentrations throughout sleep restriction therapy. This study probed potential differences in cortisol through the first 3 weeks of therapy. No significant change was found suggesting no alteration to salivary cortisol concentrations or hypothalamic–pituitary–adrenal axis activity during the first 3 weeks of therapy.
6	First use of physiological markers (including overnight plasma cortisol concentrations & core body temperature) of hypothalamic–pituitary–adrenal axis activity measured pre-to-post sleep restriction therapy for insomnia. Therapy may increase early morning levels of cortisol concentrations and decrease overall core body temperature.
7	Evaluation of brain metabolism in insomnia compared to controls using magnetic resonance spectroscopy. Results suggest no significant differences in brain neurochemistry between those groups. Objective total sleep is positively associated to creatine levels and insomnia duration is positively associated with glutamate in those with insomnia.

Table 28 An overview of key the findings from the thesis.

From the systematic review and meta-analysis in chapter three, SRT improves sleep diary continuity variables. Weighted effect sizes for sleep diary measures of sleep onset latency (SOL), wake time after sleep onset (WASO), and sleep efficiency (SE) were moderate-to-large after therapy, and total sleep time (TST) indicated a small improvement. Previous treatment studies in SRT for insomnia failed to evaluate the full impact on objective sleep variables and measures of daytime functioning, limiting finite conclusions. Future studies should now examine objective measures (actigraphy & polysomnography: PSG) and subjective measures (sleep diary) before and after therapy.

In chapter four, the use of ecological momentary assessment to probe specific temporal alterations in subjective measures of mood, alertness and sleepiness/fatigue is novel. At week one SRT did not impact negative mood statements but did reduce positive mood statements, along with increasing sleepiness/fatigue and reducing alert cognition. This reflects previous treatment data (Kyle et al., 2014; Kyle et al., 2011). At week two, scores returned to baseline levels and by week three significant improvements were found for sleepiness/fatigue and negative mood but pre-sleep levels of sleepiness/fatigue remained high. Bedtime levels of alert cognition reduced significantly and morning levels increased; suggesting an alteration to the sleep-wake experience. Overall, SRT moderated sleep through reducing alertness and increasing sleepiness, particularly prior to sleep onset.

The use of ecological momentary assessment through SRT for insomnia was expanded in chapter five to probe potential alterations in measures of salivary cortisol before and throughout treatment. This study systematically evaluated the role of salivary cortisol during SRT and proved that the protocol was possible, adhered to, and the results reflected normal circadian variation to

salivary cortisol secretion. Larger clinical trials may now look to implement similar protocol but with a longer sampling timeframe (over 6-12 months after treatment) as no significant differences were found pre-to-post therapy. This was thought to be due to the underpowered nature of the study. There was however, an increase in bedtime cortisol concentrations at three weeks after therapy and a decrease in evening cortisol, suggesting a longer assessment period (3-6 weeks) is required to fully understand changes in cortisol due to SRT for insomnia.

Chapter six builds on the results of both chapters four and five by looking to evaluate in-lab measures of objective sleep and arousal before and after SRT for insomnia. Plasma cortisol concentrations increased at post treatment in the early morning compared with baseline. This difference compared with salivary cortisol discussed in chapter five is somewhat unexpected. It would appear that plasma cortisol is more robust than home based assessments of salivary cortisol which are less likely to be contaminated (teeth brushing, cigarette smoking, or drinking orange juice) or were not taken at the right time. Bedtime plasma cortisol remained the same but the increase in morning cortisol suggests SRT improves physiological functioning (cortisol & temperature) by modifying the arousal response and may increase objective TST. There was no evidence of a significant phase shift in the circadian rhythm after SRT but the amplitude of the circadian rhythm appeared to increase. Studies evaluating changes over the course of 24 hours under constant routine conditions would further add to the body of knowledge.

Chapter seven examines brain metabolism in insomnia compared to healthy good sleeping controls. Magnetic resonance spectroscopy (MRS) was used to quantify a range of metabolites including: aspartate (ASP), creatine (CRE), glutamate (GLU), glutamine (GLN), glutathione (GSH), glycerylphosphorylcholine (GPC), *myo*-inositol (MINO), and *N*-acetylaspartate (NAA) across the left

occipital, anterior cingulate and left prefrontal cortices referenced to water. No significant differences were found between those with insomnia and controls, however exploratory correlations elucidated possible links between objective TST and brain metabolism. Insomnia duration (yrs) was positively correlated with increased levels of GLU, which is supportive of the hyperarousal theory of insomnia. This suggests that chronic sleep loss may lead to increased levels of brain metabolism with increases in glutamine (but not significantly different from controls) there is an expectation that *gamma*-Aminobutyric acid (GABA) would be reduced. Potentially, SRT in larger studies could reverse these levels of brain metabolites.

Overall, it is appropriate to integrate the findings of the thesis to existing theoretical frameworks of insomnia. In experimental studies, the most relevant theoretical perspective is the hyperarousal hypothesis (Bonnet & Arand, 2010) and the *3P* temporal model for insomnia. The *3P* provides a framework for both the development and maintenance of chronic insomnia disorder (Spielman & Glovinsky, 1991). The model suggests that individuals may harbour *predisposing* (behaviour & genetic predisposition); *precipitating* (significant & often traumatic life events that may act as a trigger for insomnia); and *perpetuating* (behaviour, mood, thoughts & beliefs) factors that contribute to insomnia disorder through time. Chronic insomnia disorder is maintained through perpetuating factors including maladaptive, thoughts, behaviours, attributions or beliefs about sleep. The individual becomes sensitised to sources of sleep disruption (e.g. noise, light or temperature, body awareness). These wake-promoting processes then become conditioned at sleep initiation, preventing sleep onset and lead to the development of psychophysiological insomnia and hyperarousal (AASM, 2005). Individuals report increased cognitive hyperarousal or an-inability to switch off a 'racing mind' for successful sleep initiation (Harvey, 2001). Results from chapter 4, suggest that SRT may normalise pre-bed time cognitive arousal in those with insomnia after three

weeks of therapy and suggest a potential mechanism for the therapeutic effect of SRT. This is paralleled with predictions from the *3P* model where cognitive arousal is normalised (a perpetuating factor) (Bonnet & Arand, 2010; Spielman & Glovinsky, 1991).

In chapter 5 salivary cortisol (SC) was examined during sleep restriction therapy (SRT) for psychophysiological insomnia. A reduction in SC concentrations is suggestive of reduced stress for the ensuing sleep period, in line with reduced physiological hyperarousal (Bonnet & Arand, 1997, 2010). Salivary cortisol concentrations did not change overall during the initial stages of therapy and more importantly, did not increase. It is therefore reassuring that SRT did not increase biological markers of stress. An increase in cortisol may have occurred as SRT is a mild stressor as time in bed was restricted. Recent studies found that salivary cortisol was a marker of stress but not sleep loss and suggested that only stressful sleep loss paradigms would increase cortisol concentrations (Pejovic et al., 2013).

A considerable challenge for the hyperarousal hypothesis is to determine when the onset of an hyperarousal response takes place in the development of insomnia. The *3P*-model may help explain the activation of this stress response (e.g. a genetic predisposition to stress that is activated by the environment and then maintained through behaviour or faulty cognitions). At present, we do not have this data. Current results suggest that more than 3 weeks is necessary for these changes to become apparent.

Night time plasma cortisol concentrations were measured in chapter 6 after at least 6 weeks of treatment. A significant rise in early morning cortisol concentrations was found suggesting a normalisation to the circadian rhythm. Backhaus et al. (2004) also found a dampened cortisol awakening response in insomnia compared to healthy controls which is not dissimilar to these

findings. This increased circadian amplitude was reflected in core body temperature data providing further evidence of circadian changes. Overall core body temperature was reduced pre-to-post therapy providing further evidence of a reduction in physiological hyperarousal after effective treatment (Bonnet & Arand, 1997, 2010).

Finally in chapter seven, it was hypothesised that concentrations of brain metabolites would display increased arousal across the brain in those with insomnia, in support of the hyperarousal hypothesis (Riemann et al., 2010; Spiegelhalder & Riemann, 2013). No differences were found between the groups. Differences may be present in other regions that are deeper within the brain (e.g. the hypothalamus). It remains unclear at this point whether this technique can identify the severity of insomnia symptomology given the heterogeneity of this disorder and variability found amongst individual sufferers as specified in the *3P* model.

8.2 Limitations

This thesis predominantly used repeated measures and would have been strengthened with placebo controls or control groups/wait-list, which was not feasible given current resources. There are some limitations regarding statistical testing which include multiple comparisons not corrected for. This method may have identified statistically significant effects (Type I error) and caution is appropriate in relation to these results. Power estimates were also not calculated prior to the beginning of these studies due not only to the experimental nature of the thesis but also the current lack of previous treatment data. This thesis is the first to successfully use ecological momentary assessment during behavioural treatment for insomnia and found significant effects. Further studies are needed to repeat this experimental method and validate these findings.

In chapter 5, no changes in salivary cortisol concentrations were found during the first 3 weeks of therapy. This study was underpowered due to time and financial constructs and is therefore vulnerable to a Type II statistical error. Subsequent studies may be able to detect changes in cortisol concentrations over a longer timeframe. In chapter 6, multiple comparisons were also not corrected for and it is quite evident that this is an exploratory pilot study that does require further validation. In chapter 7, statistical tests were run between those with insomnia and healthy controls without correction for multiple comparisons. No statistically significant differences were found at the .05 level suggesting no brain metabolic differences in insomnia. Even if differences were found multiple comparisons would still be limited by the small sample size but conservatively the *p*-values would need to be reduced to at least the .01 level.

The principal function of these studies was to test and profile the use of repeated measurements of cognition and cortisol throughout behavioural treatment for insomnia. Linear mixed-effects models were used instead of repeated-measures analysis of variance. The strength of mixed-effects models is they can be used even when data is unbalanced/missing, as well as taking into account systematic inter-individual differences which is unique (Van Dongen, Olofsen, Dinges, & Maislin, 2004). Previous studies have excluded participants without full data and in chapters four, five, and six there were small samples sizes. Therefore, it was paramount that any analysis acknowledged missing data (Olsen, Stechuchak, Edinger, Ulmer, & Woolson, 2012). Small participant numbers may have increased the probability of a Type-1 or Type-2 statistical error. In order to address this, individual participant effects were graphed pre-to-post therapy allowing for easier assessment of possible patient clinical effects. However, the small sizes do restrict generalisation of findings at this point.

In the delivery of SRT, the researcher (CBM) acted as both therapist and researcher which may have impacted on subjective outcomes. The delivery of the SRT was standardised across the thesis and was supported by a brief set of digital slides (8 in total: see Appendix B: Sleep restriction therapy presentation slides). An information manual was also used to help standardise delivery see Appendix C: Sleep restriction therapy information manual. Some caution may be needed in the interpretation of the results and a six month follow-up would have enhanced the findings of this study as only pre-to-post therapy differences were evaluated. The primary goal was to focus on the acute effects of therapy and to continue with the same protocol at the University of Sydney that had been initiated at the University of Glasgow.

In chapter eight, GABA was not examined due to the time required to detect it in the scan protocol and consequently cannot be excluded. After considerable discussion, the following metabolites were quantified: ASP, CRE, GLN, GLU, GSH, GPC, MINO, & NAA. No differences were found between those with insomnia and controls in the prefrontal, anterior cingulate and occipital cortices perhaps due to reduced statistical power. Recruitment was difficult due to financial resources. It would be very useful in future studies to evaluate differences in subtypes of insomnia (Psychophysiological / Paradoxical / Idiopathic) to fully quantify the potential impact of insomnia in a much larger sample.

Participants were sampled from the general population through tertiary sleep clinics. Participants who agreed to take part in research agree to a lengthy screening process and these individuals may not be reflective of the vast majority of those with insomnia. Only individuals with psychophysiological insomnia were recruited whereas in the general population insomnia is often comorbid with a range of other psychiatric and medical conditions. The exclusion of chronic hypnotic use may also not be generalisable to the insomnia population who continue to use hypnotics without benefit (Riemann & Perlis, 2009; Smith, Perlis, Park, et al., 2002).

8.3 Implications of research and future directions

A number of key themes have emerged from this research in relation to SRT. SRT is a clinically useful therapy (Miller et al., 2014). The American Academy of Sleep Medicine may wish to re-consider SRT as a standalone therapy given the current evidence which has not been updated since 2006 (Morin, Bootzin, et al., 2006). It is timely to evaluate objective effects of SRT which has only recently been undertaken by exploring objective impairments in sleep and vigilance (Kyle et al., 2014). Follow-up assessments with objective outcomes using PSG, actigraphy or plasma cortisol are required at 6-18 months. The delivery and titration of SRT varied between previous studies therefore evaluating different SRT delivery methods is timely. Differing methodologies for SRT inhibits the standardisation of procedures across studies which is problematic for the literature as SRT is delivered widely as part of cognitive behavioural therapy for insomnia (CBT-I). Research addressing these varying techniques of SRT will elucidate the most effective delivery for specific subtypes of insomnia allowing for better standardisation of overall CBT-I. Measuring changes in daytime cognition and quality of life throughout treatment for insomnia will allow the identification of associated impairments during the acute phase of treatment. Long term follow-up would target which aspects of cognition change and remain stable with effective SRT for insomnia.

Further targets of insomnia symptoms may only be revealed with repeated ecological valid measures of insomnia symptomology. With technology, ecological momentary assessment (EMA) can be used to map daily responses to treatment with real-time feedback to the patient. Challenging negative thoughts with this information may enhance treatment gains. With regards to measuring arousal, further studies are now required to combine point-in-time EMA techniques with longer-term follow-up times. Assessments of measures like heart rate, salivary or blood cortisol concentrations, or other measures of physiological arousal and inflammation (e.g. C-reactive

protein) in insomnia over time would be useful to capture the varying nature of this condition. This will provide ecologically valid profiles of insomnia symptoms when they do occur in the home environment which can then be targeted with treatment and evaluated for change with SRT and overall CBT-I.

Wearable devices can be repeatedly used in the home environment to track insomnia symptoms across the day and night to profile long term outcomes (Irwin et al., in press). Markers of arousal are likely to be biomarkers of insomnia but are confounded by no reliable psychiatric biomarkers and the costs of testing and development (Lakhan, Vieira, & Hamlat, 2010; Singh & Rose, 2009). The most suited marker might be one of sleep loss, reduced sleep quality or daytime performance impairments. Recent research highlighted significant daytime impairments where insomnia is described as a true 24-hour disorder (Kyle et al., 2010; Morin, LeBlanc, Daley, Gregoire, & Merette, 2006). Perhaps only an ecologically valid approach to detecting the timing of symptoms will increase the likelihood of successful measurement of sleep loss related biomarkers in insomnia. The identification of point-in-time markers would also be extremely beneficial to sleep medicine in clinical and occupational health and safety settings where detection of sleep loss and sleepiness is vital. Implementing EMA in other sleep disorders such as obstructive sleep apnea could profile the effect of treatment on important daytime outcomes including subjective sleepiness. With technology, EMA could be used to provide a robust and ecologically valid clinical outcome or serve as a marker for ineffective treatment and guide an alternate approach.

Physiological measures of arousal were evaluated before and after SRT for insomnia. Salivary cortisol was not increased during the initial acute phase of therapy. This is a positive outcome and reassuring, as patients who undergo sleep loss with SRT do not have increased cortisol levels during

the acute phase of treatment (first 3 weeks). Other mild sleep restriction therapies where patients are limited to six hours' time in bed did not acutely increase cortisol levels (Pejovic et al., 2013). Objective sleep, core body temperature and plasma cortisol concentrations were collected before and after therapy (6 weeks). TST improved with therapy whilst core body temperature was lowered along with increased cortisol concentrations and subjective morning alertness. These outcomes suggest a restoration in the amplitude of the circadian rhythm. Modifications to physiological functioning in conjunction with improvements in sleep, daytime functioning and a lessening of insomnia severity may lead researchers to uncover objective markers of insomnia severity and/or sleep loss. The use of electroencephalography before and after therapy for insomnia under constant 24-hour conditions along with plasma cortisol concentrations and core body temperature would provide a more robust evaluation of insomnia treatment and potentially limit masking effects. This would enable researchers to detangle the processes involved in treatment with CBT-I. Research should now look to identify if changes in circadian phase or reductions in physiological/cognitive arousal take place and evaluate treatment response with regards to insomnia sub-types.

Adherence is a problematic issue in SRT and evaluation of this in larger clinical effectiveness trials of SRT and CBT-I is necessary. From chapter four, the first week of therapy is very difficult with impairments in alertness being most prominent. Measuring adherence (objective & subjective) through wearable technology will feed information such as time spent in bed back to the clinician to inform of any problems with therapy. If this information were available it would enable clinicians to follow-up with the patient earlier when encouragement or changes to the schedule are required most, potentially increasing adherence and limiting dropout rates.

Insomnia is heterogeneous and although no statistical significant differences in brain metabolites were identified between insomnia and controls with MRS, this outcome is probably not unexpected in such a small study. Defining subtypes of insomnia may well enhance homogeneity in conjunction with evaluating and measuring specific regions in the prefrontal cortex. If differences do exist between insomnia subtypes and controls, MRS could be used as a marker of insomnia subtype in an ideal clinical setting. The role of GABA is important as most hypnotics act on GABA receptor sites and may identify a pathway for the development of insomnia or changes that occur as a result of insomnia.

8.4 Concluding remarks

Through experimental studies, the work presented in this thesis provides an overview and novel assessment of the effects of both SRT and brain metabolism in insomnia. SRT was an effective intervention and along with ecological momentary assessment enables a better understanding of the acute effects of therapy implementation. Objective measures including cortisol and temperature assessment probe the physiological impact of this therapy. Exploration of the cognitive and physiological changes in those who respond to SRT would further enhance our understanding of those who will respond first to behavioural or cognitive treatments. Ecological momentary assessment may be applied more widely along with overnight PSG, actigraphy, sleep diary measures, questionnaires, assessment of cortisol in saliva and blood, core body temperature, and MRS, all of which were undertaken in this study.

Appendices:

Appendix A: Sleep restriction therapy method

An example of therapy based on Spielman et al's., (1987) instructions:

Bed Restriction Therapy Method

We are going to talk a little bit about this new treatment – I want to try and explain a bit about what the treatment is about, how it would work, how you would try it out tonight, and then a little bit about how it would work when you go home as well. So we want to try and help you become a good sleeper.

Good sleepers go to bed, fall asleep, sleep pretty much through the night, then waken up. They are good sleepers, and that is not what is happening for you at the moment. Now good sleepers sleep because they are sleepy – they go to bed and they immediately fall asleep or quickly fall asleep, and they have got a certain pressure to sleep, a need to sleep, they have been awake all day, same as you have. So we want to try and find out what your sleep pressure is like at the moment, because you are not sleeping as much as a good sleeper. How much do you think you are sleeping at the moment? Just off the top of your head, think over the last week or so, on average a ballpark figure, how much sleep do you think you are getting?

Interaction

OK, so that's your estimate, and you probably think that is not nearly enough. I wonder whether that is filling your night. You are going to tell me it is not because you are in bed for much longer than that, so that is not enough to fill your night. How long is your night at the moment, how long are you in your bed? Roughly, a ballpark figure again over the past week?

Interaction *Slide one and Slide two*

So, you are telling me that you are getting 5 hours, or thereabouts, and you are in bed for 7.5 hours, so that is a lot of wakefulness during the night, and your sleep is kind of broken up.

I have got a little graph here to show you, and we can look up your number of hours of sleep here, and we can look across at the number of hours you are spending in bed, and if we draw a line across these two, it takes us to here, bang in the middle of the red zone. That tells me that your sleep is not

efficient; you have got a low sleep efficiency. It looks as if it is about 65%, certainly not 100%. Good sleepers are 90%-100% usually, up in this green zone up here. So that shows me you do have a problem with your sleep. The question is how do we get from 65 to 90+? How do we get to a position where you are like a good sleeper, you go to bed, you fall asleep, you sleep through, and you get up? There is a way to do that – it is to increase your sleep efficiency.

Slide three

Let's go back to your two figures. You have got 5, then you have got 7.5. We can either increase the 5 up to 7.5, or we can reduce what we call your "sleep window", the time you spend in bed, down to be the same as the amount of sleep you are getting at the moment, so that that amount would then fill your whole night. It would be a short night, but it would fill the whole night, that would take your sleep efficiency up. This is called "Bed Restriction". It is a difficult treatment, but it is very effective. Now we can actually look at what your sleep is at the moment like for the past week.

Slide four

Spend a bit of time with the individual with their calculator, working out their actual figures, and then return to the chart.

OK, so we want to get your sleep efficiency from 65% to 90%, and that means that we have to reduce your sleep window down to the amount of sleep you are getting at the moment. This is a difficult thing to do. Sometimes in order to reshape or rebuild people's sleep patterns, we have to take a very direct approach. You have got such a severe problem that you need this special treatment called Bed Restriction. It is a difficult thing to do. The advantage is that you are here tonight in the lab, and we can help you to do it.

So you can see now if we look at this second table that if we take your 5 hours of sleep, if you are going to have that amount of sleep each night and to sleep right through, then you could either start at this time here, and finish here, or a little bit later going to bed and getting up a little bit later, or you can go to bed earlier but it would mean you would get up very early in the morning. You can pick where that window should fall, but it will mean probably staying up later and getting up early. It is a difficult thing to do. What do you think? Which would suit you best? Just tell me your thoughts as you are thinking it through.

(Slide five & six)

Discussion

So that then would be your sleep window for night, and what we would be helping you to do is to fit into that window. There will be people around to help you to stay up, you are going to feel sleepy, sleepier than usual, and this is going to help you to sleep. If you waken during the night, it will probably be easier to fall back asleep again because you have only got a shorter window, and we will make sure you get up at that time in the morning.

One other thing to say about bedtime is that it is not just a case of going to bed exactly then, you want to make sure you are really sleepy, so we call this not your bedtime but your "threshold time". That is the time after which you can cross the threshold into your bedroom. As soon as it gets to that time (say 1.30am), any time after 1.30am you can go to bed. That is your threshold time. But you must get up at your rising time, which as we can see here according to this would be 6.30am. We will make sure you get up then. So that is your schedule for tonight. Any questions on that, any thoughts about it?

Discussion (Slide seven)

Now I have given you a lot of information here, some of it is quite challenging, and you may have questions about it. I have got a little booklet here that tells you more about it, explains more about how sleep pressure works, about how sleep timing works. We call this sleep pressure "the homeostatic drive for sleep", that is the technical term. We call the timing part your "circadian rhythm". You have maybe heard of that. You can ask me some questions about that, but read the booklet first and it will maybe explain a little bit more. Also in the booklet it tells you a little bit about other people's experiences with Sleep Restriction, and reading that may help you to understand how it works for them, and help you to understand that it isn't easy, but it is worth sticking at. So, any other questions?

Appendix B: Sleep restriction therapy presentation slides

Sleep is regulated by two processes that work in harmony together:

1.Sleep Homeostasis (Sleep Pressure)

2.Circadian Rhythm (Body Clock)

We would like to 'jump-start' these two processes in order to reset your sleep into a strong and predictable pattern.

Like a good sleeper.

Total Sleep Time (TST)

Time in Bed (TIB)

HOURS	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5
3	100													
3.5	86	100												
4	75	88	100											
4.5	67	78	89	100										
5	60	70	80	90	100									
5.5	55	64	73	82	91	100								
6	50	58	67	75	83	92	100							
6.5	46	54	62	69	77	85	92	100						
7	43	50	57	64	71	79	86	93	100					
7.5	40	47	53	60	67	73	80	87	93	100				
8	37	44	50	56	63	69	75	81	88	94	100			
8.5	35	41	47	53	59	65	71	76	82	88	94	100		
9	33	39	44	50	56	61	67	72	78	83	89	94	100	
9.5	32	37	42	47	53	58	63	68	74	79	84	89	95	100

Chart A
Sleep efficiency (SEFF)

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Working out your average Sleep Time

Look at question 9 of your diary, we will use these values to calculate your average time asleep per night.

Example:

Day	Amount Slept	(minutes)
1	**6 hr 30 min**	**390**
2	**3 hr 30 min**	**210**
3	**5 hr 15 min**	**315**
4	**6 hr 15 min**	**375**
5	**4 hr**	**240**
6	**6 hr**	**360**
7	**5 hr 30 min**	**330**

Total amount slept = $\frac{37 \text{ hrs}}{7 \text{ days}}$ or $\frac{2220 \text{ mins}}{7 \text{ days}}$

Avg sleep time = 5hrs 17 mins or (317 mins)
= 5hrs 15 mins, to nearest ¼ hr

Sleep Window

(1). First of all we must decide on a morning rising time.

(2). Second, we must decide on a time to go to bed ('threshold time').

You can adjust your sleep window to suit your own daily schedule, but remember bed time and rising time should be the same 7 days a week! e.g. if rising time = 6am, then threshold time will be = 00:45.

Important to keep a minimum of 5 hours time in bed!

For Example:
Average sleep time: 4hr 30 minutes
Set rising time: 7:00 am
Threshold time: 7:00am – 5hr = 2:00am

Time to Bed

Time to Rise	03:00	02:30	02:00	01:30	01:00	12:30	12:00	11:30	11:00	10:30
08:30	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10
08:00	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5
07:30		5	5.5	6	6.5	7	7.5	8	8.5	9
07:00			5	5.5	6	6.5	7	7.5	8	8.5
06:30				5	5.5	6	6.5	7	7.5	8
06:00		***Chart B*** Sleep window options			5	5.5	6	6.5	7	7.5
05:30						5	5.5	6	6.5	7
05:00							5	5.5	6	6.5

Sleep Efficiency

Sleep efficiency is the amount of time you spend in bed asleep

For example

Time went to bed (question 1 from diary): 10:30pm
Time got out of bed (question 5 from diary): 6:30am
Total Time in bed = 8 hrs or 480 minutes
Time asleep (question 6 from diary) = 6 hrs or 360 minutes

Sleep efficiency = time asleep ÷ time in bed x 100
= 6 ÷ 8 x 100
= 75%

Bed Restriction Therapy

Aim:

To sleep for at least 90% of the time you spend in bed

If this is achieved, we will extend your sleep window by 15 minutes.

Your new routine:

1-go to bed on or after your 'threshold' time

2-get out of bed at your rising time

3-Avoid napping during the day

4-stick to your new sleep programme 7 days a week!

University of Glasgow

Bed Restriction Therapy

Read the manual and please ask if you have any questions.

Good Luck!

Bed Restriction Therapy

Information Manual

Mr Christopher Miller

Dr Simon Kyle

Introduction

This information manual aims to help describe, in detail, bed restriction therapy, particularly the theory behind how it works, how to implement it practically, and any frequently asked questions you may have surrounding its use. If, after reading this information, you would still like to know more about Bed Restriction Therapy for insomnia please ask one of the researchers at the University of Glasgow Sleep Centre.

Regulation of sleep

Sleep is an automatic process and therefore out of our own direct, voluntary control.

Whether awake or asleep we are at the mercy of two biological processes:

(1) Sleep Homeostasis, commonly known as 'Sleep Pressure'

(2) The Circadian Rhythm, otherwise known as the 'Body Clock'

These two processes work in harmony to promote good consolidated sleep at night, and it is the goal of Bed Restriction Therapy to help restore the functioning of these two processes to enable undisturbed, good quality sleep to occur.

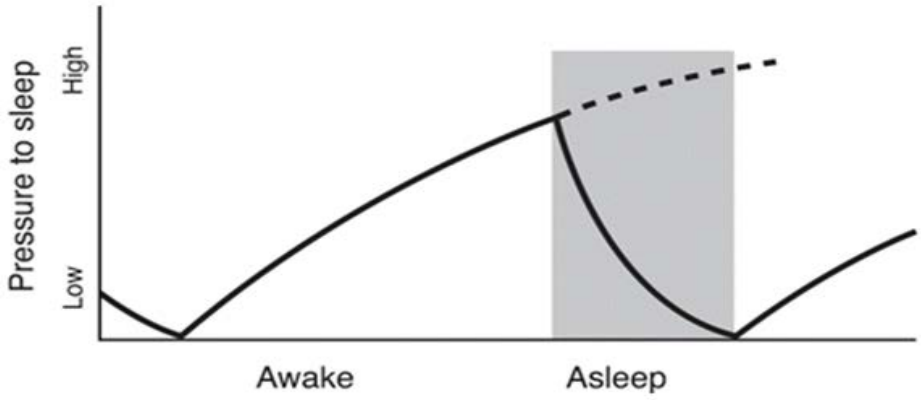
Below we describe how sleep pressure and our body clock work across a normal 24-hour day. By understanding how these processes we are able to find out what alterations may occur in insomnia, and crucially how these can be restored and improved with bed restriction therapy.

Sleep Pressure

Sleep pressure can be thought of as the brains pressure and need for sleep, which becomes greater with the increasing amount of time that we are awake. In this way, the pressure to sleep is directly related to the amount of time that we have been awake. For example, when we wake-up in the morning after a good night's sleep, we will have a very low sleep pressure or 'need to sleep'. As we continue throughout the day, sleep pressure will begin to accumulate (a bit like an hourglass egg-timer). Look at the diagram below which illustrates this increasing sleep pressure over the waking day. At the end of a full day, at bedtime, we will have a great amount of pressure to sleep. By going to bed and having another good night's sleep, then sleep pressure will be reset for the start of the next day.

Diagram of Sleep Homeostasis (Sleep Pressure)

The diagram below shows sleep pressure over the course of a day. The dashed line (---) shows that by staying awake later than your normal bedtime, you will continue to accumulate sleep pressure.



Circadian Rhythm (Body Clock)

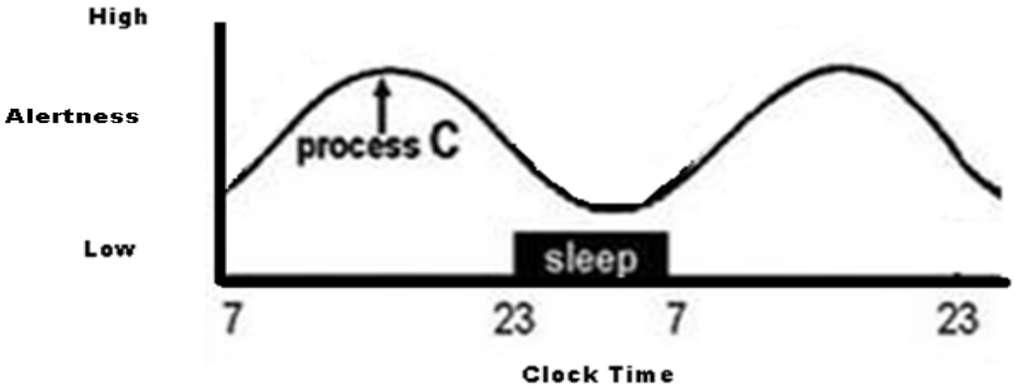
The Circadian Rhythm (Body clock) is an internally generated biological rhythm that allows a number of processes to rise and fall over the twenty four hour period. Commonly, its effects are mostly realised with jet lag when one travels through many different time zones rapidly. This is when the circadian rhythm is out of synchrony with the new environment and can take a number of days to go back to normal.

In a good sleeper, who is in-synch with the environment, the circadian rhythm will naturally rise in the early morning, promoting wakefulness and alertness - this is sometimes known as the alerting force. As the day continues, the circadian rhythm will promote wakefulness until it reaches a peak at about midday (see the diagram below showing this rise and fall in alertness). After this time, the circadian rhythm will start to dip. This initial fall is known as the 'post lunch dip' (you may be familiar with greater feelings of sleepiness after lunch) and as a time for a siesta in other cultures. As we continue through the day, the circadian rhythm continues to fall and does not promote as much arousal as before. With the onset of bedtime and sleep, the circadian rhythm drops to the lowest level and helps to maintain sleep. In this way, sleep pressure is very high, while the alerting effect of our body clock is low, creating the optimal opportunity to sleep.

After this low point, the circadian rhythm will then rise again in anticipation for the next day. The body clock is difficult to manipulate and may be disrupted in a number of poor sleep conditions.

Diagram of Circadian Rhythm (Body Clock)

The diagram below shows how our body clock controls our alertness over the course of the day.



How will this information help me sleep?

It is possible that in individuals with insomnia both sleep pressure and the body clock are not functioning optimally, and bed restriction aims to 'jump-start' these two processes to help promote consolidated and good quality sleep. Bed restriction involves:

(1). Reducing the amount of time that you spend in bed. This will lead to a build-up of sleep pressure to encourage falling asleep straight away and prevent middle-of-the-night awakenings, and improve sleep efficiency.

(2). Standardising the time you go to bed at and get up at each day. This will help create a strong circadian rhythm, with natural peaks and troughs of alertness similar to a good sleeper.

Implementing Bed Restriction Therapy

Bed Restriction Therapy begins with a one week sleep diary. This will give us an indication of the amount of time you spent awake in bed, and how much sleep you actually obtain on an average night – this is often hard to know because your sleep can vary from night-to-night. Understanding how much time you spend in bed and how much time you spend asleep will help form the foundations of Bed Restriction Therapy.

Working out your average sleep time

The first step in Bed Restriction Therapy is to work out your average sleep time from the sleep diary. **This is found in question 9 of your sleep diary**. By using your sleep diary record from the past seven nights it will be possible to calculate your average sleep time for those nights.

An example might be:

Day	**Amount Slept**	**(Minutes)**
Monday	6 hours 30 min	(390)
Tuesday	3 hours 30 min	(210)
Wednesday	5 hours 15 min	(315)
Thursday	6 hours 15 min	(375)
Friday	4 hours	(240)
Saturday	6 hours	(360)
Sunday	5 hours 30 min	(330)

Therefore, by adding up the total amount of time slept on each night, and by dividing that by the number of nights (in this case seven), we are able to calculate your average sleep time. By doing the following:

Total amount slept = 37 hours or (2220 minutes)
÷ ÷
Number of days (7) Number of days (7)
Average Sleep Time = 5 hours 17 minutes or (317 minutes)
= 5 hours 15 minutes, to the nearest 15 minutes

This example suggests that this person has slept approximately on average five hours and 15 minutes per night. It is often the case that poor sleepers spend much longer in bed compared with the actual amount of time they spend sleeping. Bed Restriction Therapy aims to improve the efficiency of sleep by restricting the amount of time that you spend awake in bed.

Getting your sleep into a regular pattern

The first modification to your sleep within Bed Restriction Therapy is to set a morning rising time, a time to get out of bed. It is best to calculate a time to rise from bed in the morning as this is something that we can control. In the example patient above, it was decided that due to work reasons the set morning rising time would be at 6 am. We call this the Set Rising Time or Anchor Time as this should be the time that you rise from bed everyday of the week (even weekends!).

With this new set Rising Time, we then work backwards around the clock with the amount of time that you, on average, slept for the preceding week (in the patient above it was previously worked out to be five hours and 15 minutes from the sleep diary). This enables us to decide on a 'Threshold Time'.

The Threshold time is the time after which you can now retire to your bedroom and to bed. In this example, with a Set rising time of 6am and an average sleep time of 5 hours and 15 minutes, the Threshold Time is set at 00:45am; on or after this time you can go to bed.

You can adjust your preferred threshold and rising times e.g. if this patient decide to set his/her rising time at 7am, then the threshold time would be 1:45am. This period between going to bed and rising from bed is called the 'sleep window'.

However, it is vitally important to keep a minimum of Five hours of time spent in bed.

For example, if your average total sleep time is equal to 4 hours and 30 minutes then the minimum of five hours of time spent in bed must be applied. An example might be setting a rising time of 7:00 am, and so a threshold time would then be worked out to be 7:00am – **five hours** = 2:00am.

Sleep Efficiency

One of the main goals of bed restriction therapy is to make your sleep more efficient. What we mean by this is that, when you go to bed, you fall asleep quickly and have very little wake time during the night. Sleep efficiency therefore refers to the amount of time that you spend asleep as a percentage of the time that you spend in bed. The example below shows how this can be calculated.

Go to bed: 10:30pm
Get to sleep: 12:30am
Wake up: 6:30am
Time asleep: 6 hours (or 360 minutes)
Time in bed: 8 hours (or 480 minutes)

Sleep efficiency = time asleep ÷ time in bed (x 100)

= 6 ÷ 8 x 100 = 75%

We will use the Sleep Efficiency ratio to help study weekly changes in your sleep pattern, over the course of Bed Restriction Therapy. A 'good sleep efficiency' is around 90%, however this can be variable even in a

good sleeper. Sleep efficiency scores less than this suggest a poor sleep. If your sleep efficiency improves to equal to or greater than 90% we will extend your sleep window by 15 minutes. If your sleep efficiency works out to be lower than 85% on average, over seven days, we will decrease your sleep window by 15 minutes. This will help ensure that you are having more efficient sleep, eliminating wakefulness during the night and helping you have a consolidated block of sleep.

Recap of your new Bed Restriction Routine.

*** Stay up and out of bed until your threshold time**

*** Go to bed at or after your set threshold time**

*** Get up in the morning at your rising time**

*** Follow this programme every night, even at weekends.**

Making these changes

These changes to your sleep wake schedule can be very difficult to make and to adhere to. However, Old habits do die hard and the initial two weeks of this therapy can be especially difficult.

But if you can adhere to the intervention we are sure that you will see improvements in your sleep efficiency.

In addition, weekends can be difficult especially when you have more hours of wakefulness in the morning. However, you should do your best to try to stick with the programme and stay motivated about changing your sleep.

You may find that the mornings will provide you with new opportunities to do exercise or catch up with things that you have long put off. It is also beneficial to get as much light as possible in the morning to help synchronise your internal Circadian rhythm to the morning rising time.

Bed Restriction Therapy also stops negative associations about the bedroom environment - as it strengthens the idea that the bedroom should only be used for sleeping or intimacy. With this therapy you should (hopefully!) no longer worry about trying to get to sleep in the bedroom. Instead you will relish going to bed and it will now become a place for you to finally fall asleep.

Questions and Answers

When will I start to get more sleep?

- Once you are sleeping 90% (sleep efficiency) of your time in bed. After this we will be able to Increase your time in bed by 15 minutes.
- You will then be asked to stay with this new pattern for at least another week.
- We will review your progress and make changes each week for the next 4 weeks.

What do I do with this extra evening time?

- Continue with normal daily tasks, whatever you want to do.
- But do not fall asleep before 'threshold time'
- Safety: do not take risks.

Can I nap during the day?

- Napping may reduce the effectiveness of bed restriction therapy.
- Only take a short nap (15-20 minutes) if you are struggling to stay awake during the day.

Is Bed Restriction Therapy Safe?

- Yes! However, you may feel sleepier and more fatigued in the early days and weeks of treatment. It is important that, if you feel very sleepy, you avoid driving or operating heavy machinery.

Can I really make the change?

- Bed Restriction Therapy is tough, but can be incredibly effective at improving sleep pattern and quality.
- Think of it as a surgical treatment for your sleep pattern, which will help you rediscover how to sleep in a consolidated undisturbed block.
- Remember to work hard at it and stay positive.

Previous Patient Quotes

Below we have provided some quotes from real patients that have taken part in Bed Restriction Therapy. These are to give you a flavour of what it is like to implement the prescribed sleep window, as well as any difficulties that patients have encountered when adhering to the programme, and finally what impact it can have on sleep and daytime functioning. If you have any questions about these quotes please ask Dr Simon Kyle.

"..the sort of limited amount of sleep that you were giving us in the first night sounded pretty horrific, and it was, the first week was really tough, eh, but I think I could see the sense then, but I didn't see it immediately you know, it didn't hit me immediately that it was going to work, that sort of came in the second week' [David, 16-19]

"driving was a nightmare, and I've never ever had an issue with driving before" [Bill, 84]

"I suppose rationally and logically, it did seem a good idea, but then I think the first week of actually doing it, I felt worse, and so you kinda, there's a temptation there to think 'och this is not working', like 'give up now'" [Lisa, 17-19]

"my husband was determined I was sticking at it, you know, cos he, when I was sitting at night time, and I was like almost falling asleep…he kept shouting at me 'get up', 'wake up, don't go to sleep', you know it was kinda like that, but I felt it very difficult to get up and do anything, I was actually too tired to" [Gillian, 135-138]

"…there's been a few mornings where you're em, oh you're thinking, especially like Saturday and Sunday, 'there's just no way I want to get out of my bed', but em, then you think 'well no', especially at the weekend cos then if I lie long this morning then I don't get to sleep tonight, it's just going to start the whole thing again, that's, I suppose, the motivation, the fact that you think 'well if this makes you sleep five hours through the night, then just get up'" [Lisa, 273-278]

"I'm sleeping longer, and going into a deeper sleep, I think, when I wake during the night it's only…it's less frequent, and it's easier to get back over again…previously if I woke up during the night

I'd be worried about trying to get back over again, and I'd be thinking about it, but because you're so tired by this sort of programme then you actually get back over much quicker and it seems to work" [David, 62-66]

"you're so knocked that you don't have the anxiety to be anxious at that time of night, really, I'm so looking forward to going to my bed, when I get to whichever hour my times up, I say 'Yes, times up, going to bed' [laughs] so that's probably the highlight of the day" [Bill, 167-170]

"I think I've altered my, I just seem to have gone onto a different plain when it comes to my attitude to sleep, em, another thing though I've realised is that em it's possibly true that I just don't need 8 hours of sleep, or even seven and a half hours sleep, or even seven, possibly I only need about six and a half hours sleep." [Louise, 78-81]

"I'm not concerned, I'm not worried about not sleeping, because I know that when I go to bed I will sleep" [Sarah, 188-189]

"I do feel like a normal sleeper, which is bizarre and great, this has been huge for...like driving, I feel like I'm calmer you know I don't get road rage, I don't…I'm not as bad as what I was, I'm taking less risks in the car, I'm not in a rush, because I'm not as anxious, I'm not on edge, I'm just a bit more chilled I think, and I think the sleep helps to centre yourself…" [Hannah, 353-357]

"much more sort of…quite motivated for work and stuff, eh, it definitely has had a very positive effect on my sort of daily life" [David, 87-88]

" I think now I'm more likely if I've planned something for after work, to do it, em, I'm meant to, I've paid for most of this year west Dunbartonshire council money for a gym membership, that I ['ve] never been in, em, so I'm now back three times a week!" [Lisa, 185-187]

Total Sleep Time (TST)

Time in Bed (TIB)

HOURS	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5
3	100													
3.5	86	100												
4	75	88	100											
4.5	67	78	89	100										
5	60	70	80	90	100									
5.5	55	64	73	82	91	100								
6	50	58	67	75	83	92	100							
6.5	46	54	62	69	77	85	92	100						
7	43	50	57	64	71	79	86	93	100					
7.5	40	47	53	60	67	73	80	87	93	100				
8	37	44	50	56	63	69	75	81	88	94	100			
8.5	35	41	47	53	59	65	71	76	82	88	94	100		
9	33	39	44	50	56	61	67	72	78	83	89	94	100	
9.5	32	37	42	47	53	58	63	68	74	79	84	89	95	100

Chart A
Sleep efficiency (SEFF)

Time to Bed

Time to Rise	03:00	02:30	02:00	01:30	01:00	12:30	12:00	11:30	11:00	10:30
08:30	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10
08:00	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5
07:30		5	5.5	6	6.5	7	7.5	8	8.5	9
07:00			5	5.5	6	6.5	7	7.5	8	8.5
06:30				5	5.5	6	6.5	7	7.5	8
06:00		***Chart B*** Sleep window options			5	5.5	6	6.5	7	7.5
05:30						5	5.5	6	6.5	7
05:00							5	5.5	6	6.5

Appendix D: Ethical approval for Chapters 4 & 5

WoSRES
West of Scotland Research Ethics Service

West of Scotland REC 3
Ground Floor – The Tennent Institute
Western Infirmary
38 Church Street
Glasgow G11 6NT
www.nhsggc.org.uk

Professor Colin Espie
Director, University of Glasgow Sleep Research Laboratory
Southern General Hospital
Neurosurgery Building 2nd floor
1345 Govan Road
Glasgow G51 4TF

Date 10th December 2010
Your Ref
Our Ref
Direct line 0141 211 2123
Fax 0141 211 1847
E-mail Liz.Jamieson@ggc.scot.nhs.uk

Dear Professor Espie

Study Title: **Objective impact on sleep and daytime functioning of sleep restriction therapy: a brief behavioural intervention for persistent insomnia.**

REC reference number: **10/S0701/85**

The Research Ethics Committee reviewed the above application at the meeting held on 02 December 2010. Thank you for attending to discuss the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Sponsors are not required to notify the Committee of approvals from host organisations.

Other Conditions

Participant Information Sheet to be amended as follows:

- In the introduction it should be made clear to participants that this study is on the back of

another study so that they know what they are signing up for.
- The timings stated for completing the questionnaires are not accurate and should be amended to give a true reflection of what is involved.
- The use of the acti-watch should be mentioned.
- There is no mention of swabs being taken.
- If the interviews are being taped then this must be stated.
- The name of the Committee is wrong. This should be 'West of Scotland Research Ethics Committee 3'.

Consent Form to be amended as follows:

- The Consent Form is not in the standard format and should have Initial boxes and not 'Yes/No' boxes.
- Consent to take swabs must be obtained.
- If the interviews are being taped then consent must be obtained.

General

In discussion with the Researcher, the Committee noted agreed that whilst there were no material ethical issues there should be a mechanism in place to ensure that participants held on the database are not being 'over-researched'. Apart from the inconvenience to participants this could bias the results from a statistical point of view. The researcher agreed to review how participants are selected and develop a monitoring mechanism. The Committee was concerned that this might be a general problem with Sleep Centre research due to the fact that participants are given the opportunity to opt-in to further research when consent is taken for a study.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*	
Participant Information Sheet: Poor Sleeper	1.1	05 November 2010	
REC application		16 November 2010	
Participant Consent Form: Additional Study for Poor Sleepers	1.1	05 November 2010	
Questionnaire: Validated - Alcohol Use Disorders Identification Test			
Questionnaire: Validated - FIRST			
Questionnaire: Validated - Sleep Diary			
Questionnaire: Validated - Life			
Questionnaire: Validated - Dysfunctional Beliefs and Attitudes about Sleep			
Questionnaire: Validated - Karolinska Sleepiness Scale			
Questionnaire: Validated - Sleep Restriction Therapy			
Questionnaire: Validated - Mood20			
Letter from Funder		22 July 2010	
Validated Questionnaire - SF36			
Validated Questionnaire - Fatigue Scale			
Participant Information Sheet: Good Sleeper	1.1	05 November 2010	
Advertisement			
CV Student - Christopher Miller			
CV Co-Investigator - Christine Salveta			

Investigator CV			
Participant Information Sheet: Additional Study for Poor Sleeper	1.1	05 November 2010	
Participant Consent Form: Good Sleeper	1.1	05 November 2010	
Participant Consent Form: Poor Sleeper	1.1	05 November 2010	
Protocol	1.1	05 November 2010	
Validated Questionnaire - PHQ		14 November 2005	
Validated Questionnaire - SAS			
Covering Letter		16 November 2010	
Questionnaire: Validated - Epworth Sleepiness Scale			
Questionnaire: Validated - Glasgow Sleep Effort Scale			
Questionnaire: Validated - Symptom Checklist			
Participant Enquiry and Preliminary Screening Form		13 February 2010	
Validated Questionnaire - ISI			
Validated Questionnaire - CFQ			
Validated Questionnaire - HADS			
Acti-watch Instructions			
CV - Co-Investigator Dr Simon Kyle			
Validated Questionnaire - PSQI			
Validated Questionnaire - Glasgow Content of Thoughts Inventory			
Instructions taking Cortisol Saliva Sample			
Sleep Restriction Protocol - Training for GPs			

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/S0701/85	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Liz Jamieson

Committee Co-ordinator

On behalf of Dr Paul Fleming, Chair

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to: Dr Simon Kyle, University of Glasgow

Dr Steven Burke, R&D

West of Scotland REC 3

Attendance at Committee meeting on 02 December 2010

Committee Members:

Name	*Profession*	*Present*	*Notes*	
Dr Jim Brooks	Lay Member	No		
Dr Adam Burnel	Consultant Psychiatrist	No		
Mrs Bernadette Campbell	Primary Care Support Nurse	Yes		
Ms Lorna Cuthbertson	Senior Clinical Pharmacist	Yes		
Dr Paul Fleming	Consultant Clinical Psychologist	Yes		
Ms Susan Fleming	Public Health Researcher	Yes		
Ms Catriona Kent	Nurse Consultant	No		
Mr Eoin MacGillivray	Lay Member	Yes		
Dr Paul Mattison	Consultant Physician in Rehabilitation Medicine	Yes		
Dr Angus McFadyen	Reader in Health Statistics	Yes		
Canon Matt McManus	Lay Member	Yes		
Dr Stephen Noble	Consultant Anaesthetist	Yes		
Mrs Gillian Notman	Joint Occupational Therapy Lead Advisor	Yes		
Mrs Helen Ross	Lay Member	Yes		
Mrs Rosie Rutherford	Lay Member	Yes		

Appendix E: Participant sampling instructions for salivary cortisol concentrations

Dear

Additional Study Component

I have supplied a timetable and a description of the procedures for the Additional Study Component. It is hoped by taking part in this Additional Study Component that you may find out more about your own sleep pattern changes over the treatment intervention period. You will also be helping to inform the science about sleep research further. I hope you will be able to carry this out.

Also, if you have any questions regarding any of the procedures or wish to visit the Sleep Centre to learn and find out more about the Additional Study Component process please do not hesitate to get in touch with myself.

Best regards,

Mr Christopher Miller

PhD Research Student

University of Glasgow Sleep Centre

Sackler Institute of Psychobiological Research/Institute of Neuroscience and Psychology

Southern General Hospital, Glasgow G51 4TF, Scotland, UK

Tel: +44(0)141 232 7699/7700 Fax: +44(0)141 232 7697

Email: c.miller.2@research.gla.ac.uk www.glasgowsleepcentre.co.uk

The University of Glasgow, charity number SC004401

CSO Additional Study Component Study: Cortisol Timeline

Please fill in box with the time on completion

Sample One: Monday the _____at two hours before bedtime. ☐

Label code: Green

Sample Two: Monday the _____at bedtime (within the bedroom store in freezer then brush teeth). ☐

Label code: Red

Sample Three: Tuesday the _____ in the morning immediately upon ☐

awakening (Within first 15 minutes of awakening).

Label code: Blue

Sample Four: Tuesday the _____at two hours before bedtime. ☐

Label code: Green

Sample Five: Tuesday the _____ at bedtime. ☐

Label code: Red

Sample Six: Wednesday the_ in the morning immediately upon ☐

Awakening (Within first 15 minutes of awakening).

Label code: Blue

*The next samples will be collected at the Sleep Centre.

**Another three samples will be completed at home after your stay.

***This procedure will be repeated for each overnight stay.

CSO Additional Study Component Study: Cortisol Timeline Part II

Please fill in the time in the box

Sample Seven: Wednesday _____(in Sleep Centre) two hours before bedtime. ☐

Label code: Green

Sample Eight: Wednesday _____(in Sleep Centre) at bedtime ☐

Label code: Red

Sample Nine: Thursday _____in the morning immediately upon Awakening (in Sleep Centre). ☐

Label code: Blue

Sample Ten: Thursday_____ at two hours before bedtime. ☐

Label code: Green

Sample Eleven: Thursday _____ at bedtime. ☐

Label code: Red

Sample Twelve: Friday _____ in the morning immediately upon ☐

Awakening (Within first 15 minutes of awakening).
Label code: Blue

END of Week One

Week Two

Sample One: Monday _____ at two hours before bedtime.

Label code: Green

Sample Two: Monday _____ at bedtime (within the bedroom store in freezer then brush teeth).

Label code: Red

Sample Three: Tuesday _____ in the morning immediately upon awakening (Within first 15 minutes of awakening).

Label code: Blue

Sample Four: Tuesday _____ at two hours before bedtime.

Label code: Green

Sample Five: Tuesday _____ at bedtime.

Label code: Red

Sample Six: Wednesday _____ in the morning immediately upon Awakening (Within first 15 minutes of awakening).
Label code: Blue

CSO Additional Study Component Study: Cortisol Timeline Part III

Please fill in the time in the box

Sample Seven: Wednesday _____(in Sleep Centre) two hours before bedtime. ☐

Label code: Green

Sample Eight: Wednesday _____(in Sleep Centre) at bedtime ☐

Label code: Red

Sample Nine: Thursday _____in the morning immediately upon Awakening (in Sleep Centre). ☐

Label code: Blue

Sample Ten: Thursday _____ at two hours before bedtime. ☐

Label code: Green

Sample Eleven: Thursday _____ at bedtime. ☐

Label code: Red

Sample Twelve: Friday _____ in the morning immediately upon ☐

Awakening (Within first 15 minutes of awakening).
Label code: Blue

END of Week Two

Week Three

Sample One: Monday _____ at two hours before bedtime. ☐

Label code: Green

Sample Two: Monday _____ at bedtime (within the bedroom store in freezer then brush teeth). ☐

Label code: Red

Sample Three: Tuesday _____ in the morning immediately upon awakening (Within first 15 minutes of awakening). ☐

Label code: Blue

Sample Four: Tuesday _____ at two hours before bedtime. ☐

Label code: Green

Sample Five: Tuesday _____ at bedtime. ☐

Label code: Red

Sample Six: Wednesday _____ in the morning immediately upon ☐

Awakening (Within first 15 minutes of awakening).
Label code: Blue

CSO Additional Study Component Study: Cortisol Timeline Part IV

Please fill in the time in the box

Sample Seven: Wednesday _____(in Sleep Centre) two hours before bedtime. ☐

Label code: Green

Sample Eight: Wednesday _____ (in Sleep Centre) at bedtime ☐

Label code: Red

Sample Nine: Thursday _____ in the morning immediately upon Awakening (in Sleep Centre). ☐

Label code: Blue

Sample Ten: Thursday _____ at two hours before bedtime. ☐

Label code: Green

Sample Eleven: Thursday _____ at bedtime. ☐

Label code: Red

Sample Twelve: Friday _____in the morning immediately upon ☐

Awakening (Within first 15 minutes of awakening).
Label code: Blue

END of Cortisol testing

Instructions for taking the Cortisol saliva sample cotton swab:

Saliva Cortisol must be sampled at specific time points throughout this study. If you are not sure about any aspect of this procedure please call/ask the researcher Christopher Miller on 07950737669 (out of office hours) / 0141 232 7699 (office hours)

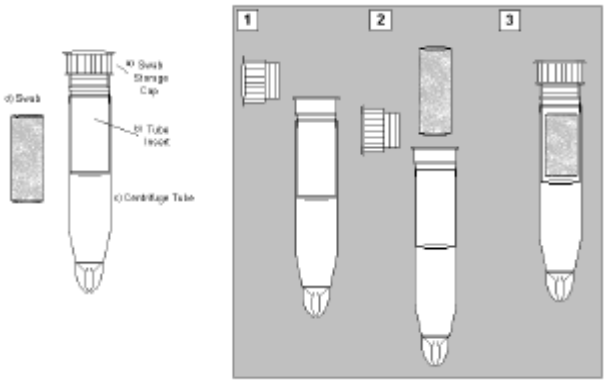
To take a Cortisol sample:

The cotton bud (found inside the sample container under the purple cap) must be placed in the right hand side of the mouth for a period of two-three minutes or until completely saturated.

Once this time is up you must put the sample into the specified sampling tube.

This is done by:

1. Removing the purple cap (whilst the smaller tube is still in place inside the larger tube).
2. Place the swab into the top compartment.
3. Seal the top of the tube with the purple cap.



Then the tube must be stored in the storage bag inside your freezer as soon as possible.

For the three different time points:

1. In the morning you must on wake up (when you are sure that you have finally woken and are about to begin your day) take the first cotton swab as indicated on the sample tube. It would be best to have this tube beside your bed as this must be completed immediately on wake-up.
2. The second sample is due to be taken two hours before your scheduled time for bed. Again, you will repeat the saliva collection with the cotton swab and store the sample in the provided tube for this time. Please store the sample in the provided fridge.
3. Finally, the last sample should be collected once you are in bed, placed in the correct tube and stored in the fridge.

Appendix F: Ethical approval for Chapter 6

ADDRESS FOR ALL CORRESPONDENCE
RESEARCH DEVELOPMENT OFFICE
ROYAL PRINCE ALFRED HOSPITAL
CAMPERDOWN NSW 2050

TELEPHONE: (02) 9515 6766
FACSIMILE: (02) 9515 7176
EMAIL: lesley.townsend@email.cs.nsw.gov.au
REFERENCE: X11-0408 & HREC/11/RPAH/634

NSW GOVERNMENT Health
Sydney
Local Health District

20 January 2012

A/Professor D Bartlett
Woolcock Institute of Medical Research
PO Box M77
CAMPERDOWN NSW 2050

Dear Professor Bartlett,

Re: Protocol No X11-0408 & HREC/11/RPAH/634 - "Sleep Restriction Therapy (SRT) for chronic insomnia disorder: physiological, cognitive & objective sleep alterations after six weeks of therapy intervention – a pilot study"

The Executive of the Ethics Review Committee, at its meeting of 18 January 2012, considered your correspondence of 11 January 2012. In accordance with the decision made by the Ethics Review Committee, at its meeting of 14 December 2011, approval is granted to proceed.

The proposal meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

This approval includes the following:

- Testing Protocol (Version 2, 11 January 2012)
- Information for Participants (Master Version 2, 10 January 2012)
- Consent Form (Master Version 2, 10 January 2012)

General Correspondence
PO Box M30
Missenden Road, NSW, 2050
Email: slhn.esu@sswahs.nsw.gov.au
Website: www.health.nsw.gov.au/sydlhn/

Sydney Local Health District
ABN 17 520 269 052
Level 11 North, King George V Building
83 Missenden Rd
CAMPERDOWN, NSW, 2050
Tel 612 9515 9600 Fax 612 9515 9610

- Sleep Diary (Version 2, 11 January 2012)
- Epworth Sleepiness Scale (ESS) (Version 2, 11 January 2012)
- DASS21 (Version 2, 11 January 2012)
- ISI: The Insomnia Severity Index (Version 2, 11 January 2012)
- Ford Insomnia Response to Stress Test (FIRST) (Version 2, 11 January 2012)
- The Glasgow Content of Thoughts Inventory (Version 2, 11 January 2012)
- Pittsburgh Sleep Quality Index (Version 2, 11 January 2012)
- The Glasgow Sleep Effort Scale (Version 2, 11 January 2012)
- Fatigue Scale (Version 2, 11 January 2012)
- Sleep Arousal Scale (SAS) (Version 2, 11 January 2012)
- Dysfunctional Beliefs and Attitudes about Sleep (14 January 2008)

You are asked to note the following:

- The study is authorised to be conducted at the following site(s):
    - Woolcock Institute of Medical Research
- This approval is valid for four years, and the Committee requires that you furnish it with annual reports on the study's progress beginning in February 2013.
- You must immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.
- You must notify the HREC of proposed changes to the research protocol or conduct of the research in the specified format.
- You must notify the HREC, giving reasons, if the project is discontinued before the expected date of completion.
- You are responsible for the following:
    - arranging a Criminal Record Check and a SLHD identity pass for any researcher who is not employed by the Sydney Local Health District. You should contact the Ethics Officer on 02 9515 7899 for advice on this matter, and

- if appropriate, informing the study sponsor that this human research ethics committee (HREC) has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review and is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

- If you or any of your co-investigators are University of Sydney employees or have a conjoint appointment, you are responsible for informing the University's Risk Management Office of this approval, so that you can be appropriately indemnified.

- Where appropriate, the Committee recommends that you consult with your Medical Defence Union to ensure that you are adequately covered for the purposes of conducting this study.

Yours sincerely,

Lesley Townsend
Executive Officer
Ethics Review Committee (RPAH Zone)

Research Governance Officer
SLHD (RPAH Zone)

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Appendix G: Individual data for Chapter 6

Figure 1: Sleep onset latency

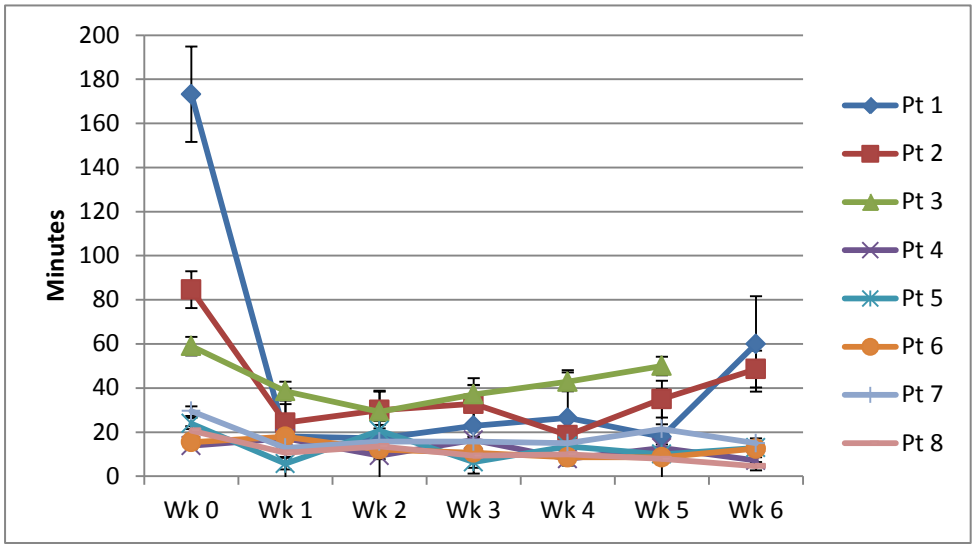

Figure 1: Displays the average sleep onset latency (minutes) from the sleep diary for each participant (Pt 1-8) throughout the weeks of the study (baseline to week 6).

Figure 2: Wake-time after sleep onset

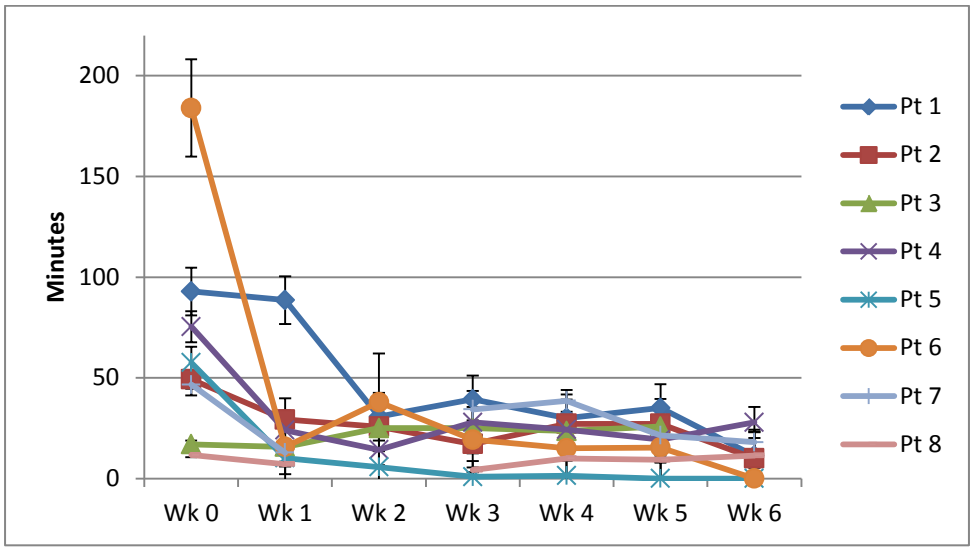

Figure 2: Displays the average wake-time after sleep onset (minutes) from the sleep diary for each participant (Pt 1-8) throughout the weeks of the study (baseline to week 6). Error bars display one standard error of the mean.

Figure 3: Total sleep time

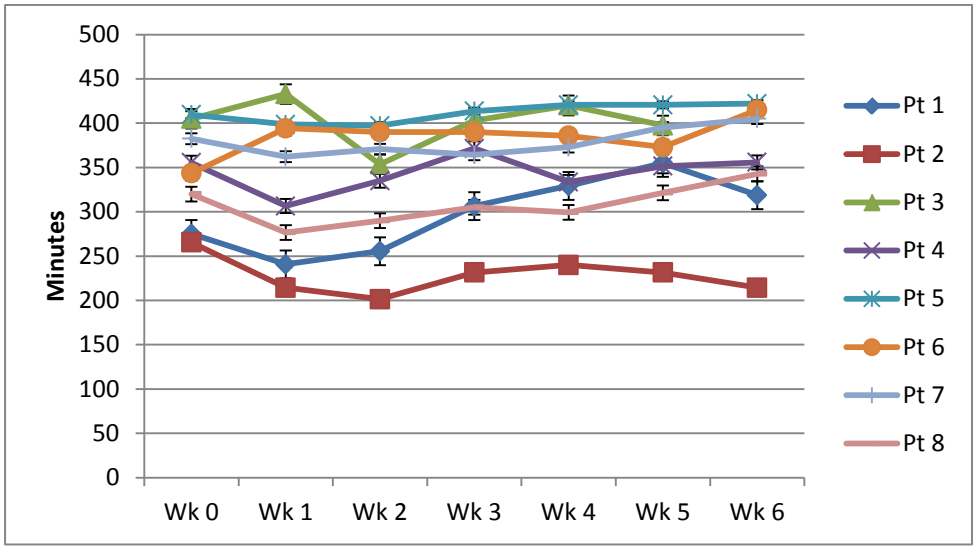

Figure 3: Displays the average total sleep time (minutes) from the sleep diary for each participant (Pt 1-8) throughout the weeks of the study (baseline to week 6). Error bars display one standard error of the mean.

Figure 4: Sleep efficiency

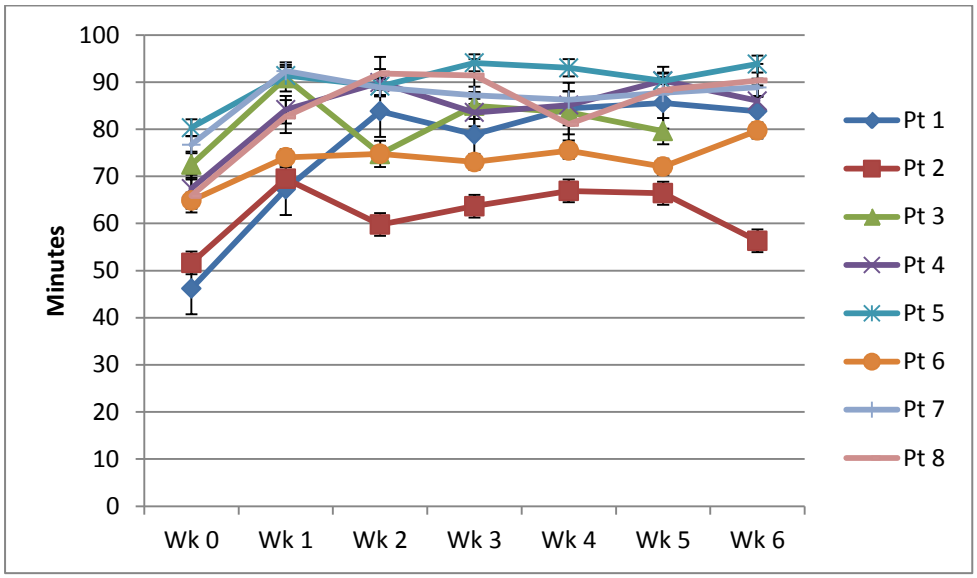

Figure 4: Displays the average sleep efficiency (minutes) from the sleep diary for each participant (Pt 1-8) throughout the weeks of the study (baseline to week 6). Error bars display one standard error of the mean.

Figure 5: Sleep onset latency

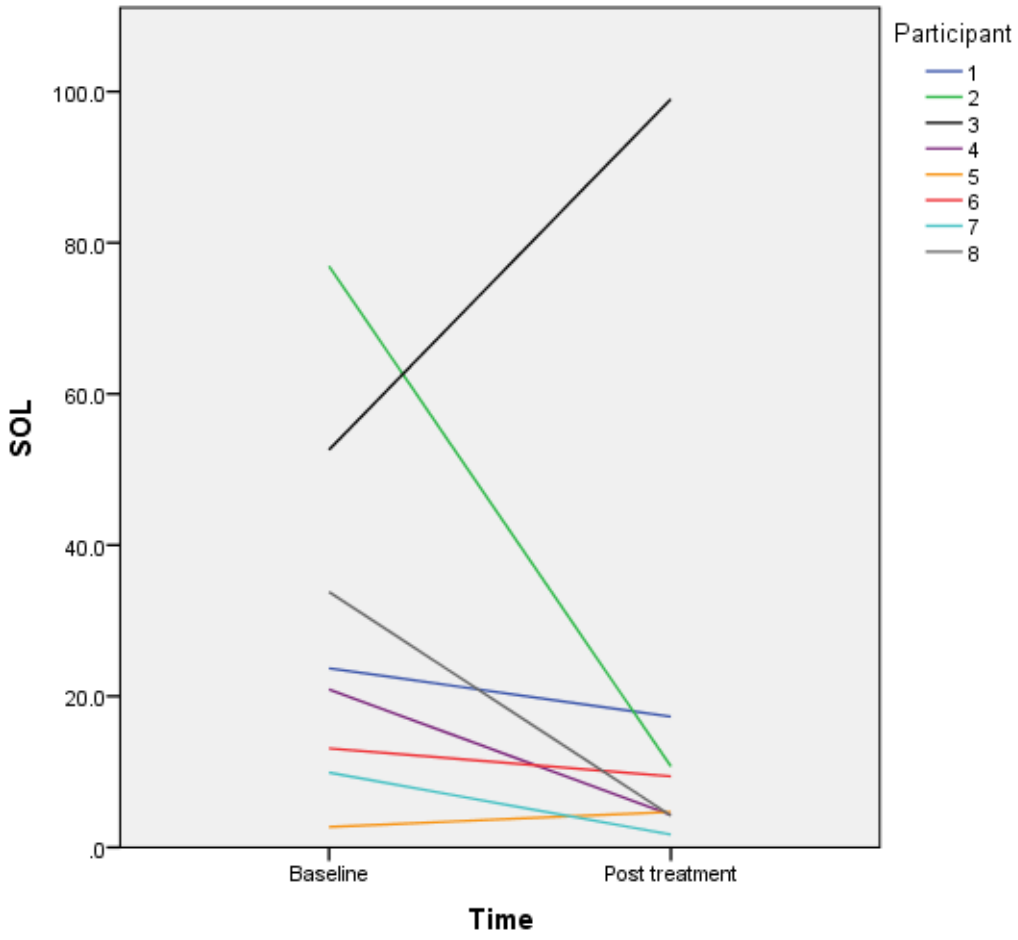

Figure 5: Displays sleep onset latency (minutes) from polysomnography for each participant (Participant 1-8) throughout the weeks of the study (baseline to week 6).

Figure 6: Total sleep time

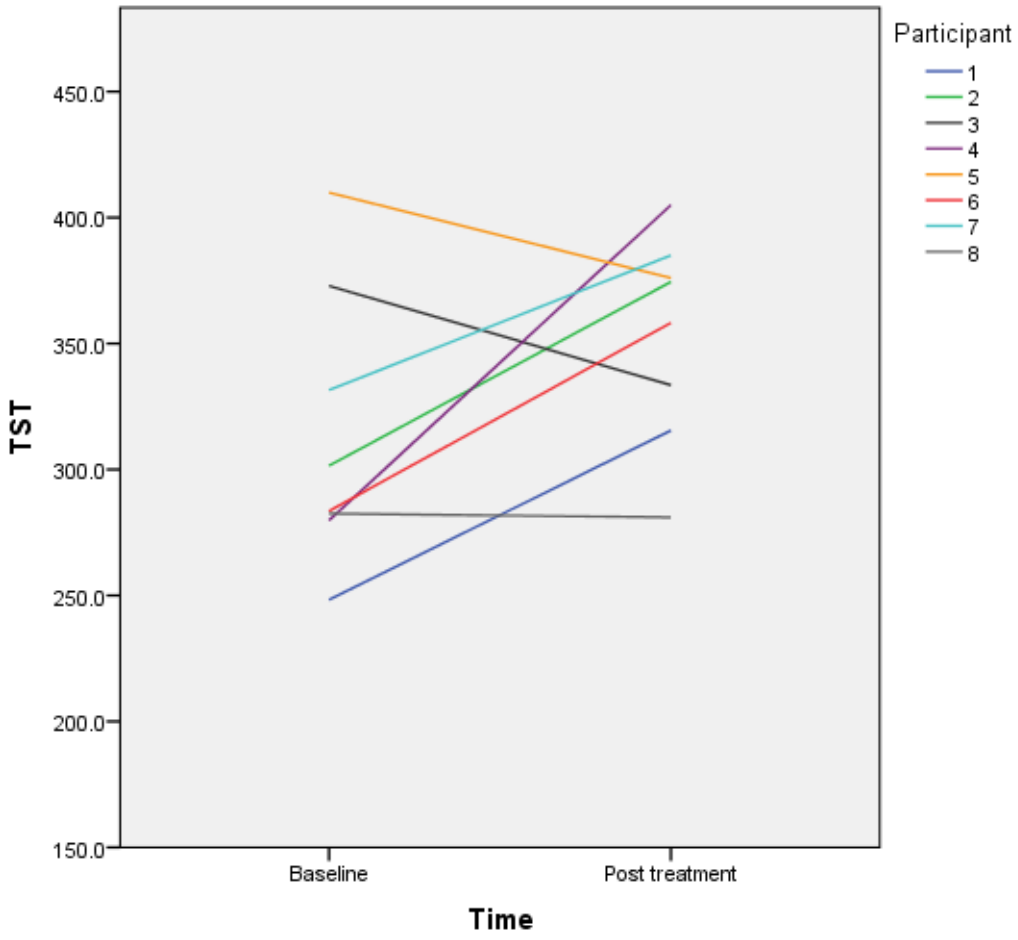

Figure 6: Displays total sleep time (minutes) from polysomnography for each participant (Participant 1-8) throughout the weeks of the study (baseline to week 6).

Figure 7: Wake-time after sleep onset

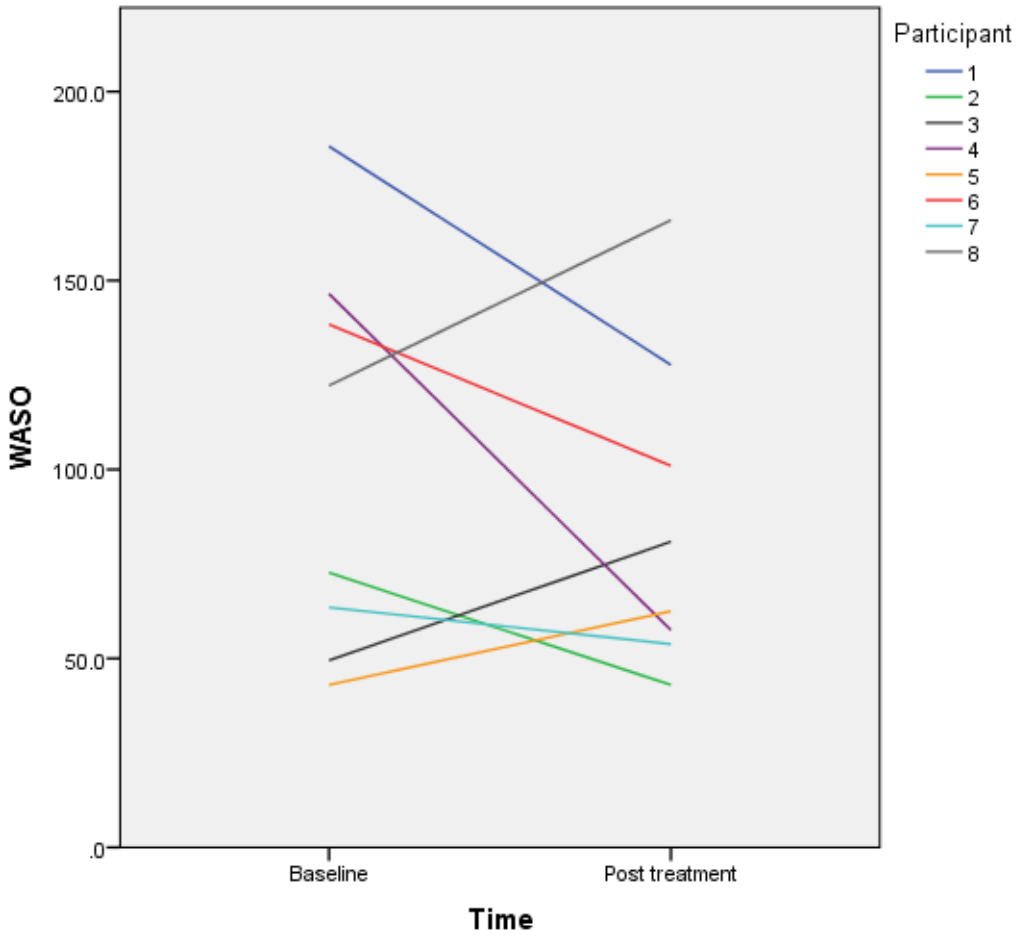

Figure 7: Displays the wake-time after sleep onset (minutes) from polysomnography for each participant (Participant 1-8) throughout the weeks of the study (baseline to week 6).

Figure 8: Sleep efficiency

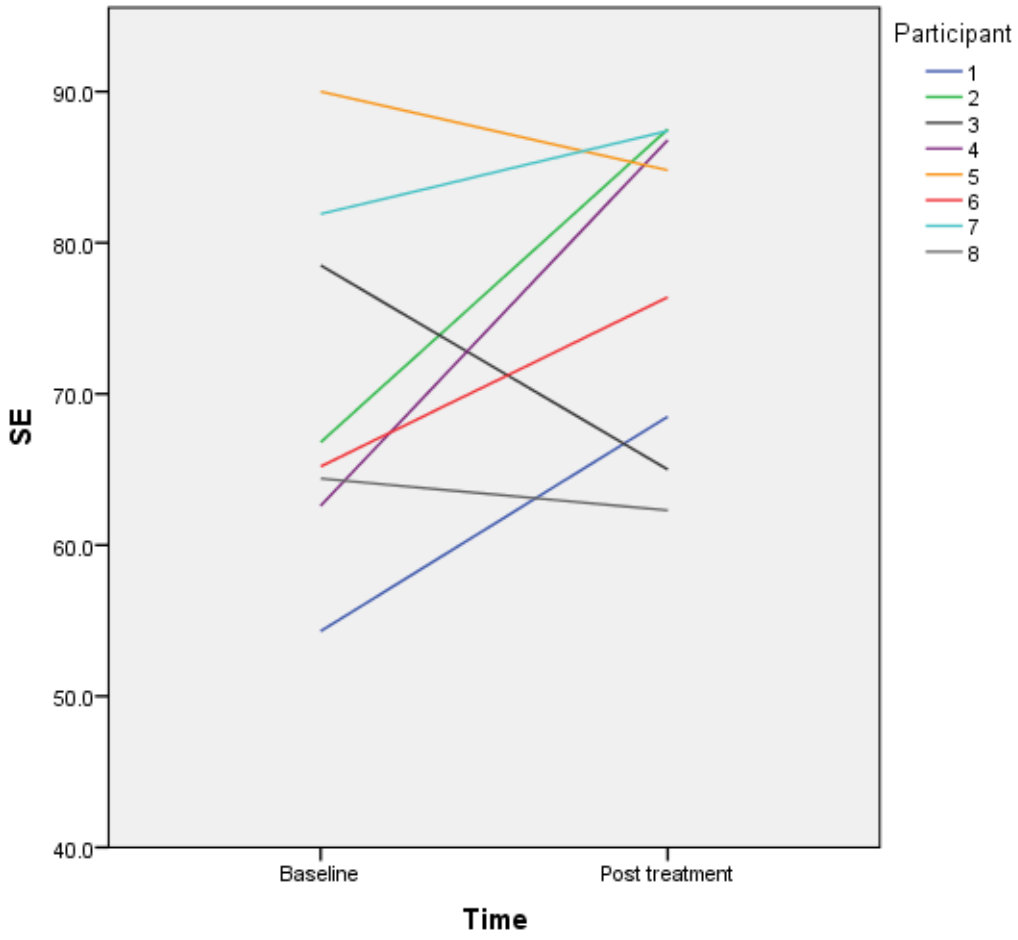

Figure 8: Displays % sleep efficiency (SE) from polysomnography for each participant (Participant 1-8) throughout the weeks of the study (baseline to week 6).

Figure 9: Rapid eye movement sleep

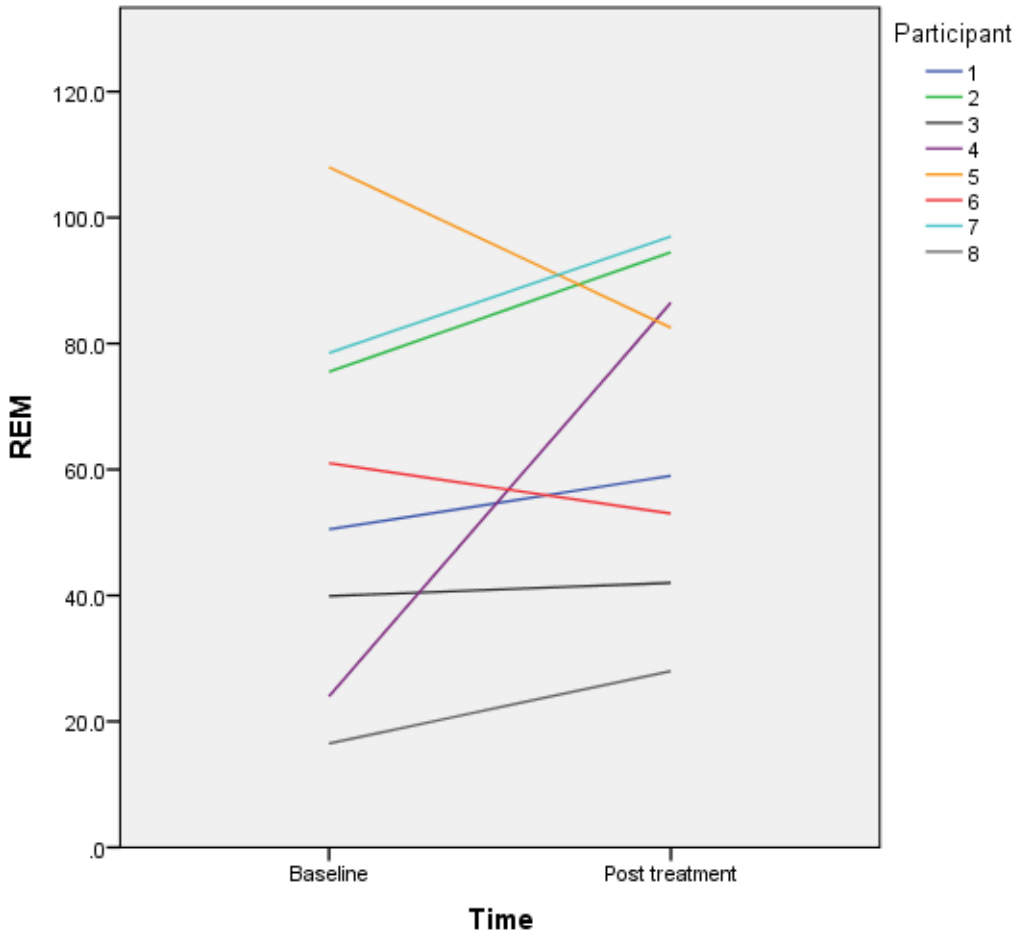

Figure 9: Displays rapid eye movement sleep (REM) in minutes from polysomnography for each participant (Participant 1-8) throughout the weeks of the study (baseline to week 6).

Figure 10: Stage 1 sleep

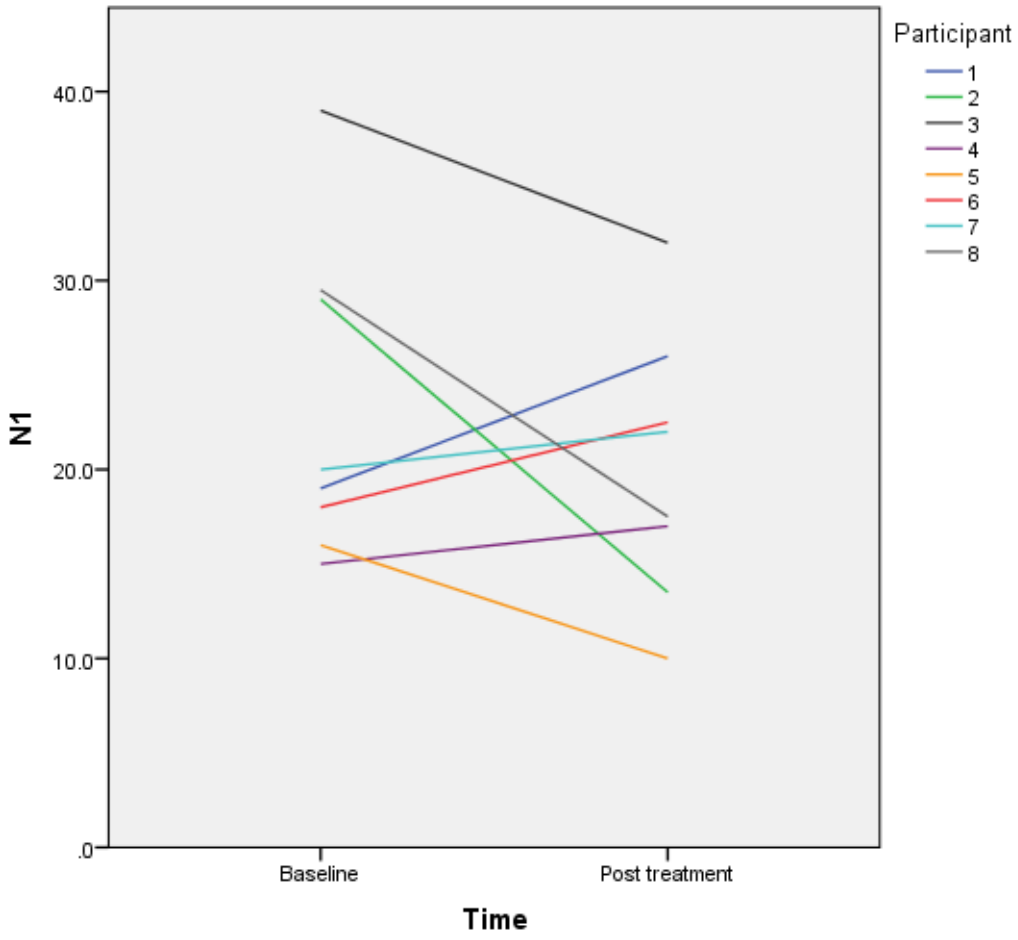

Figure 10: Displays Stage 1 sleep (N1) in minutes from polysomnography for each participant (Participant 1-8) throughout the weeks of the study (baseline to week 6).

Figure 11: Stage 2 sleep

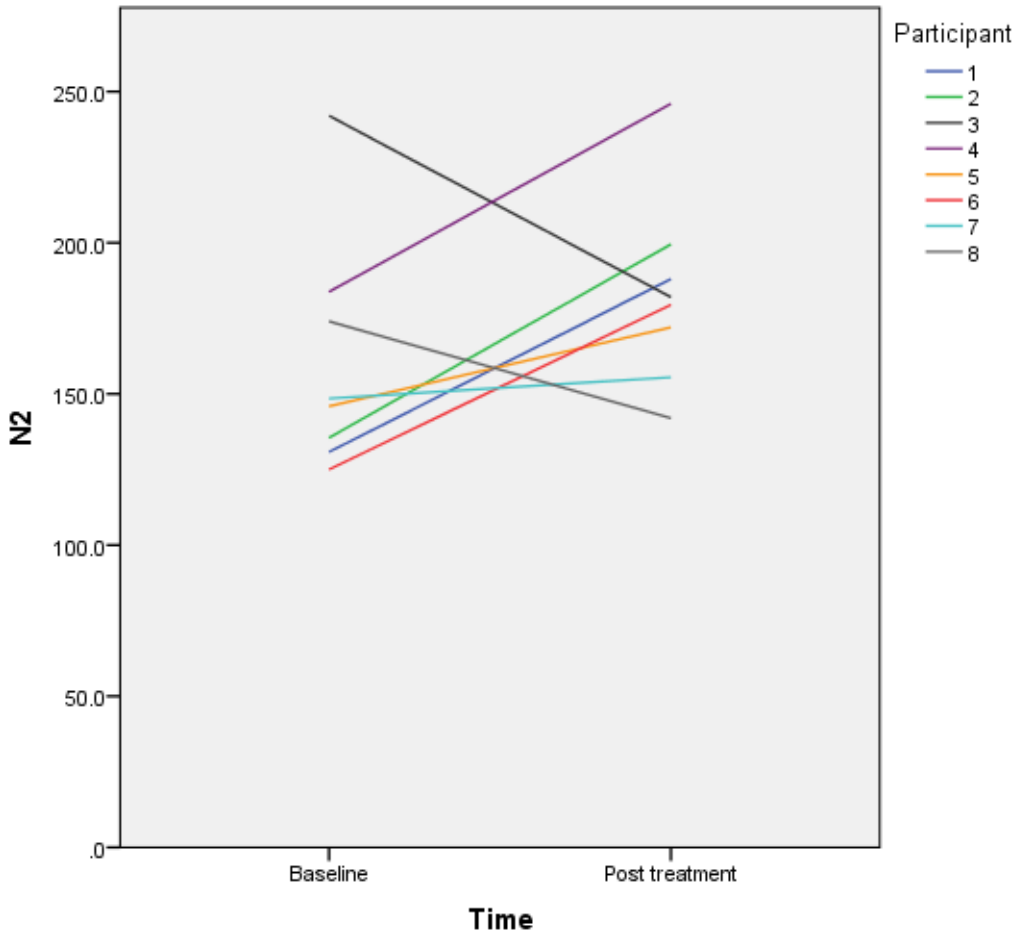

Figure 11: Displays Stage 2 sleep (N2) in minutes from polysomnography for each participant (Participant 1-8) throughout the weeks of the study (baseline to week 6).

Figure 12: Slow wave sleep

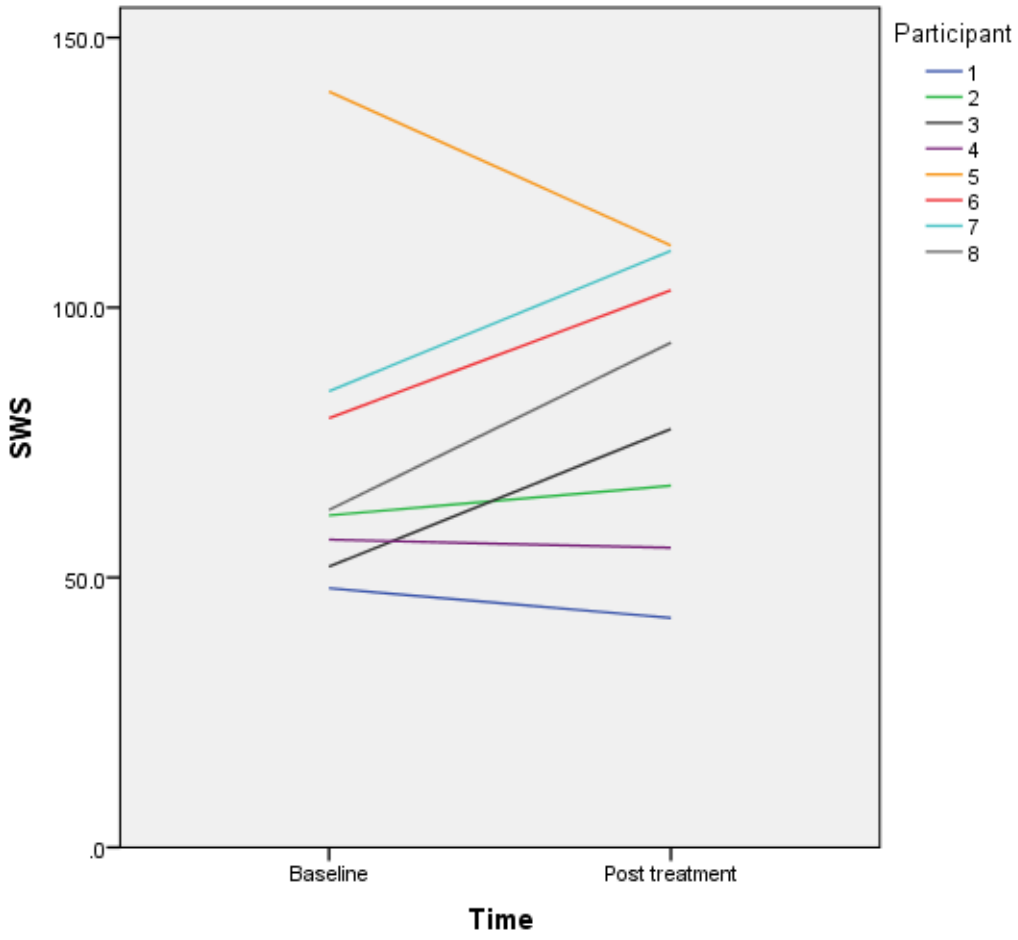

Figure 12: Displays slow wave sleep (SWS) in minutes from polysomnography for each participant (Participant 1-8) throughout the weeks of the study (baseline to week 6).

Figure 13: Cortisol concentrations before therapy

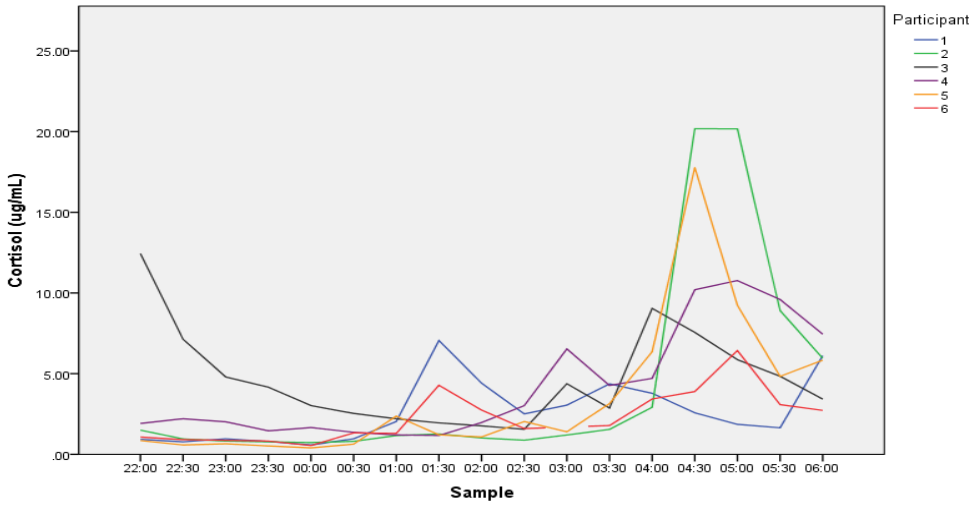

Figure 13: Displays nocturnal cortisol secretion (*n*=6) for each sample collection time point at baseline over the course the night (22:00-06:00). Cortisol (µg/dL).

Figure 14: Cortisol concentrations after therapy

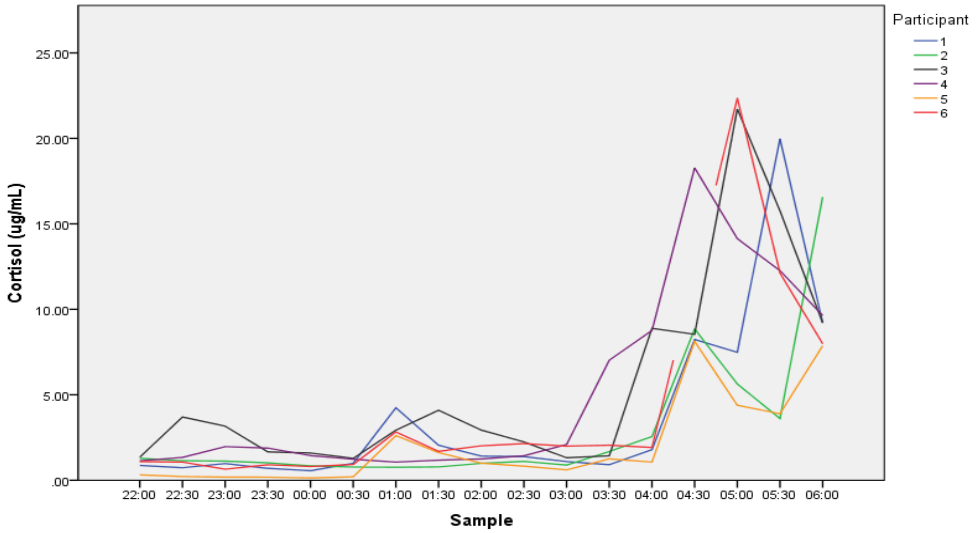

Figure 14: Displays nocturnal cortisol secretion (*n*=6) for each sample collection time point at post treatment over the course the night (22:00-06:00). Cortisol (µg/dL).

Figure 15: Baseline core body temperature data

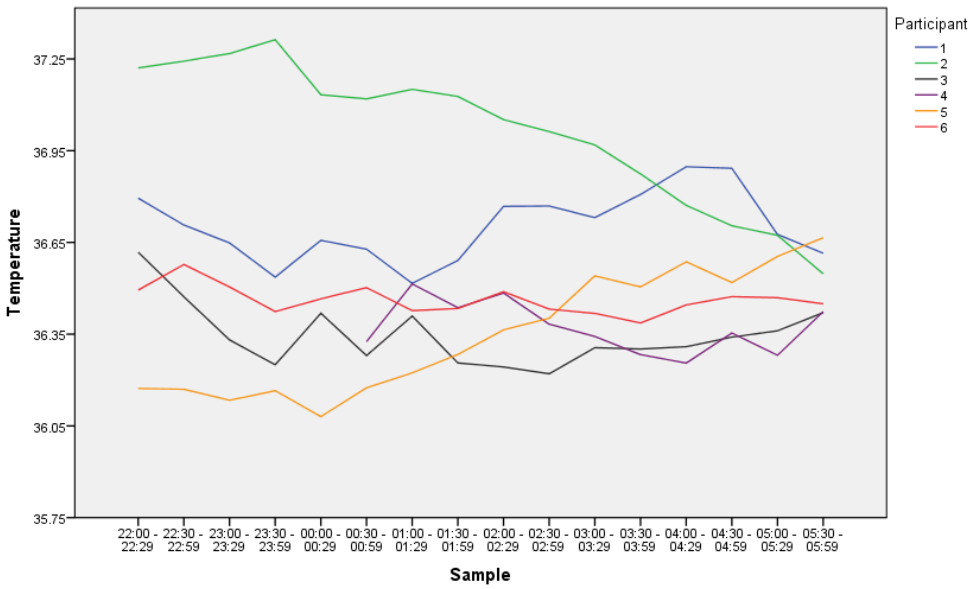

Figure 15: Displays nocturnal core body temperature data (*n*=6) for each sample collection time point at baseline over the course the night (22:00-06:00). Temperature (°C).

Figure 16: Post treatment core body temperature data

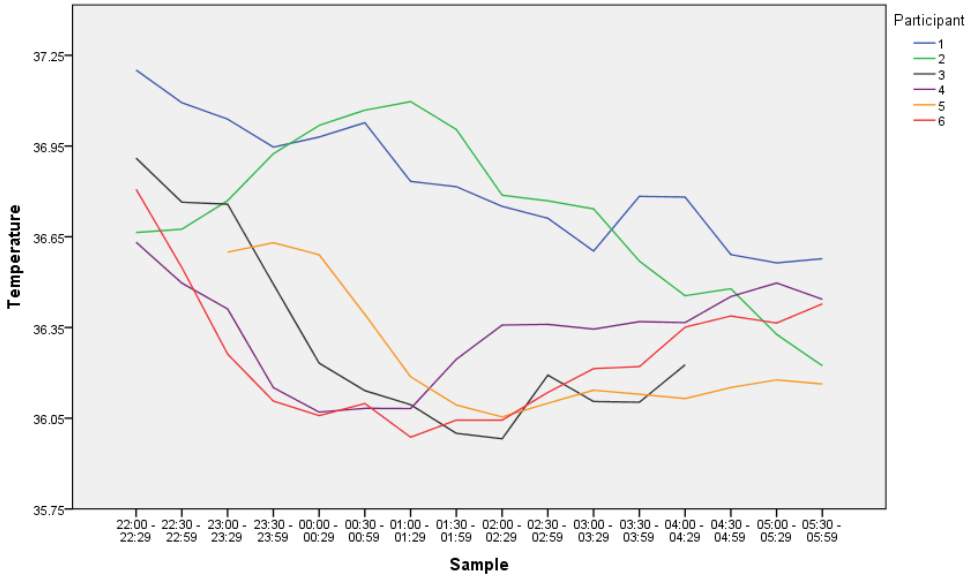

Figure 16: Displays nocturnal core body temperature data (*n*=6) for each sample collection time point at baseline over the course the night (22:00-06:00). Temperature (°C).

Appendix H: Ethical approval for Chapter 7

ADDRESS FOR ALL CORRESPONDENCE
RESEARCH DEVELOPMENT OFFICE
ROYAL PRINCE ALFRED HOSPITAL
CAMPERDOWN NSW 2050

TELEPHONE: (02) 9515 6766
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EMAIL: lesley.townsend@email.cs.nsw.gov.au
REFERENCE: X11-0391 & HREC/11/RPAH/638

NSW GOVERNMENT Health
Sydney
Local Health District

20 January 2012

Professor R Grunstein
Woolcock Institute of Medical Research
PO Box M77
CAMPERDOWN NSW 2050

Dear Professor Grunstein,

Re: Protocol No X11-0391 & HREC/11/RPAH/638 - "An MRS study of the brain in insomnia disorder"

The Executive of the Ethics Review Committee, at its meeting of 18 January 2012, considered your correspondence of 11 January 2012. In accordance with the decision made by the Ethics Review Committee, at its meeting of 14 December 2011, approval is granted to proceed.

The proposal meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

This approval includes the following:

- Testing Protocol (Version 2, 11 January 2012)
- Information for Participants (Version 2, 16 January 2012)
- Participant Consent Form (Version 2, 16 January 2012)
- Recruitment Flyer ((Version 2, 11 January 2012)

General Correspondence
PO Box M30
Missenden Road, NSW, 2050
Email: slhn.esu@sswahs.nsw.gov.au
Website: www.health.nsw.gov.au/sydlhn/

Sydney Local Health District
ABN 17 520 269 052
Level 11 North, King George V Building
83 Missenden Rd
CAMPERDOWN, NSW, 2050
Tel 612 9515 9600 Fax 612 9515 9610

- Fatigue Scale ((Version 2, 11 January 2012)
- ISI: The Insomnia Severity Index ((Version 2, 11 January 2012)
- Ford Insomnia Response to Stress Test (FIRST) (Version 2, 11 January 2012)
- Assessment of menstrual cycle characteristics ((Version 2, 11 January 2012)
- DASS21 (Version 2, 11 January 2012)
- Epworth Sleepiness Scale (ESS) (Version 2, 11 January 2012)
- Sleep Diary (Version 2, 11 January 2012)
- Dysfunctional Beliefs and Attitudes about Sleep (14 January 2008)
- Sleep Arousal Scale (SAS) ((Version 2, 11 January 2012)
- The Glasgow Sleep Effort Scale ((Version 2, 11 January 2012)
- The Glasgow Content of Thoughts Inventory ((Version 2, 11 January 2012)

You are asked to note the following:

- The study is authorised to be conducted at the following site(s):
    - Woolcock Institute of Medical Research
- This approval is valid for four years, and the Committee requires that you furnish it with annual reports on the study's progress beginning in February 2013.
- You must immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.
- You must notify the HREC of proposed changes to the research protocol or conduct of the research in the specified format.
- You must notify the HREC, giving reasons, if the project is discontinued before the expected date of completion.
- You are responsible for the following:
    - arranging a Criminal Record Check and a SLHD identity pass for any researcher who is not employed by the Sydney Local Health District. You should contact the Ethics Officer on 02 9515 7899 for advice on this matter, and

- if appropriate, informing the study sponsor that this human research ethics committee (HREC) has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review and is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

- If you or any of your co-investigators are University of Sydney employees or have a conjoint appointment, you are responsible for informing the University's Risk Management Office of this approval, so that you can be appropriately indemnified.

- Where appropriate, the Committee recommends that you consult with your Medical Defence Union to ensure that you are adequately covered for the purposes of conducting this study.

Yours sincerely,

[redacted]

Lesley Townsend
Executive Officer
Ethics Review Committee (RPAH Zone)

Research Governance Officer
SLHD (RPAH Zone)

HERC\EXCOR\12-02

References:

AASM. (2005). *ICSD-2 International classification of sleep disorders: Diagnostic and coding manual* (2nd ed. ed.). Westchester, Ill.: American Academy of Sleep Medicine (AASM).

AASM. (2014). *ICSD-3 International classification of sleep disorders: Diagnostic and coding manual* (3rd ed. ed.). Darien, IL: American Academy of Sleep Medicine (AASM).

Achermann, P., Dijk, D. J., Brunner, D. P., & Borbely, A. A. (1993). A model of human sleep homeostasis based on EEG slow-wave activity: quantitative comparison of data and simulations. *Brain Res Bull, 31*(1-2), 97-113.

Agnew, H. W., Webb, Wilse B., & Williams, Robert L. (1966). The First Night Effect: An EEG Study of Sleep. *Psychophysiology, 2*(3), 263-266. doi: 10.1111/j.1469-8986.1966.tb02650.x

Akers, J., Aguiar-Ibáñez, A., Baba-Akbari Sari, A., Beynon, S., & Booth, A. (2009). *Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care*. University of York, York, UK.

Allen, R. P., Barker, P. B., Horská, A., & Earley, C. J. (2013). Thalamic glutamate/glutamine in restless legs syndrome Increased and related to disturbed sleep. *Neurology, 80*(22), 2028-2034.

Altena, E., Van Der Werf, Y. D., Sanz-Arigita, E. J., Voorn, T. A., Rombouts, S. A. R. B., Kuijer, J. P. A., & Van Someren, E. J. W. (2008). Prefrontal hypoactivation and recovery in insomnia. *Sleep, 31*(9), 1271-1276.

Altena, E., Vrenken, H., Van Der Werf, Y. D., van den Heuvel, O. A., & Van Someren, E. J. W. (2010). Reduced Orbitofrontal and Parietal Gray Matter in Chronic Insomnia: A Voxel-Based Morphometric Study. *Biological Psychiatry, 67*(2), 182-185. doi: DOI 10.1016/j.biopsych.2009.08.003

Ancoli-Israel, S., Cole, R., Alessi, C., Chambers, M., Moorcroft, W., & Pollak, C. P. (2003). The role of actigraphy in the study of sleep and circadian rhythms. *Sleep, 26*(3), 342-392.

Antic, N. A., Catcheside, P., Buchan, C., Hensley, M., Naughton, M. T., Rowland, S., . . . McEvoy, R. D. (2011). The Effect of CPAP in Normalizing Daytime Sleepiness, Quality of Life, and Neurocognitive Function in Patients with Moderate to Severe OSA. *Sleep, 34*(1), 111-119.

APA. (2000). *DSM-IV-TR–Diagnostic and statistical manual of mental disorders* (Vol. Vol. 4th ed-TR). Washington, D.C.: American Psychiatric Association.

APA. (2013). DSM-V–Diagnostic and statistical manual of mental disorders (Vol. 5th ed). Arlington, VA: American Psychiatric Publishing.

Arborelius, L., Owens, M. J., Plotsky, P. M., & Nemeroff, C. B. (1999). The role of corticotropin-releasing factor in depression and anxiety disorders. *J Endocrinol, 160*(1), 1-12.

Aserinsky, E., & Kleitman, N. (1953). Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science, 118*(3062), 273-274.

Association, American Psychological. (1995). Task Force on Promotion and Dissemination of Psychological Procedures (1995). Training in and dissemination of empirically-validated psychological treatments. Report and recommendations. *Clinical Psychologist, 48*, 3-23.

Auer, D. P, Pütz, B., Kraft, E., Lipinski, B., Schill, J., & Holsboer, F. (2000). Reduced glutamate in the anterior cingulate cortex in depression: an in vivo proton magnetic resonance spectroscopy study. *Biological psychiatry, 47*(4), 305-313.

Backhaus, J., Junghanns, K., & Hohagen, F. (2004). Sleep disturbances are correlated with decreased morning awakening salivary cortisol. *Psychoneuroendocrinology, 29*(9), 1184-1191. doi: 10.1016/j.psyneuen.2004.01.010

Baglioni, C., Battagliese, G., Feige, B., Spiegelhalder, K., Nissen, C., Voderholzer, U., . . . Riemann, D. (2011). Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord, 135*(1-3), 10-19. doi: 10.1016/j.jad.2011.01.011

Baglioni, C., Regen, W., Teghen, A., Spiegelhalder, K., Feige, B., Nissen, C., & Riemann, D. (2014). Sleep changes in the disorder of insomnia: A meta-analysis of polysomnographic studies. *Sleep Medicine Reviews*(0). doi: http://dx.doi.org/10.1016/j.smrv.2013.04.001

Balbo, M., Leproult, R., & Van Cauter, E. (2010). Impact of Sleep and Its Disturbances on Hypothalamo-Pituitary-Adrenal Axis Activity. *International Journal of Endocrinology, 2010*. doi: 10.1155/2010/759234

Bartlett, D. J., Rae, C., Thompson, C. H., Byth, K., Joffe, D. A., Enright, T., & Grunstein, R. R. (2004). Hippocampal area metabolites relate to severity and cognitive function in obstructive sleep apnea. *Sleep Medicine, 5*(6), 593-596. doi: 10.1016/j.sleep.2004.08.004

Bartlett, DJ, Marshall, NS, Williams, A, & Grunstein, RR. (2008). Sleep health New South Wales: chronic sleep restriction and daytime sleepiness. *Internal medicine journal, 38*(1), 24-31.

Bastien, Célyne H, Vallières, Annie, & Morin, Charles M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine, 2*(4), 297-307. doi: 10.1016/S1389-9457(00)00065-4

Belenky, G., Wesensten, N. J., Thorne, D. R., Thomas, M. L., Sing, H. C., Redmond, D. P., . . . Balkin, T. J. (2003). Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *J Sleep Res, 12*(1), 1-12.

Bennett, Maxwell R, & Balcar, Vladimir J. (1999). Forty years of amino acid transmission in the brain. *Neurochemistry international, 35*(4), 269-280.

Bhagwagar, Zubin, Wylezinska, Marzena, Jezzard, Peter, Evans, John, Boorman, Erie, M Matthews, Paul, & J Cowen, Philip. (2008). Low GABA concentrations in occipital cortex and anterior cingulate cortex in medication-free, recovered depressed patients. *The International Journal of Neuropsychopharmacology, 11*(02), 255-260.

Blagrove, Mark, Farmer, Laura, & Williams, Elvira. (2004). The relationship of nightmare frequency and nightmare distress to well-being. *Journal of Sleep Research, 13*(2), 129-136. doi: 10.1111/j.1365-2869.2004.00394.x

Bliwise, Donald L., Friedman, Leah, Nekich, Jamie C., & Yesavage, Jerome A. (1995). Prediction of outcome in behaviorally based insomnia treatments. *Journal of Behavior Therapy and Experimental Psychiatry, 26*(1), 17-23. doi: 10.1016/0005-7916(94)00073-u

Bonnet, M. H., & Arand, D. L. (1996). The consequences of a week of insomnia. *Sleep, 19*(6), 453-461.

Bonnet, M. H., & Arand, D. L. (1997). Hyperarousal and insomnia. *Sleep Med Rev, 1*(2), 97-108.

Bonnet, M. H., & Arand, D. L. (2010). Hyperarousal and insomnia: state of the science. *Sleep Med Rev, 14*(1), 9-15. doi: 10.1016/j.smrv.2009.05.002

Bonnet, M. H., & Webb, W. B. (1976). Effect of two experimental sets on sleep structure. *Percept Mot Skills, 42*(2), 343-350.

Bootzin, Richard R. (1973). *Stimulus control treatment for insomnia.* Paper presented at the APA 80th Annual Convention, Honolulu, HI, September 2-8, 1972.

Bora, Emre, Fornito, Alex, Pantelis, Christos, & Yücel, Murat. (2012). Gray matter abnormalities in major depressive disorder: a meta-analysis of voxel based morphometry studies. *Journal of affective disorders, 138*(1), 9-18.

Borbély, A. A. (1982). A two process model of sleep regulation. *Hum Neurobiol, 1*(3), 195-204.

Borbély, A. A., & Achermann, P. (1999). Sleep homeostasis and models of sleep regulation. *Journal of Biological Rhythms, 14*(6), 557-568.

Brooks, J. O., Friedman, L., Bliwise, D. L., & Yesavage, J. A. (1993). Use of the Wrist Actigraph to Study Insomnia in Older Adults. *Sleep, 16*(2), 151-155.

Broomfield, N. M, & Espie, C. A. (2005). Towards a valid, reliable measure of sleep effort. *Journal of sleep research, 14*(4), 401-407.

Buckley, T. M., & Schatzberg, A. F. (2005). On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis activity and circadian rhythm, exemplary sleep disorders. *J Clin Endocrinol Metab, 90*(5), 3106-3114. doi: 10.1210/jc.2004-1056

Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Lichstein, K. L., & Morin, C. M. (2006). Recommendations for a standard research assessment of insomnia. *Sleep, 29*(9), 1155-1173.

Buysse, D. J., Germain, A., Hall, M., Monk, T. H., & Nofzinger, E. A. (2011). A Neurobiological Model of Insomnia. *Drug Discov Today Dis Models, 8*(4), 129-137. doi: 10.1016/j.ddmod.2011.07.002

Buysse, D. J., Germain, A., Moul, D. E., Franzen, P. L., Brar, L. K., Fletcher, M. E., . . . Monk, T. H. (2011). Efficacy of Brief Behavioral Treatment for Chronic Insomnia in Older Adults. *Archives of Internal Medicine, 171*(10), 887-895.

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index - a New Instrument for Psychiatric Practice and Research. *Psychiatry Research, 28*(2), 193-213. doi: 10.1016/0165-1781(89)90047-4

Buysse, D. J., Thompson, W., Scott, J., Franzen, P. L., Germain, A., Hall, M., . . . Kupfer, D. J. (2007). Daytime symptoms in primary insomnia: A prospective analysis using ecological momentary assessment. *Sleep Medicine, 8*(3), 198-208. doi: 10.1016/j.sleep.2006.10.006

Campbell, Scott S, & Broughton, Roger J. (1994). Rapid decline in body temperature before sleep: fluffing the physiological pillow? *Chronobiology international, 11*(2), 126-131.

Cano, G., Mochizuki, T., & Saper, C. B. (2008). Neural circuitry of stress-induced insomnia in rats. *J Neurosci, 28*(40), 10167-10184. doi: 10.1523/JNEUROSCI.1809-08.2008

Carney, C. E., Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Krystal, A. D., Lichstein, K. L., & Morin, C. M. (2012). The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep, 35*(2), 287-302. doi: 10.5665/sleep.1642

Carskadon, Mary A., & Dement, William C. (2011). *Chapter 2 - Normal Human Sleep: An Overview* M. H. Kryger, T. Roth & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine (Fifth Edition)* (pp. 16-26). doi:10.1016/B978-1-4160-6645-3.00002-5

Castillo, Mauricio, Kwock, Lester, & Mukherji, Suresh K. (1996). Clinical applications of proton MR spectroscopy. *American journal of neuroradiology, 17*, 1-16.

Castillo, Mauricio, Kwock, Lester, Scatliff, James, & Mukherji, Suresh K. (1998). Proton MR spectroscopy in neoplastic and non-neoplastic brain disorders. *Magnetic resonance imaging clinics of North America, 6*(1), 1-20.

Cervena, K., Dauvilliers, Y., Espa, F., Touchon, J., Matousek, M., Billiard, M., & Besset, A. (2004). Effect of cognitive behavioural therapy for insomnia on sleep architecture and sleep EEG power spectra in psychophysiological insomnia. *Journal of sleep research, 13*(4), 385-393.

Chang, F. C., & Opp, M. R. (2001). Corticotropin-releasing hormone (CRH) as a regulator of waking. *Neurosci Biobehav Rev, 25*(5), 445-453.

Chen, Wei, Zhu, Xiao-Hong, Adriany, Gregor, & Uğurbil, Kămil. (1997). Increase of creatine kinase activity in the visual cortex of human brain during visual stimulation: a 31P NMR magnetization transfer study. *Magnetic resonance in medicine, 38*(4), 551-557.

Chesson Jr, Andrew L, Anderson, WM, Littner, Michael, Davila, David, Hartse, Kristyna, Johnson, Stephen, . . . Rafecas, Jose. (1999). Practice parameters for the nonpharmacologic treatment

of chronic insomnia. An American Academy of Sleep Medicine report. Standards of Practice Committee of the American Academy of Sleep Medicine. *Sleep, 22*(8), 1128-1133.
Choi, Dennis W. (1988). Glutamate neurotoxicity and diseases of the nervous system. *Neuron, 1*(8), 623-634.
Clow, A., Thorn, L., Evans, P., & Hucklebridge, F. (2004). The awakening cortisol response: Methodological issues and significance. *Stress-the International Journal on the Biology of Stress, 7*(1), 29-37. doi: Doi 10.1080/10253890410001667205
Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*: Lawrence Erlbaum.
Colrain, I. M. (2011). Sleep and the Brain. *Neuropsychology Review, 21*(1), 1-4. doi: DOI 10.1007/s11065-011-9156-z
Conroy, Deirdre A, Spielman, Arthur J, & Scott, Rebecca Q. (2005). Daily rhythm of cerebral blood flow velocity. *Journal of circadian rhythms, 3*(3), 32-37.
Czeisler, Charles A, Duffy, Jeanne F, Shanahan, Theresa L, Brown, Emery N, Mitchell, Jude F, Rimmer, David W, . . . Emens, Jonathan S. (1999). Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science, 284*(5423), 2177-2181. doi: 10.1126/science.284.5423.2177
Daley, M., Morin, C. M., LeBlanc, M., Gregoire, J. P., & Savard, J. (2009). The Economic Burden of Insomnia: Direct and Indirect Costs for Individuals with Insomnia Syndrome, Insomnia Symptoms, and Good Sleepers. *Sleep, 32*(1), 55-64.
Daley, M., Morin, C. M., LeBlanc, M., Gregoire, J. P., Savard, J., & Baillargeon, L. (2009). Insomnia and its relationship to health-care utilization, work absenteeism, productivity and accidents. *Sleep Medicine, 10*(4), 427-438. doi: DOI 10.1016/j.sleep.2008.04.005
Dalgleish, T., & Watts, F. N. (1990). Biases of attention and memory in disorders of anxiety and depression. *Clinical Psychology Review, 10*(5), 589-604.
Dement, William, & Kleitman, Nathaniel. (1957). Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. *Electroencephalography and Clinical Neurophysiology, 9*(4), 673-690. doi: 10.1016/0013-4694(57)90088-3
Dibner, Charna, Schibler, Ueli, & Albrecht, Urs. (2010). The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annual review of physiology, 72*, 517-549. doi: 10.1146/annurev-physiol-021909-135821
Diekelmann, Susanne, & Born, Jan. (2010). The memory function of sleep. *Nature Reviews Neuroscience, 11*(2), 114-126. doi: 10.1038/nrn2762
Dinges, D. F., Pack, F., Williams, K., Gillen, K. A., Powell, J. W., Ott, G. E., . . . Pack, A. I. (1997). Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep, 20*(4), 267-277.
Dringen, Ralf, Gutterer, Jan M, & Hirrlinger, Johannes. (2000). Glutathione metabolism in brain. *European Journal of Biochemistry, 267*(16), 4912-4916.
Dunlap, William P, Cortina, Jose M, Vaslow, Joel B, & Burke, Michael J. (1996). Meta-analysis of experiments with matched groups or repeated measures designs. *Psychological Methods, 1*(2), 170.
Eddy, D. M. (1992). *A manual for assessing health practices & designing practice policies: the explicit approach*: American College of Physicians Philadelphia.
Edinger, J. D., Bonnet, M. H., Bootzin, R. R., Doghramji, K., Dorsey, C. M., Espie, C. A., . . . American Academy of Sleep Medicine Work, Group. (2004). Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. *Sleep, 27*(8), 1567-1596.

Edinger, J. D., & Means, M. K. (2005). Cognitive-behavioral therapy for primary insomnia. *Clin Psychol Rev, 25*(5), 539-558. doi: 10.1016/j.cpr.2005.04.003

Edinger, J. D., Wohlgemuth, W. K., Krystal, A. D., & Rice, J. R. (2005). Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial. *Archives of internal medicine, 165*(21), 2527-2535. doi: 10.1001/archinte.165.21.2527

Edinger, Jack D, Wohlgemuth, William K, Radtke, Rodney A, Marsh, Gail R, & Quillian, Ruth E. (2001). Cognitive behavioral therapy for treatment of chronic primary insomnia. *JAMA: the journal of the American Medical Association, 285*(14), 1856-1864.

Ekstedt, M., Akerstedt, T., & Soderstrom, M. (2004). Microarousals during sleep are associated with increased levels of lipids, cortisol, and blood pressure. *Psychosom Med, 66*(6), 925-931. doi: 10.1097/01.psy.0000145821.25453.f7

Elder, Greg J., Wetherell, Mark A., Barclay, Nicola L., & Ellis, Jason G. (2014). The cortisol awakening response – Applications and implications for sleep medicine. *Sleep Medicine Reviews, 18*(3), 195-204. doi: http://dx.doi.org/10.1016/j.smrv.2013.05.001

Eller, N. H., Netterstrom, B., & Hansen, A. M. (2006). Psychosocial factors at home and at work and levels of salivary cortisol. *Biological Psychology, 73*(3), 280-287. doi: DOI 10.1016/j.biopsycho.2006.05.003

Ellis, J. G., Perlis, M. L., Bastien, C. H., Gardani, M., & Espie, C. A. (2014). The natural history of insomnia: acute insomnia and first-onset depression. *Sleep, 37*(1), 97-106. doi: 10.5665/sleep.3316

Epstein, D. R., Sidani, S., Bootzin, R. R., & Belyea, M. J. (2012). Dismantling multicomponent behavioral treatment for insomnia in older adults: a randomized controlled trial. *Sleep, 35*(6), 797-805. doi: 10.5665/sleep.1878

Espie, C. A. (2002). Insomnia: conceptual issues in the development, persistence, and treatment of sleep disorder in adults. *Annu Rev Psychol, 53*, 215-243. doi: 10.1146/annurev.psych.53.100901.135243

Espie, C. A. (2007). Understanding insomnia through cognitive modelling. *Sleep Med, 8 Suppl 4*, S3-8. doi: 10.1016/S1389-9457(08)70002-9

Espie, C. A. (2009). "Stepped care": a health technology solution for delivering cognitive behavioral therapy as a first line insomnia treatment. *Sleep, 32*(12), 1549-1558.

Espie, C. A., Broomfield, N. M., MacMahon, K. M., Macphee, L. M., & Taylor, L. M. (2006). The attention-intention-effort pathway in the development of psychophysiologic insomnia: a theoretical review. *Sleep Med Rev, 10*(4), 215-245. doi: 10.1016/j.smrv.2006.03.002

Espie, C. A., Hames, P., & McKinstry, B. (2013). Use of the Internet and Mobile Media for Delivery of Cognitive Behavioral Insomnia Therapy. *Sleep Medicine Clinics, 8*(3), 407-419. doi: http://dx.doi.org/10.1016/j.jsmc.2013.06.001

Espie, C. A., Kyle, S. D., Hames, P., Cyhlarova, E., & Benzeval, M. (2012). The daytime impact of DSM-5 insomnia disorder: comparative analysis of insomnia subtypes from the Great British Sleep Survey. *J Clin Psychiatry, 73*(12), e1478-1484. doi: 10.4088/JCP.12m07954

Espie, C. A., Kyle, S. D., Williams, C., Ong, J. C., Douglas, N. J., Hames, P., & Brown, J. S. L. (2012). A Randomized, Placebo-Controlled Trial of Online Cognitive Behavioral Therapy for Chronic Insomnia Disorder Delivered via an Automated Media-Rich Web Application. *Sleep, 35*(6), 769-781. doi: Doi 10.5665/Sleep.1872

Evans, Christopher John, McGonigle, David John, & Edden, Richard Anthony Edward. (2010). Diurnal stability of γ-aminobutyric acid concentration in visual and sensorimotor cortex. *Journal of Magnetic Resonance Imaging, 31*(1), 204-209.

Fernando III, Antonio, Arroll, Bruce, & Falloon, Karen. (2013). A double-blind randomised controlled study of a brief intervention of bedtime restriction for adult patients with primary insomnia. *On the basis of their personhood, patient s and clinicians are moral equals.*, 5.

Follenius, M., Brandenberger, G., Bandesapt, J. J., Libert, J. P., & Ehrhart, J. (1992). Nocturnal Cortisol Release in Relation to Sleep Structure. *Sleep, 15*(1), 21-27.

Fonnum, Frode. (1984). Glutamate: a neurotransmitter in mammalian brain. *Journal of neurochemistry, 42*(1), 1-11.

Foulkes, William David. (1962). Dream reports from different stages of sleep. *The Journal of Abnormal and Social Psychology, 65*(1), 14. doi: 10.1037/h0040431

Friedman, L., Benson, K., Noda, A., Zarcone, V., Wicks, D. A., O'Connell, K., . . . Yesavage, J. A. (2000). An actigraphic comparison of sleep restriction and sleep hygiene treatments for insomnia in older adults. *Journal of Geriatric Psychiatry and Neurology, 13*(1), 17-27.

Friedman, L., Bliwise, D.L., Yesavage, J.A., & Salom, S.R. (1991). A preliminary study comparing sleep restriction and relaxation treatments for insomnia in older adults. *Journal of gerontology, 46*(1), P1-P8.

Garbarino, S., De Carli, F., Nobili, L., Mascialino, B., Squarcia, S., Peneo, M. A., . . . Ferrillo, F. (2002). Sleepiness and sleep disorders in shift workers: A study on a group of Italian police officers. *Sleep, 25*(6), 648-653.

Germain, A, Moul, DE, Franzen, PL, Miewald, JM, Reynolds 3rd, CF, Monk, TH, & Buysse, DJ. (2006). Effects of a brief behavioral treatment for late-life insomnia: preliminary findings. *J Clin Sleep Med, 2*(4), 403-406.

Gonnissen, Hanne KJ, Rutters, Femke, Mazuy, Claire, Martens, Eveline AP, Adam, Tanja C, & Westerterp-Plantenga, Margriet S. (2012). Effect of a phase advance and phase delay of the 24-h cycle on energy metabolism, appetite, and related hormones. *The American journal of clinical nutrition, 96*(4), 689-697.

Gottesmann, Claude. (2002). GABA mechanisms and sleep. *Neuroscience, 111*(2), 231-239.

Govindaraju, Varanavasi, Young, Karl, & Maudsley, Andrew A. (2000). Proton NMR chemical shifts and coupling constants for brain metabolites. *NMR in Biomedicine, 13*(3), 129-153. doi: 10.1002/1099-1492(200005)13:3<129::AID-NBM619>3.0.CO;2-V

Gradisar, M., Lack, L., Wright, H., Harris, J., & Brooks, A. (2006). Do chronic primary insomniacs have impaired heat loss when attempting sleep? *Am J Physiol Regul Integr Comp Physiol, 290*(4), R1115-1121. doi: 10.1152/ajpregu.00266.2005

Guyon, A., Balbo, M., Morselli, L. L., Tasali, E., Leproult, R., L'Hermite-Balériaux, M., . . . Spiegel, K. (in press). Adverse effects of two nights of sleep restriction on the hypothalamic-pituitary-adrenal axis in healthy men. *The Journal of Clinical Endocrinology & Metabolism, 0*(0), jc.2013-4254. doi: doi:10.1210/jc.2013-4254

Han, Jilin, Cheng, Fu-Chou, Yang, Zhaoliang, & Dryhurst, Glenn. (1999). Inhibitors of Mitochondrial Respiration, Iron (II), and Hydroxyl Radical Evoke Release and Extracellular Hydrolysis of Glutathione in Rat Striatum and Substantia Nigra. *Journal of neurochemistry, 73*(4), 1683-1695.

Harper, David G, Plante, David T, Jensen, J Eric, Ravichandran, Caitlin, Buxton, Orfeu M, Benson, Kathleen L, . . . Winkelman, John W. (2013). Energetic and cell membrane metabolic products in patients with primary insomnia: a 31-phosphorus magnetic resonance spectroscopy study at 4 Tesla. *Sleep, 36*(4), 493.

Harris, Jodie, Lack, Leon, Kemp, Kristyn, Wright, Helen, & Bootzin, Richard. (2012). A Randomized Controlled Trial of Intensive Sleep Retraining (ISR): A Brief Conditioning Treatment for Chronic Insomnia. *Sleep, 35*(1), 49-60.

Harvey, A. G. (2001). I Can't Sleep, My Mind Is Racing! An Investigation of Strategies of Thought Control in Insomnia. *Behavioural and Cognitive Psychotherapy, 29*(1), 3-11. doi: Doi 10.1017/S1352465801001023

Harvey, A. G. (2002). A cognitive model of insomnia. *Behaviour research and therapy, 40*(8), 869-893.

Harvey, Allison G, & Tang, NK. (2003). Cognitive behaviour therapy for primary insomnia: can we rest yet? *Sleep medicine reviews, 7*(3), 237.

Harvey, Christopher-James, Gehrman, Phil, & Espie, Colin A. (2014). Who is predisposed to insomnia: A review of familial aggregation, stress-reactivity, personality and coping style. *Sleep Medicine Reviews, 18*(3), 217-227. doi: http://dx.doi.org/10.1016/j.smrv.2013.11.004

Harvey, Linda, Inglis, Stephanie J, & Espie, Colin A. (2002). Insomniacs' reported use of CBT components and relationship to long-term clinical outcome. *Behaviour research and therapy, 40*(1), 75-83.

Hasler, Gregor, van der Veen, Jan Willem, Tumonis, Toni, Meyers, Noah, Shen, Jun, & Drevets, Wayne C. (2007). Reduced prefrontal glutamate/glutamine and γ-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. *Archives of General Psychiatry, 64*(2), 193-200.

Hauri, P. J. (1983). A cluster analysis of insomnia. *Sleep, 6*(4), 326-338.

Hellhammer, D. H., Wust, S., & Kudielka, B. M. (2009). Salivary cortisol as a biomarker in stress research. *Psychoneuroendocrinology, 34*(2), 163-171. doi: DOI 10.1016/j.psyneuen.2008.10.026

Henry, Julie D, & Crawford, John R. (2005). The short-form version of the Depression Anxiety Stress Scales (DASS-21): Construct validity and normative data in a large non-clinical sample. *British Journal of Clinical Psychology, 44*(2), 227-239.

Hiller-Sturmhofel, S., & Bartke, A. (1998). The endocrine system: an overview. *Alcohol Health Res World, 22*(3), 153-164.

Hirshkowitz, Max. (2004). Normal human sleep: an overview. *Medical Clinics of North America, 88*(3), 551-565. doi: 10.1016/j.mcna.2004.01.001

Hoaglin, David C, & Iglewicz, Boris. (1987). Fine-tuning some resistant rules for outlier labeling. *Journal of the American Statistical Association, 82*(400), 1147-1149.

Hoch, C. C., Reynolds, C. F., 3rd, Buysse, D. J., Monk, T. H., Nowell, P., Begley, A. E., . . . Dew, M. A. (2001). Protecting sleep quality in later life: a pilot study of bed restriction and sleep hygiene. *The journals of gerontology. Series B, Psychological sciences and social sciences, 56*(1), P52-59.

Hoelscher, Timothy J., & Edinger, Jack D. (1988). Treatment of Sleep-Maintenance Insomnia in Older Adults: Sleep Period Reduction, Sleep Education, and Modified Stimulus Control. *Psychology and Aging, 3*(3), 258-263.

Hueston, C. M., & Deak, T. (2014). The inflamed axis: the interaction between stress, hormones, and the expression of inflammatory-related genes within key structures comprising the hypothalamic-pituitary-adrenal axis. *Physiol Behav, 124*, 77-91. doi: 10.1016/j.physbeh.2013.10.035

Iber, C., Ancoli-Israel, S., Chesson, A., Quan SF. (2007). The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specification. For the American Academy of Sleep Medicine 1st ed. .

Ioannides, Andreas A, Kostopoulos, George K, Liu, Lichan, & Fenwick, Peter BC. (2009). MEG identifies dorsal medial brain activations during sleep. *Neuroimage, 44*(2), 455-468.

Irwin, M. R., Cole, J. C., & Nicassio, P. M. (2006). Comparative meta-analysis of behavioral interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+ years of age. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association, 25*(1), 3-14. doi: 10.1037/0278-6133.25.1.3

Irwin, M. R., Olmstead, R., Carrillo, C., Sadeghi, N., Breen, E. C., Witarama, T., . . . Nicassio, P. (in press). Cognitive Behavioral Therapy vs. Tai Chi for Late Life Insomnia and Inflammatory Risk: A Randomized Controlled Comparative Efficacy Trial *SLEEP*.

Jasper, H. H. (1958). The ten twenty electrode system of the international federation. *Electroencephalography and Clinical Neurophysiology, 10*, 371-375.

Johns, M. W. (1992). Reliability and Factor-Analysis of the Epworth Sleepiness Scale. *Sleep, 15*(4), 376-381.

Joo, Eun Yeon, Noh, Hyun Jin, Kim, Jeong-Sik, Koo, Dae Lim, Kim, Daeyoung, Hwang, Kyoung Jin, . . . Hong, Seung Bong. (2013). Brain gray matter deficits in patients with chronic primary insomnia. *Sleep, 36*(7), 999.

Kales, A., Caldwell, A. B., Soldatos, C. R., Bixler, E. O., & Kales, J. D. (1983). Biopsychobehavioral correlates of insomnia. II. Pattern specificity and consistency with the Minnesota Multiphasic Personality Inventory. *Psychosom Med, 45*(4), 341-356.

Kalivas, Peter W. (2009). The glutamate homeostasis hypothesis of addiction. *Nature Reviews Neuroscience, 10*(8), 561-572.

Kalueff, Allan V, & Nutt, David J. (2007). Role of GABA in anxiety and depression. *Depression and anxiety, 24*(7), 495-517.

Kamba, M., Inoue, Y., Higami, S., Suto, Y., Ogawa, T., & Chen, W. (2001). Cerebral metabolic impairment in patients with obstructive sleep apnoea: an independent association of obstructive sleep apnoea with white matter change. *Journal of Neurology Neurosurgery and Psychiatry, 71*(3), 334-339. doi: 10.1136/jnnp.71.3.334

Kaplan, Katherine A, & Harvey, Allison G. (2013). Behavioral Treatment of Insomnia in Bipolar Disorder. *American Journal of Psychiatry, 170*(7), 716-720.

Kirschbaum, C., & Hellhammer, D. H. (1994). Salivary Cortisol in Psychoneuroendocrine Research - Recent Developments and Applications. *Psychoneuroendocrinology, 19*(4), 313-333. doi: Doi 10.1016/0306-4530(94)90013-2

Kivlighan, K. T., Granger, D. A., Schwartz, E. B., Nelson, V., Curran, M., & Shirtcliff, E. A. (2004). Quantifying blood leakage into the oral mucosa and its effects on the measurement of cortisol, dehydroepiandrosterone, and testosterone in saliva. *Hormones and Behavior, 46*(1), 39-46. doi: DOI 10.1016/j.yhbeh.2004.01.006

Kmet, L. M., Lee, R. C., & S., Cook L. (2004). Standard quality assessment criteria for evaluating primary research papers from a variety of fields.

Koenigs, Michael, Holliday, Jessica, Solomon, Jeffrey, & Grafman, Jordan. (2010). Left dorsomedial frontal brain damage is associated with insomnia. *The Journal of Neuroscience, 30*(47), 16041-16043.

Koga, Minori, Serritella, Anthony V, Messmer, Marcus M, Hayashi-Takagi, Akiko, Hester, Lynda D, Snyder, Solomon H, . . . Sedlak, Thomas W. (2011). Glutathione is a physiologic reservoir of neuronal glutamate. *Biochemical and biophysical research communications, 409*(4), 596-602.

Koolschijn, PCMP, van Haren, Neeltje EM, Lensvelt-Mulders, Gerty JLM, Pol, Hulshoff, Hilleke, E, & Kahn, René S. (2009). Brain volume abnormalities in major depressive disorder: A

meta-analysis of magnetic resonance imaging studies. *Human brain mapping, 30*(11), 3719-3735.

Kräuchi, Kurt. (2007). The thermophysiological cascade leading to sleep initiation in relation to phase of entrainment. *Sleep medicine reviews, 11*(6), 439-451.

Kravitz, R. L., Hays, R. D., Sherbourne, C. D., DiMatteo, M. R., Rogers, W. H., Ordway, L., & Greenfield, S. (1993). Recall of recommendations and adherence to advice among patients with chronic medical conditions. *Arch Intern Med, 153*(16), 1869-1878.

Krieger, D. T., & Glick, S. M. (1974). Sleep EEG stages and plasma growth hormone concentration in states of endogenous and exogenous hypercortisolemia or ACTH elevation. *J Clin Endocrinol Metab, 39*(6), 986-1000. doi: 10.1210/jcem-39-6-986

Kripke, D. F., Mullaney, D. J., Messin, S., & Wyborney, V. G. (1978). Wrist actigraphic measures of sleep and rhythms. *Electroencephalography and Clinical Neurophysiology, 44*(5), 674-676. doi: 10.1016/0013-4694(78)90133-5

Krystal, A. D. (2007). Treating the health, quality of life, and functional impairments in insomnia. *J Clin Sleep Med, 3*(1), 63-72.

Krystal, Andrew D, & Edinger, Jack D. (2010). Sleep EEG predictors and correlates of the response to cognitive behavioral therapy for insomnia. *Sleep, 33*(5), 669.

Kunz-Ebrecht, S. R., Kirschbaum, C., Marmot, M., & Steptoe, A. (2004). Differences in cortisol awakening response on work days and weekends in women and men from the Whitehall II cohort. *Psychoneuroendocrinology, 29*(4), 516-528. doi: Doi 10.1016/S0306-4530(03)00072-6

Kushida, C. A., Littner, M. R., Morgenthaler, T., Alessi, C. A., Bailey, D., Coleman, J., . . . Wise, M. (2005). Practice parameters for the indications for polysomnography and related procedures: An update for 2005. *Sleep, 28*(4), 499-521.

Kushida, Clete A., Chang, Arthur, Gadkary, Chirag, Guilleminault, Christian, Carrillo, Oscar, & Dement, William C. (2001). Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. *Sleep Medicine, 2*(5), 389-396. doi: 10.1016/S1389-9457(00)00098-8

Kyle, S. D., Crawford, M. R., Morgan, K., Spiegelhalder, K., Clark, A. A., & Espie, C. A. (2013). The Glasgow Sleep Impact Index (GSII): a novel patient-centred measure for assessing sleep-related quality of life impairment in Insomnia Disorder. *Sleep Medicine, 14*(6), 493-501. doi: 10.1016/j.sleep.2012.10.023

Kyle, S. D., Espie, C. A., & Morgan, K. (2010). "...Not just a minor thing, it is something major, which stops you from functioning daily": quality of life and daytime functioning in insomnia. *Behavioral sleep medicine, 8*(3), 123-140. doi: 10.1080/15402002.2010.487450

Kyle, S. D., Miller, C. B., Roger, Z., Siriwardena, M., Mac Mahon, K. M., & Espie, C. A. (2014). Sleep restriction therapy for insomnia is associated with reduced objective total sleep time, increased daytime somnolence, and objectively-impaired vigilance: implications for the clinical management of insomnia disorder. *Sleep, 37*(2), 229-237. doi: 10.5665/sleep.3386

Kyle, Simon D., Morgan, Kevin, Spiegelhalder, Kai, & Espie, Colin A. (2011). No pain, no gain: an exploratory within-subjects mixed-methods evaluation of the patient experience of sleep restriction therapy (SRT) for insomnia. *Sleep Medicine, 12*(8), 735-747.

Lack, L. C., Gradisar, M., Van Someren, E. J. W., Wright, H. R., & Lushington, K. (2008). The relationship between insomnia and body temperatures. *Sleep Medicine Reviews, 12*(4), 307-317. doi: DOI 10.1016/j.smrv.2008.02.003

Lack, L. C., & Wright, H. R. (2007). Treating chronobiological components of chronic insomnia. *Sleep Medicine, 8*(6), 637-644. doi: http://dx.doi.org/10.1016/j.sleep.2006.10.003
Lack, L., & Wright, H. (1993). The effect of evening bright light in delaying the circadian rhythms and lengthening the sleep of early morning awakening insomniacs. *Sleep, 16*(5), 436-443.
Lakhan, Shaheen E, Vieira, Karen, & Hamlat, Elissa. (2010). Biomarkers in psychiatry: drawbacks and potential for misuse. *Int Arch Med, 3*(1).
Landis, J Richard, & Koch, Gary G. (1977). The measurement of observer agreement for categorical data. *biometrics*, 159-174.
Leger, D., & Bayon, V. (2010). Societal costs of insomnia. *Sleep Med Rev, 14*(6), 379-389. doi: 10.1016/j.smrv.2010.01.003
Lehnert, H., Schulz, C., & Dieterich, K. (1998). Physiological and neurochemical aspects of corticotropin-releasing factor actions in the brain: The role of the locus coeruleus. *Neurochemical Research, 23*(8), 1039-1052. doi: Doi 10.1023/A:1020751817723
Leslie, E. M, Deeley, R. G, & Cole, S. P.C. (2001). Toxicological relevance of the multidrug resistance protein 1, MRP1 (ABCC1) and related transporters. *Toxicology, 167*(1), 3-23.
Levitt, H., Wood, A., Moul, D. E., Hall, M., Germain, A., Kupfer, D. J., & Buysse, D. J. (2004). A pilot study of subjective daytime alertness and mood in primary insomnia participants using ecological momentary assessment. *Behavioral sleep medicine, 2*(2), 113-131. doi: 10.1207/s15402010bsm0202_3
Lewis, D. A., Hashimoto, T., & Volk, D. W. (2005). Cortical inhibitory neurons and schizophrenia. *Nature Reviews Neuroscience, 6*(4), 312-324.
Li, Belinda SY, Wang, Hao, & Gonen, Oded. (2003). Metabolite ratios to assumed stable creatine level may confound the quantification of proton brain MR spectroscopy. *Magnetic resonance imaging, 21*(8), 923-928.
Lichstein, K. L., Stone, K. C., Donaldson, J., Nau, S. D., Soeffing, J. P., Murray, D., . . . Aguillard, N. (2006). Actigraphy validation with insomnia. *Sleep, 29*(2), 232-239.
Lichstein, K.L. (1988). Sleep compression treatment of an insomnoid. *Behavior Therapy, 19*(4), 625-632.
Lin, Alexander, Ross, Brian D, Harris, Kent, & Wong, Willis. (2005). Efficacy of proton magnetic resonance spectroscopy in neurological diagnosis and neurotherapeutic decision making. *NeuroRx, 2*(2), 197-214.
Liu, J., Yu, B., Neugebauer, V., Grigoriadis, D. E., Rivier, J., Vale, W. W., . . . Gallagher, J. P. (2004). Corticotropin-releasing factor and Urocortin I modulate excitatory glutamatergic synaptic transmission. *J Neurosci, 24*(16), 4020-4029. doi: 10.1523/JNEUROSCI.5531-03.2004
Longbottom, RT, & Pleuvry, BJ. (1984). Respiratory and sedative effects of triazolam in volunteers. *British journal of anaesthesia, 56*(2), 179-185.
Loomis, A. L., Harvey, E. N., & Hobart, G. A. (1938). Distribution of disturbance-patterns in the human electroencephalogram with special reference to sleep. *Journal of Neurophysiology, 1*, 413-430.
Lowson, E., Middleton, B., Arber, S., & Skene, D. J. (2013). Effects of night work on sleep, cortisol and mood of female nurses, their husbands and children. *Sleep and Biological Rhythms, 11*(1), 7-13. doi: DOI 10.1111/j.1479-8425.2012.00585.x
Lushington, K., Dawson, D., & Lack, L. (2000). Core body temperature is elevated during constant wakefulness in elderly poor sleepers. *Sleep, 23*(4), 504-510.
Maes, J., Verbraecken, J., Willemen, M., De Volder, I., van Gastel, A., Michiels, N., . . . Cluydts, R. (2014). Sleep misperception, EEG characteristics and Autonomic Nervous System activity in

primary insomnia: A retrospective study on polysomnographic data. *Int J Psychophysiol, 91*(3), 163-171. doi: 10.1016/j.ijpsycho.2013.10.012
Manber, Rachel, & Ong, Jason C. (2010). Clinical assessment of insomnia: Primary insomnias. *Insomnia: Diagnosis and treatment*, 113-125.
Meerlo, P., Sgoifo, A., & Suchecki, D. (2008). Restricted and disrupted sleep: Effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Medicine Reviews, 12*(3), 197-210. doi: DOI 10.1016/j.smrv.2007.07.007
Mendelson, W. B., James, S. P., Garnett, D., Sack, D. A., & Rosenthal, N. E. (1986). A psychophysiological study of insomnia. *Psychiatry Res, 19*(4), 267-284.
Merica, H., Blois, R., & Gaillard, J. M. (1998). Spectral characteristics of sleep EEG in chronic insomnia. *Eur J Neurosci, 10*(5), 1826-1834.
Mescher, M, Merkle, H, Kirsch, J, Garwood, M, & Gruetter, R. (1998). Simultaneous in vivo spectral editing and water suppression. *NMR in Biomedicine, 11*(6), 266-272.
Meyerhoff, D. J., Mon, A., Metzler, T., & Neylan, T. C. (2014). Cortical gamma-aminobutyric Acid and glutamate in posttraumatic stress disorder and their relationships to self-reported sleep quality. *Sleep, 37*(5), 893-900. doi: 10.5665/sleep.3654
Miller, C. B., Espie, C. A., Epstein, D. R., Friedman, L., Morin, C. M., Pigeon, W. R., . . . Kyle, S. D. (2014). The evidence base of sleep restriction therapy for treating insomnia disorder. *Sleep Medicine Reviews*. doi: http://dx.doi.org/10.1016/j.smrv.2014.01.006
Miller, C. B., Kyle, S. D., Marshall, N. S., & Espie, C. A. (2013). Ecological momentary assessment of daytime symptoms during sleep restriction therapy for insomnia. *J Sleep Res, 22*(3), 266-272. doi: 10.1111/jsr.12024
Möhler, H. (2006). GABAA receptor diversity and pharmacology. *Cell and tissue research, 326*(2), 505-516.
Möller-Levet, C. S., Archer, S. N., Bucca, G., Laing, E. E., Slak, A., Kabiljo, R., . . . Smith, C. P. (2013). Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome. *Proceedings of the National Academy of Sciences, 110*(12), E1132-E1141.
Montgomery, P, & Dennis, J. (2003). Cognitive behavioural interventions for sleep problems in adults aged 60+. *Cochrane Database Syst Rev, 1*.
Morgan, P. T., Pace-Schott, E. F., Mason, G. F., Forselius, E., Fasula, M., Valentine, G. W., & Sanacora, G. (2012). Cortical GABA levels in primary insomnia. *Sleep, 35*(6), 807.
Morgenthaler, T., Alessi, C., Friedman, L., Owens, J., Kapur, V., Boehlecke, B., . . . Swick, T. J. (2007). Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: An update for 2007. *Sleep: Journal of Sleep and Sleep Disorders Research, 30*(4), 519-529.
Morgenthaler, T., Kramer, M., Alessi, C., Friedman, L., Boehlecke, B., Brown, T., . . . Swick, T. J. (2006). Practice parameters for the psychological and behavioral treatment of insomnia: an update. An american academy of sleep medicine report. *Sleep, 29*(11), 1415-1419.
Morin, C. M. (1993). *Insomnia: Psychological assessment and management*. New York, NY: Guilford Press.
Morin, C. M, & Espie, C. A. (2003). *Insomnia: A clinician's guide to assessment and treatment* (Vol. 1): Springer.
Morin, C. M., Belanger, L., LeBlanc, M., Ivers, H., Savard, J., Espie, C. A., . . . Gregoire, J. P. (2009). The natural history of insomnia: a population-based 3-year longitudinal study. *Archives of internal medicine, 169*(5), 447-453. doi: 10.1001/archinternmed.2008.610

Morin, C. M., & Benca, R. (2012). Chronic insomnia. *Lancet, 379*(9821), 1129-1141. doi: 10.1016/S0140-6736(11)60750-2

Morin, C. M., Bootzin, R. R., Buysse, D. J., Edinger, J. D., Espie, C. A., & Lichstein, K. L. (2006). Psychological and behavioral treatment of insomnia: Update of the recent evidence (1998-2004). *Sleep, 29*(11), 1398-1414.

Morin, C. M., Culbert, J. P., & Schwartz, S. M. (1994). Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. *The American journal of psychiatry, 151*(8), 1172-1180.

Morin, C. M., Hauri, P. J., Espie, C. A., Spielman, A. J., Buysse, D. J., & Bootzin, R. R. (1999). Nonpharmacologic treatment of chronic insomnia. *Sleep, 22*(8), 1134-1156.

Morin, C. M., Kowatch, R. A., & Oshanick, G. (1990). Sleep Restriction for the Inpatient Treatment of Insomnia. *Sleep, 13*(2), 183-186.

Morin, C. M., Vallieres, A., Guay, B., Ivers, H., Savard, J., Merette, C., . . . Baillargeon, L. (2009). Cognitive Behavioral Therapy, Singly and Combined With Medication, for Persistent Insomnia A Randomized Controlled Trial. *Jama-Journal of the American Medical Association, 301*(19), 2005-2015.

Morin, Charles M, & Jarrin, Denise C. (2013). Epidemiology of insomnia: prevalence, course, risk factors, and public health burden. *Sleep Medicine Clinics, 8*(3), 281-297.

Morin, Charles M, LeBlanc, M, Daley, M, Gregoire, JP, & Merette, C. (2006). Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. *Sleep medicine, 7*(2), 123-130.

Morphy, H., Dunn, K. M., Lewis, M., Boardman, H. F., & Croft, P. R. (2007). Epidemiology of insomnia: a longitudinal study in a UK population. *SLEEP, 30*(3), 274.

Mountford, C. E., Stanwell, P., Lin, A., Ramadan, S., & Ross, B. (2010). Neurospectroscopy: the past, present and future. *Chemical reviews, 110*(5), 3060-3086.

Murphy, M., Riedner, B. A., Huber, R., Massimini, M., Ferrarelli, F., & Tononi, G. (2009). Source modeling sleep slow waves. *Proc Natl Acad Sci U S A, 106*(5), 1608-1613. doi: 10.1073/pnas.0807933106

Murtagh, D. R., & Greenwood, K. M. (1995). Identifying effective psychological treatments for insomnia: a meta-analysis. *Journal of consulting and clinical psychology, 63*(1), 79-89.

National Institutes of Health State-of-the-Science Conference Statement on manifestations and management of chronic insomnia in adults. (2005). *NIH Consens State Sci Statements, 22*(2), 1-30.

Nemeroff, C. B., Bissette, G., Akil, H., & Fink, M. (1991). Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy. Corticotrophin-releasing factor, beta-endorphin and somatostatin. *Br J Psychiatry, 158*, 59-63.

Neylan, Thomas C, Mueller, Susanne G, Wang, Zhen, Metzler, Thomas J, Lenoci, Maryann, Truran, Diana, . . . Schuff, Norbert. (2010). Insomnia severity is associated with a decreased volume of the CA3/dentate gyrus hippocampal subfield. *Biological psychiatry, 68*(5), 494-496.

Neylan, Thomas C. (2011). Time to disseminate cognitive behavioral treatment of insomnia: comment on "Efficacy of brief behavioral treatment for chronic insomnia in older adults". *Archives of Internal Medicine, 171*(10), 895-896.

Nofzinger, E. A., Buysse, D. J., Germain, A., Price, J. C., Miewald, J. M., & Kupfer, D. J. (2004). Functional neuroimaging evidence for hyperarousal in insomnia. *American Journal of Psychiatry, 161*(11), 2126-2129. doi: 10.1176/appi.ajp.161.11.2126

Nofzinger, E. A., Nissen, C., Germain, A., Moul, D. E., Hall, M., Price, J. C., . . . Buysse, D. J. (2006). Regional cerebral metabolic correlates of WASO during NREM sleep in insomnia. *J Clin Sleep Med, 2*(3), 316-322.

O'Brien, C., Hoyt, R. W., Buller, M. J., Castellani, J. W., & Young, A. J. (1998). Telemetry pill measurement of core temperature in humans during active heating and cooling. *Med Sci Sports Exerc, 30*(3), 468-472.

Ohayon, M. M., Guilleminault, C., Zulley, J., Palombini, L., & Raab, H. (1999). Validation of the sleep-EVAL system against clinical assessments of sleep disorders and polysomnographic data. *Sleep, 22*(7), 925-930.

Ohayon, M. M., & Hong, S. C. (2002). Prevalence of insomnia and associated factors in South Korea. *J Psychosom Res, 53*(1), 593-600.

Okajima, I., Komada, Y., & Inoue, Y. (2011). A meta-analysis on the treatment effectiveness of cognitive behavioral therapy for primary insomnia. *Sleep and Biological Rhythms, 9*(1), 24-34.

Okun, Michele L, Kravitz, Howard M, Sowers, Mary Fran, Moul, Douglas E, Buysse, Daniel J, & Hall, Martica. (2009). Psychometric evaluation of the Insomnia Symptom Questionnaire: a self-report measure to identify chronic insomnia. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine, 5*(1), 41.

Olsen, Maren K, Stechuchak, Karen M, Edinger, Jack D, Ulmer, Christi S, & Woolson, Robert F. (2012). Move over LOCF: principled methods for handling missing data in sleep disorder trials. *Sleep medicine, 13*(2), 123-132.

Omisade, Antonina, Buxton, Orfeu M., & Rusak, Benjamin. (2010). Impact of acute sleep restriction on cortisol and leptin levels in young women. *Physiology & Behavior, 99*(5), 651-656. doi: http://dx.doi.org/10.1016/j.physbeh.2010.01.028

Ong, J. C., Ulmer, C. S., & Manber, R. (2012). Improving sleep with mindfulness and acceptance: a metacognitive model of insomnia. *Behav Res Ther, 50*(11), 651-660. doi: 10.1016/j.brat.2012.08.001

Oostenveld, Robert, & Praamstra, Peter. (2001). The five percent electrode system for high-resolution EEG and ERP measurements. *Clinical Neurophysiology, 112*(4), 713-719. doi: 10.1016/S1388-2457(00)00527-7

Ozminkowski, R. J., Wang, S., & Walsh, J. K. (2007). The direct and indirect costs of untreated insomnia in adults in the United States. *Sleep, 30*(3), 263-273.

Palagini, L., Biber, K., & Riemann, D. (2014). The genetics of insomnia – Evidence for epigenetic mechanisms? *Sleep Medicine Reviews, 18*(3), 205-215. doi: http://dx.doi.org/10.1016/j.smrv.2013.05.002

Pallesen, S., Sivertsen, B., Nordhus, I. H., & Bjorvatn, B. (2014). A 10-year trend of insomnia prevalence in the adult Norwegian population. *Sleep Medicine, 15*(2), 173-179. doi: DOI 10.1016/j.sleep.2013.10.009

Pejovic, S., Basta, M., Vgontzas, A. N., Kritikou, I., Shaffer, M. L., Tsaoussoglou, M., . . . Chrousos, G. P. (2013). Effects of recovery sleep after one work week of mild sleep restriction on interleukin-6 and cortisol secretion and daytime sleepiness and performance. *American Journal of Physiology-Endocrinology and Metabolism, 305*(7), E890-E896. doi: DOI 10.1152/ajpendo.00301.2013

Perlis, M. L., Giles, D. E., Mendelson, W. B., Bootzin, R. R., & Wyatt, J. K. (1997). Psychophysiological insomnia: the behavioural model and a neurocognitive perspective. *J Sleep Res, 6*(3), 179-188.

Perlis, M. L., Smith, M. T., Orff, H. J., Andrews, P. J., & Giles, D. E. (2001). The mesograde amnesia of sleep may be attenuated in subjects with primary insomnia. *Physiol Behav, 74*(1-2), 71-76.

Perlis, M., Shaw, P. J., Cano, G., & Espie, Colin A. (2011). Chapter 78 - Models of Insomnia. In M. H. Kryger, T. Roth & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine (Fifth Edition)* (pp. 850-865). Philadelphia: W.B. Saunders.

Pigeon, W. R., & Perlis, M. L. (2006). Sleep homeostasis in primary insomnia. *Sleep Med Rev, 10*(4), 247-254. doi: 10.1016/j.smrv.2005.09.002

Plante, David T, Jensen, J Eric, Schoerning, Laura, & Winkelman, John W. (2012). Reduced γ-Aminobutyric Acid in Occipital and Anterior Cingulate Cortices in Primary Insomnia: a Link to Major Depressive Disorder? *Neuropsychopharmacology, 37*(6), 1548-1557.

Plante, David T, Jensen, J Eric, & Winkelman, John W. (2012). The role of GABA in primary insomnia. *Sleep, 35*(6), 741.

Price, Rebecca B, Shungu, Dikoma C, Mao, Xiangling, Nestadt, Paul, Kelly, Chris, Collins, Katherine A, . . . Mathew, Sanjay J. (2009). Amino acid neurotransmitters assessed by proton magnetic resonance spectroscopy: relationship to treatment resistance in major depressive disorder. *Biological psychiatry, 65*(9), 792-800.

Puts, N. A. J., & Edden, R. A. E. (2012). < i> In vivo</i> magnetic resonance spectroscopy of GABA: A methodological review. *Progress in nuclear magnetic resonance spectroscopy, 60*, 29-41.

Rae, C., Bartlett, D. J., Yang, Q., Walton, D., Denotti, A., Sachinwalla, T., & Grunstein, R. R. (2009). Dynamic changes in brain bioenergetics during obstructive sleep apnea. *Journal of Cerebral Blood Flow and Metabolism, 29*(8), 1421-1428. doi: 10.1038/jcbfm.2009.57

Rae, C. D. (2014). A Guide to the Metabolic Pathways and Function of Metabolites Observed in Human Brain H-1 Magnetic Resonance Spectra. *Neurochemical Research, 39*(1), 1-36. doi: 10.1007/s11064-013-1199-5

Rae, Caroline, Digney, Alison L, McEwan, Sally R, & Bates, Timothy C. (2003). Oral creatine monohydrate supplementation improves brain performance: a double–blind, placebo–controlled, cross–over trial. *Proceedings of the Royal Society of London. Series B: Biological Sciences, 270*(1529), 2147-2150.

Rechtschaffen, Allan, & Kales, Anthony. (1968). A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. doi: 10.1234/12345678

Reynolds, A. C., & Banks, S. (2010). Total sleep deprivation, chronic sleep restriction and sleep disruption. *Progress in brain research, 185*, 91-103. doi: 10.1016/B978-0-444-53702-7.00006-3

Richardson, G. S. (2007). Human physiological models of insomnia. *Sleep Med, 8 Suppl 4*, S9-14. doi: 10.1016/S1389-9457(08)70003-0

Richardson, G. S., & Roth, T. (2001). Future directions in the management of insomnia. *J Clin Psychiatry, 62 Suppl 10*, 39-45.

Riedel, B. W., & Lichstein, K. L. (2001). Strategies for evaluating adherence to sleep restriction treatment for insomnia. *Behaviour Research and Therapy, 39*(2), 201-212. doi: 10.1016/s0005-7967(00)00002-4

Riedel, B. W., Lichstein, K. L., & Dwyer, W. O. (1995). Sleep Compression and Sleep Education for Older Insomniacs: Self-Help Versus Therapist Guidance. *Psychology and Aging, 10*(1), 54-63.

Riemann, D., Baglioni, C., Feige, B., & Spiegelhalder, K. (2014). Insomnia - state of the science. *Nervenarzt, 85*(1), 43-49. doi: DOI 10.1007/s00115-013-3892

Riemann, D., & Perlis, M. L. (2009). The treatments of chronic insomnia: a review of benzodiazepine receptor agonists and psychological and behavioral therapies. *Sleep medicine reviews, 13*(3), 205-214. doi: 10.1016/j.smrv.2008.06.001

Riemann, Dieter, Spiegelhalder, Kai, Feige, Bernd, Voderholzer, Ulrich, Berger, Mathias, Perlis, Michael, & Nissen, Christoph. (2010). The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep medicine reviews, 14*(1), 19-31.

Rodenbeck, A., Cohrs, S., Jordan, W., Huether, G., Ruther, E., & Hajak, G. (2003). The sleep-improving effects of doxepin are paralleled by a normalized plasma cortisol secretion in primary insomnia. A placebo-controlled, double-blind, randomized, cross-over study followed by an open treatment over 3 weeks. *Psychopharmacology (Berl), 170*(4), 423-428. doi: 10.1007/s00213-003-1565-0

Rodenbeck, A., & Hajak, G. (2001). Neuroendocrine dysregulation in primary insomnia. *Revue Neurologique, 157*(11), S57-S61.

Rodenbeck, A., Huether, G., Ruther, E., & Hajak, G. (2002). Interactions between evening and nocturnal cortisol secretion and sleep parameters in patients with severe chronic primary insomnia. *Neuroscience Letters, 324*(2), 159-163. doi: 10.1016/S0304-3940(02)00192-1

Romeijn, N., Verweij, I. M., Koeleman, A., Mooij, A., Steimke, R., Virkkala, J., . . . Van Someren, E. J. W. (2012). Cold hands, warm feet: sleep deprivation disrupts thermoregulation and its association with vigilance. *Sleep, 35*(12), 1673.

Rosekind, M. R., & Gregory, K. B. (2010). Insomnia risks and costs: health, safety, and quality of life. *Am J Manag Care, 16*(8), 617-626.

Rosen, Y., & Lenkinski, R. E. (2007). Recent advances in magnetic resonance neurospectroscopy. *Neurotherapeutics, 4*(3), 330-345.

Rosenthal, N. E., Josephvanderpool, J. R., Levendosky, A. A., Johnston, S. H., Allen, R., Kelly, K. A., . . . Starz, K. E. (1990). Phase-Shifting Effects of Bright Morning Light as Treatment for Delayed Sleep Phase Syndrome. *Sleep, 13*(4), 354-361.

Roth, T. (2001). The relationship between psychiatric diseases and insomnia. *Int J Clin Pract Suppl*(116), 3-8.

Roth, T. (2007a). Introduction - Advances in our understanding of insomnia and its management. *Sleep Medicine, 8*, S25-S26. doi: DOI 10.1016/j.sleep.2007.10.001

Roth, T. (2007b). The nature of Insomnia. *Cns Spectrums, 12*(7), 1-+.

Roth, T. (2007c). Understanding neuronal pathways: Novel targets for the management of insomnia - Introduction. *Journal of Clinical Psychiatry, 68*, 4-5.

Roth, T., Roehrs, T., & Pies, R. (2007). Insomnia: pathophysiology and implications for treatment. *Sleep Med Rev, 11*(1), 71-79. doi: 10.1016/j.smrv.2006.06.002

Sackett, D. L. (1989). Rules of evidence and clinical recommendations on the use of antithrombotic agents. *CHEST Journal, 95*(2_Supplement), 2S-4S.

Sadeh, A., & Acebo, C. (2002). The role of actigraphy in sleep medicine. *Sleep Medicine Reviews, 6*(2), 113-124. doi: 10.1053/smrv.2001.0182

Salas, RE, Galea, JM, Gamaldo, AA, Gamaldo, CE, Allen, RP, Smith, MT, . . . Celnik, PA. (2013). Increased use-dependent plasticity in chronic insomnia. *Sleep, 37*(3), 535-544.

Satoh, T., & Yoshioka, Y. (2006). Contribution of reduced and oxidized glutathione to signals detected by magnetic resonance spectroscopy as indicators of local brain redox state. *Neuroscience research, 55*(1), 34-39.

Scheer, Frank AJL, Hilton, Michael F, Mantzoros, Christos S, & Shea, Steven A. (2009). Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proceedings of the National Academy of Sciences, 106*(11), 4453-4458.

Schenck, C. H., Bundlie, S. R., & Mahowald, M. W. (1996). Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. *Neurology, 46*(2), 388-393. doi: 10.1212/WNL.46.2.388

Schenck, C. H., Hurwitz, T. D., & Mahowald, M. W. (1993). REM sleep behaviour disorder: an update on a series of 96 patients and a review of the world literature. *Journal of Sleep Research, 2*(4), 224-231. doi: 10.1111/j.1365-2869.1993.tb00093.x

Schmid, S. M., Hallschmid, M., Jauch-Chara, K., Wilms, B., Lehnert, H., Born, J., & Schultes, B. (2011). Disturbed glucoregulatory response to food intake after moderate sleep restriction. *Sleep, 34*(3), 371-377.

Schramm, E., Hohagen, F., Grasshoff, U., Riemann, D., Hajak, G., Weess, H. G., & Berger, M. (1993). Test-retest reliability and validity of the Structured Interview for Sleep Disorders According to DSM-III—R. *The American Journal of Psychiatry, 150*(6), 867-872.

Schulz, P., Kirschbaum, C., Prussner, J., & Hellhammer, D. (1998). Increased free cortisol secretion after awakening in chronically stressed individuals due to work overload. *Stress Medicine, 14*(2), 91-97. doi: Doi 10.1002/(Sici)1099-1700(199804)14:2<91::Aid-Smi765>3.0.Co;2-S

Schutte-Rodin, Sharon, Broch, Lauren, Buysse, Daniel, Dorsey, Cynthia, & Sateia, Michael. (2008). Clinical guideline for the evaluation and management of chronic insomnia in adults. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine, 4*(5), 487.

Seelig, E., Keller, U., Klarhofer, M., Scheffler, K., Brand, S., Holsboer-Trachsler, E., . . . Bilz, S. (2013). Neuroendocrine regulation and metabolism of glucose and lipids in primary chronic insomnia: a prospective case-control study. *PLoS One, 8*(4), e61780. doi: 10.1371/journal.pone.0061780

Shaver, J. L. F., Johnston, S. K., Lentz, M. J., & Landis, C. A. (2002). Stress exposure, psychological distress, and physiological stress activation in midlife women with insomnia. *Psychosomatic Medicine, 64*(5), 793-802. doi: Doi 10.1097/01.Psy.0000024235.11538.9a

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annu Rev Clin Psychol, 4*, 1-32.

Sibson, Nicola R, Dhankhar, Ajay, Mason, Graeme F, Rothman, Douglas L, Behar, Kevin L, & Shulman, Robert G. (1998). Stoichiometric coupling of brain glucose metabolism and glutamatergic neuronal activity. *Proceedings of the National Academy of Sciences, 95*(1), 316-321.

Siebern, A. T., & Manber, R. (2010). Insomnia and its effective non-pharmacologic treatment. *Med Clin North Am, 94*(3), 581-591. doi: 10.1016/j.mcna.2010.02.005

Singh, Ilina, & Rose, Nikolas. (2009). Biomarkers in psychiatry. *Nature, 460*(7252), 202-207.

Sivertsen, B., Lallukka, T., & Salo, P. (2011). The economic burden of insomnia at the workplace. An opportunity and time for intervention? *Sleep, 34*(9), 1151-1152. doi: 10.5665/SLEEP.1224

Sivertsen, B., Salo, P., Mykletun, A., Hysing, M., Pallesen, S., Krokstad, S., . . . Overland, S. (2012). The bidirectional association between depression and insomnia: the HUNT study. *Psychosom Med, 74*(7), 758-765. doi: 10.1097/PSY.0b013e3182648619

Smith, M. T., Huang, M. I., & Manber, R. (2005). Cognitive behavior therapy for chronic insomnia occurring within the context of medical and psychiatric disorders. *Clinical Psychology Review; Clinical Psychology Review*.

Smith, M. T., Perlis, M. L., Chengazi, V. U., Pennington, J., Soeffing, J., Ryan, J. M., & Giles, D. E. (2002). Neuroimaging of NREM sleep in primary insomnia: a Tc-99-HMPAO single photon emission computed tomography study. *Sleep, 25*(3), 325-335.

Smith, M. T., Perlis, M. L., Park, A., Smith, M. S., Pennington, J., Giles, D. E., & Buysse, D. J. (2002). Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *American Journal of Psychiatry, 159*(1), 5-11.

Snyder, J., & Wilman, A. (2010). Field strength dependence of PRESS timings for simultaneous detection of glutamate and glutamine from 1.5 to 7T. *Journal of Magnetic Resonance, 203*(1), 66-72.

Soares, DP, & Law, M. (2009). Magnetic resonance spectroscopy of the brain: review of metabolites and clinical applications. *Clinical radiology, 64*(1), 12-21.

Spiegel, K., Leproult, R., & Van Cauter, E. (1999). Impact of sleep debt on metabolic and endocrine function. *The Lancet, 354*(9188), 1435-1439. doi: 10.1016/S0140-6736(99)01376-8

Spiegelhalder, K., Regen, W., Baglioni, C., Riemann, D., & Winkelman, J. W. (2013). Neuroimaging Studies in Insomnia. *Current Psychiatry Reports, 15*(11). doi: 10.1007/S11920-013-0405-0

Spiegelhalder, Kai, Regen, Wolfram, Baglioni, Chiara, Klöppel, Stefan, Abdulkadir, Ahmed, Hennig, Jürgen, . . . Feige, Bernd. (2013). Insomnia does not appear to be associated with substantial structural brain changes. *Sleep, 36*(5), 731.

Spiegelhalder, Kai, & Riemann, Dieter. (2013). Hyperarousal and Insomnia. *Sleep Medicine Clinics, 8*(3), 299-307.

Spielman, A., J., Chien-Ming, Y., & Glovinsky, P., B. (2010). Insomnia: Sleep Restriction Therapy. In J. Sateia M. & J. Buysse D. (Eds.), *Insomnia: Diagnosis and Treatment* (Vol. 1, pp. 277- 289). London: Medical Psychiatry Series Informa Healthcare.

Spielman, A., J., & Glovinsky, P., B. (1991). The Varied Nature of Insomnia. In H. P. J (Ed.), *Case Studies in Insomnia* (pp. 1-15). New York: Kluwer Academic (Plenum Medical Book Company).

Spielman, A. J., Saskin, P., & Thorpy, M. J. (1987). Treatment of Chronic Insomnia by Restriction of Time in Bed. *Sleep, 10*(1), 45-56.

Stagg, C. J., Bestmann, S., Constantinescu, A. O., L., Moreno M., Allman, C., Mekle, R., . . . Rothwell, J. C. (2011). Relationship between physiological measures of excitability and levels of glutamate and GABA in the human motor cortex. *The Journal of physiology, 589*(23), 5845-5855.

Stephan, Friedrich K., & Nunez, Antonio A. (1977). Elimination of circadian rhythms in drinking, activity, sleep, and temperature by isolation of the suprachiasmatic nuclei. *Behavioral Biology, 20*(1), 1-16. doi: 10.1016/S0091-6773(77)90397-2

Sumner, Petroc, Edden, Richard AE, Bompas, Aline, Evans, C John, & Singh, Krish D. (2010). More GABA, less distraction: a neurochemical predictor of motor decision speed. *Nature neuroscience, 13*(7), 825-827.

Szuba, Martin P, Guze, Barry H, & Baxter Jr, Lewis R. (1997). Electroconvulsive therapy increases circadian amplitude and lowers core body temperature in depressed subjects. *Biological psychiatry, 42*(12), 1130-1137.

Taylor, D. J., Mallory, L., Lichstein, K. L., Durrence, H. H., Riedel, B. W., & Bush, A. J. (2007). Comorbidity of chronic insomnia with medical problems. (vol 30, pg 213, 2007). *Sleep, 30*(7), Cp2-Cp2.

Taylor, D. J., Schmidt-Nowara, W., Jessop, C. A., & Ahearn, J. (2010). Sleep restriction therapy and hypnotic withdrawal versus sleep hygiene education in hypnotic using patients with insomnia. *J Clin Sleep Med, 6*(2), 169-175.

Theysohn, Jens M, Maderwald, Stefan, Kraff, Oliver, Moenninghoff, Christoph, Ladd, Mark E, & Ladd, Susanne C. (2008). Subjective acceptance of 7 Tesla MRI for human imaging. *Magnetic Resonance Materials in Physics, Biology and Medicine, 21*(1-2), 63-72.

Troxel, W.M., Germain, A., & Buysse, D.J. (2012). Clinical Management of Insomnia with Brief Behavioral Treatment (BBTI). *Behavioral sleep medicine, 10*(4), 266-279.

Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research, 53*(4), 865-871. doi: Pii S0022-3999(02)00429-4
Doi 10.1016/S0022-3999(02)00429-4

Uhlig, Benjamin Langsæter, Sand, Trond, Ødegård, Siv Steinsmo, & Hagen, Knut. (2014). Prevalence and associated factors of DSM-V insomnia in Norway: the Nord-Trøndelag Health Study (HUNT 3). *Sleep medicine*.

Vallieres, A., Ceklic, T., Bastien, C. H., & Espie, C. A. (2013). A preliminary evaluation of the physiological mechanisms of action for sleep restriction therapy. *Sleep Disord, 2013*, 726372. doi: 10.1155/2013/726372

Van Dongen, H. P. A., Baynard, M. D., Maislin, G., & Dinges, D. F. (2004). Systematic interindividual differences in neurobehavioral impairment from sleep loss: Evidence of trait-like differential vulnerability. *Sleep, 27*(3), 423-433.

Van Dongen, H. P. A., & Dinges, D. F. (2005). Sleep, Circadian Rhythms, and Psychomotor Vigilance. *Clinics in Sports Medicine, 24*(2), 237-249. doi: 10.1016/j.csm.2004.12.007

Van Dongen, H. P. A., Kerkhof, G. A., & Souverijn, J. H. M. (1998). Absence of seasonal variation in the phase of the endogenous circadian rhythm in humans. *Chronobiology international, 15*(6), 623-632.

Van Dongen, H. P., Maislin, G., Mullington, J. M., & Dinges, D. F. (2003). The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep, 26*(2), 117-126.

Van Dongen, H. P.A., Olofsen, E., Dinges, D. F., & Maislin, G. (2004). Mixed-model regression analysis and dealing with interindividual differences. *Essential Numerical Computer Methods*, 225.

Varkevisser, M., & Kerkhof, G. A. (2005). Chronic insomnia and performance in a 24-h constant routine study. *J Sleep Res, 14*(1), 49-59. doi: 10.1111/j.1365-2869.2004.00414.x

Varkevisser, M., Van Dongen, H. P., Van Amsterdam, J. G., & Kerkhof, G. A. (2007). Chronic insomnia and daytime functioning: an ambulatory assessment. *Behav Sleep Med, 5*(4), 279-296. doi: 10.1080/15402000701557425

Vgontzas, A. N., Bixler, E. O., Lin, H. M., Prolo, P., Mastorakos, G., Vela-Bueno, A., . . . Chrousos, G. P. (2001). Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: Clinical implications. *Journal of Clinical Endocrinology & Metabolism, 86*(8), 3787-3794. doi: 10.1210/Jc.86.8.3787

Vgontzas, A. N., Fernandez-Mendoza, J., Liao, D., & Bixler, E. O. (2013). Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. *Sleep Med Rev, 17*(4), 241-254. doi: 10.1016/j.smrv.2012.09.005

Vgontzas, A. N., Pejovic, S., Zoumakis, E., Lin, H. M., Bixler, E. O., Basta, M., . . . Chrousos, G. P. (2007). Daytime napping after a night of sleep loss decreases sleepiness, improves performance, and causes beneficial changes in cortisol and interleukin-6 secretion. *American Journal of Physiology-Endocrinology and Metabolism, 292*(1), E253-E261. doi: DOI 10.1152/ajpendo.00651.2005

Vgontzas, A. N., Tsigos, C., Bixler, E. O., Stratakis, C. A., Zachman, K., Kales, A., . . . Chrousos, G. P. (1998). Chronic insomnia and activity of the stress system: A preliminary study. *Journal of Psychosomatic Research, 45*(1), 21-31. doi: 10.1016/S0022-3999(97)00302-4

Vgontzas, A., Trakada, G., Bixler, E., Lin, H., Zoumakis, E., Chrousos, G., & Legro, R. (2004). Plasma IL-6 and TNF alpha levels are elevated in polycystic ovary syndrome independent of obesity and sleep disturbance. *Sleep, 27*, 334-334.

Vincent, N., Lewycky, S., & Finnegan, H. (2008). Barriers to engagement in sleep restriction and stimulus control in chronic insomnia. *Journal of consulting and clinical psychology, 76*(5), 820-828.

Vincent, N., & Lionberg, C. (2001). Treatment preference and patient satisfaction in chronic insomnia. *Sleep, 24*(4), 411-417.

Vinkers, C. H., van Bogaert, M. J., Klanker, M., Korte, S. M., Oosting, R., Hanania, T., . . . Groenink, L. (2008). Translational aspects of pharmacological research into anxiety disorders: the stress-induced hyperthermia (SIH) paradigm. *Eur J Pharmacol, 585*(2-3), 407-425. doi: 10.1016/j.ejphar.2008.02.097

Vitiello, M. V., McCurry, S. M., & Rybarczyk, B. D. (2013). The Future of Cognitive Behavioral Therapy for Insomnia: What Important Research Remains to Be Done? *Journal of clinical psychology*.

Walsh, JK, & Engelhardt, CL. (1999). The direct economic costs of insomnia in the United States for 1995. *Sleep, 22*, S386-393.

Walter, M., Henning, A., Grimm, S., Schulte, R. F., Beck, J., Dydak, U., . . . Northoff, G. (2009). The relationship between aberrant neuronal activation in the pregenual anterior cingulate, altered glutamatergic metabolism, and anhedonia in major depression. *Archives of General Psychiatry, 66*(5), 478-486.

Weibel, L., Follenius, M., Spiegel, K., Ehrhart, J., & Brandenberger, G. (1995). Comparative effect of night and daytime sleep on the 24-hour cortisol secretory profile. *Sleep, 18*(7), 549-556.

Williams, R. L., Agnew Jr, H. W., & Webb, W. B. (1964). Sleep patterns in young adults: an EEG study. *Electroencephalography and clinical neurophysiology, 17*(4), 376-381. doi: 10.1016/0013-4694(64)90160-9

Wilson, S. J., Nutt, D. J., Alford, C., Argyropoulos, S. V., Baldwin, D. S., Bateson, A. N., . . . Wade, A. G. (2010). British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol, 24*(11), 1577-1601. doi: 10.1177/0269881110379307

Winkelman, J. W, Plante, D. T, Schoerning, L., Benson, K., Buxton, O. M., O'Connor, S. P., . . . Gonenc, A. (2013). Increased rostral anterior cingulate cortex volume in chronic primary insomnia. *Sleep, 36*(7), 991.

Winkelman, J. W., Buxton, O. M., Jensen, J. E., Benson, K. L., O'Connor, S. P., Wang, W., & Renshaw, P. F. (2008). Reduced brain GABA in primary insomnia: preliminary data from 4T proton magnetic resonance spectroscopy (1H-MRS). *Sleep, 31*(11), 1499.

Woods, H. C., Scheepers, C., Ross, K. A., Espie, C. A., & Biello, S. M. (2013). What are you looking at? moving toward an attentional timeline in insomnia: a novel semantic eye tracking study. *Sleep, 36*(10), 1491-1499. doi: 10.5665/sleep.3042

Wu, H., Zhao, Z., Stone, W. S., Huang, L., Zhuang, J., He, B., . . . Li, Y. (2008). Effects of sleep restriction periods on serum cortisol levels in healthy men. *Brain Res Bull, 77*(5), 241-245. doi: 10.1016/j.brainresbull.2008.07.013

Wyss, M., & Schulze, A. (2002). Health implications of creatine: can oral creatine supplementation protect against neurological and atherosclerotic disease? *Neuroscience, 112*(2), 243-260.

Xia, L., Chen, G. H., Li, Z. H., Jiang, S., & Shen, J. (2013). Alterations in hypothalamus-pituitary-adrenal/thyroid axes and gonadotropin-releasing hormone in the patients with primary insomnia: a clinical research. *PLoS One, 8*(8), e71065. doi: 10.1371/journal.pone.0071065

Yanovski, J. A., Cutler, G. B., Jr., Chrousos, G. P., & Nieman, L. K. (1993). Corticotropin-releasing hormone stimulation following low-dose dexamethasone administration. A new test to distinguish Cushing's syndrome from pseudo-Cushing's states. *Jama, 269*(17), 2232-2238.

Zee, P. C., Badr, M. S., Kushida, C., Mullington, J. M., Pack, A. I., Parthasarathy, S., . . . Watson, N. F. (2014). Strategic opportunities in sleep and circadian research: report of the Joint Task Force of the Sleep Research Society and American Academy of Sleep Medicine. *Sleep, 37*(2), 219-227. doi: 10.5665/sleep.3384