The Mechanisms of Sleep Restriction Therapy for Insomnia Disorder



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A thesis submitted for the degree of

Doctor of Philosophy

Michaelmas 2019

By learning the laws of science, a person is able to behave effectively under the contingencies of an extraordinarily complex world. Science carries him beyond experience and beyond the defective sampling of nature inevitable in a single lifetime. It also brings him under the control of conditions which could play no part in shaping and maintaining his behaviour.

B.F. Skinner (1974, p.124)

Acknowledgements

I would like to express my sincerest gratitude to Dr Simon Kyle and Professor Colin Espie, who have supported me throughout the duration of this three-year project. Thank you Simon, for the time you have dedicated to me, your endless guidance, patience and inspirational determination to ensure that this project would succeed. Colin, thank you for your out the box thinking, experience and wisdom, which has helped me to see the bigger picture over the course of these last three years. In addition, I would like to add that I am truly grateful for the kindness and positive push (g'aun yersel) which has helped and inspired me to think and work as a scientific researcher. Of course, not to mention your wonderful Scottish whit. I could not have wished for better supervision.

I would also like to thank Dr Ximena Omlin for pathing the way for all my research conducted during my DPhil. You were always one step ahead of me making sure I would not stumble. Thanks for your personal support, your scientific advice and your endless encyclopaedia of fun facts.

Thanks to Dr Suzanne Ftouni for the co-supervision of the ESPRIT study. Without you, this project would not have been possible, and I am very grateful for the time you spent with me working on the study protocol, the analysis of the data and the graphical illustration of all of that. Your circadian insights were inspiring and helped to see through the entangled data.

I am truly grateful for the help and support of Dr Rachel Sharman. Thanks Rachel, for sharing your endless knowledge of actigraphy and polysomnography data with me and for spending so much time on teaching and double checking my records. You make the SCNi a lively place and I enjoy listening to all your sleep and non-sleep stories.

Further thanks go to other valuable members of the SCNi. Matthew Reid and Lampros Bisdounis, I am truly thankful for the time you spent helping me out with data collection, visiting participants and the organisation around it. I could not have conducted my projects without you. I am very grateful for having you placed around me always up for cheering me

up, explaining the English language or joining me in the suffering of a DPhil student. Thanks to Dimitri Gavriloff for clinical and personal advice, for being chatty at any time, lighting up the atmosphere - if visiting a participant or sitting at high table. Thanks to Dr Jules Schneider for last minute writing advice, listening to my problems and for making me laugh. Thanks to the VV lab and Teele Palumaa for personal support and stimulating scientific conversations throughout the last three years and for reminding me how great human research is.

A huge thankyou goes to all the participants volunteering for my research studies. You have let me into your houses, you came to our lab, you shared your insomnia experience with me, you tracked your sleep every day, you let me stick electrodes on your head, you sat in dim light for more than eight hours, you filled out many questionnaires, you were truly motivated, and you taught me what it means to have sleepless nights seven days a week.

Last but not least, thanks to my family and friends if local or abroad. I am very grateful for your support on a day to day basis, for asking me about sleep, for sharing your compassion, for cheering me up and for telling me to keep going. Special thanks goes to the Maurer-Basecamp, for discussing everything with me until the very very end. As much as you dislike it, I am sure it helped me grow as a scientific researcher and lead me to where I am. Thanks to 53 Fairacres for being there whenever research let me down. Thanks to Katharina Lawall, Alicia Smith and Adam Mabrouk for your very valuable English knowledge. Adam, I am truly grateful for your unconditional love and your endless patience which have carried me through these past three years. Finally, I would also like to thank my grandfathers, Guenther Maurer and Heinz Lutz, who have pathed my way and to whom this work is dedicated.

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List of Abbreviations

BC-CCI ..... British Columbia cognitive complaints inventory
BCT ..... Bedtime consistency therapy
BT ..... Behavioural therapy
CBT-I ..... Cognitive behavioural therapy for insomnia
CEQ ..... Credibility/expectancy questionnaire
CI ..... Confidence interval
CT ..... Controlled trial
CT' ..... Cognitive therapy
DBAS ..... Dysfunctional beliefs about sleep
DISS ..... Daytime insomnia symptom scale
DLMO ..... Dim light melatonin onset
DPT ..... Dot probe task
DSM-V ..... Diagnostic and statistical manual of mental disorders
ECG ..... Electrocardiography
EEG ..... Electroencephalography
EMG ..... Electromyography
EOG ..... Electrooculography
ESRS ..... European sleep research society
ES ..... Effect size
ESS ..... Epworth sleepiness scale
GCTI ..... Glasgow content of thoughts inventory
GSII ..... Glasgow sleep impact index
HADS ..... Hospital anxiety and depression scale
ICD-10 ..... International statistical classification of diseases and related health problems
ICSD-3 ..... International classification of sleep disorders
ITT ..... Intention to treat
ISI ..... Insomnia severity index
MSLT ..... Multiple sleep latency test
N1 ..... Stage 1 sleep
N2 ..... Stage 2 sleep
N3 ..... Stage 3 sleep
NREM ..... Non-rapid eye movement sleep

PSAS..... Pre-sleep arousal scale
PSG.....Polysomnography
PVT.....Psychomotor vigilance task
RCT ..... Randomised controlled trial
REM .....Rapid eye movement sleep
RMMSD .....Root mean squared successive difference
RT ..... Reaction time
SC ..... Symptom checklist
SCN .....Suprachisamatic nuclei
SCNi ..... Sleep and Circadian Neuroscience institute
SE ..... Sleep efficiency
SOL..... Sleep onset latency
SRT.....Sleep restriction therapy
SSS .....Stanford sleepiness scale
SWA ..... Slow wave activity
SWS..... Slow wave sleep
SWS-L ..... Slow wave sleep latency
TIB..... Time in bed
TST..... Total sleep time
TWT .....Total wake time
UCT ..... Uncontrolled trial
WASO ..... Wake after sleep onset
WMZ .....Wake maintenance zone

Thesis overview

Insomnia is one of the most common health burdens world-wide. While pharmacological treatment is available, the current recommended first-line intervention is a multi-component psychological therapy called cognitive behavioural therapy for insomnia (CBT-I). Although randomised-controlled trials support the efficacy of CBT-I, its treatment mechanisms are not well understood.

This thesis sought to addresses this gap by focusing on the mechanisms of one of the chief components of CBT-I, Sleep restriction therapy (SRT). The first chapter introduces the subject matter and familiarises the reader with the complexity of insomnia. A systematic literature review then summarises theoretical and empirical evidence for putative mechanisms of SRT. This work concludes by introducing a new testable model of the SRT mechanisms-of-action followed by practice points and a research agenda (chapter two).

Chapter three describes the first randomised-controlled trial to systematically test the mechanisms of SRT. The restriction element of SRT was isolated by comparing a restricted time in bed with consistent bedtimes, showing treatment effects for insomnia severity and quality of life in favour of SRT. High-resolution measurements of sleep and daytime functioning further reveal improved sleep continuity, increased sleep pressure, diminished cognitive arousal, reduced sleep-related mentation and normalised subjective-objective sleep discrepancy, again in favour of SRT.

The fourth chapter extends this work by focusing on the impact of SRT on circadian phase. The presented study is the first to obtain dim light melatonin onset (DLMO) before and after two weeks of SRT and the first to conduct repeated measurements of subjective and objective vigilance. The study shows that SRT increases the phase angle between attempted sleep and DLMO. Furthermore, medium to large impairments are reported for subjective and objective vigilance measurements.

Finally, chapter five synthesises and critically reflects on results from the preceding chapters. Emphases are placed on methodological considerations, future research and implications for clinical practice.

CHAPTER 1:

INTRODUCTION

1 Preface

This chapter informs about the current understanding of insomnia disorder by first explaining the principles of sleep-wake regulation and subsequently summarising prevalence, costs, pathophysiology, aetiology and treatment of insomnia.

The content of section 3.4 about the aetiology of insomnia is published as follows: Omlin, X., Spiegelhalder, K., Maurer, L., & Kyle, S. (2018). Chapter 23, Psychobiology of Insomnia. In P.N. Murphy (Ed.). The Routledge International Handbook of Psychobiology (pp. 414-418). Edge Hill University, UK.

The contents of section 3.5.1 about sleep restriction therapy are published here: Maurer, L. F., Espie, C. A., & Kyle, S. D. (2018). How does sleep restriction therapy for insomnia work? A systematic review of mechanistic evidence and the introduction of the Triple-R model. Sleep Medicine Reviews.

2 Sleep and sleep-wake regulation

Sleep is a phenomenon that is shared by multiple creatures ubiquitous across evolution[1]. Considering that humans spend about one third of their lifetime asleep, it seems that sleep fulfils important functions[2]. Indeed, sleep is a fundamental behavioural state, characterised by the loss of consciousness and behavioural control[3]. It has a critical role in many important somatic and cognitive processes, as well as in maintaining the normal body and brain homeostasis[4].

Polysomnographic (PSG) measurement, which includes electroencephalography (EEG), electrooculography (EOG) and electromyography (EMG), is the gold-standard method to determine distinct sleep stages that alternate throughout the night[5]. In humans, sleep is depicted by the cyclic occurrence of rapid eye movement (REM) sleep and non-REM (NREM) sleep. Rapid eye movement sleep is featured by a rapid, desynchronised pattern of EEG (similar to waking EEG), rapid eye movements in the EOG and low muscle tone in

EMG[6]. Non-REM sleep includes slow wave sleep (SWS, stages 3 and 4 or N3) and lighter sleep stages 1 and 2 (N1 and N2) which are subdivided in the proportion of the low-frequency, high amplitude waves in the EEG[7]. All sleep stages alternate over the course of the sleep period in a regular manner. A sleep period is typically starting from N1, deepening through N2 to N3 and then proceeding to REM sleep. In adults, one cycle takes about 90 minutes and is repeated consecutively between four and six times during each night[6]. The amount of SWS is more prominent during the first half of the night, whereas the amount of REM sleep increases towards the end of the night[8]. Furthermore, the time course of slow wave activity (SWA) during N2 and N3, a quantitative measure of EEG slow waves (EEG spectral power in the frequency range of 0.75-4.5Hz), is used as a parameter for the homeostatic process. The homeostatic process is considered to reflect sleep pressure or sleep need and can be felt when wakefulness is maintained beyond the habitual bedtime into the night. Sleep pressure is assumed to build up during wakefulness and dissipates during sleep, symbolising recovery obtained from sleep[9,10]. When the homeostatic process increases progressively during wakefulness above a certain threshold, sleep is induced and when it decreases during (non-REM) sleep, wakefulness is invoked. Typically, SWA is initially high - in the first sleep episode - and exhibits an exponential decline across the successive non-REM episodes. This reflects the overnight dissipation of sleep inclination[9,10].

Another process that influences our wakefulness is the circadian rhythm. The circadian rhythm is controlled by the biological clock, located in the suprachiasmatic nuclei (SCN) of the hypothalamus[11]. The SCN receives photic information from the eye via the retinohypothalamic tract and has enabled humans to anticipate environmental change throughout evolution[12]. The circadian rhythm is mostly entrained by the environmental light-dark circle and can be detected in almost all variables that describe sleepiness and neurobehavioral performance[13,14]. Together, the homeostatic and the circadian regulating process describe the temporal profile of sleep and wakefulness, and consequently, determine the waking neurobehavioral functions as expressed in measurements of alertness and performance[15].

Though, sleep needs and sleep patterns are not the same for everyone. Instead, they differ from person to person, across a human lifespan[16] and from day to day[17]. Daily variability in sleep can often be a response to external factors, such as worry, medication, or medical symptoms[18]. Consequently, occasional sleepless nights are something most people have experienced at one point. However, if sleep difficulties occur more frequently or even persistently, and if they are accompanied by impaired daytime functioning, the person may have developed a sleep-wake disorder named insomnia[19].

3 Insomnia

3.1 Definition of insomnia

The term insomnia (Latin: insomnis = sleepless) is used in a variety of ways in the medical literature and popular press. It can occur as an independent disorder, as an isolated symptom or as a syndrome closely related to, or even directly caused by, other mental, somatic or physiological disorders[20]. Insomnia disorder refers to the occurrence of sleep problems, whereby sleep cannot be initiated, maintained or is disrupted by early morning awakenings[21].

To date, the classification criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V)[20], the International Classification of Sleep Disorders (ICSD-3)[22] and the International Statistical Classification of Diseases and Related Health Problems (ICD-10) are used for diagnosis[22]. At the time this research was planned, the criteria of the DSM-V prevailed and hence were applied to this thesis. In comparison to the previous version (DSM-IV/TR), the DSM-V has now given up the distinction between primary and secondary insomnia and only includes one diagnostic category named *Insomnia Disorder*. In order to be diagnosed with insomnia disorder, one must report the following criteria that are described in Table 1 below and derived from the DSM-V, p. 362.

Table 1. Criteria for insomnia disorder according to the DSM-V

A	A predominant complaint of dissatisfaction with sleep quantity or sleep quality with one or more of the following sleep difficulties: difficulty initiating sleep, difficulty maintaining sleep, and early morning awakenings.
B	The sleep difficulties cause significant distress or impairment in social, occupational, educational, academic, behavioural, or other important areas of functioning.
C	The sleep difficulties occur at least 3 nights per week.
D	The sleep difficulties have been present for at least 3 months.
E	The sleep difficulties occur despite adequate opportunity for sleep (e.g. adequate time and circumstances for sleep and a safe, quiet, and dark bedroom).
F	The symptoms are not better explained by and do not occur exclusively during the course of another sleep-wake disorder (e.g. hypersomnolence disorder; narcolepsy; breathing-related sleep disorders such as obstructive sleep apnea; circadian rhythm sleep-wake disorders such as delayed sleep-wake phase and shift work; parasomnias such as sleepwalking, sleep terrors, and nightmares; and restless legs syndrome).
G	The symptoms cannot be attributed to the effects of a substance (e.g. drug abuse and medication).
H	Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

3.2 Prevalence

Insomnia disorder is one of the most common health complaints worldwide and was ranked 11th in the list of important brain disorders with respect to global burden[23]. At symptom level (i.e. sleep difficulties are present but do not meet the full criteria for insomnia disorder), insomnia is very common (>50% of the population in a year), but often remits, for example after the cessation of an acute stressor[24,25]. In contrast to its symptomatic presentation, chronic insomnia (meeting full criteria) typically occurs persistently with a median duration of three years[26]. The persistence rates range from 56% to 74% at one year and 46% at three-year follow-up[27-29]. The worldwide point in time prevalence for insomnia depends on the diagnostic criteria that are applied and varies from 3.9% to 22.1%. In industrialised countries it is assumed that ~10% of the population suffer from insomnia disorder[30]. In the English population, where the research for this thesis was undertaken, the prevalence is estimated to be 5.8%[31].

3.3 Costs

Since insomnia was evaluated to have a high impact on global burden, it can be assumed that the disorder must present a high financial load on the healthcare systems, either through direct costs (i.e. medical consultations, hospitalisation, and treatments) or indirect costs (i.e. reduced productivity, sick leave or early retirement)[32]. No study has yet evaluated the financial costs of insomnia in the UK, however, a review of the costs of brain disorders in the UK refers to two studies conducted in France[33]. These studies reveal an estimate of the direct medical costs at €1.5 billion[34] and indirect costs of insomnia-associated work absenteeism at €1,472 (± 545) per employee, per year, reflecting a high financial burden to the society[35]. In the United States, the total cost of insomnia is estimated to exceed $100 billion per year, with most being spent on indirect costs[36].

Beyond financial costs, insomnia also affects general health[37] and quality of life[36,38,39]. Research has shown that symptoms of insomnia are related to adverse changes in health-related behaviours, such as smoking, high-risk alcohol consumption, and lack of physical inactivity[40]. Henceforth, insomnia has been associated with an increased risk for diabetes[41] and cardiovascular disease[42]. Additionally, the sleep-wake disorder has been linked to adverse changes in energy and mood levels[43], increased sensitivity to stress[44], sleep related accidents[45], impaired daytime functioning[46], deficits in memory, attention, alertness, and problem-solving[47], as well as to impairments in social and emotional functioning[48,49]. Moreover, insomnia is closely related to psychiatric disorders, such as depression[50] and anxiety[51].

3.3 Pathophysiology

Insomnia disorder is typically classified as a psychobiological disorder whereby psychological processes, such as thoughts, emotions and behaviours can dysregulate the biology and in turn, biological processes, such as circadian rhythm and sleep, can affect related psychobiological processes[25,52]. Hence, the sleep difficulties that insomnia patients experience are assumed to result from the interactions of both processes that manifest in

cognitive attributions like the inability to *shut off the brain*[53], but also in alterations of sleep physiology[54,55]. Cognitive and physiological factors have been extensively researched. On the one hand, it has been shown that experiences of intrusive and uncontrollable thoughts, but also the monitoring of bodily sensation at sleep times, contribute to the complaint of poor sleep by insomnia patients[56,57]. On the other hand, meta-analytic data revealed that the sleep of those with insomnia is characterised by disrupted sleep continuity, which in turn is reflected in decreased sleep efficiency, increased sleep onset latency and increased wake time, but also by diminished SWS and REM sleep[55]. Additionally, results from studies which applied spectral analysis to the electric brain activity during sleep showed that insomnia patients display an increase in fast EEG rhythms during NREM sleep[58-62]. This activity has been associated with higher cortical activation (*hyperarousal*) and might therefore interfere with the initiation and maintenance of sleep[25,63]. Besides hyperarousal, a small body of research has linked circadian dysrhythmia and homeostatic dysregulation to the symptoms of insomnia[64]. With regards to circadian dysrhythmia, studies have shown that sleep onset difficulties in insomnia patients are associated with a circadian phase delay[65], while early morning awakenings occur in relation to a circadian phase advance[66]. Evidence for a dysregulation of the homeostatic sleep drive in insomnia is currently limited with some studies indicating a deficiency in SWA[61] and others showing no difference between good sleepers and people with insomnia[67].

3.4 Aetiology

While higher cortical arousal may characterise the manifestation of insomnia, several conceptual models have been proposed to account for the development and maintenance of insomnia from an acute-to-chronic problem. Richard R. Bootzin[68] proposed a stimulus control account of insomnia in the 1970s, which has served as the foundation for successive theoretical models. He refers to the behavioural principle of a simple conditioning history, whereby the pairing of a stimulus with a specific behaviour will lead to a higher probability of this stimulus to trigger only one response. In insomnia, Bootzin proposes that cues normally associated with sleep are paired with activities other than sleep (stimulus

dyscontrol) leading to a dysfunctional bed-sleep association. Seminal models since this early work include the 3P Model[69], the Neurocognitive Model[70], the Psychobiological Inhibition Model/Attention-Intention-Effort Pathway[71,72], the Cognitive Model of Insomnia[52] and a recent Neurobiological Model of Insomnia[73]. Since the understanding of the aetiology is essential for the treatment of insomnia, and hence for the development of this thesis, the *main* insomnia models are summarised in more detail below.

The 3P Model (also known as *Diathesis-stress Model*)[69] was the first fully articulated model of insomnia to gain broad acceptance. It proposes that insomnia is based on the interaction of three different factors starting with the letter 'P' (see Figure 1 below).

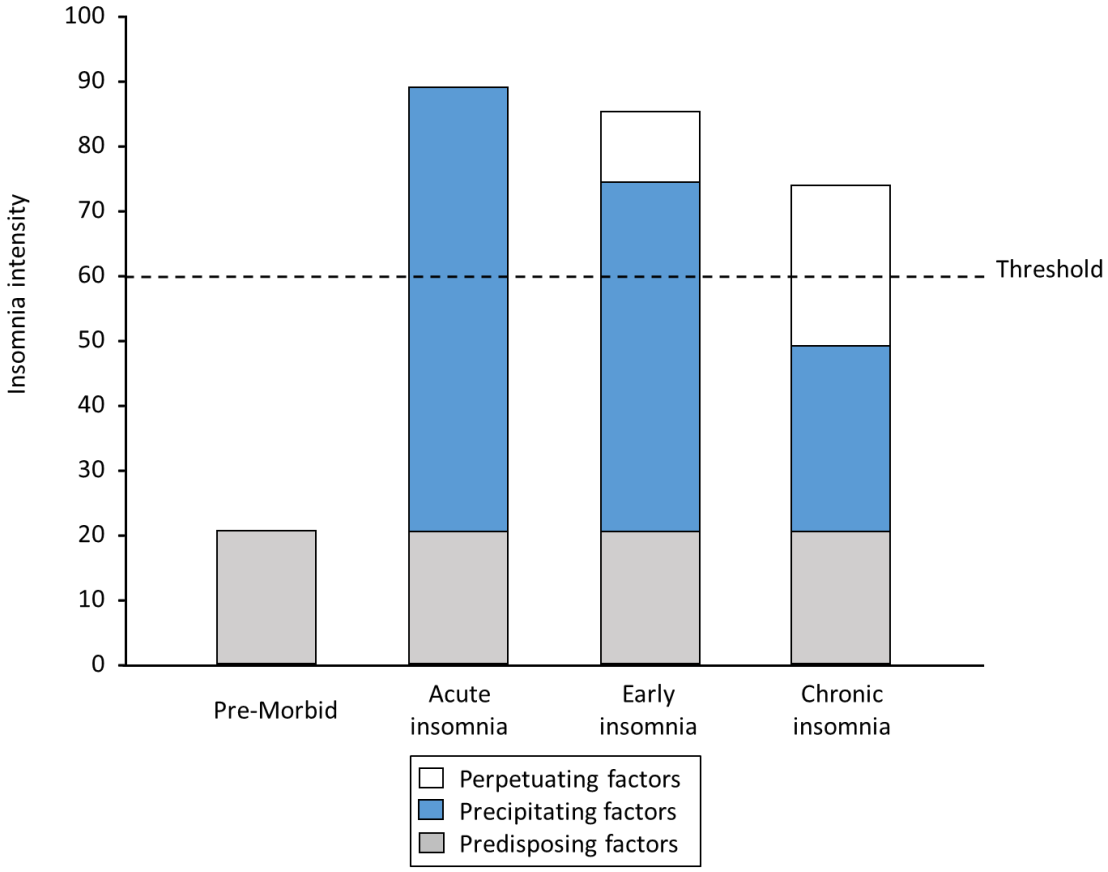


Figure 1. The classic representation of the 3P Model. It proposes that the development and maintenance of insomnia disorder is based on the interaction of predisposing, precipitating and perpetuating factors. Redrawn version from Espie CA, Kyle SD, Cognitive and behavioural psychological therapies for chronic insomnia, in: Barkoukis TJ, Matheson JK, Ferber R, Dohramji K (Ed.), Therapy in Sleep Medicine, pp. 161–171.

First, there are predisposing factors from the biopsychosocial spectrum. These are considered as a vulnerability to develop insomnia (e.g. a family history of sleep disorders, certain personality traits). Second, precipitating factors like life stressors interact with this predisposition, triggering acute disturbances in sleep. Critically, what determines the course of insomnia, and the maintenance of persistent poor sleep, is a number of perpetuating factors. These can be coping strategies like practicing non-sleep activities (e.g. ruminating) in the bedroom and the tendency to spend excessive amounts of time in bed. As a result, normal cues associated with sleep (like the bed) are paired with activities other than sleep. This may lead to stimulus dyscontrol, whereby the bedroom environment triggers wakefulness, and mismatch between sleep opportunity and sleep ability, leading to weakened sleep drive and fragmented sleep.

Perlis et al. extended the *3P Model* to the *Neurocognitive Model*[70] and integrated neurobiological and neurophysiological observations (see Figure 2). The authors state that classical conditioning of hyperarousal can also serve as a perpetuating factor for chronic insomnia, whereby hyperarousal contains cognitive, somatic and cortical components. When the coupling of sleep-related stimuli (like the bed) and insomnia related wakefulness gets repeated, the sleep-related stimuli conclusively provokes higher levels of cortical arousal than usual. This manifests as increased high-frequency (beta and gamma) EEG activity at sleep onset and during sleep. It precipitates the rise of cognitive and somatic arousal; that is, cognitive arousal is the *by-product* of cortical arousal rather than the primary determinant of insomnia. The conditioned cortical arousal further contributes to enhanced sensory processing and long-term memory formation. Enhanced sensory processing during NREM sleep is suggested to blur the distinction between sleep and wakefulness and therefore leads to a *sleep state misperception* or *paradoxical insomnia,* in which insomnia patients underestimate the time they spent asleep[74,75]. The enhanced long-term memory formation around sleep onset and during NREM sleep is thought to interfere with sleep initiation and maintenance, which are considered two main symptoms of insomnia[76].

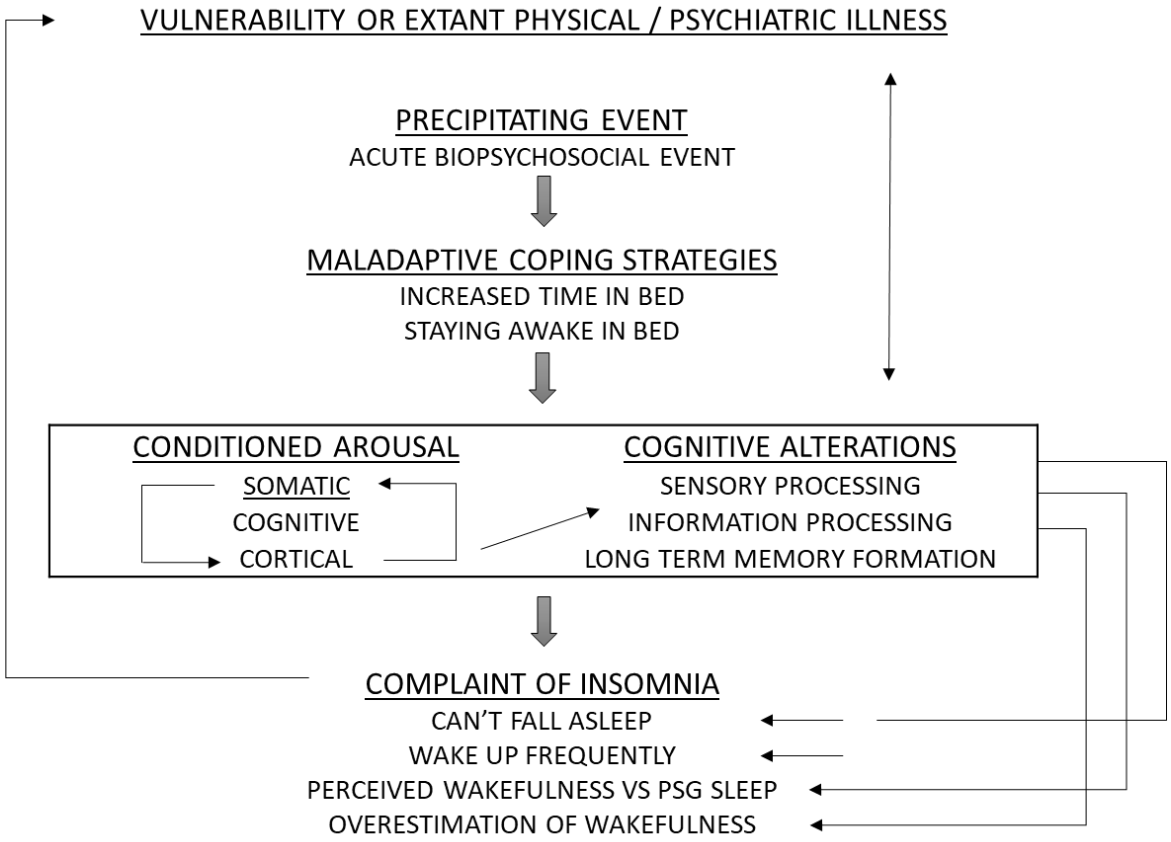


Figure 2. A schematic representation of the neurocognitive model. The classical conditioning of hyperarousal and sleep-related stimuli enhances sensory processing and long-term memory formation around sleep onset and during sleep. Therefore, insomnia gets manifested. Redrawn version from Perlis, M., et al., Psychophysiological insomnia: the behavioural model and a neurocognitive perspective. Journal of sleep research, 1997. 6(3): p. 179-188.

The *Psychobiological Inhibition Model*[71] attributes an important role to selective attention in the development and maintenance of insomnia (see Figure 3). The model states that stressful life events lead to physiologic and psychological arousal, which drives selective attention towards life stressors and towards the occurrence of insomnia symptoms. During acute insomnia, the arousal is sufficient to interfere with the normal regulation of sleep and to prevent the normal inhibition of wakefulness. The acute insomnia might then resolve or be perpetuated according to the natural course of the stress state. The transfer from acute to chronic insomnia is hypothesised to result from an attention-intention-effort (A-I-E) pathway[72]. First, when the person cannot fall asleep, the attention shifts from the life stressor

to the sleep itself and attention is drawn to an otherwise automatic process. Second, the attention promotes an action and an intentional process is initiated. The normal downregulation of arousal becomes inhibited. Furthermore, the inability to sleep contributes to an active effort to try falling asleep and further prevents the inhibition of wakefulness. These processes are antithetical to sleep: the good sleeper passively abandons wakefulness, a process devoid of effort, intention or pre-occupation.

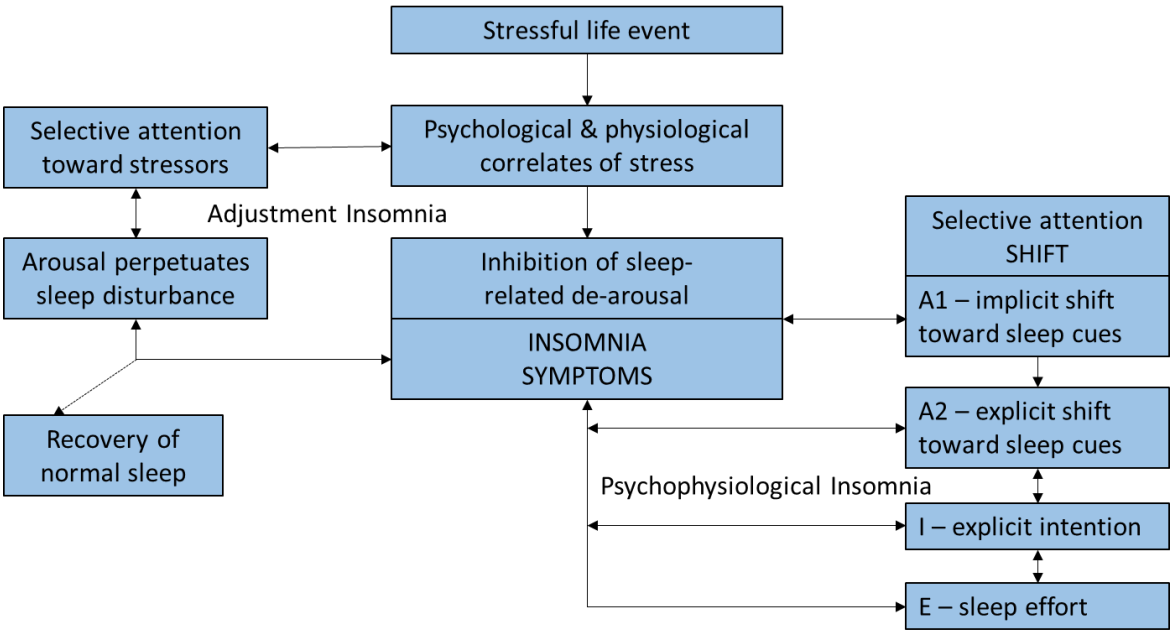


Figure 3. A schematic representation of the development and maintenance of insomnia according to the attention-intention-effort (A-I-E) pathway. The model proposes that each of the three cognitive phenomena act in a hierarchical manner to transit stress-induced sleep problems into chronic insomnia. Redrawn version from Espie, C.A., et al., The attention-intention-effort pathway in the development of psychophysiological insomnia: a theoretical review. Sleep Med Rev, 2006. 10(4): p. 215-45.

Buysse and colleagues claim that the previous models of insomnia are clinically useful but lack neurobiological specificity. In the proposed *Neurobiological model*[73] insomnia is considered a disorder of sleep-wake regulation characterised by constant wake-like activity in neural structures during NREM sleep. The model acknowledges that neural structures and circuits that regulate sleep and wakefulness also produce homeostatic sleep drive, circadian rhythms and psychobiological arousal. These structures include hypothalamic centres that control the *switch* between wakefulness and sleep. Furthermore, they involve brainstem hypothalamic arousal centres innervating cortico-limbic systems, which regulate cognitive

and emotional arousal as well as the default-mode network that may regulate self-awareness. These brain systems and processes are highly interactive and have extensive feedback loops among themselves and with each other. In insomnia, however, the authors hypothesize over-activation of cortico-limbic and brainstem hypothalamic centres, as well as a relative increase in psychobiological arousal. Consequently, the normal circadian and homeostatic functions may become impaired. Increased arousal coupled with reduced circadian and homeostatic sleep drive may contribute to both night-time (sleep initiation and maintenance problems, misperception of sleep) and daytime (fatigue, emotional reactivity) features of insomnia. A poor function of the sleep-wake switch (i.e., a simultaneous activation of wake- and sleep promoting neurons) that reflects in more high-frequency brain signals during sleep[63,77], could also result in increased wakefulness or poorer sleep quality experienced by insomnia patients.

3.5 Cognitive behavioural therapy for insomnia and its components

In 2017, the European Sleep Research Society (ESRS) published treatment guidelines for the diagnosis and treatment of insomnia. The guidelines were based on a systematic review of meta-analyses of various pharmacological and non-pharmacological interventions[78]. While benzodiazepines, benzodiazepine receptor agonists and a range of antidepressants are effective in the short term treatment of insomnia (≤ four weeks; weak recommendation, moderate-quality evidence)[79], a recent meta-analysis revealed that more than 60% of the response to medication was also observed with placebo[80]. These large placebo effects can be explained by the optimisation of placebo mechanisms through which therapeutic effects might have been achieved. Potential placebo mechanisms are discussed by the authors of the meta-analysis and include regression to the mean, treatment expectancy, social desirability, actual ingestion of a pill, the Hawthorne effect, cognitive dissonance and participation in research[80].

In line with other established recommendations, such as the American College of Physicians and the British Association for Psychopharmacology[81-84], the authors of the ESRS guidelines

recommended CBT-I as the first-line treatment because it reveals high-quality evidence and results in sustainable improvements in sleep variables[78]. The multi-component therapy involves cognitive and behavioural aspects that target the perpetuating factors of insomnia (see Table 2). The cognitive components of CBT-I can be related to the cognitive model of insomnia[52] and typically include strategies designed to identify, challenge and change misconceptions about sleep, faulty beliefs about insomnia and daytime consequences[85]. Behavioural components involve sleep hygiene, relaxation therapy, stimulus control and sleep restriction therapy. Sleep hygiene education commonly informs about bedroom and lifestyle factors that promote or disrupt sleep[86], but has insufficient evidence as a single-component intervention[87]. Relaxation therapy refers to procedures aimed at reducing tension and intrusive thoughts such as progressive muscle relaxation, autogenic training or meditation[87].

Table 2. Components of Cognitive behavioural therapy

CBT-I component	Content
Sleep hygiene	Aims to make people more aware of behavioural, environmental, and temporal factors that may be detrimental or beneficial to sleep.
Relaxation therapy	Aims at reducing tension or minimising intrusive thoughts that may interfere with sleep.
Stimulus control	Aims to help the person to re-associate the bed and bedroom with sleep, and to re-establish a consistent sleep/wake pattern.
Sleep restriction therapy	Involves limiting the amount of time spent in bed to the actual amount of time spent asleep, creating a mild sleep deprivation, and then increasing sleep time as the efficiency of sleep improves.
Cognitive therapy	Aims to examine and change the person's beliefs and attitudes about insomnia.

Note. CBT-I=Cognitive behavioural therapy; this table is adapted from the guidelines of the National Institute for Health and Care Excellence (NICE) for the management of long-term insomnia (>4 weeks; https://cks.nice.org.uk).

Based on Bootzin's model, the objective of stimulus control is to re-condition the association between the bed and bedroom with sleep by advising the patient to (1) go to bed only when sleepy; (2) leave the bed when unable to sleep; (3) use the bed/bedroom only for sex and sleeping; (4) rise at the same time every day, and (5) not to nap during the day[68]. The final component, sleep restriction therapy, was built upon the 3P model and has also been shown to be effective as a standalone intervention[88]. It curtails the amount of time in bed to the actual amount of time spent asleep, thereby creating a mild sleep deprivation, and then lengthening sleep time as sleep efficiency improves (see detailed description below)[89]. It is international consensus that CBT-I is the first-line treatment for insomnia, but despite its support from multiple randomised-controlled trials, its treatment mechanisms are currently not well understood[90]. Hence, it is not clear if every patient needs cognitive and behavioural treatment, if one of the components could be sufficient for successful treatment, or if the treatment should be tailored to the individual[91].

3.5.1 Sleep restriction therapy

Relative to the other components of CBT-I, SRT is believed to be one of the most active elements[78,92]. It is considered as a guideline intervention by the American Academy of Sleep Medicine practice parameters[93], provides a cost-efficient solution to treat insomnia and has been shown to be effective on its own[88].

Arthur Spielman first formulated the concept of SRT in 1987[94]. His approach was guided by the idea that addressing factors that perpetuate insomnia is essential for therapeutic success[95]. People suffering from insomnia often feel that extending their time in bed (TIB) will help compensate for long sleep latencies or disrupted sleep. Excessive TIB is assumed to be one important factor that sustains insomnia[69] because it can lead to more fragmented sleep[96,97]. Sleep restriction therapy aims to improve the consolidation of sleep and compels its occurrence to a specific time by restricting TIB. After filling out a sleep diary for two weeks, an upper limit of the TIB is set to equal the average sleep time and lower the chances of spending TIB awake. For example, a patient who reports to spend nine hours in bed, but

only reports six of those sleeping would be assigned a six-hour sleep window. In agreement with the patient, the therapist establishes the time for rising first and then sets the time for retiring at night to equal the new prescribed TIB (typically no less than $\leq$ 5hrs). With the continuation of the treatment, sleep efficiency (SE) is used as a criterion for making weekly changes to TIB for the duration of the treatment (about four to six weeks). It is calculated by dividing the total sleep time (TST) by the TIB and therefore takes into account the wake time that occurs before and after sleep onset. High SE, reflecting less wakefulness during TIB, is regarded as an aspect of satisfactory and consolidated sleep[94]. Therefore, only when patients report a high SE, the TIB will be increased (see Table 3 below).

Table 3. Sleep window titration according to Spielman et al. (1987)

Sleep efficiency	=>	**Sleep window (time in bed)**
Less than 85%	=>	Decrease by 15 minutes
85-90%	=>	Keep sleep window
More than 90%	=>	Increase by 15 minutes

Through a series of weekly adjustments to TIB, an optimal bedtime length is reached, with the aim of maintaining high SE without excessively curtailing the length of sleep, while delivering improvements in daytime functions. However, variability in the implementation of SRT is present at every level (sleep window generation, minimum TIB, SE titration criteria, positioning of the sleep window) and may therefore result in different sleep window trajectories. That is, adaptation of the sleep window over time (to improve sleep quality and/or may vary markedly depending on what SRT criteria are applied[98]. Sleep restriction therapy is routinely applied as part of cognitive-behavioural therapy for insomnia (CBT-I)[78,90,92], but also as an independent, single-component intervention[88,93]. The efficacy of SRT was recently reviewed by Miller et al.[88]. The authors identified nine studies, four of which met adequate methodological strength. Results revealed moderate-to-large effect sizes for sleep diary measures of sleep onset latency (SOL), wake-time after sleep onset (WASO), and SE, as well as a small effect size for increased TST. While effective, the implementation

of SRT may also be associated with short-term side effects. It can lead to transient increases in somnolence, fatigue, and impaired vigilance[99].

4 Thesis rationale

This chapter has illustrated the importance of insomnia treatment. Insomnia is common in the population, increases the risk for other health conditions, comes with costs for the society, reduces quality of life and manifests in psychobiological symptoms. Insomnia models inform about the aetiology of the disorder and have led to the design of an effective treatment targeting cognitive and behavioural pathways. Although multiple randomised-controlled trials demonstrate the effectiveness of CBT-I, they neither inform about how the treatment exerts its effects, nor do they test the models the treatment is based upon. Literature across different clinical fields in psychology has emphasised to bridge this gap by conducting more mechanistic-based research[100,101]. Researchers argue that understanding the processes accounting for treatment effects would allow investigators to refine current treatment protocols and tailor treatments more effectively[102]. Treatment mechanisms can be derived from aetiological models and assessed by mediators in randomised-controlled trials. In the insomnia field, the authors Schwartz and Carney reviewed potential mediators of full CBT-I in insomnia patients[90]. They identified nine different mediators categorised by behaviour, cognition and hyperarousal, and extracted results of respective measurements from eligible CBT-I trials. The authors found some evidence for accordance between mechanisms and research findings, but their results were limited by the lack of consensus regarding the most important mediators to explore, and the limited application of mediation analysis within trials. Schwartz and Carney focused exclusively on the mediators of studies that implemented full CBT-I, hence it was not possible to draw conclusions for the impact of each of the components. Consequently, the mechanisms of the multi-component therapy could not be teased apart. This is especially problematic as CBT-I is conceptualised as one treatment, yet it is constituted by a system of cognitive-behavioural *therapeutics*. Consequently, to understand how the system works, these components need to be delineated. Likewise, for testing models.

The here presented thesis was developed in order to bridge this gab. Building upon the work from Schwartz and Carney, it became clear that multiple components thwart the investigation of treatment mechanisms. Hence, the focus of this research is on only one component of CBT-I, sleep restriction therapy. Sleep restriction therapy is the component of choice as it is assumed to be the most effective ingredient of CBT-I, it is used as a standalone therapy and is not just based upon a theoretical model of insomnia (the 3P model), but also on testable hypotheses on sleep regulation. The focus on one component also allows a complex investigation of mechanisms on various levels (e.g. cognitive, behavioural and physiological), which previous CBT-I studies did not embrace[90], but that enables an integrated research approach on a psychobiological disorder.

5 Aims

The overall aim of this thesis is to elucidate the mechanisms of actions of SRT in order to better understand how the systematic restriction and titration of time in bed exerts treatment effects in people with insomnia disorder. This research aims to develop a theory and evidence based driven framework of potential pathways of SRT to facilitate empirical mechanistic research that teases cognitive-behavioural and physiological factors apart. By doing so, we hope to test our current understanding of insomnia as a psychobiological disorder and provide a base for improving insomnia treatment and potentially tailoring it to the individual.

This thesis investigates the underlying mechanisms of SRT by (a) deriving treatment mediators of SRT from the theoretical insomnia literature; (b) evaluating empirical evidence for the proposed mediators from the SRT literature; (c) introducing a new model of how SRT engenders therapeutic change; (d) experimentally testing such a model; and (e) elaborating acute circadian effects (see Table 4).

Table 4. Specific aims

Study	Specific Aims
Chapter 2 Systematic literature review	- To derive mechanisms of SRT from the insomnia literature - To evaluate evidence for these putative mechanisms - To introduce a new testable model of SRT mechanism-of-action - To set out a research agenda aimed at stimulating prospective investigations
Chapter 3 The MARTINI study	- To develop a dismantling trial design that enables the systematic evaluation of treatment mechanisms of SRT - To investigate clinical treatment effects and the importance of the restriction component of SRT - To evaluate mechanistic treatment effects of SRT in comparison to a control group
Chapter 4 The ESPRIT study	- To develop an exploratory within-subjects study design in order to determine the acute treatment effects of SRT on the relationship of the circadian system and the sleep-wake cycle

CHAPTER 2:

EVIDENCE FROM THE LITERATURE FOR THE PUTATIVE MECHANISMS OF SLEEP RESTRICTION THERAPY

1 Preface

This chapter informs about the evidence from the literature for the putative mechanisms of SRT and introduces a new framework for its mechanistic pathways. The contents of this chapter are published as follows: Maurer, L. F., Espie, C. A., & Kyle, S. D. (2018). How does sleep restriction therapy for insomnia work? A systematic review of mechanistic evidence and the introduction of the Triple-R model. Sleep Medicine Reviews.

2 Abstract

For over 30 years sleep restriction therapy has been used to treat insomnia but we know very little about how this therapy exerts its effects. When SRT was first described, it was hypothesised to treat insomnia by addressing four key factors: strengthening homeostatic sleep pressure, inhibiting perpetuating practices (excessive time in bed), attenuating hyperarousal and tightening regulatory control of sleep by the endogenous circadian pacemaker.

We conducted a systematic literature review in search of evidence for these putative mechanisms-of-action. A total of 15 randomised and non-randomised studies investigating SRT met inclusion criteria. For each study, we extracted all variables associated with the proposed mechanisms and assessed study quality using a structured appraisal tool. The extracted variables were time in bed (TIB), napping, variability in sleep, markers of circadian rhythmicity, measurements of sleep pressure/sleepiness, and assessments of arousal.

Overall study quality was poor as indicated by a mean quality score of 17 (out of a possible range of 0 to 31). No study indicated, or indeed was designed to test, whether changes in the proposed mechanisms act as *mediators* of treatment outcomes. Of all reviewed studies, most reported a reduction in TIB (10/10) and/or revealed a decrease in sleep onset latency (10/14), indexing increased sleep pressure. However, such changes were most often reported at the end of treatment, reflecting an outcome and not a mechanism of SRT per se. Evidence for reduction in arousal (4/4) and night-to-night sleep variability (2/2) was found in only a small number of uncontrolled studies while there was no evidence for change in circadian phase or periodicity (0/1).

Our review suggests that SRT targets some of the hypothesised processes but specifically designed mechanistic evaluations are needed. We introduce a new testable model of SRT mechanism-of-action (*Triple-R*) and set out a research agenda aimed at stimulating prospective investigations.

3 Introduction

The '3P model' (also known as 'Diathesis-stress model')[69] has served as the conceptual basis for the application of SRT. It proposes that predisposing factors precede the onset of sleep difficulties and increase individuals' vulnerability to insomnia; precipitating factors typically involve acute stressors that trigger the onset of insomnia; and perpetuating factors maintain symptoms by mismatching sleep opportunity and sleep ability (see Figure 1 in chapter one). When Spielman, Saskin and Thorpy first fully articulated SRT in 1987[94], they stated that SRT therapeutically addresses one of the key factors that they believe perpetuates insomnia: the tendency to remain in bed while awake. By restricting TIB, sleep opportunity is curtailed, resulting in partial sleep deprivation that may be crucial for therapeutic effects. Results of the seminal SRT study revealed that patients experienced an increase in TST as well as improvements in SOL, SE, and subjective insomnia symptoms after eight weeks of treatment. When discussing the results of this first trial, the authors proposed several mechanisms that may have led to sleep improvements:

> *'The mild sleep loss produced at the beginning of sleep restriction therapy may be crucial for its effectiveness. The partial sleep deprivation may have consolidated sleep directly, produced daytime fatigue that dampened the insomniacs' chronic state of hyperarousal, or reduced maladaptive conditioning because less time was spent lying awake in bed […]. Getting into bed early, staying in bed late, and napping are short-sighted strategies that foster the fluctuations in the distribution and amounts of sleep and waking that are characteristic of the sleep of insomniacs. The present approach of restricting TIB stabilizes sleep.'* (pages 53-54[94])

In 2011, Spielman, Yang and Glovinsky similarly emphasised that SRT may work through strengthening homeostatic sleep drive, inhibiting perpetuating practices (excessive TIB and napping), attenuating hyperarousal and tightening regulatory control of sleep by the endogenous circadian pacemaker[103]. Each of these pathways can be indexed via commonly employed

measurements in sleep research (see Table 5 below) permitting appraisal of mechanistic change. Building upon the importance of understanding mechanisms-of-action of psychological treatments[101], we conducted a systematic review of the available literature with the aim of identifying mechanistic variables associated with SRT outcomes. Finally, we conclude with a new expanded and testable model of SRT mechanism of action.

Table 5. Theoretical mechanisms of SRT and proposed mediator measurements.

Mechanism	Measurements
Perpetuating practices (excessive TIB and napping)	Time in Bed/ Napping during T/ at PT (e.g. sleep diary, actigraphy)
Circadian sleep-wake cycle	Variability in sleep and bedtime parameters during T/ at PT (e.g. sleep diary, actigraphy) Markers of circadian rhythmicity during T/ at PT (e.g. phase/periodicity/amplitude of body temperature)
Homeostatic sleep drive	Sleep pressure during T/ at PT (e.g. SOL, SWA, subjective and objective sleepiness)
Hyperarousal/conditioned arousal	Cognitive/ physiological Arousal during T/ at PT (e.g. Pre-Sleep-Arousal Scale, cortisol concentration, high-frequency EEG)

Notes. T=Treatment; PT=Post-Treatment; PSG=Polysomnography; SOL=Sleep onset latency, SWA=Slow wave activity; TIB=Time in bed; EEG=Electroencephalography

4 Methodology

4.1 Search strategy

The systematic review was undertaken in compliance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for the reporting of systematic reviews[104] to evaluate evidence regarding mechanisms involved in SRT. We therefore searched for both randomised and non-randomised single-component SRT studies which implemented therapy guidelines consistent with the approach of Spielman and colleagues[94]. To identify relevant articles, we conducted a thorough search of Web of Knowledge, PubMed, and Scopus. Databases were accessed via the University of Oxford Ovid and EBSCO online system, with a

final search date of February 2018. Additional records were identified by accessing journals focused on sleep research, namely: 'Journal of Sleep Research', 'Sleep', 'Sleep Medicine' and 'Behavioral Sleep Medicine'. We applied the same subject and text word strategy as Miller et al. [88], with 'insomnia' and' sleep restriction' or 'sleep compression' as the primary search terms. Sleep compression was included as a primary search term to capture articles that might have used a form of sleep restriction that is similar to SRT or used SRT as a control group. If the titles included 'insomnia', 'behavior/ behaviour' or 'treatment' the online article was accessed, and the abstract examined. We included randomised controlled (RCT), controlled (CT) and uncontrolled trials (UCT) as long as SRT was applied in adults with insomnia. We included studies that combined SRT with sleep hygiene because there is currently no evidence that sleep hygiene is an active single-component treatment[93,105,106].

4.1.1 Inclusion criteria

a) Adults ($\geq$ 18 years)
b) Whole sample met criteria for insomnia disorder or insomnia symptoms, as verified by diagnostic criteria; self-report; or objective measures in the sleep laboratory
c) Investigated a standalone intervention (or combination with sleep hygiene) involving restriction of TIB for the treatment of insomnia, consistent with the approach of Spielman[94]
d) Examined sleep-wake outcomes before and after treatment
e) Peer reviewed paper published in English between 1987 and February 2018
f) Reported data on at least one variable associated with one of four proposed mechanisms (homeostatic sleep drive, circadian sleep-wake cycle, perpetuating practices, hyperarousal/conditioned arousal; see Table 5)

4.1.2 Exclusion criteria

a) Conference abstract, dissertation, letter, case study, review or case series
b) Applied sleep compression as the intervention

4.2 Quality assessment

The Downs and Black checklist[107] was used to assess the methodological quality of all included studies by the first author (LFM). It is considered one of the 'best' tools for evaluating randomised and non-randomised intervention studies[108]. The checklist includes 27 items assessing study reporting, external and internal validity, and has good inter-rater reliability[107]. Item 14, regarding participant blinding to intervention was removed given the nature of behavioural treatment. Thus, the possible score ranged from zero to 31, with higher scores indicating better methodological quality.

4.3 Data extraction

Articles were screened based on title, abstract and full text by the first author (LFM). Search results were exported to a reference management software (EndNote X7) and duplicates were removed. Eligibility of the papers was finalised following review and discussion between authors (SDK). We extracted information from each study in relation to the four mechanistic pathways proposed by Spielman and colleagues. We then organised review results by these four pathways and measurements used to index them (see Table 5).

5 Results

Records identified through database searching with keywords yielded 1671 papers (WEB OF KNOWLEDGE = 786, PubMed = 600, SCOPUS = 284). An additional 582 records were identified through journal specific search. Duplicates were removed, and 1620 titles were screened; of which 358 abstracts were acquired. From these, 27 studies were deemed potentially eligible and a full version of the article was therefore accessed. Of these 27 studies, 12 were excluded as they did not meet the inclusion/exclusion criteria. The selection process is shown in Figure 4.

5.1 Study characteristics

Fifteen studies met all criteria and were included in the synthesis. This comprised seven controlled[109-115] and eight uncontrolled trials[94,99,116-121]. Studies took place at various sites

worldwide: seven in the USA, four in Great Britain, two in Australia, one in New Zealand, and one in China. Seven studies had less than 18 participants, four yielded between 32 and 46 participants, and four reported over 70 participants. The total number of participants included in the analyses was 598. The average age of participants ranged from 36 to 69 years. All studies included mixed-gender groups, however there was a greater proportion of women reported in the descriptions of the study population (66.21%). Six studies implemented SRT in combination with sleep hygiene[110,112,113,115,116,122].

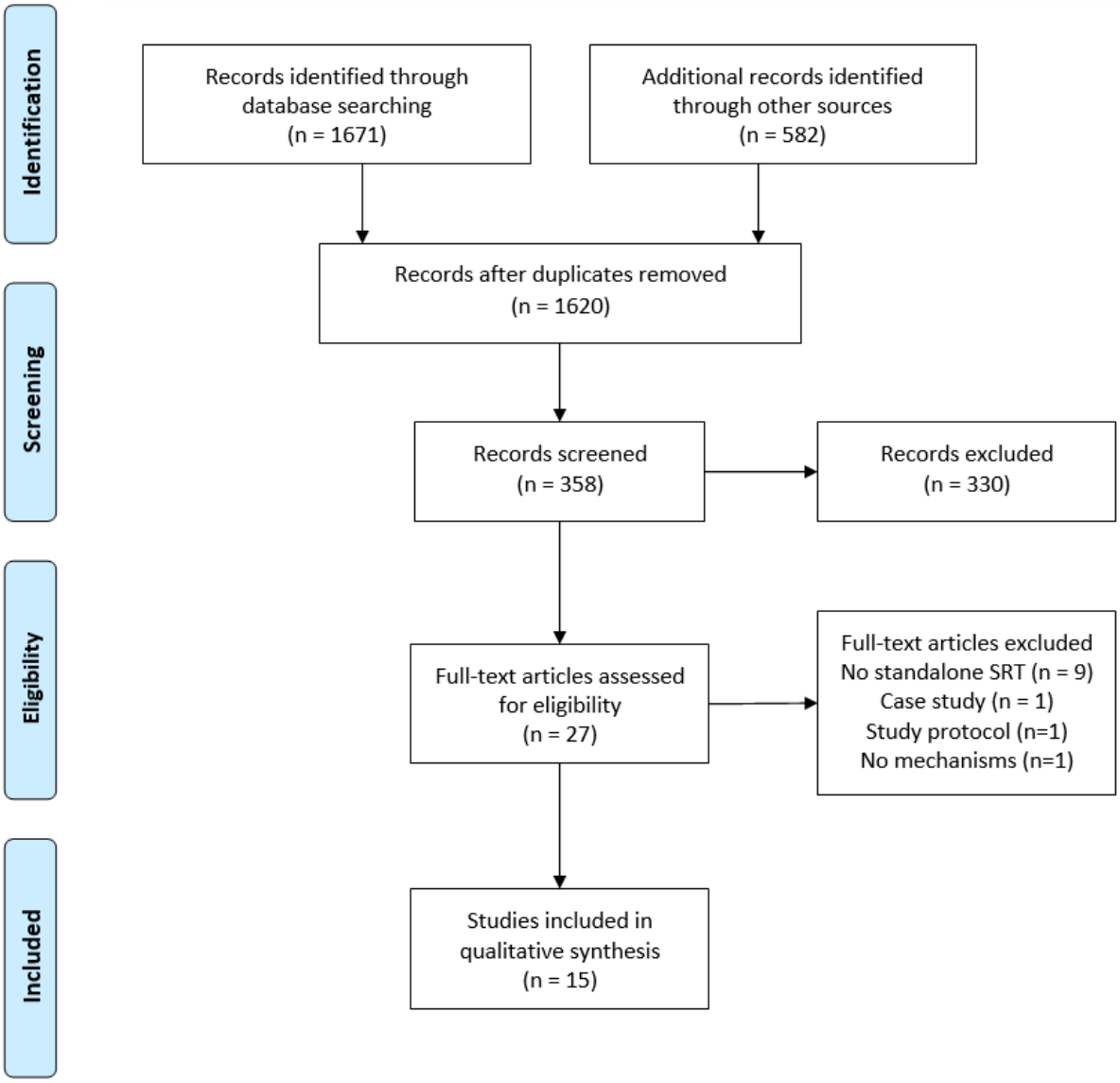


Figure 4. Prisma flowchart[104] showing the process of selecting studies

Assessment of study quality by the *Black and Downs* questionnaire revealed that overall study quality was poor, scoring between 13 and 21 (mean score 17.38 $\pm$ 2.33, see Appendix A) out of

a possible 31. More than half of the studies did not employ a randomised-controlled design and therefore lacked internal validity. Reports of side effects, treatment delivery (therapist, facilities) and detailed descriptions of the recruitment processes were typically missing, resulting in low scores on external validity.

5.2 Narrative synthesis

No study reported, or was designed to report, whether changes in the proposed mechanisms act as mediators of treatment outcomes. Nevertheless, in line with the inclusion criteria, all studies reported information on at least one of the proposed mechanisms. Hence, ten studies reported information regarding perpetuating practices (i.e. TIB and napping), four on arousal (physiological and cognitive measurements), 14 on markers of homeostatic sleep drive (mainly SOL) and three on the circadian sleep-wake cycle (variability in sleep parameters and markers of circadian rhythmicity). However, changes in variables were most often reported at the end of treatment, reflecting an outcome and not necessarily a mechanism of SRT. In fact, only five studies (33%; mostly uncontrolled) obtained measurements of hypothesised mechanisms *during* the course of SRT, in addition to measurements after treatment completion. An overview of all included studies and their mechanistic findings can be found in Table 6.

Table 6. Description of mediator variables in SRT trials.

Study	Design	Insomnia sample	Mediator measures (T&PT)	Mediator findings within the SRT group	Quality rating
Bliwise et al., 1995[109]	SRT vs RLT	32 elderly people with insomnia (community)	Homeostatic sleep pressure (SOL)	SOL decreased significantly from baseline to post-treatment.	17/31
Brooks et al., 1993[116]	SRT vs RLT	9 elderly people with insomnia (community)	Perpetuating practices (TIB) & homeostatic sleep pressure (SOL)	TIB decreased significantly from baseline to post-treatment (sleep diary & actigraphy). SOL showed a trend to decrease (sleep diary).	15/31
Epstein et al., 2012[110]	SCT vs SRT vs MCI vs WLC	179 elderly people with insomnia (community)	Perpetuating practices (TIB) & homeostatic sleep pressure (SOL)	TIB and SOL decreased significantly from baseline to post-treatment (sleep diary).	18/31
Friedman et al., 1991[112]	SRT vs RLT	22 elderly people with insomnia (community)	Perpetuating practices (TIB), homeostatic sleep pressure (SOL) & circadian sleep-wake cycle	The SRT group displayed significant reductions in TIB, TIB variability and SOL from baseline to post-treatment (sleep diary).	14/31
Friedman et al., 2000[113]	SRT vs NSRT vs SH	39 elderly people with insomnia (community)	Perpetuating practices (TIB) & homeostatic sleep pressure (SOL & sleepiness)	TIB and SOL decreased significantly from baseline to post-treatment (sleep diary). Subjective sleepiness decreased from baseline to end of treatment and follow-up, while objective sleepiness seemed to be increased after treatment.	18/31
Kyle et al., 2011[99]	SRT	18 people with insomnia (community)	Homeostatic sleep pressure (SOL & sleepiness) & arousal	SOL (sleep diary) and sleep effort (indicator for arousal) decreased significantly from baseline to post-treatment. Ninety-four percent of the participants reported “extreme sleepiness” during SRT.	20/31

Kyle et al., 2014[123]	SRT	16 people with insomnia (community)	Perpetuating practices (TIB) & homeostatic sleep pressure (SOL & sleepiness, RT)	TIB decreased significantly during the first week of treatment and increased by 15min over the following three weeks of the treatment. SOL decreased significantly from baseline to post-treatment (sleep diary). Sleepiness (obtained by ESS and RT) increased significantly from baseline to week one, week two and week three of SRT but decreased at post-treatment.	19/31
Miller et al., 2013[118]	SRT	9 people with insomnia (community)	Perpetuating practices (TIB), homeostatic sleep pressure (SOL & sleepiness) & arousal	TIB and SOL decreased significantly from baseline to post-treatment (sleep diary). Subjective sleepiness (DISS) increased from baseline to week one but decreased from baseline to week three of SRT. Overall alert cognition decreased from baseline to week one. Alert cognition at bedtime decreased from baseline to week three of SRT.	16/31
Miller et al., 2015[119]	SRT	11 (8) people with insomnia (community)	Perpetuating practices (TIB), homeostatic sleep pressure (SOL), arousal & circadian timing of core body temperature (N=6)	TIB decreased significantly from baseline to post-treatment (sleep diary). SOL displayed a trend to decrease. Core body temperature decreased significantly, especially in the pre-sleep period. No individual changes in phase or periodicity were detected. Cortisol concentrations in the morning increased from baseline to post-treatment. No change was observed in the pre-sleep phase/early night.	16/31
Spielman, Saskin & Thorpy, 1987[94]	SRT	35 patients with chronic insomnia	Perpetuating practices (TIB), homeostatic sleep pressure (SOL) & circadian sleep-wake cycle	TIB, SOL and variability in sleep parameters decreased significantly from baseline to post-treatment (sleep diary).	13/31
Taylor et al., 2010[114]	SRT + HW vs SH	46 people with insomnia (community)	Homeostatic sleep pressure (SOL)	SOL decreased significantly from baseline to post-treatment (sleep diary).	17/31

Vallières et al., 2013[120]	SRT	5 people with insomnia (community)	Homeostatic sleep pressure (SOL, SWA & sleepiness) & hyperarousal (high-frequency EEG/cortisol)	SOL decreased in responders from baseline to post-treatment and at the beginning of the treatment (PSG). There was no change in SWA. Subjective sleepiness correlated with sleep improvements. High frequencies in EEG seemed to decrease. Morning and evening cortisol levels seemed to be lower by the 2nd week of SRT.	16/31
Wang et al., 2015[115]	PASR vs SRT	71 patients with chronic insomnia	Perpetuating practices (TIB) & homeostatic sleep pressure (SOL)	TIB and SOL decreased significantly from baseline to post-treatment (sleep diary).	21/31
Whittall, Pillion & Gradisar, 2017[121]	SRT	16 insomnia participants	Perpetuating practices (TIB) & homeostatic sleep pressure (SOL, sleepiness, RT)	TIB and SOL decreased significantly from baseline to post-treatment (sleep diary). No significant changes in ESS and RT scores from baseline to mid-treatment and post-treatment.	18/31

Notes. DISS=Daytime insomnia symptom scale; ESS=Epworth sleepiness scale; HW=Hypnotic withdrawal; MCI=Multicomponent intervention; NSRT=Nap-modified SRT; PASR=Physical activity counselling with SRT; PSG=Polysomnography; RLT=Relaxation therapy; RT=Reaction time; SCT=Stimulus control therapy; SE=Sleep efficiency; SH=Sleep hygiene, SRT=Sleep restriction therapy; SOL=Sleep onset latency; TIB=Time in bed; TST=Total sleep time; TWT=Total wake time.

5.3 Perpetuating practices

All studies[94,110,112,113,115,116,118,119,121,123] (3 RCTs, 7 UCTs) that reported on perpetuating practices found that participants spent less TIB at the end of treatment. Only four studies (all uncontrolled) revealed a reduction of TIB during the course of SRT[112,118,121,123] and only two studies (1 RCT, 1 UCT) reported data on napping[94,113]. Time in bed decreased by an average of 94.42 (± 17.83) minutes from baseline to post-treatment and about 107 (± 30.15) minutes during treatment, as indicated by sleep diary analysis. In addition, actigraphy data from two controlled studies showed a reduction of 78.64 (± 30.67) minutes in TIB after SRT[110,116].

Friedman et al.[113] described a reduction in TIB from baseline to post-treatment by both actigraphy (~73 min) and polysomnography (PSG, ~ 56 min). However, those reductions were not reported to be significant, likely due to the low sample size (N=8). No detailed description of how PSG was conducted or how long participants were asked to stay in bed was provided. Nap data from the same study revealed that six participants in the SRT group stopped napping entirely during treatment, eight remained non-nappers and two remained nappers (reported napping ≥ 6 min/day), indicating an overall reduction in napping consistent with treatment instructions.

Additionally, Spielman, Saskin and Thorpy[94] reported that ten participants napped at baseline (for a mean time of 26.5 minutes) compared with only two (for an average of 13.3 minutes) on completion of treatment. The authors also analysed whether mild relapses in sleep at follow-up could be accounted for by an increase in TIB. Results showed that change in TIB from the end of treatment to follow-up was positively correlated with change in total wake time and sleep latency, suggesting that the degree to which TIB is increased following treatment is related to the degree to which sleep deteriorates.

Overall, TIB seems to be reliably decreased from pre- to post-treatment, across both controlled and uncontrolled studies. Data on TIB reductions during treatment and changes in napping are limited and have not been investigated as mediators of treatment outcome.

5.4 Hyperarousal/conditioned arousal

Four uncontrolled studies reported data on arousal measurements[99,118-120] but all investigated different aspects of arousal. In the study of Miller et al.[118] participants completed the 'Daytime insomnia symptom scale' (DISS)[124] at four assessment points per day (rise-time, 12:00 hours, 18:00 hours and bedtime) for one week before-, and for three weeks during the intervention. Alert cognition is one of the DISS subscales, comprised of five items (Forgetful, Clear-headed, Concentrate, Effort, Alert). Compared with baseline, alert cognition decreased during the first week of SRT. At week three of SRT, alert cognition was significantly increased at rise-time but significantly decreased at bedtime, resembling those of good sleeping controls. The authors suggest that modification to alert cognition may reflect a re-structuring of cognitive arousal by SRT; inhibiting it before bedtime and restoring it in the morning. These changes could reveal a potential mechanism by which SRT exerts its therapeutic effect. However, the interpretation of the results is limited by the small sample size (N=9) and the lack of a control group.

Vallières, Ceklic, Bastien and Espie[120] investigated physiological mechanisms of action of SRT. In this study, five participants underwent a treatment protocol with daily sleep measurements, actigraphy, PSG and daily cortisol assays. The authors conducted power spectral analysis on PSG nights across baseline and treatment focussing on change in high frequency patterns. There was an overall decrease across the three nights in beta-1 power during stages two and three, as well as total NREM sleep among responders (N=3). For beta-2, significant reductions from baseline to treatment night one and two were observed during NREM sleep. Furthermore, *visual inspection* of morning and evening cortisol levels suggested that by the second week of treatment levels were lower than at baseline. The authors concluded that these results demonstrate a potential action of SRT on cortisol levels although it should be noted that cortisol levels showed a tendency to increase after treatment. While interesting, this study is preliminary given the small sample size and absence of a control group.

Another study investigated physiological markers of arousal during SRT[119]. Overnight measures of temperature and cortisol in six participants were collected at baseline and at 6-weeks post-treatment. Results revealed that core body temperature decreased significantly by 0.09°C, suggesting that SRT may reduce physiological arousal in insomnia after six weeks of treatment. Contrary to the hypothesis, cortisol concentrations were found to be higher in the morning at post-treatment. The authors suggest that this might represent normalisation of the cortisol awakening response. However, the reliability of these results is limited by the quality of the study (N=8, [6 with complete overnight data], no control group).

Kyle et al.[99] conducted a mixed methods study focussing on the patient experience of SRT. The questionnaire battery included the 'Glasgow sleep effort scale' (GSES[125]), which purports to measure sleep effort, a construct thought to be closely linked to cognitive and emotional arousal[72]. Results revealed that the mean GSES score decreased significantly with SRT from baseline to post-treatment. The pattern remained robust at 3-month follow-up. However, reduction in sleep effort was not investigated as a predictor of clinical improvement, and the study results are limited by the absence of a control group.

In summary, there is no strong evidence for a reduction in cognitive or physiological arousal. The only studies reporting data on change in measures of arousal with SRT are uncontrolled with sample sizes of $n \leq 18$ and therefore no reliable conclusions can be drawn.

5.5 Homeostatic sleep drive

All studies were reviewed for subjective and objective markers of homeostatic sleep drive. The finding most consistently reported was a reduction in SOL. Fourteen studies reported SOL at baseline and post-treatment. Ten of them (five RCTs) indicated a significant decrease in SOL of 23.93 minutes ($\pm$ 6.54) as obtained by sleep diaries. In addition, Vallières et al.[120] reported a reduction in SOL of 38.8 minutes during the first two days of treatment and a reduction of 37 minutes at post-treatment in treatment responders (N=3), as measured by PSG. Non-responders (N=2) did not show a decrease in SOL during the first two days of treatment (+ 0.9 minutes), but a reduction of 11.8 minutes at the end of treatment. Given the

small sample size these results were not tested for statistical significance. Reductions in SOL were also reported by six studies presenting follow-up data[94,99,109,112,123,126], indicating that SRT may lead to stable change in SOL. All other markers of sleep pressure were obtained by different measurements across studies and are summarised below.

Vallières et al.[120] measured SWA at five time-points in five participants (two at baseline, three during treatment). Participants were also asked to monitor their sleepiness and alertness levels in the morning and evening using a 0-4 Likert scale as part of the sleep diary. *Visual inspection* of PSG recordings did not indicate a greater homeostatic response during SRT, but analysis of subjective sleepiness indicated that greater sleepiness at night was associated with higher SE and shorter WASO during the subsequent night. While both measurements provide an opportunity to test an association between sleepiness and treatment outcome, a stronger study design is needed to investigate if sleep pressure as indicated by SWA or sleepiness is a) reliably observed in SRT versus an appropriate control group; and b) a mediator of clinical treatment effects.

Friedman et al.[113] compared three groups (SRT, nap-modified SRT, sleep hygiene) on subjective sleepiness using the Stanford sleepiness scale (SSS) and objective sleep propensity using the Multiple sleep latency test (MSLT). For the SSS, participants were asked to rate their sleepiness every two hours during days in which the actigraph was worn (four consecutive days at baseline, treatment and follow-up). Analysis revealed an overall significant treatment x time interaction on SSS scores. The authors interpreted this result as evidence of a treatment-related decrease in sleepiness for both the SRT and sleep hygiene groups but not the nap modified SRT group. In contrast, data from the MSLT indicated that participants across all groups were somewhat sleepier at the end of treatment, although statistical significance was not reported. Again, associations between sleepiness and treatment outcome were not tested and results are clearly limited by the small sample size (N=6 in the SRT group).

Kyle et al.[99] assessed sleep-restriction related side effects finding that 94% (18 participants) reported ‘extreme sleepiness’ during the first week of treatment. In addition, exploratory correlation analysis revealed that higher frequency of side-effects was associated with a greater magnitude of change in symptom severity and SE. However, this relationship was not specifically tested for sleepiness.

In a follow-up study by Kyle et al.[123], the psychomotor vigilance task (PVT) and the ‘Epworth sleepiness scale’ (ESS)[127] were assessed at baseline, during treatment (week one to four), and after three months follow-up. Compared to baseline, results showed that the ESS score increased significantly during treatment (from baseline to week one, week two and week three) but was not different at the end of treatment [week four (post-treatment) and week 12 (follow-up)]. A similar pattern was observed for reaction times (RT) obtained by the PVT. Analysis revealed that participants were slower during the acute treatment, returning to baseline levels at follow-up. The aim of the study was to investigate whether implementation of SRT was associated with increased daytime somnolence and impaired vigilance; therefore, no analyses were conducted to link sleepiness with improvements in insomnia. Furthermore, the results are limited by the small sample size (N=16) and the lack of a control group.

Conversely, Whittall et al.[121] did not observe increased sleepiness during SRT. Sixteen participants underwent a brief SRT phase (two weeks) and completed the ESS and a Go/NoGo task at pre-, mid- (i.e. after one week of SRT) and post-SRT (after two weeks of SRT). The authors found no significant changes in ESS scores, RTs or accuracy in the Go/NoGo task. Yet, the interpretation of these results is limited by several factors. The implementation of SRT was very brief and modified to prevent extreme daytime sleepiness, TST did not decrease significantly during the two weeks of treatment, there was no control group and the sample size was small (N=16).

In a small, uncontrolled study (N=9) Miller et al.[118] tested the hypothesis that daytime symptoms would deteriorate during SRT. Daily sleepiness was measured by the

'sleepiness/fatigue' subscale of the DISS (containing the adjectives sleepy, fatigued, and exhausted) and compared between baseline, week one and week three of SRT. Consistent with the hypothesis, sleepiness increased in the beginning of the treatment (week one) but decreased towards the end of the treatment (week three). A time of day × week interaction revealed that sleepiness/fatigue was increased at bedtime. The authors suggest that this result is indicative of heightened sleep pressure, which may help to overcome cognitive arousal to facilitate the initiation of sleep. The interpretation of results is limited by the uncontrolled study design and small sample size (N=9, no control group), and because *fatigue* and *sleepiness* were subsumed within one domain of functioning.

Overall, while most studies obtained some indicator of homeostatic sleep pressure, there is little standardisation in measurements, studies are of low quality (small sample size, no control group) and only one study assessed EEG markers of sleep pressure.

5.6 Circadian sleep-wake cycle

In this systematic review, only three studies reported results on circadian markers and sleep variability estimates. Spielman, Saskin and Thorpy[94] measured change in night-to-night variability of self-reported SOL, total wake time (TWT), TST and SE, between baseline and end of treatment. All variables showed a decrease from baseline to the end of treatment, indicating stabilised sleep parameters.

Second, the study of Friedman et al.[112] compared TIB variability between a relaxation and a sleep restriction arm in 22 elderly participants. Only participants in the sleep restriction group showed a significant change in TIB variability, reporting a 22-minute reduction in TIB in the final two weeks of treatment relative to baseline. However, there was no treatment x time interaction reported and the results are limited by the small sample size (N=10 in the SRT group).

Lastly, Miller et al.[119] assessed changes in core body temperature from pre to post six-week SRT in a small sample of patients (N=6). However, there was no change in estimates of

circadian phase or periodicity as indicated by model parameters for the fitted overnight data. The lack of findings could be explained by the small sample size and the absence of a control group.

In sum, only two studies reported a decrease in sleep or TIB variability even though SRT is proposed to stabilise sleep. As sleep diaries (and actigraphy) are standard measurements in clinical sleep research[128], data on sleep variability were likely collected in most of the studies described in this review but not reported.

6 Discussion

6.1 Summary

The primary objective of this review was to systematically examine empirical evidence for four proposed mechanistic pathways involved in SRT treatment response[94,129]. One of the most consistent observations across studies was that TIB was reliably decreased both during and at the end of SRT, in comparison to baseline values and relative to control groups. Spielman et al. proposed that reduced TIB increases sleep pressure and subsequently inhibits arousal. However, we did not find research evidence for this temporal pathway, principally because no study sought to investigate it directly. Instead, reviewed studies showed that SOL was reliably decreased from baseline to post-treatment, as well as from baseline to the first weeks of SRT implementation, potentially reflecting increased sleep pressure. In addition, five studies reported increased subjective sleepiness during treatment but only one study assessed homeostatic sleep pressure through quantitative EEG. In this small study (N=5), participants showed a reduction in high frequencies but no change in SWA. Limited assessment of homeostatic sleep pressure is surprising given that 1) sleep homeostasis may be dysfunctional in insomnia[64]; and 2) partial sleep deprivation has well-described effects on sleep homeostatic processes[130,131]. Equally surprising is the lack of investigation of arousal, which is considered a key maintenance factor in the expression of persistent insomnia[54,132]. Physiological arousal was investigated by two uncontrolled studies, indexed by core body temperature[119] and cortisol levels[119,120]. While core body temperature

significantly decreased, there was no reliable change in evening cortisol, and an increase in morning cortisol levels. Evidence for decreased cognitive arousal was limited. Only three small, uncontrolled studies reported results for a decrease in sleep effort, alert cognition and cortical arousal. Finally, while a regular TIB is proposed to stabilise sleep-wake timing, only two studies reported changes in sleep or TIB variability, indicating less variability at the end of treatment. Importantly, no study showed change in objective measures of circadian rhythmicity, but only one study included such measures.

In summary, then, the principal conclusion from this review is that the field lacks high quality evidence that SRT achieves therapeutic success through its proposed mechanistic pathways. That is, despite a strong evidence-base for single component SRT we do not know which mechanisms account for change in key insomnia outcomes.

6.2 Methodological considerations

To the authors' knowledge this is the first systematic review to investigate the mechanisms of SRT by focusing on its theoretical underpinnings. A systematic review applying selective criteria for identification and screening of relevant literature was chosen as the main methodological approach. Studies using SRT as a partial treatment were excluded, ensuring that we were able to examine the effects of SRT in the absence of possible influence from other evidence-based components of CBT-I, such as stimulus control therapy or relaxation.

There are several limitations of this review. First, uncontrolled studies, secondary analyses and studies with small sample sizes (47% with $n \leq 18$) were included to increase the quantity rather than the quality of studies. Consequently, the reliability of the combined research findings is undermined by limitations in internal and external validity[133]. Furthermore, heterogeneity in both study design and measurement of proposed mediator variables precluded meta-analysis. A second limitation is that only published studies were included, and so our analysis may be influenced by potential publication bias. Third, this review did not consider adherence to the SRT protocol or protocol variability. We hypothesise that these factors could significantly influence measurements associated with mechanisms and

contribute to variability in findings across studies (e.g. sleepiness). Fourth, we pre-defined possible mechanisms consistent with the seminal SRT literature and screened research articles accordingly. It is possible that other putative treatment mechanisms have been investigated in the SRT field. However, given the small size of the SRT literature, and the fact that we sought and read all published SRT studies, we consider this highly unlikely.

The identification of variables associated with mechanisms was hindered by overlapping constructs and the lack of distinction between mediators, indicators of adherence, and outcome variables. For example, reduction of TIB is not just part of SRT, it indexes adherence and functions as a mechanism. Increased homeostatic sleep pressure is hypothesised to be central to treatment effects and manifests as increased sleepiness before sleep and increased SWA during sleep. However subjective sleepiness is also a symptom of insomnia and expected to be improved by successful treatment. Therefore, sleepiness would be expected to increase during treatment (particularly in the evening) but decrease at the end of treatment as a sign of good quality and restorative sleep (particularly in the morning). Moreover, reviewed variables can often be associated with more than one mechanism, for example core body temperature and cortisol can reflect measurements of arousal as well as measurements of circadian rhythmicity[25,134]. Without conducting appropriately powered and hypothesis-driven mediational analyses in RCTs, it becomes difficult to assess the temporal order of these relationships, especially across studies with variable treatment implementation periods (e.g. treatment outcome after two vs four weeks of SRT)[100].

6.3 Towards a mechanistic model of SRT

When SRT was first developed it was principally based on the 3-P account of insomnia development and maintenance. This pragmatic (and generic) model has provided a very useful ‘wide-angle lens’ approach to understanding insomnia chronicity and the factors that require modification (e.g. excessive TIB) to achieve therapeutic success[69,94]. We believe that the field is now ripe for a more fine-grained analysis of SRT (a ‘zoom lens’ approach), to fully elucidate mechanisms and drive treatment refinement and innovation. Below we

outline a testable model, specific to SRT, which integrates Spielman's key observations but also introduces new hypotheses based on contemporary understanding of insomnia and basic sleep-wake regulation.

6.4 The Triple-R model of SRT: Restricting, Regularising, and Re-conditioning

Insomnia is a psychobiological disorder that can be examined across several levels of brain and behaviour. Psychological processes (thoughts, emotions, behaviours) serve to dysregulate sleep biology and in turn, modifications to sleep can feed-back onto key cognitive-behavioural and physiological processes. This interaction maintains insomnia over time. We propose that SRT effectively treats insomnia because it influences cognitive-behavioural and physiological pathways simultaneously and reciprocally. However, it primarily exerts its effects by doing three key things:

1. Restricting time in bed awake,
2. Regularising timing of sleep and wake, and consequently
3. Re-conditioning the association between bedroom factors and sleep.

Targeted modification of these key processes subsequently drives a cascade of change in subsidiary physiological and cognitive-behavioural components that serves to weaken insomnia maintenance factors and restore normal sleep (see Figure 5). The immediate and subsequent effects of the three R's are described below, with respect to both physiological and cognitive-behavioural pathways.

6.4.1 Physiological pathway

During SRT, participants are asked to keep a fixed bed and rise time seven nights a week with only small variations over successive weeks of treatment. Hence, a regular TIB will tighten the regulatory control of sleep by the endogenous circadian pacemaker and standardise exposure to other zeitgebers (i.e. light, mealtimes). It is recognised that the circadian pacemaker is in permanent interaction with homeostatic sleep pressure[10] and thus, a regular TIB will make sleep more predictable and stabilise the circadian sleep-wake cycle[103,135]. The restricted TIB prescription is based on subjective estimates of participants'

TST and will, therefore, result in mild sleep deprivation since people with insomnia tend to underestimate sleep time[136]. Moreover, even if the patient accurately judges TST, they would not be expected to sleep 100% of their TIB because good sleepers also spend some time awake during the night[55,69,94]. Accordingly, sleep pressure (measured for example by SWA) will increase, reflecting a strengthened homeostatic response to accumulated sleep loss[137,138], which will concurrently feed-back onto the circadian drive[139].

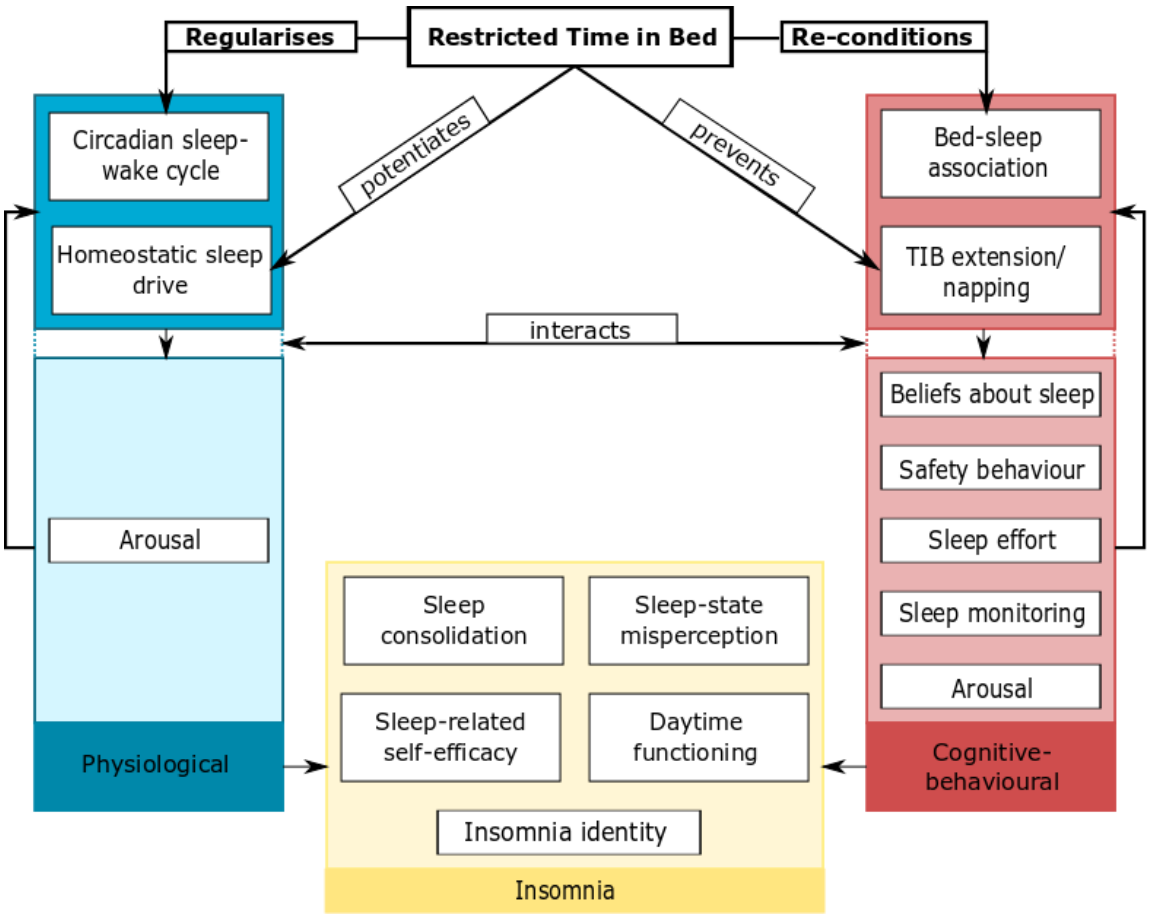


Figure 5. The Triple-R model states that SRT exerts its treatment effects by doing three key things: restricting time in bed awake, regularising timing of sleep and wake, and reconditioning the association between bedroom factors and sleep. Targeted modification of these key processes subsequently drives a cascade of change in subsidiary physiological (e.g. diminished arousal) and cognitive-behavioural factors (e.g. reduced sleep effort) that serve to weaken insomnia maintenance factors and restore normal sleep. Interaction between cognitive-behavioural and physiological pathways improves sleep consolidation, reduces sleep-state misperception and ensures that sleep-related psychological agency (which in insomnia serves to disrupt sleep) surrenders to the two-process model of sleep-wake regulation. Consequently, those with insomnia will have a positive sleep experience that enhances sleep self-efficacy. With continued experience of predictable and restorative sleep, alongside sleep window extension and improved daytime function, the insomnia identity is challenged and ultimately revised.

During sleep, homeostatic pressure for sleep dissipates in synchrony with decreasing circadian pressure for wakefulness, possibly leading to a greater alignment between the processes[140,141]. Consequently, there is little remaining wake pressure throughout the night, which results in a consolidated period of sleep[142]. On a neurobiological level, strong inputs generated by the gradual build-up of the circadian and homeostatic pressures may lead to changes in the *imbalance* between sleep-promoting areas (i.e., ventrolateral preoptic nucleus) and arousal-promoting neurons in the lateral hypothalamus[73,143]. Thus, circadian and homeostatic drives, together, enhance the activity of the sleep-promoting areas and simultaneously inhibit the arousal system, favouring the sleep state[144]. As a result, cortical (e.g. high-frequency EEG) and cognitive arousal (e.g. 'racing mind') prior to sleep and throughout the sleep period will diminish[72,140,145]. This strengthened homeostatic sleep drive may suppress *conscious awareness* during NREM sleep through activity reductions in the left frontoparietal and posterior cingulate, regions that have been associated with cognition and self-referential processes[54,146]. In healthy participants it is known that sleep restriction principally reduces time spent in stage 2 and REM sleep[147,148]; sleep stages which have been linked to subjective-objective sleep discrepancy (sleep-state misperception) in insomnia[149,150]. Restriction and consolidation of these sleep stages may, therefore, drive reduction in subjective-objective sleep discrepancies [54,151]. We assume that SRT takes advantage of relatively intact, though perhaps poorly co-ordinated, homeostatic and circadian processes[64,138]. In sum, strengthened homeostatic sleep drive, regularised circadian sleep-wake timing and reduced arousal will lead to more consolidated and predictable sleep, and ultimately improved perceptions of sleep.

6.4.2 Cognitive-behavioural pathway

Sleep restriction therapy has parallel effects on cognitive-behavioural processes. Initial restriction of TIB aims to reduce time spent in bed awake which, if adhered to, ensures that bed and sleepiness are paired more consistently than bed and wakefulness, promoting counterconditioning against the typical bed-wake association presumed to characterise insomnia[68]. Over time, SRT changes the conditioning history and therefore increases the

probability that sleep-related stimuli will trigger the desired response of sleepiness and sleep[68,70,152]. Extending TIB or taking a nap to compensate for poor sleep are considered counterproductive safety behaviours that reinforce erroneous beliefs about sleep and, together with sleep related worries, exacerbate insomnia (e.g. 'I have to stay in bed to get more sleep, I need to nap to cope during the day')[52,153]. However, blockade of TIB extension provides the opportunity to directly challenge the need for such behaviour, or specific notions that one needs to sleep eight hours a night. That is, during SRT, sleep can be short but deep and more restorative. Furthermore, partial sleep deprivation caused by decreased TIB potentiates homeostatic sleep pressure to a point whereby sleep will occur inevitably, without attention, intention, or effort; processes which typically serve to dysregulate sleep in insomnia (see Figure 3 in chapter one)[72,144,154,155]. The accumulation and discharge of sleep pressure also helps demonstrate that the sleep system is not irreversibly damaged and challenges the belief that sleep is entirely uncontrollable[156,157]. In this way SRT may be considered a behavioural experiment, helping to test out and challenge beliefs presumed to underlie insomnia and related distress. We postulate that targeting such core beliefs, in synchrony with reduced night-time arousal and improved sleep consolidation (direct physiological effects of restricted TIB), will feedback onto daytime cognitive processes (e.g. sleep-related monitoring) and safety behaviours, and help improve perceptions of daytime functioning.

6.4.3 Becoming a good sleeper

We see the psychobiological interaction as central to the effects of SRT. Modification of both the cognitive-behavioural and physiological pathways serves to improve sleep consolidation, reduce subjective-objective sleep discrepancy and remove (maladaptive) psychological agency. Consequently, those with insomnia will have a positive sleep experience that enhances sleep-related self-efficacy[158]. A feedback loop could arise, whereby the knowledge provided early in the intervention (i.e. 'this is how sleep is regulated', 'it is inevitable that I will sleep', 'I have the capacity to sleep like a good sleeper') may initially increase feelings of sleep self-efficacy and deliver a sense of sleep normalcy.

This subsequently motivates the individual to continue to implement the new (and often challenging) schedule, which then delivers improved sleep and further enhances the patient's confidence that they can make positive changes to sleep and behaviour, encouraging further adherence[159]. These processes initially change sleep, but over successive weeks begin to modify daytime symptoms[99]. That is, a lag likely exists between sleep and daytime functioning improvement because of the side effects of restricted sleep time, especially at the beginning of treatment[99,123]. With continued experience of predictable and restorative sleep, alongside sleep window extension and improved daytime function, the insomnia identity is challenged (and ultimately revised) despite only modest increases to TST[88,160].

Consistent with Spielman[94], we assume that restricted sleep is central to the rapidity and effectiveness of SRT. While SRT has circumscribed targets, it has generalised effects on a range of cognitive-behavioural and physiological processes. We assume, therefore, that SRT has the capacity to address different phenotypes of insomnia, consistent with recent work showing that behavioural insomnia treatments can drive robust cognitive change, similar in magnitude to targeted cognitive therapy[91].

6.5 Summary

This review sought to investigate the mechanisms of SRT. Evidence for mechanistic relations between proposed mediators and treatment outcomes is limited, principally because studies have not been specifically designed to elucidate them. We suggest several areas for future research with the aim of advancing understanding of SRT (see research agenda). The *Triple-R* model, based upon Spielman's seminal work, provides a framework specific to SRT from which mechanisms of action can be systematically interrogated through empirical evaluation.

6.5.1 Practice points

- Understanding treatment mechanisms has the potential to refine treatment protocols and tailor therapies to presenting phenotype and to maximise efficacy
- Mechanisms underlying the effects of SRT have been proposed in the literature but only rarely investigated
- There is a lack of distinction between mediators and outcome variables in the insomnia (and SRT) literature
- A new testable model (Triple-R) is introduced that proposes that SRT primarily exerts its effects by regularising, restricting and re-conditioning TIB, followed by subsequent changes in physiological and cognitive-behavioural pathways

6.5.2 Research agenda

- Adequately powered and controlled evaluations of single-component SRT are needed which embed mechanistic measurements to determine mediating effects on clinical outcomes
- Accordingly, the following four conditions should be tested and satisfied: (a) SRT must be related to therapeutic change (e.g. improvement in insomnia severity); (b) SRT must be related to the proposed mediator (e.g. homeostatic sleep drive); (c) The proposed mediator must be related to therapeutic change and; (d) The relationship between SRT and therapeutic change must be reduced after controlling statistically for the proposed mediator
- High resolution and continuous measurement throughout treatment is needed to track trajectories in sleep and putative mediators
- Key pathways of the proposed Triple-R model of SRT should be interrogated through the integration of physiological and cognitive-behavioural measurements.

CHAPTER 3:

EMPIRICAL EVIDENCE FOR THE PUTATIVE MECHANISMS OF SLEEP RESTRICTION THERAPY

1 Preface

Building upon the previous chapter, this chapter presents the first randomised controlled trial to test the centrality of the sleep restriction component of SRT and to systematically investigate its mechanisms of action in comparison to a well-matched control group.

2 Abstract

Sleep restriction therapy is considered to be a primary active ingredient of CBT for insomnia, yet it remains unclear how this component exerts its therapeutic effects. Theoretical models posit that mild sleep deprivation, created by TIB restriction, is essential, and potential underlying mechanisms have been proposed. To isolate the role of TIB restriction and investigate underlying processes, we designed a parallel, randomised-controlled, dismantling trial to compare SRT with bedtime consistency therapy (BCT), which involves prescription of a regular, but not reduced, TIB.

Participants aged 25-55 who met DSM-V diagnostic criteria for insomnia disorder were block-randomised to four weeks of SRT or BCT (1:1). The primary clinical outcome measure was insomnia severity, assessed with the Insomnia severity index (ISI) at baseline, and 4- and 12-weeks post-randomisation. Secondary clinical outcomes included sleep-diary derived continuity, quality of life, cognitive complaints, depression and anxiety. The primary mechanistic outcome was PSG-defined sleep continuity, assessed at baseline, and 1- and 4-weeks post-randomisation. Secondary mechanistic outcomes included actigraphy-derived sleep continuity, pre-sleep arousal, vigilance, sleep variability, attention bias, sleep related mentation and sleep misperception. Intention-to treat analyses was performed using linear mixed models.

Fifty-six participants (39 females, mean age = 41.11 ± 9.08) were assigned to SRT (N = 27) or BCT (N = 29). At 4-weeks post-randomisation the estimated adjusted mean difference for

the ISI was -4.49 and -4.35 at 12-weeks, indicating that the SRT group reported reduced insomnia severity relative to BCT. Treatment effects in favour of SRT were also found for sleep-related quality of life and daytime sleepiness at 12-weeks (*d* range 0.41-1.29) and for sleep continuity variables, indexed via polysomnography, actigraphy and diary during the four-week treatment phase (*d* range = 0.40 - 0.92). Analysis of other secondary mechanistic variables revealed that SRT reduced pre-sleep arousal, nigh-to-night sleep variability and underestimation of sleep time when compared to BCT. However, participants in the SRT group experienced more sleepiness in the evening, more side effects and impairments in vigilance. No effects were found for attentional bias.

In conclusion, TIB restriction demonstrates superior efficacy to bedtime consistency in isolation. The results underscore the centrality of the restriction component to SRT and give evidence for proposed mechanistic variables.

3 Introduction

The previous chapters have illustrated that SRT is an effective treatment for insomnia, but its mechanisms of action are not well understood. Sleep restriction therapy involves prescribing a restricted TIB that matches patient-reported sleep duration[89]. While total sleep time is not directly targeted, the prescribed TIB often engenders mild sleep deprivation[123] as patients tend to underestimate their time asleep[136] and may still experience awakenings and long sleep onsets during early implementation[123]. Over the course of treatment, TIB is systematically expanded – contingent on sleep efficiency thresholds (see Table 3) – and hence, provides opportunity for more sleep[89]. However, at the end of treatment, the gain in total sleep time barely exceeds[88] or even equals the amount of sleep reported at baseline[113,123]. Despite its potential for some sleep loss, studies show that SRT robustly decreases insomnia severity[88]. Furthermore, research evidence from the same studies revealed reliable improvements in diary measures of sleep latency, wake-time after sleep

onset and sleep efficiency[88], suggesting that changes in sleep continuity are driving the effects of SRT.

When Arthur Spielman first described and tested the implementation of SRT in 1987, he hypothesised that the initial sleep deprivation, caused by the restriction component, is essential because of its effects on sleep consolidation and arousal (see chapter two)[94]. This is supported by theoretical models which state that initial sleep deprivation strengthens the homeostatic sleep drive[137,138]. Enhanced sleep drive may then help dial down cognitive (e.g. patients are too sleepy to be worried) and physiological arousal (e.g. brain activity in the attentional system decreases)[161,145], obviating sleep effort[72] and enhancing the consolidation and predictability of sleep[129,162]. While many studies have shown that TIB (see chapter two) and time asleep[113,123] is reduced during SRT, only two correlational studies have linked the effects of sleep deprivation (indexed by self-reported sleepiness and self-reported side effects) with sleep improvements[99,120].

Importantly, Spielman also emphasised that the regularisation of bed times, intrinsic to SRT, may be important for therapeutic effects[94,129]. During the intervention, patients are asked to keep a fixed bed and rise time, typically for seven nights a week with only small variations over successive weeks of treatment. Consequently, studies have revealed that the implementation of SRT is associated with significantly reduced TIB variability[112,163]. Moreover, Riedel and Lichstein showed that greater consistency of time spent in bed and a more consistent rise time, *but not the degree of bedtime reduction*, were correlated with better treatment outcomes[163]. This suggests that the regularity and not the restriction of sleep opportunity per se may be sufficient for the success of the treatment. Indeed, studies in the student population have shown that (a) the frequency of irregular bedtimes is associated with poorer sleep quality[164], and (b) regularisation of bedtimes can reduce sleep onset latency,

daytime sleepiness and increase sleep efficiency[165]. Theories support the beneficial effects of consistent bedtimes and hypothesise that a regular TIB tightens the regulatory control of sleep by the endogenous circadian pacemaker and standardises the exposure to other zeitgebers (e.g. light, mealtimes)[129]. It is recognised that the circadian pacemaker is in permanent interaction with the homeostatic sleep drive[10] and thus, a regular TIB may enhance the predictability of sleep, stabilise the circadian sleep-wake cycle and improve sleep consolidation[103,135].

In summary, theoretical models and research evidence illustrate how both restricted and consistent TIB contribute to the efficacy of SRT[137,164]. Additionally, the Triple-R model has been introduced (see chapter 2) and illustrates how SRT may exert its effects beyond the immediate effects of restriction and regularisation. Based on this model, the following additional variables are expected to be targeted by downstream effects: bed-sleep association, beliefs about sleep, safety behaviour, sleep effort, sleep monitoring, arousal, sleep-state misperception, sleep-related self-efficacy, daytime functioning and insomnia identity. However, without data from specifically designed experimental investigations it remains an empirical question if restricted sleep opportunity (and by implication, sleep time) is required to bring about improvements in insomnia. To date, research on predictors and mechanisms of treatment response in SRT is limited, and to our knowledge no study has hitherto assessed the mechanisms of SRT in a systematic manner. We conducted a parallel, randomised, controlled trial comparing SRT with a dismantled version of SRT, named bedtime consistency therapy (BCT), to test the centrality of the restriction component for the treatment of insomnia with SRT and to allow for an exploratory investigation of its proposed mechanisms of action.

4 Methods

4.1 Study design

The MARTINI (MechAnisms of sleep Restriction Therapy IN Insomnia) trial was a randomised, controlled, mechanistic evaluation of SRT versus a specific factors component control arm (BCT). The study was based on the principles of a dismantling study design, which involves comparing a full treatment protocol to a *dismantled* comparator, whereby one or more aspects of the original treatment protocol - that are thought to be an active change agent(s) - are removed (see Figure 6). All other aspects of the study design and implementation were held constant across groups, and attempts were made to ensure equivalence across other aspects of care delivery such as therapist time and attention[166].

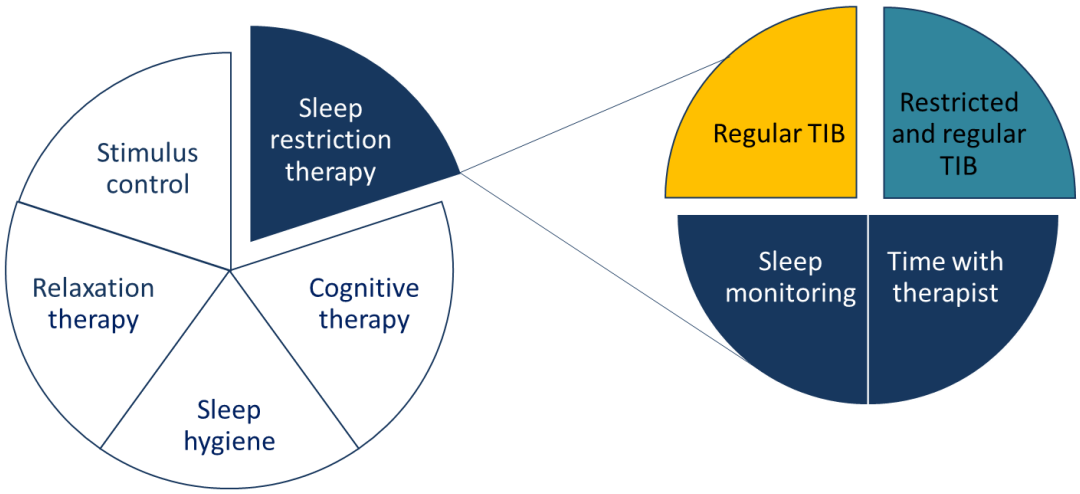


Figure 6. Dismantling of CBT-I and SRT. The pie chart on the left represents CBT-I and the pie chart on the right displays the dismantling of SRT. Here, we compared a regular time in bed plus unspecific factors (sleep monitoring and time with therapist) against restricted (and regular) time in bed plus unspecific factors.

In the MARTINI study, participants meeting criteria for insomnia disorder were randomly assigned to the experimental group, SRT, or the control group, BCT (1:1). Bedtime consistency therapy is the dismantled comparator of choice, because – similar to SRT – it involves sleep monitoring via daily sleep diary, adherence to behavioural advice, and permits matching for therapist time and attention. However, unlike SRT, it does not aim to increase sleep efficiency, reduce TIB or tailor sleep opportunity to circadian preference or pattern of

sleep disruption. Comparable to SRT, BCT prescribes a regular bed and rise time. In this way, BCT can also be described as a specific factors component control[167]. The study was conducted in Oxfordshire, UK and the Central University Research Ethics Committee of the University of Oxford approved the study protocol (CUREC R51331/RE005).

4.2 Objectives

The MARTINI study is designed to dismantle the treatment effects of restriction and regularisation of TIB and to allow for the mechanistic evaluation of SRT. Hence, the study objectives are twofold and include clinical as well as mechanistic hypotheses. All hypotheses were pre-defined and have been registered at ISRCTN (ISRCTN10974094). In total, six clinical and seven mechanistic objectives were formulated for this thesis and are summarised below.

4.2.1 Clinical objectives

4.2.1.1 Primary clinical objective

The primary clinical objective of the MARTINI study was to assess whether delivering SRT for the treatment of insomnia reduces self-reported insomnia severity at the end of treatment (4- and 12-weeks) relative to BCT. Self-reported insomnia severity was measured by the Insomnia severity index (ISI[168]) at baseline, post-treatment (4-weeks) and follow-up (12-weeks).

4.2.1.2 Secondary clinical objectives

The MARTINI study aimed to investigate the following secondary clinical hypotheses:

1. SRT reduces sleep-diary reported WASO, SOL and SE during the treatment phase relative to BCT. All sleep variables were derived from continuous daily sleep diary for two weeks during the baseline phase and four weeks during active treatment.
2. SRT improves sleep-related quality of life relative to BCT. Quality of life was measured by the Glasgow sleep impact index (GSII[169]) at baseline, post-treatment (4-weeks) and follow-up (12-weeks).

3. SRT reduces self-reported symptoms of depression and anxiety relative to BCT. Self-reported symptoms of depression and anxiety were measured by the Hospital anxiety and depression scale (HADS[170]) at baseline, post-treatment (4-weeks) and follow-up (12-weeks).
4. SRT reduces self-reported cognitive complaints relative to BCT. Self-reported cognitive complaints were measured with the British Columbia cognitive complaints inventory (BC-CCI[171]) at baseline, post-treatment (4-weeks) and follow-up (12-weeks).

Additionally, this study aimed to compare self-reported adverse events between SRT and BCT groups. Self-reported adverse events were measured by the side-effects checklist at the end of treatment week 1, 2, 3 and 4.

4.2.2 Mechanistic objectives

4.2.2.1 Primary mechanistic objective

The primary mechanistic objective was to assess whether the restriction of TIB increases PSG-defined sleep continuity during (week one) and at the end of treatment (week four) compared to standardising the sleep schedule. Consequently, we hypothesised that SRT would increase PSG-defined sleep continuity relative to BCT. Sleep continuity comprised the following three dependent variables: SOL, WASO and SE.

4.2.2.2 Secondary mechanistic objectives

The MARTINI study has several secondary objectives, these being to investigate whether restriction of time in bed would impact a range of behavioural and self-report estimates of sleep continuity, and related variables such as sleepiness, arousal and sleep-related cognition. The following secondary mechanistic hypotheses were proposed:

1. The restriction of TIB improves actigraphy-defined sleep continuity during the treatment phase relative to BCT. Objective sleep continuity (SOL, WASO, and SE)

was obtained by continuous actigraphy (two weeks baseline and four weeks treatment).

2. SRT increases subjective and objective measures of sleepiness during the treatment phase relative to BCT. Subjective sleepiness was measured by:
   2.1. Daily self-reported sleep diary (two weeks baseline, four weeks treatment)
   2.2. The Epworth sleepiness scale (ESS[127]) at baseline and weekly during treatment phase weeks one to four and at 12-weeks follow-up
   2.3. Objective sleepiness as obtained by the psychomotor vigilance task (PVT[172]) at baseline and at the end of treatment week one and four.
3. SRT decreases the subjective-objective sleep discrepancy for TST relative to BCT. Objective-subjective discrepancy of sleep estimates were derived from continuous sleep diary and actigraphy estimates over a six-week period (two weeks baseline, four weeks treatment) and polysomnography measurements at baseline and at the end of treatment week one and four.
4. SRT reduces night-to-night sleep variability for SOL, WASO and TST relative to BCT. Variability estimates of sleep variables were extracted from continuous sleep diary and actigraphy over a six-week period (two weeks baseline, four weeks treatment).
5. SRT reduces attention bias to sleep stimuli during and at the end of treatment relative to BCT. Attention bias to sleep stimuli was measured with the sleep related dot-probe task (DPT[173]) performed at baseline and at the end of treatment week one and four.
6. SRT reduces self-reported pre-sleep arousal and sleep-related mentation relative to BCT. Self-reported pre-sleep arousal and sleep-related mentation were measured:
   6.1. Continuously with five items of the pre-sleep arousal scale (PSAS[174]) included in the sleep diary
   6.2. With full versions of the PSAS and the Glasgow content of thoughts inventory (GCTI[175]) that were obtained at baseline and at the end of treatment (week four) and at follow-up (week 12).

4.3 Study population

4.3.1 Strategies for recruitment and retention

The study aimed to recruit a sample size of N=56 (~28 in each arm). Extrapolating from previously reported effects of behavioural treatment for insomnia[176,177], the study was powered to detect a minimum standardised effect size of .80 at post-treatment (week four) at a 5% level of significance with 80% power. Accounting for 10% attrition the study sought to recruit 56 participants. The primary mechanistic outcome, PSG derived sleep continuity, has received scant attention in the published SRT literature. However, there is evidence for large effect sizes on PSG derived changes in WASO and SE when comparing CBT-I to a placebo intervention with n<16 in each group[178].

The study recruited through several channels. These included online, print and broadcast media announcements or advertisements and the use of contact lists where adults who had previously volunteered to be involved in research were re-contacted. If participants were interested in participating in the study, they were contacted by e-mail and received the participant information sheet (Appendix B). If recruited via social media, they accessed the participant information sheet online and were then referred to the screening (see Table 7).

4.3.2 Screening and eligibility assessment

Before entering the study protocol, participants completed an online screening questionnaire using ‘Qualtrics survey tool’ (Qualtrics, Provo, UT) to assess age, insomnia, internet use, regular phone use, location, anxiety, depression, pregnancy, shift work and additional sleep disorders criteria. In order to take part in the study it was essential that participant’s home was accessible by the researcher to conduct home visits and that the participant was reachable via phone and e-mail to facilitate research assessments. Furthermore, we excluded for depression, anxiety and pregnancy due to potential side effects of SRT and because the impact those conditions have on sleep. Shift-workers had to be excluded as the

implementation of a sleep schedule requires the participants to set up the new bed and rise times seven days a week for four weeks.

Table 7. Inclusion/Exclusion criteria and screening information

Inclusion criteria	**Screener**	**Included if:**	**Online**	**Phone**
Participant gives consent	yes/no	Yes	*x*	
Age	OQ	>25 and <55	*x*	*x*
Persistent insomnia disorder	SCI[179]	item criteria*	*x*	
Access to the internet	OQ	Yes	*x*	
Regular phone use	yes/no	Yes	*x*	
Living proximal to Oxford	MC	≤ 10 miles	*x*	*x*
Exclusion criteria	**Screener**	**Excluded if:**		
Other psychiatric diagnoses	OQ	Yes		*x*
Caseness for anxiety	HADS[170]	> 10	*x*	
Caseness for depression	PHQ[180]	≥ 10	*x*	
Pregnancy	MC	Yes	*x*	
Shift work	MC	Yes	*x*	
Current substance misuse	Modified AUDIT[181]	**		*x*
	Caffeine (OQ)	> 300 mg/day		*x*
	Nicotine (OQ)	> 5 cigarettes/week		*x*
Additional sleep disorders	Screening algorithm[182]	see algorithm	*x*	*x*
Sleep-disruptive medical comorbidity	OQ	Yes		*x*
Current prescription of CNS/sleep medication or psychotherapy for sleep	OQ	Yes		*x*

Notes: SCI=Sleep condition indicator; MC=Multiple choice; OQ=Open question; HADS=Hospital anxiety and depression score; PHQ=Patient health questionnaire; AUDIT=Alcohol use disorders identification test; CNS=Central nervous system. *Item criteria for the SCI: scoring ≤2 on item 1 (sleep latency) or item 2 (wakefulness during the night) + scoring ≤2 on item 3 (frequency of disturbance) + scoring ≤1 on item 4 (sleep quality) + scoring ≤2 on daytime functioning items 5 or 6 + scoring ≤2 on item 8 (chronicity of problem). ** Decisions were made on telephone interview using items from the AUDIT.

Participants who screened positively online were followed up with a brief, structured telephone interview to confirm age, location and additional sleep disorders criteria, and to address other psychiatric diagnoses, current substance misuse, sleep-disruptive medical comorbidities or psychotherapy for sleep. We also excluded for current prescriptions of medication that acts on the central nervous system such as anti-depressants (e.g. Fluoxetine) or sleep-specific medications (e.g. Zolpidem). All of those conditions would have affected our primary mechanistic outcome, PSG-defined sleep continuity.

Once deemed eligible, participants were invited for their study induction at the Sleep and Circadian Neuroscience Institute (SCNi) to discuss study procedures, obtain written consent and commence baseline assessments. An overview of inclusion/exclusion criteria and the respective screening measurements and procedures can be found in Table 7 above.

4.4 Study assessments and procedures

All assessments and procedures of the MARTINI study are summarised below and can be found in the flow chart of study procedures (see Figure 7).

4.4.1 Baseline assessments

Eligible participants came to a first visit at the SCNi for the study induction. Printed versions of the participant information sheet (see Appendix B) and consent form were presented to participants. All participants were told that they would be randomised to one of two behavioural interventions, SRT or BCT, that are believed to be beneficial for sleep but have never been compared in one study before. The name ‘bedtime consistency therapy’ was chosen to account for the possibility that participants might search for the intervention in the internet and find plausible results. Hence, participants were aware about being randomised to one of two behavioural interventions that aim to improve sleep and expectations were kept the same for both arms. On signing the consent form, participants were provided with an actigraph watch (MotionWatch 8, Camntech Ltd.) and a sleep diary. All participants were given a briefing on their use.

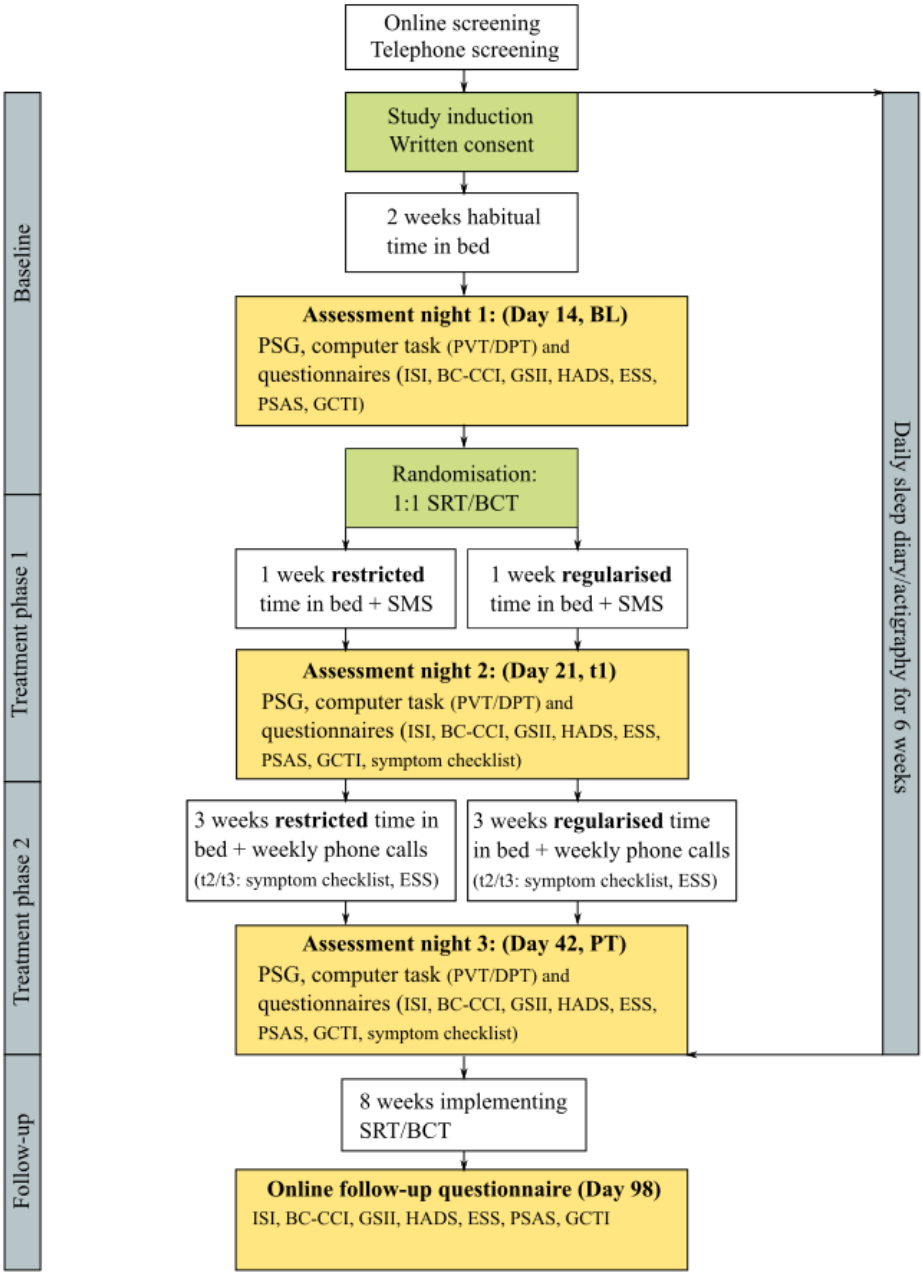


Figure 7. Flow chart of study procedures.

Notes: BL=Baseline; t1=treatment week one; t2=treatment week two; t3=treatment week 3; PT=Post treatment (after four weeks of treatment); PVT=Psychomotor vigilance task; DPT=Dot-probe task; ISI=Insomnia severity index; BC-CCI=British-Columbia cognitive complaints inventory; GSII=Glasgow sleep impact index; HADS=Hospital anxiety and depression scale; ESS=Epworth sleepiness scale; PSAS=Pre-sleep arousal scale; GCTI=Glasgow content of thoughts inventory; SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy.

The participants were asked to keep their habitual sleep-wake patterns and to fill out the sleep diary every morning after awakening and every evening before going to bed. They were further instructed to wear the actiwatch 24 hours a day (other than during wet activities)

and to press the event button on the watch whenever they went to sleep (‘lights off’) and whenever they were rising from bed (‘lights on’). Two weeks after study induction, the baseline PSG measurement was obtained. The researcher (LM) arrived two hours before habitual bedtime to administer questionnaires, set up the PSG measurement and computerised tasks to assess vigilance and sleep-related attentional bias. The researcher left before the habitual bedtime of the participant. Participants were asked to fill out their sleep diaries in the morning and evening as usual. Participants were given instructions to safely remove the electrodes in the morning.

4.4.2 Randomisation and masking

On completion of all baseline assessments, participants were randomly assigned (1:1) to either the SRT or the BCT group using a computer-generated randomisation sequence (sealedenvelope.com), stratifying by age (25-40 vs 41-55) and gender (female/male), with varying block size (two to six) to minimise prediction of future allocations and reduce confounding effects of gender and age. The randomisation sequence was kept by a departmental colleague (MG) who had no formal involvement with the MARTINI study and no interaction with participants. While participants (and therapist) knew what group they had been allocated to, the positioning of the two study treatments as both effective helped to minimise bias due to participant expectations (see Table 8 and Table 9 below).

4.4.3 Study intervention

Treatment for both groups was delivered in a one-hour one to one session (session one) by a trained researcher (LM) at the SCNi according to a manualised protocol, workbooks and personalised treatment slides (PowerPoint, 2013, see Appendix C). Both interventions, SRT and BCT, followed a set structure for each session, required a similar amount of time with the therapist and were matched as closely as possible, including rationales, side effects and treatment expectations (see Table 8). The intervention took place in a meeting room of the SCNi which was equipped with a table, chairs and a TV screen. Latter one was connected to a laptop and facilitated the presentation of the intervention slides. Researcher and participant

were typically seated at the table and in opposition to each other, whereby the researcher made sure the participants could also see the TV screen. Treatment slides and workbooks were used interactively; e.g. after hearing about different sleep hygiene advice, the participant was instructed to make decisions about those he/she wanted to address in the upcoming weeks.

Table 8. Contents of treatment per session

Session	SRT	BCT
Session 1 (60 min)	- Sleep hygiene instructions - Treatment rationale: homeostatic sleep drive & master clock - Review average *sleep times* - Set a sleep window and discuss action plan	- Sleep hygiene instructions - Treatment rationale: master clock - Review average *bedtimes* - Set a sleep window and discuss action plan
Sessions 2 -4 (15 min)	- Review sleep efficiency - Adjust sleep window - Discuss side effects/challenges to adherence	- Review bedtime consistency - Adjust sleep window - Discuss side effects/challenges to adherence

Notes: SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy

Both interventions were referred to as 'sleep scheduling' and started with sleep hygiene instructions. These included: caffeine, alcohol, diet, exercise, nicotine, noise, light, comfort, temperature and air quality. Sleep hygiene advice is commonly delivered as part of usual care for insomnia[183] but has not been shown to be an effective monotherapy[184,185]. It was incorporated in order to ensure that both groups had equivalent awareness of the effects of lifestyle and bedroom factors on sleep. After setting the goals to improve sleep hygiene, the key principles of sleep scheduling were explained and new bed and rise times were implemented according to standardised criteria (see Table 9). Rationales for both interventions included the explanation of our 'master clock', while participants in the SRT group also received an illustration of the sleep homeostat.

To track sleep efficiency on a weekly basis (SRT group only), the use of sleep efficiency grids was explained whereby the total sleep time is divided by the time in bed and multiplied

by 100 for each day. The grid allows participants to have an overview of their sleep efficiency and aids treatment standardisation[186]. Participants in the BCT group were introduced to a bedtime consistency checklist, whereby they had to check if the previously reported daily bed and rise times were within ten minutes of the scheduled bed and rise times (see Appendix C). We also audio-recorded the first treatment session for all participants, during which the chief therapeutic ingredients were explained, to evaluate treatment fidelity. A random sample of 10% of recordings in both arms was then selected for quality appraisal. The evaluation was conducted by an independent clinical psychologist (DG) experienced in the cognitive behavioural treatment of insomnia.

Table 9. Sleep scheduling criteria

Criteria	SRT	BCT
Initial sleep window (TIB)	Average TST over the last 2 weeks with a minimum of 5 hrs	Average TIB over the last 2 weeks
Time to rise	Time to rise that fits working schedule	
Time to bed	Time to bed was set to equal the new prescribed TIB	
Weekly adjustments	a) SE $\geq$ 90%=> TIB + 15 min b) SE < 85%=> TIB – 15min c) 85% $\leq$ SE < 90% => TIB	Minimal adjustments ($\pm$15min) if difficulties with work schedule/ changes in circumstances

Notes: SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy; TIB=Time in bed; SE=Sleep efficiency (total sleep time/time in bed*100)

4.4.4 Treatment phase one

Treatment phase one only comprised the first week of treatment to obtain the effects of the initial sleep window and its effects on mechanistic variables. During the first week of treatment, participants continued to wear the actiwatch and completed the daily sleep diary as before. Both groups were asked to adhere to their scheduled sleep-wake pattern and received daily check-in text messages to support schedule adherence. The messages were personalised and enclosed a reminder of the scheduled bed and rise time. For example: *'Dear XXX, we hope you're getting on well with your new sleep schedule. Please remember, it is*

important that you don't go to bed before XX:XX and that you rise from bed no later than XX:XX. Adhering to this schedule will help you to establish a new improved sleep pattern. Keep going!'

One week after randomisation, the researcher visited the participant's home to set up the second PSG measurement and to administer questionnaires related to associated side-effects, sleepiness, and computerised tasks. Before the PSG set-up, sleep diary and sleep efficiency of the previous seven days were reviewed and the sleep window (in the SRT group) was titrated according to sleep efficiency thresholds (see Table 9). In the BCT group, sleep diaries were checked for adherence to the protocol and experienced difficulties were discussed. The PSG set-up occurred in the same manner as previously. The researcher arrived at the same time as at the baseline measurement to ensure standardised timing for questionnaires and computer tasks, but participants went to bed according to their new prescribed sleep schedule.

4.4.5 Treatment phase two

Participants continued to complete daily sleep measurements (actigraphy and sleep diary). Both groups were contacted weekly by telephone (twice in total) in order to review the sleep diary and adapt the sleep window. During these calls, participants gave verbal responses to two standardised questionnaires assessing experienced side-effects of the treatment and daytime sleepiness. In the evening of the last day of treatment (end of week four, post-randomisation) a final at-home PSG assessment took place. Questionnaires and computerised tasks were also administered in the evening. At the end of the assessment, participants in both groups were given a leaflet comprising instructions and worksheets to keep and adjust (SRT group only) their new sleep schedule (see Appendix D).

4.4.6 Follow-up

Twelve weeks after randomisation, participants were sent a link to an online questionnaire in Qualtrics (Qualtrics, Provo, UT). On completion of the questionnaire, participants were

thanked for their involvement in the study, their reimbursement was set up and they received a personalised sleep report about their first two weeks of sleep, recorded by sleep diary and actiwatch. Additionally, they were provided with a free access code to a digital cognitive-behavioural treatment as a 'thank you' for participation and in order that the BCT group received an evidence based treatment (Sleepio, BigHealth).

4.5 Measures

4.5.1 Questionnaires, indices and checklists

4.5.1.1 Insomnia severity

Insomnia severity was measured by the Insomnia severity index (ISI[187]). The ISI comprises seven items assessing the severity of sleep onset, sleep maintenance and early morning awakening difficulties. It measures satisfaction with the current sleep pattern, interference with daily functioning, noticeability of impairment, and degree of distress or concern attributed to the sleep problem. Each item is rated on a zero to four scale and the total score ranges from 0 to 28 with a higher score indicating more severe insomnia and a cut-off score of ten for detecting insomnia cases in the community sample. The ISI has a high internal consistency ($\alpha \geq 0.90$)[188]. In the clinical sample, a change score of −8.4 points has been associated with moderate improvements[188].

4.5.1.2 Quality of life

Sleep-related quality of life was measured with the Glasgow sleep impact index (GSII)[169]. The GSII asks participants to generate, and rate, three domains of impairment affected by their sleep. These three generated areas of impairment are ranked in order of concern (1–3; i.e. 1 = the most concerning impairment), and then rated on a 0-100 visual analogue scale in relation to impact in the past two weeks (0 = very bothered, 100 = not bothered). Participants re-rated these specified areas of impairment at post-treatment and follow-up. We calculated the average rating per and across the three areas of concern with lower scores indicating

poorer sleep-related quality of life. The measurement has shown sensitivity to CBT-I interventions[169,189].

4.5.1.3 Depression and anxiety symptoms

We measured symptoms of depression and anxiety with the Hospital anxiety and depression scale (HADS)[170]. The questionnaire consists of 14 items (seven covering depressive symptoms; seven covering anxiety symptoms), scored zero to three, to give a range between zero and 21 with higher scores indicating greater severity. The questionnaire reveals acceptable internal consistencies for both, the anxiety (α = 0.68-0.93) and the depression scale (α = 0.67-0.90)[190]. It also displays a good concurrent validity (0.60-0.80) with other measures of anxiety and depression[190] and has been used in the insomnia population[191,192].

4.5.1.4 Cognitive complaints

Self-reported cognitive complaints were obtained by the British Colombia cognitive complaints inventory (BC-CCI)[171]. The questionnaire comprises six questions where each is scored between zero and three, and the total score ranges from zero to 18 with higher scores indicating higher cognitive impairment. The measurement reveals a high internal consistency ($\alpha \geq 0.82$)[171].

4.5.1.5 Pre-sleep arousal

The Pre-sleep arousal scale (PSAS) is a 16-item self-report questionnaire categorised into cognitive and somatic subscales (each eight items)[174]. Each item is scored between one and five (1 = not at all, 5 = extremely) and the sum score for each subscale ranges from eight to 40 with higher scores indicating higher arousal. The PSAS shows good internal consistency for both subscales in the insomnia population ($\alpha \geq 0.72$)[174]. Here, we report results from the weekly version of the PSAS, hence referring to the arousal experienced in the previous week.

4.5.1.6 Sleep related mentation

The Glasgow content of thoughts inventory (GCTI) is a 25-item scale that lists thoughts people commonly have when they cannot sleep[175]. Participants are asked to tick an answer that indicates the sleep interference of each thought (not at all, a little, a fair amount, a great

deal). Answers are scored from zero to three, giving a maximum score of 75. In this study, we report results from the weekly version (referring to the last seven days) of the GCTI. The inventory reveals high internal consistency in the insomnia population ($\alpha = .87$)[175].

4.5.1.7 Treatment credibility and expectancy

The credibility/expectancy questionnaire (CEQ) is a scale for measuring treatment expectancy and rationale credibility for use in clinical outcome studies[193]. The questionnaire contains six items (three indexing expectancy, three indexing credibility) divided into two sections that differ in their instructions. The first section of the questionnaire (first four items) is answered in terms of what the participant *thinks* about the treatment, the second section is answered in terms of what the participant *feels* about the treatment. The CEQ utilises two different response formats: items 1, 2, 3 and 5, are scored on a 1-9 scale, while items 4 and 6 are scored on 0–100% scale. For analysis, all items were standardised on the same 1-9 scale in order to derive sum scores for expectancy (items 1-3) and credibility (items 4-6) with a possible range from 3 to 27, respectively.

4.5.1.8 Self-reported side-effects

The side-effects checklist[99] is a 14-item measure which asks participants to answer yes/no questions regarding whether implementing the new sleep schedule has resulted in any of the 14 listed side-effects. Items include low mood, bodily pain, headache/migraine, difficulty concentrating, changes in hunger/appetite, blurred vision and dizziness. If the participant indicates the presence of unwanted symptoms, they are prompted to rate the extent to which this has interfered with their everyday functioning on a scale from ‘not at all’ to ‘very much’ (0-4). Hence, the scale measures frequency and daytime interference of side effects associated with the intervention. The principal outcome is number of endorsed symptoms per participant. The scale was administered weekly throughout treatment; participants filled out the paper copy of the checklist in weeks one and four, while they completed it over the phone for weeks two and three.

4.5.1.9 Daytime sleepiness

The Epworth sleepiness scale (ESS) is a self-administered questionnaire to obtain daytime sleepiness[127]. Participants are asked to rate on a scale from zero to three how likely they are to doze off or fall asleep in eight different scenarios when referring to their last seven days. The sum score ranges from zero to 24. The measurement has a good internal consistency (α=.88)[194] and has been used in the insomnia population[195].

4.5.2 Computerised tasks

Computerised tasks were programmed in E-prime 3.0 software (Psychology Software Tools, Pittsburgh, PA) and completed on a Dell laptop computer set up on an available surface in the participant's home (e.g. kitchen table, dining table, desk); the viewing distance was kept constant at approximately 45cm. The size of the screen was 32cm (diagonally).

4.5.2.1 Psychomotor vigilance task

The Psychomotor vigilance task (PVT) is frequently used to assess vigilance in the insomnia population[196] and to assess effects of sleep restriction[197]. Participants are instructed to respond as quickly as possible to the presence of a red asterisk, located in the centre of the computer screen, with a left laptop mouse button click. Interval onset for asterisks varied between one and ten seconds across 110 experimental trials. Participants completed five practice trials at the beginning of each session and the task lasts for approximately 12 minutes. The PVT has been shown to reveal reliable performance measures across repeated administration[198].

4.5.2.2 Sleep-related dot probe task

Participants were instructed to respond to two simultaneously presented dots ('probe') that were either aligned horizontally or vertically by pressing the left arrow key or the down arrow key, respectively. Each trial consisted of the following consecutive events: a) a fixation cross appeared in the centre of the screen for 500 milliseconds, b) a pair of words appeared for 500 milliseconds; c) two dots appeared in either the upper or lower position for

500 milliseconds. In case of an incorrect response, an error feedback showed up with a subsequent three second delay, otherwise the screen was cleared, and the next trial started after 500 milliseconds. Each session consisted of 16 practice trials, followed by 192 experimental trials, resulting in a total of 208 trials with an inter trial interval of 1000 milliseconds. Each word pair either comprised of a neutral and a sleep related word (e.g. '*Islanders-Sleepless'*) or a neutral and a threat related pair (e.g. '*Bottles-Assault*'). Pairs of words were presented in a 1:1 random order. The same word pairs were used across repeated measures, however the order of the word pairs differed between trials. The appearance of the dots occurred in an equal probability replacing either the sleep/threat related or the neutral word. The task lasted for approximately eight minutes and was based on Milkins, Notebaert, MacLeod, and Clarke[199]. The DPT has previously been used to assess attention bias in the insomnia population[173,199].

4.5.3 Daily measurements

4.5.3.1 Self-reported sleep continuity

Participants were instructed to complete a sleep diary that was based on the consensus sleep diary[200] in the morning (just after waking up) and in the evening (just before switching off the light) for 14 days during the baseline and 28 days during the treatment phase. Participants provided subjective estimates of the following sleep continuity variables: (1) SOL – time from initial lights out until sleep onset; (2) WASO – time spent awake after initial sleep onset until last awakening and attempted sleep after; (3) TST – total time spent in bed asleep. To compare sleep variables across a similar amount of days, the treatment phase (28 days) was split into two 14-day time-points, reflecting early (weeks 1-2) and late (weeks 3-4) treatment. Self-reported sleep continuity outcomes of interest were SOL, WASO and SE, which were averaged across the 14-day periods (baseline, early treatment, late treatment). We also performed analysis on TST to evaluate the extent of sleep restriction during the acute phase of the treatment.

4.5.3.2 Daily measurements of cognitive arousal and sleepiness

The sleep diary included additional questions about sleepiness (‘*Right now: How sleepy do you feel?*), and cognitive arousal (item 10,12,13,14,&15 of the PSAS[201]). Similar to self-reported sleep continuity, data was compressed to three 14-day time points. Sleepiness was measured on a visual analogue scale from 0-100. Cognitive arousal items were given a score from zero to four (0=not at all; 4=extremely).

4.5.3.3 Actigraphy

Participants were provided with an actigraph watch (MotionWatch 8, Camntech Ltd.) for six weeks (two weeks baseline, four weeks treatment). The watch was set to record activity in tri-axial mode and light in 60 second epochs, comparable to recording settings in other sleep studies[202].

4.5.4 Treatment fidelity and adherence

We developed a content checklist for both treatments, whereby a maximum score of two was given if the content was fully covered, and a score of one if the content was mentioned, but not covered. No score was given if the content was left out. The checklist was based on the developed treatment manual and implemented treatment slides. This resulted in a maximum score of 156 for SRT and 138 for BCT (see Appendix E). A research team member not involved in any study procedures (DG) rated 10% of all recorded treatment session for each group and rated those according to the developed content checklist.

To investigate if participants followed their new sleep schedule as prescribed, we compared self-reported and actigraphy-derived TIB during the four weeks of intervention.

4.5.5 Adverse events measures

Serious adverse events were defined as: (1) death, (2) suicide attempt, (3) admission to hospital, and (4) formal complaints about the behavioural intervention and were recorded when a member of the research team was made aware of their occurrence.

4.5.6 Polysomnography

Participants' sleep was recorded with the portable PSG system, SOMNO HD (Somnomedics GmbH, Germany). The set up included six scalp electrodes (F3, F4, C3, C4, O3, O4), one ground electrode (forehead), one scalp reference electrode (CZ) and two reference electrodes placed on each mastoid (A1,A2). Eye movements were recorded by two standard EOG electrodes and muscle activity by three EMG electrodes on the chin. Impedances were checked before the participant went to bed. They were recorded at 32 Hz and required to be below 5k. Sampling rate for all channels was set to 256 Hz, with a high pass filter at .20 for eye and scalp electrodes and a low pass filter at 10.0 for eye channels and 35.0 for scalp electrodes. EMG channels had a high pass at 10.0 and a low pass at 128 Hz. The participant's position was recorded by a sensor in the recording device with 4 Hz. To define *lights off*, all participants were instructed to move their eyes five times from the left to the right just after having switched off the light. Lights on was determined by an upright position or by the event marker of the actiwatch on that morning.

4.6 Data processing

4.6.1 Questionnaires

All questionnaire entries were first checked to ensure that each score was valid. Once the individual items had been confirmed as valid inputs, composite scores were calculated according to the manual of the applied questionnaire (see Table 10).

Table 10. Overview of measurements obtained by questionnaires, indices and scales

Outcome	Measurement	Properties	Score
Insomnia severity	ISI[168]	7 items (0-4)	Sum score (0-28); higher scores indicating higher severity
Quality of life	GSII[169]	3 visual analogue scales (0-100)	Average (0-100); higher scores indicating lower impairment
Anxiety	HADS[170]	7 items (0-3)	Sum score (0-21); higher scores indicating higher anxiety
Depression	HADS[170]	7 items (0-3)	Sum score (0-21); higher scores indicating higher depression
Cognitive complaints	BC-CCI[171]	6 items (0-3)	Sum score (0-18); higher scores indicating more cognitive complaints
Daytime sleepiness	ESS[127]	8 items (0-3)	Sum score (0-24); higher scores indicating more daytime sleepiness
Somatic arousal	PSAS[174]	8 items (1-5)	Sum score (8-40); higher scores indicating higher somatic arousal
Cognitive arousal	PSAS[174]	8 items (1-5)	Sum score (8-40); higher scores indicating higher cognitive arousal
Overall arousal	PSAS[174]	16 items (1-5)	Sum score (16-80); higher scores indicating higher arousal
Sleep related thoughts	GCTI[175]	25 items (0-3)	Sum score (0-75); higher scores indicating more sleep related thoughts
Side effects	SC[99]	14 side-effects	Sum score (0-14); higher scores indicating more side effects

Notes: ISI=Insomnia severity index; GSII=Glasgow sleep impact index; HADS=Hospital anxiety and depression scale; BC-CCI=British-Columbia cognitive complaints inventory; ESS=Epworth sleepiness scale; PSAS=Pre-sleep arousal scale; GCTI=Glasgow content of thoughts inventory; SC=Symptom checklist

4.6.2 Sleep diary

Sleep diary entries were only entered into the database if the answer was valid or could be estimated by other given answers (e.g. time awake after the final awakening could be calculated by subtracting the time of the final awakening from the time of getting up). When a question about a number (e.g. *'How long did it take you to fall asleep?'*) was answered with wording (e.g. *'Ages'*) it was considered an invalid response and excluded from analysis. Answers reported on a visual analogue scale (e.g. '*How sleepy do you feel?*') were measured with a millimetre scale and the number representing the placed mark was entered into the

database. Of special interest were the sleep continuity variables SOL, WASO, and SE. Sleep onset latency was directly extracted from the question: *'How long did it take you to fall asleep?*. Wake after sleep onset was calculated by the sum score of answers given to the questions '*How long did these awakenings last*?' and '*After your final awakening, how long did you spend in bed trying to sleep*?'. Sleep efficiency was calculated by dividing the time spent in bed (extracted from attempted sleep and rise times) by the time spent asleep (extracted from the question: *'In total, how long did you sleep?'*) and multiplied by 100. To analyse sleep variability, we calculated the root mean squared successive difference (RMMSD) extracted from continuous sleep diary and actigraphy variables (see section below). Only data sets with valid actigraphy data for at least three consecutive days were included in the analysis[203]. The RMSSD serves as an index of night-to-night variability and uses the following formula:

$$RMMSD = \sqrt{\frac{\sum_{i=1}^{n-1}(x_{i+1} - x_i)^2}{n-1}}$$

Here, RMSSD calculation was conducted in R software[204] using the package *varian*[205].

4.6.3 Actigraphy

Actigraphy data were analysed using MotionWare Software 1.1.26 (Camntech Ltd.). Piloting tests of the in-built sleep analysis of the tri-axial recording mode revealed high sensitivity for movements during sleep when compared to *mode 1* which is the company's recommended recording mode for sleep analysis. To account for the increased sensitivity, we raised the activity threshold from low to medium, which showed the best match in our pilot data. We defined each sleep period, using the bed and rise times from the sleep diary or by event markers. Each recording was visually analysed and checked for congruency of reported sleep times with motion and light recordings according to a standardised hierarchical approach developed at the SCNi, which enabled time in bed to be determined (see Appendix F). Only nights where the watch was worn, and where markers could be identified were extracted for statistical analysis. All sleep variables of interest (SOL, WASO,

TST, TIB, SE) were calculated by the validated in-build algorithm of the MotionWare software 1.1.26[206] and defined as described in Table 11 below.

Table 11. Definition of actigraphy derived sleep variables

Sleep variable	Definition according to the software (MotionWare)
Sleep latency (SOL)	The time between *Lights Out* and *Fell Asleep*
Actual wake time (WASO)	The total time spent in wake according to the epoch-by-epoch wake/sleep categorisation
Actual sleep time (TST)	The total time spent in sleep according to the epoch-by-epoch wake/sleep categorisation
Time in bed (TIB)	The total elapsed time between the "Lights Out" and "Got Up" times
Sleep efficiency (%)	Actual sleep time expressed as a percentage of time in bed

4.6.4 Polysomnography

Only polysomnographic recordings that covered the full length of the sleep period (*lights off* to *lights on*) were considered for analysis. While the recording period at baseline was based on habitual sleep patterns, recording periods for the treatment session were based on the prescribed sleep window of the participant. Recordings were blinded and scored according to AASM 2017 guidelines[207]. Reliability of sleep scoring was confirmed by an experienced scorer (RS), who double-scored 10% of all recordings (agreement = 91.5%). We derived the same sleep continuity variables as described above. In addition, we extracted the macrostructure of sleep, i.e. the time spent in the different stages of sleep (stage 1, stage 2, stage 3, NREM and REM) and slow wave sleep latency (SWS-L). Slow wave sleep latency has previously been used as one measure of slow wave sleep pressure[208]. There are different definitions of SWS-L, here the latency to the first epoch of stage 3 was extracted. SWS-L has previously been shown to differ between insomnia patients and healthy controls[64] and was extracted as a proxy for sleep pressure.

Subjective-objective discrepancy. The mismatch between the subjective and the objective estimates of total sleep time was measured by the following formula: Misperception index (MI) = (objective TST−subjective TST) / objective TST. The MI describes the direction of misperception, being positive when objective TST > subjective TST (underestimation) and negative when objective TST < subjective TST (overestimation)[209]. For actigraphy, the MI was averaged across time points (baseline, early treatment, and late treatment). For PSG, we compared the sleep diary of the night of the overnight measurement with the respective recording.

4.6.5 Psychomotor vigilance task

Data from the PVT were extracted and checked for valid responses. Responses < 200 ms were excluded and responses ≥ 500 ms were considered as attentional lapses[210]. Average reaction times and attentional lapses were calculated for each participant at each time point and extracted for statistical analysis.

4.6.6 Sleep related dot-probe task

Outliers in the dot-probe task were defined as reaction times that were larger than two times the individual standard deviation and were removed before the sleep related attentional bias score was calculated. Attentional bias scores were calculated for each participant by subtracting participants' mean response latency to discriminate probes replacing sleep-related stimuli from their mean response latency to discriminate probes replacing neutral words. Hence, a greater negative index implies a greater bias towards sleep stimuli[211]. *Attentional bias score=mean (RT (neutral)) - mean (RT (sleep))*

4.6.7 Definition of population for analysis

The intention to treat (ITT) population consists of participants who were randomised to a study arm[212,213]. All completed outcomes were analysed according to the study arm assigned, assuming missing data was missing at random. No adjustment was made for multiple testing

for the analyses performed on the primary and secondary outcomes as these hypotheses were pre-specified and are highly correlated and related to each other[214].

4.7 Statistical analysis

4.7.1 General approach

Summary statistics (means and standard deviations or medians & lower and upper quartiles for continuous variables, frequencies and percentages for binary and categorical variables) are presented by intervention group. All analysis was conducted in SPSS.25 (IBM) and statistical methods were reviewed by a statistician with expertise in clinical trials (RE).

4.7.2 Analysis of pre-defined endpoints

Consistent with CONSORT guidelines on the reporting of RCTs[215], all data from all randomised participants, including those who dropped out or were noncompliant, were analysed using the ITT principle[213]. A linear mixed effects regression model was fitted for the primary outcome in SPSS.25 (IBM) with fixed effects of group and time point. The outcomes at 4- and 12-weeks were included as the response. Following the guidelines from Landau and Everitt[216], we included the centred baseline score as a covariate and a participant specific random intercept to account for repeated measures and their non-independence. The covariance structure for random effects, here participant, was set to variance components as this is the default for a mixed model with one random effect[217]. An interaction between time point and randomised group was included to evaluate treatment effects separately at each time point. Ninety-five % confidence interval (CI) and two-sided p values are reported with estimated effects. Cohen's d statistics were calculated as the adjusted treatment effect divided by the baseline standard deviation of the ISI for the combined treatment groups[218]. Secondary outcomes were analysed in the same way. For continuously measured sleep variables, responses were entered as averages of week 1-2 (early treatment) and week 3-4 (late treatment). Unadjusted means and SDs are also reported. For treatment side effects, outcomes at week one, two, three and four were included as the response. In the absence of

baseline values, effects sizes were calculated with ES = Diff/((SD[1]+SD[2])/2 [218]. Differences in treatment credibility and expectancy were tested for normal distribution, homogeneity of variances and analysed by independent t-tests.

5 Results

5.1 Participant characteristics

Participants were recruited between July 2017 and January 2019, when planned sample size was achieved. Five-hundred-twenty-nine individuals were screened online, 58 were deemed eligible, of whom 56 completed all baseline assessments. Main reasons for exclusion were other psychiatric symptoms (depression/anxiety), not meeting insomnia criteria or experiencing other sleep problems. See Figure 8 for the CONSORT (Consolidated Standards of Reporting Trials) flow diagram. Session attendance was high in both arms, with just one participant in the SRT arm withdrawing from the trial due to lack of benefit. Hence, 55 participants completed all post-treatment and follow-up assessments. Twenty-seven participants were randomised to SRT, while 29 were randomised to BCT. The sample was predominantly middle-aged (mean = 41.11 $\pm$ 9.08; range 26-55 years), comprised of females (70%), and was university-educated (79%). Consistent with inclusion criteria, insomnia severity index scores were in the clinical range (mean = 14.9 $\pm$ 3.21).

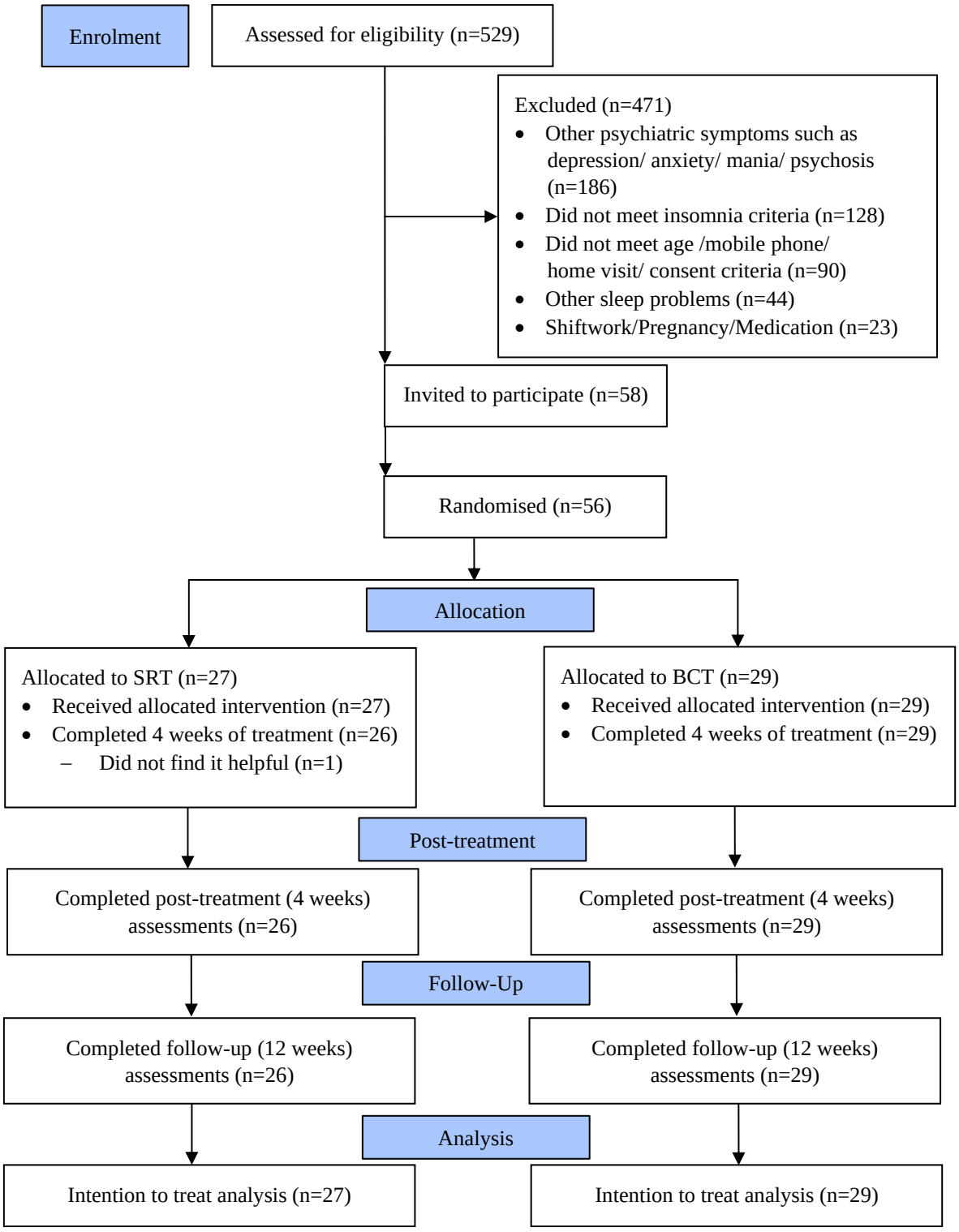


Figure 8. Participant recruitment CONSORT-style flow diagram.

Table 12 provides the baseline characteristics and clinical outcomes at baseline of the participants recruited into each of the treatment arms. The two groups were well-matched on demographic and clinical outcomes at baseline.

Table 12. Participant characteristics and clinical outcomes at baseline by group

	SRT		BCT	
	N=27		N=29	
Baseline characteristics				
Age, years; M(SD)	40.6	9.1	40.9	9.2
Female (n; %)	19	70.4	20	69.0
Marital status (n;%)				
Married	13	48.1	19	65.5
Single	8	29.6	7	24.1
Divorced	5	18.5	3	10.3
Separated	1	3.7	0	0.0
Employment status (n;%)				
Employed for wages	25	92.6	20	69.0
Student	1	3.7	4	13.8
Self-employed	0	0.0	4	13.8
Homemaker	1	3.7	1	3.4
Highest level of qualification (n;%)				
GCSE	1	3.7	0	0.0
A-Levels, diploma or the equivalent	2	7.4	0	0.0
Some college credit, no degree	1	3.7	1	3.4
Trade/technical/vocational training	1	3.7	2	6.9
Associate degree	0	0.0	1	3.4
Bachelor's degree	8	29.6	9	31.0
Master's degree	5	18.5	6	20.7
Professional degree	3	11.1	0	0.0
Doctoral degree	6	22.2	10	34.5
Health characteristics				
BMI, M (SD)	25.3	4.2	25.2	5.4
Sleep problem duration, years, M (SD)	12.5	8.0	9.1	8.1
Clinical outcomes at baseline				
Insomnia severity index, M (SD)	15.6	2.8	14.2	3.7
Quality of life, M (SD)	31.1	12.4	34.1	13.4
Anxiety, M (SD)	3.9	3.3	4.9	3.7
Depression, M (SD)	6.2	3.0	6.7	3.6
Cognitive complaints, M (SD)	7.7	3.3	8.0	4.1
Sleep diary variables, min, M (SD)				
Sleep onset latency	26.0	15.0	22.8	22.3
Wake after sleep onset	62.9	31.6	76.3	51.7
Sleep efficiency, %	79.1	8.1	79.3	10.2

Notes: SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy; GCSE=General certificate of secondary education; BMI=Body mass index

5.2 Clinical outcomes

5.2.1 Primary clinical outcome – Insomnia severity

Insomnia severity. We analysed results from the ISI to assess whether delivering SRT for the treatment of insomnia reduces self-reported insomnia severity. As shown in Table 14 and Figure 9, there were significant group effects at 4- and 12-weeks post-randomisation. At 4-weeks post randomisation, the estimated adjusted mean difference in outcome was -4.49 (p <.001, d = -1.40), indicating that participants in the SRT group reported a lower ISI total score than those in the BCT group. Treatment effects were maintained at 12-weeks, illustrated by an adjusted mean difference of -4.35 (p < .001, d = -1.36).

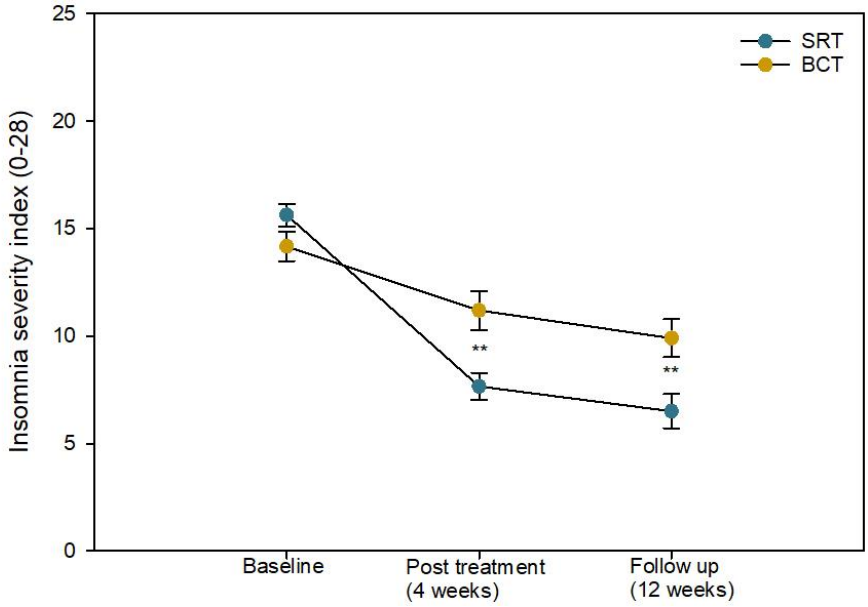


Figure 9. Changes in the primary outcome, insomnia severity, across groups and time points. SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy. Raw means (+/- 1 SE) are presented for both groups at each time point. Statistical group differences are derived from linear mixed models and represented by a double asterisk (**=p<.01).

5.2.2 Secondary clinical outcomes

5.2.2.1 Self-reported sleep continuity

To test if SRT reduces self-reported sleep continuity we analysed continuous sleep diary data. Between-group comparisons (see Table 14) revealed significant group differences for

WASO at both time points (early and late treatment). Moderate effect sizes were observed for early treatment ($p < .001$, $d = -.62$) and late treatment ($p < .001$, $d = -.69$), showing lower WASO in the SRT group. Moderate effect sizes were also found for between-group comparisons of SOL ($p_{\text{early treatment}} = .007$, $d = -.45$; $p_{\text{late treatment}} = .001$, $d = -.57$), favouring SRT.

5.2.2.2 Sleep-related quality of life

We further hypothesised that SRT improves sleep-related quality of life relative to BCT. Our analysis revealed no significant between-group effects on the GSII at post-treatment. However, at follow-up (12-weeks post-randomisation), participants in the SRT group reported reduced impairment to sleep-related quality of life in comparison to the BCT group ($p = .001$, $d = 1.29$; see Figure 10).

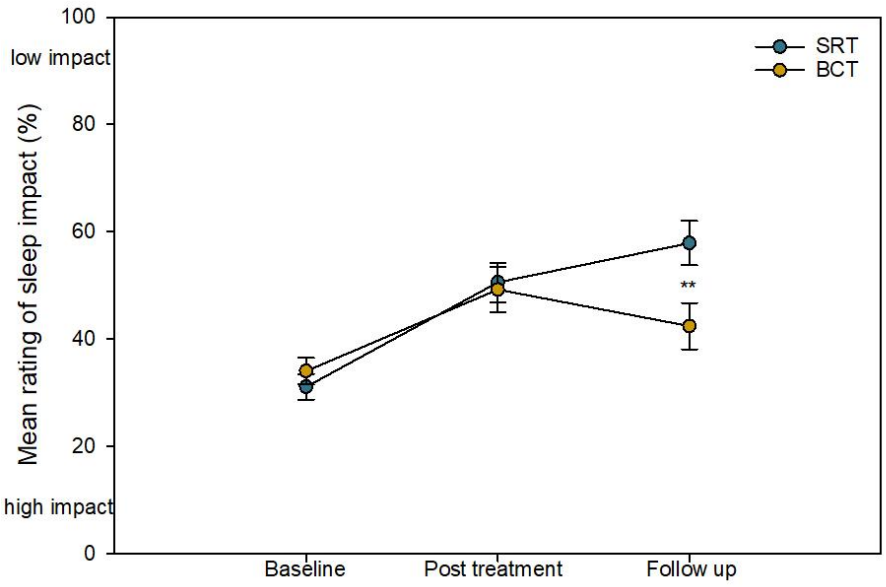


Figure 10. Changes in the Glasgow sleep impact index, across groups and time points. SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy. Raw means (+/- 1 SE) are presented for both groups at each time point. Statistical group differences are derived from linear mixed models and represented by a double asterisk (**=p<.01).

Similar results were found when we analysed group differences of impairment ratings separated by their ranking (see Table 13).

Table 13.Glasgow sleep impact index separated by ranking

		SRT (26)		BCT (29)						
		M	SD	*M*	SD	$Diff_{adj}$	95% CI		*p*	ES
GSII-1	week 4	48.6	22.1	45.5	27.6	4.3	-6.2	14.8	0.417	0.26
	week 12	55.9	23.6	40.0	25.3	17.1	6.6	27.6	**0.002**	1.01
GSII-2	week 4	49.9	53.4	47.8	25.8	1.8	-10.1	13.7	0.761	0.11
	week 12	60.8	22.0	42.8	23.9	17.8	5.9	29.7	**0.004**	1.04
GSII-3	week 4	53.4	22.8	54.5	24.3	-1.4	-13.3	10.6	0.824	-0.08
	week 12	57.1	23.5	44.8	25.8	12.0	0.1	24.0	**0.049**	0.70

Notes: SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy; GSII=Glasgow sleep impact index (1=highest impact, 3=lowest impact); $Diff_{adj}$=Mean difference adjusted for baseline, 95% CI=95% confidence interval of the adjusted mean difference; ES=Effect size (Cohen's d). Significant p-values are displayed in bold.

5.2.2.3 Symptoms of depression and anxiety.

Subscale scores from the HADS were analysed to test if SRT reduces self-reported symptoms of depression and anxiety relative to BCT. Linear mixed models revealed that there were no between-group effects of symptoms of depression or anxiety at post-treatment (*p* anxiety = .249; *p* depression = .218) or follow-up (*p* anxiety = .186; *p* depression = .093). These results are also summarised in Figure 11 and Table 14 below.

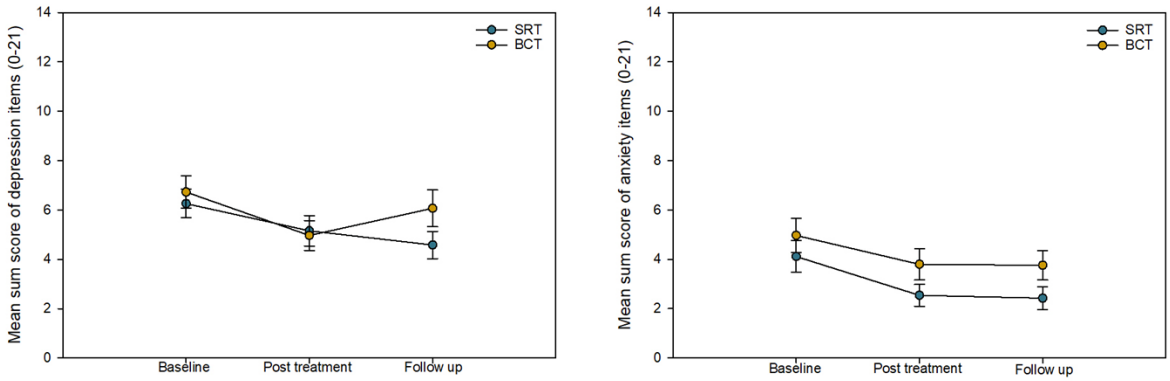


Figure 11. Changes in the Hospital anxiety and depression scale, across groups, subscales (left=depression scores, right=anxiety scores) and time points. SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy. Raw means (+/- 1 SE) are presented for both groups at each time point.

Table 14. Means and standard deviations for self-reported clinical outcomes

		SRT (26)		**BCT (29)**						
		M	SD	*M*	SD	$Diff_{adj}$	95% CI		*p*	ES
ISI	week 4	7.7	3.2	11.2	4.9	-4.5	-6.2	-2.8	**<.001**	-1.40
	week 12	6.5	4.0	9.9	4.7	-4.4	-6.0	-2.7	**<.001**	-1.36
GSII	week 4	50.6	18.8	49.3	22.7	2.5	-6.8	11.9	0.595	0.20
	week 12	57.9	21.1	42.5	23.4	16.7	7.3	26.0	**0.001**	1.29
HADS-A	week 4	2.5	2.3	3.8	3.4	-0.5	-1.5	0.4	0.249	-0.15
	week 12	2.4	2.4	3.8	3.2	-0.6	-1.5	0.3	0.186	-0.18
HADS-D	week 4	5.2	3.2	5.0	3.3	0.7	-0.7	1.9	0.218	0.18
	week 12	4.6	2.8	6.1	4.0	-1.1	-2.3	0.2	0.093	-0.33
BC-CCI	week 4	5.7	4.4	6.1	5.0	-0.2	-1.9	0.2	0.864	-0.04
	week 12	3.2	3.0	5.0	4.0	-1.5	-3.2	0.1	0.071	-0.41
SOL (min)	week 1-2	17.0	21.3	22.7	17.9	-8.4	-14.5	-2.4	**0.007**	-0.45
	week 3-4	13.1	8.9	21.0	17.7	-10.1	-16.8	-4.6	**0.001**	-0.57
WASO (min)	week 1-2	27.3	17.7	61.8	51.5	-25.6	-36.6	-14.7	**<.001**	-0.62
	week 3-4	19.5	14.0	56.8	42.6	-28.5	-39.5	-17.6	**<.001**	-0.69
SE (%)	week 1-2	88.2	6.2	83.0	10.3	5.5	2.6	8.4	**<.001**	0.60
	week 3-4	90.3	4.4	82.3	10.6	8.3	5.6	11.3	**<.001**	0.92

Notes: SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy; ISI=Insomnia severity index; GSII=Glasgow sleep impact index; HADS-A=Hospital anxiety and depression scale – anxiety subscale; HADS-D=Hospital anxiety and depression scale – depression subscale; BC-CCI=British Columbia cognitive complaints inventory; SOL=sleep onset latency; WASO=Wake after sleep onset; SE=Sleep efficiency; $Diff_{adj}$=Mean difference adjusted for baseline; 95% CI=95% confidence interval of the adjusted mean difference; ES=Effect size (Cohen's d). Significant p-values are displayed in bold.

5.2.2.4 Cognitive complaints

We further tested whether SRT reduces self-reported cognitive complaints relative to BCT. However, between-group comparisons showed that there were no between-group effects of

cognitive complaints at post-treatment (p = .864) or follow-up (p = .071). Results are summarised in Figure 12 (see below) and Table 14 (see above).

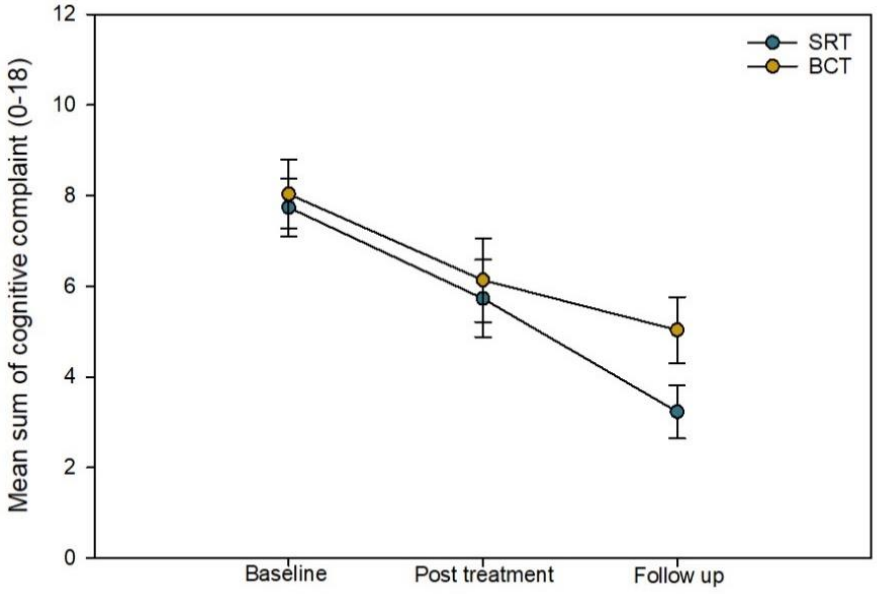


Figure 12. Changes in the British-Columbia cognitive complaints inventory, across groups and time points. SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy. Raw means (+/- 1 SE) are presented for both groups at each time point.

5.2.2.5 Treatment expectations, fidelity and TIB manipulation check

There were group differences for ratings of treatment credibility (SRT = 22.44±2.38 vs BCT = 20.83±3.28; $t_{1,54}$ = 2.10, p = .041, d = 0.57). Group differences for expectancy were of similar magnitude (d = 0.52) but did not reach significance (SRT = 18.68±4.64 vs 16.18±5.0; $t_{1,54}$ = 1.62, p = .058). Treatment fidelity ratings revealed high content accuracy for both interventions (SRT = 99%; BCT = 97%).

To investigate if participants followed their new sleep schedule as prescribed, we compared self-reported and actigraphy-derived TIB during the four weeks of intervention (see Figure 13). Self-reported average TIB was significantly lower in the SRT group during early treatment (SRT = 421.82 ± 54.26 vs BCT = 497.74 ± 45.10; p < .001, d = -1.98) and late treatment (SRT = 432.84 ± 50.41 vs BCT = 501.25 ± 39.29; p < .001, d = -1.83). Consistent with this, actigraphy-derived TIB revealed a significant reduction of TIB in the SRT group during early treatment (SRT = 413.51 ± 39.60 vs BCT = 452.96 ± 42.31; p < .001, d = -1.98)

and late treatment (SRT = 427.03 ± 45.12 vs BCT = 483.58 ± 40.36; $p < .001$, $d = -1.63$). This was in line with their average *prescribed* TIB across early (SRT = 411.35 ± 67.75 min; BCT = 495.60 ± 39.98 min), and late (SRT = 414.02 ± 43.54 min; BCT = 492.07 ± 38.81 min) treatment, indicating that participants adhered to their new sleep schedule.

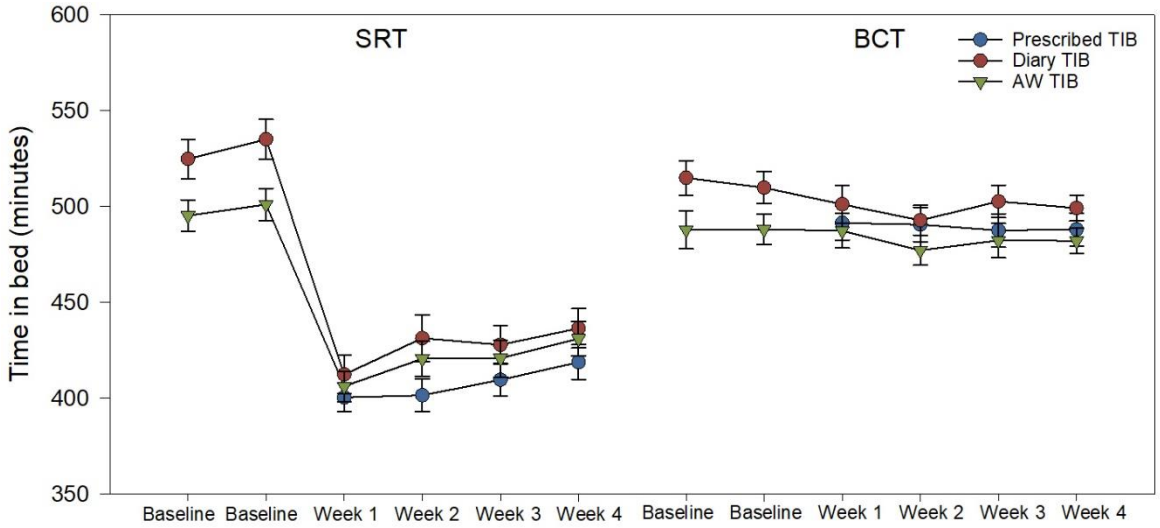


Figure 13. Prescribed, self-reported (Diary TIB) and actigraphy-derived time in bed (AW TIB) across baseline (two weeks) and treatment weeks (week 1-4) divided by group (left: SRT=Sleep restriction therapy, right: BCT=Bedtime consistency therapy). Raw means (+/- 1 SE) are presented for both groups at each time point. In the SRT group, TIB decreased from baseline weeks to treatment weeks, while in the BCT group, TIB remained consistent.

5.2.2.6 Treatment side-effects

The research team was not made aware of any serious adverse events. However, side-effects were commonly reported by both groups across the four-week treatment period (see Table 15). The most frequently reported symptoms were 'fatigue/exhaustion', 'extreme sleepiness', and 'difficulty concentrating and focusing' (see Table 16). Between-group comparisons revealed significant differences in total symptom frequency at week two, indicating that the SRT group reported more side effects ($p = .032$, $d = .61$). A similar, though non-significant pattern was found at week three ($p = .060$). There were no clear group differences at week one ($p = .278$) or four ($p = .403$).

Table 15. Reported number of symptoms during treatment weeks one to four

	SRT (26)		BCT (29)						
	M	SD	*M*	SD	$Diff_{adj}$	95% CI		*p*	ES*
Week 1	6.80	2.43	5.93	2.64	0.87	-0.6	2.3	.231	.34
Week 2	5.69	2.87	4.21	2.36	1.49	0.6	2.9	**.041**	.57
Week 3	5.42	2.96	3.89	2.62	1.38	-0.1	2.8	.064	.49
Week 4	6.54	2.28	6.03	3.01	0.50	-0.9	1.9	.485	.19

Notes: SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy;*ES=Diff/((SD[1]+SD[2])/2); $Diff_{adj}$=Mean difference adjusted for missing values at week 3 and week 4. Significant p-values are displayed in bold.

Both groups had the opportunity to list up to three symptoms in addition to the 14 that were pre-defined. In the SRT group, participants added the symptoms ‘feeling angry’ (N = 1), ‘struggle to get out of bed’ (N = 1), ‘nausea’ (N = 1), ‘twitching muscle in face’ (N = 1), ‘cold’ (N = 2), ‘anxiety’ (N = 2), ‘ability to stay awake’ (N = 1), ‘falling asleep accidentally’ (N = 1), ‘coughing’ (N = 1), ‘eyes itchy’ (N = 1),’indigestion’ (N = 1), ‘sleepy when driving’ (N = 1), ‘more difficult to deal with stress’ (N = 1), and ‘emotional/tearful’ (N = 1).

In the BCT group, participants added the symptoms ‘waking earlier’ (N = 1), ‘measurements make sleep problems more prominent’ (N = 1), ‘stress/anxiety’ (N = 2), ‘losing things’ (N = 1), ‘restlessness’ (N = 1), ‘need to nap and doze’ (N = 1), and ‘disturbed sleep’ (N = 1). An overview of frequency ratings per pre-defined symptom can be found in Table 16 below.

Table 16. Frequencies of reported symptoms during treatment weeks 1-4

Symptom	Week 1				Week 2				Week 3				Week 4			
	SRT (26)		BCT (29)		SRT (26)		BCT (29)		SRT (24)		BCT (27)		SRT (26)		BCT (29)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Low mood	11	42.3	17	58.6	10	38.5	10	34.5	10	41.7	8	29.6	17	65.4	17	58.6
Fatigue/exhaustion	26	100.0	27	93.1	21	80.8	21	72.4	20	83.3	18	66.7	22	84.6	23	79.3
Extreme sleepiness	22	84.6	20	69.0	16	61.5	12	41.4	13	54.2	8	29.6	21	80.8	21	72.4
Feeling agitated	10	38.5	16	55.2	10	38.5	9	31.0	9	37.5	7	25.9	15	57.7	12	41.4
Difficulty remembering	16	61.5	15	51.7	13	50.0	8	27.6	11	45.8	7	25.9	15	57.7	16	55.2
Bodily pain	5	19.2	4	13.8	3	11.5	1	3.4	3	12.5	2	7.4	6	23.1	4	13.8
Headache/migraine	11	42.3	6	20.7	7	26.9	8	27.6	8	33.3	6	22.2	8	30.8	9	31.0
Euphoria	5	19.2	1	3.4	2	7.7	1	3.4	1	4.2	2	7.4	4	15.4	5	17.2
Difficulty concentrating	21	80.8	19	65.5	17	65.4	16	55.2	15	62.5	14	51.9	18	69.2	18	62.1
Reduced motivation	19	73.1	19	65.5	17	65.4	14	48.3	16	66.7	16	59.3	16	61.5	19	65.5
Changes in hunger	9	34.6	5	17.2	7	26.9	4	13.8	6	25.0	2	7.4	9	34.6	8	27.6
Blurred vision	1	3.8	1	3.4	4	15.4	2	6.9	1	4.2	0	0.0	1	3.8	1	3.4
Dizziness	4	15.4	1	3.4	2	7.7	2	6.9	3	12.5	2	7.4	2	7.7	2	6.9
Feeling irritable	17	65.4	21	72.4	19	73.1	14	48.3	14	58.3	13	48.1	16	61.5	20	69.0

Notes: SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy

5.3 Mechanistic outcomes

5.3.1 Primary mechanistic outcome – PSG defined sleep continuity

Polysomnographically-defined sleep continuity. Our primary mechanistic objective was to assess whether delivering SRT improves PSG-defined sleep continuity relative to BCT. The variables TIB, TST, SOL, WASO and SE were extracted and are summarised in Table 17.

Table 17. Polysomnography-derived sleep continuity variables

		SRT (26)		**BCT (27)**						
		M	SD	*M*	SD	$Diff_{ad}$	95% CI		p	ES
TIB	Baseline	478.6	51.1	464.0	54.0					
(min)	Week 1	404.3	38.9	476.9	46.5	-77.9	-98.5	-57.3	**<.001**	-1.48
	Week 4	432.0	47.3	467.2	44.9	-42.3	-62.7	-21.9	**<.001**	-0.81
TST	Baseline	413.9	47.6	420.4	47.8					
(min)	Week 1	372.4	33.4	425.7	40.9	-48.0	-69.7	-26.3	**<.001**	-1.01
	Week 4	394.6	49.1	415.1	50.0	-16.6	-38.1	4.9	0.129	-0.35
SOL*	Baseline	8.7	7.6	8.4	7.0					
(min)	Week 1	5.6	5.0	10.9	13.3	-5.4	-10.5	-0.2	**0.041**	-0.74
	Week 4	7.2	7.4	11.5	14.7	-4.4	-9.5	0.7	0.091	-0.61
WASO	Baseline	64.6	56.0	42.9	25.8					
(min)	Week 1	31.9	20.5	51.2	32.8	-32.3	-45.8	-18.9	**<.001**	-0.79
	Week 4	37.4	35.4	52.0	34.4	-27.9	-41.2	-14.6	**<.001**	-0.68
SE	Baseline	87.0	9.8	90.1	6.2					
(%)	Week 1	92.3	4.4	89.5	5.9	4.5	1.7	7.4	**0.002**	0.56
	Week 4	91.5	7.2	88.8	7.2	4.5	1.7	7.3	**0.002**	0.56

Notes: SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy; TIB=Time in bed (time from *lights off* to *lights on*); TST=Total sleep time; SOL=Sleep onset latency; WASO=Wake after sleep onset; SE=Sleep efficiency; $Diff_{adj}$=Mean difference adjusted for baseline; 95% CI=95% confidence interval of the adjusted mean difference; ES=Effect size (Cohen's d).*All 29 participants of the BCT group were included in the analysis of PGS-derived SOL. Significant p-values are displayed in bold.

Only two recordings from two different participants were excluded from WASO, TST and SE analysis (one baseline [BCT] and one week-1 recording [BCT]) due to data loss. Between-group comparisons revealed significant group differences for WASO at week one ($p < .001$, $d = -.79$) and week four ($p < .001$, $d = -.68$) in favour of SRT. Similar findings were found for SE at week one ($p = .002$, $d = .56$) and week four ($p = .002$, $d = .56$). Sleep onset latency was shorter at week one ($p = .041$, $d = -.74$), however, there were no significant group differences for SOL at week four ($p = .091$). To analyse the extent to which sleep was restricted, we analysed TST. Results from linear mixed models revealed a significant reduction at week one ($p < .001$, $d = 1.01$), but no between-group effects at week four ($p = .129$), indicating that participants in the SRT group underwent a stronger sleep restriction during the early phase of the treatment.

5.3.2 Secondary mechanistic outcomes

5.3.2.1 Polysomnographically-defined sleep architecture

An overview of changes in the sleep architecture can be found in Table 18. Exploratory analysis was conducted to test the effects of SRT on sleep architecture. In the SRT group, results revealed that the decrease in TST (see above) was further reflected in a decrease of time spent in NREM sleep at week one ($p < .001$, $d = -1.11$) and week four ($p = .049$, $d = -.043$) when compared to BCT. Furthermore, at week one, participants in the SRT group spent less time in stage 1 ($p < .001$, $d = -0.78$) and stage 2 sleep ($p < .001$, $d = -0.92$), while REM sleep and stage 3 sleep did not differ when compared to the BCT group ($ps \geq .290$). These results indicate that the reduction of TST was reflected in a decrease of lighter sleep stages and preservation of deeper sleep stages. However, these effects were not maintained at week four (Stage 1: $p = 0.158$; Stage 2: $p = .082$)

Furthermore, we compared SWS-L at week one and week four post-randomisation. Analysis revealed significant group differences at week one, reflected in a shorter latency to the occurrence of stage 3 sleep in the SRT group. At week one, results showed that participants in the SRT group entered stage 3 sleep about 12 minutes earlier than participants in the BCT

group (p = .002, d = -.81). No significant group differences were detected at week four (p = .09).

Table 18. Polysomnography-derived variables of sleep architecture

		SRT (26)			BCT (27)							
		M	*%*	SD	*M*	*%*	SD	$Diff_{adj}$	95% CI		p	ES
Stage 1	Baseline	34.3	*8.3*	20.5	42.2	*10.1*	26.5					
(min)	Week 1	20.8	*5.6*	11.0	43.8	*10.3*	28.5	-18.2	-26.9	-9.6	**<.001**	-0.78
	Week 4	28.8	*7.3*	14.0	39.7	*9.6*	26.8	-6.2	-14.8	2.4	0.158	-0.26
Stage 2	Baseline	203.8	*49.2*	38.1	208.8	*49.7*	47.6					
(min)	Week 1	173.5	*46.6*	31.2	217.5	*51.1*	40.1	-39.4	-57.5	-21.2	**<.001**	-0.92
	Week 4	191.3	*48.5*	39.9	208.1	*50.1*	41.8	-15.9	-33.9	2.1	0.082	-0.37
Stage 3	Baseline	77.5	*18.7*	30.1	67.6	*16.1*	29.0					
(min)	Week 1	86.0	*23.1*	29.8	70.6	*16.6*	43.9	6.3	-5.4	18.0	0.290	0.21
	Week 4	79.4	*20.1*	33.1	70.5	*17.0*	42.5	0.3	-11.3	12.0	0.963	0.01
NREM	Baseline	315.6	*76.2*	42.8	318.7	*75.8*	44.1					
(min)	Week 1	280.3	*75.3*	29.3	331.9	*78.0*	38.2	-48.4	-67.3	-29.5	**<.001**	-1.11
	Week 4	299.4	*75.9*	42.5	318.3	*76.7*	38.4	-18.9	-37.6	-0.1	**0.049**	-0.43
REM	Baseline	98.3	*23.8*	24.7	101.7	*24.2*	28.6					
(min)	Week 1	92.1	*24.7*	22.4	93.8	*22.0*	20.1	1.1	-9.8	11.9	0.845	0.04
	Week 4	95.2	*24.1*	24.3	96.8	*23.5*	29.8	2.8	-8.0	13.5	0.613	0.10
SWS-L	Baseline	27.9		17.3	26.6		12.3					
(min)	Week 1	20.1		9.6	31.8		21.1	-12.0	-19.4	-4.6	**0.002**	-0.81
	Week 4	27.0		10.3	32.9		16.9	-6.3	-13.6	1.0	0.090	-0.43

Notes: REM=Rapid eye movement sleep; NREM=Non-REM sleep; SWS-L=Slow wave sleep latency; $Diff_{adj}$=Mean difference adjusted for baseline, 95% CI=95% confidence interval of the adjusted mean difference; ES=Effect size (Cohen's d). Significant p-values are displayed in bold.

5.3.2.2 Actigraphy-defined sleep continuity

We hypothesised that SRT improves actigraphy-defined sleep continuity during the treatment phase and relative to BCT. Between-group comparisons revealed significant group differences for WASO at both time points (early and late treatment, see Table 19).

Table 19. Overview of changes in actigraphy-derived sleep variables

		SRT (26)		BCT (29)						
		M	SD	*M*	SD	$Diff_{adj}$	95% CI		p	ES
WASO	Baseline	72.7	28.4	71.7	22.9					
(min)	Early treatment	58.0	22.2	71.1	20.6	-14.5	-20.9	-8.2	**<.001**	-0.57
	Late treatment	59.8	21.7	73.8	20.4	-14.8	-21.1	-8.4	**<.001**	-0.58
SOL	Baseline	8.4	9.2	10.4	8.6					
(min)	Early treatment	4.4	2.7	12.4	12.7	-7.0	-11.6	-2.4	**0.003**	-0.78
	Late treatment	5.0	3.4	13.5	16.6	-7.8	-12.4	-3.2	**0.001**	-0.87
SE	Baseline	82.4	6.3	82.1	5.3					
(%)	Early treatment	84.1	5.0	81.7	5.2	2.3	0.8	3.9	**0.003**	0.40
	Late treatment	84.1	4.6	81.2	5.1	2.8	1.3	4.3	**<.001**	0.48
TST	Baseline	404.9	36.7	398.9	39.0					
(min)	Early treatment	345.7	32.1	391.3	37.2	-50.9	-62.9	-38.8	**<.001**	-1.33
	Late treatment	359.5	35.4	393.6	28.4	-38.6	-50.6	-26.6	**<.001**	-1.01

Notes: SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy; WASO=Wake after sleep onset; SOL=Sleep onset latency; SE=Sleep efficiency; TST=Total sleep time; $Diff_{adj}$=Mean difference adjusted for baseline; 95% CI=95% confidence interval of the adjusted mean difference; ES=Effect size (Cohen's d). Significant p-values are displayed in bold.

The treatment effects were of moderate size ($p_{\text{early treatment}} < .001$, $d = -.57$; $p_{\text{late treatment}} < .001$, $d = -.58$) and in favour of the SRT group. Moderate to large effect sizes were found for between-group comparisons of SOL ($p_{\text{early treatment}} = .003$, $d = -.78$; $p_{\text{late treatment}} = .001$, $d = -.87$), favouring the SRT group. These results were also reflected in group differences for SE ($p_{\text{early treatment}} = .003$, $d = .40$; $p_{\text{late treatment}} < .001$, $d = .48$), revealing higher SE for the SRT group. Additional analysis revealed that restriction of TIB (see Figure 13) also resulted in a decrease of TST in the SRT group. Compared to the BCT group, participants following SRT experienced a significantly shorter sleep duration during early ($p < .001$, $d = -1.33$) and late treatment ($p < .001$, $d = -1.01$). See Figure 14 for an overview of all obtained sleep continuity variables across measurements (sleep diary, actigraphy and PSG).

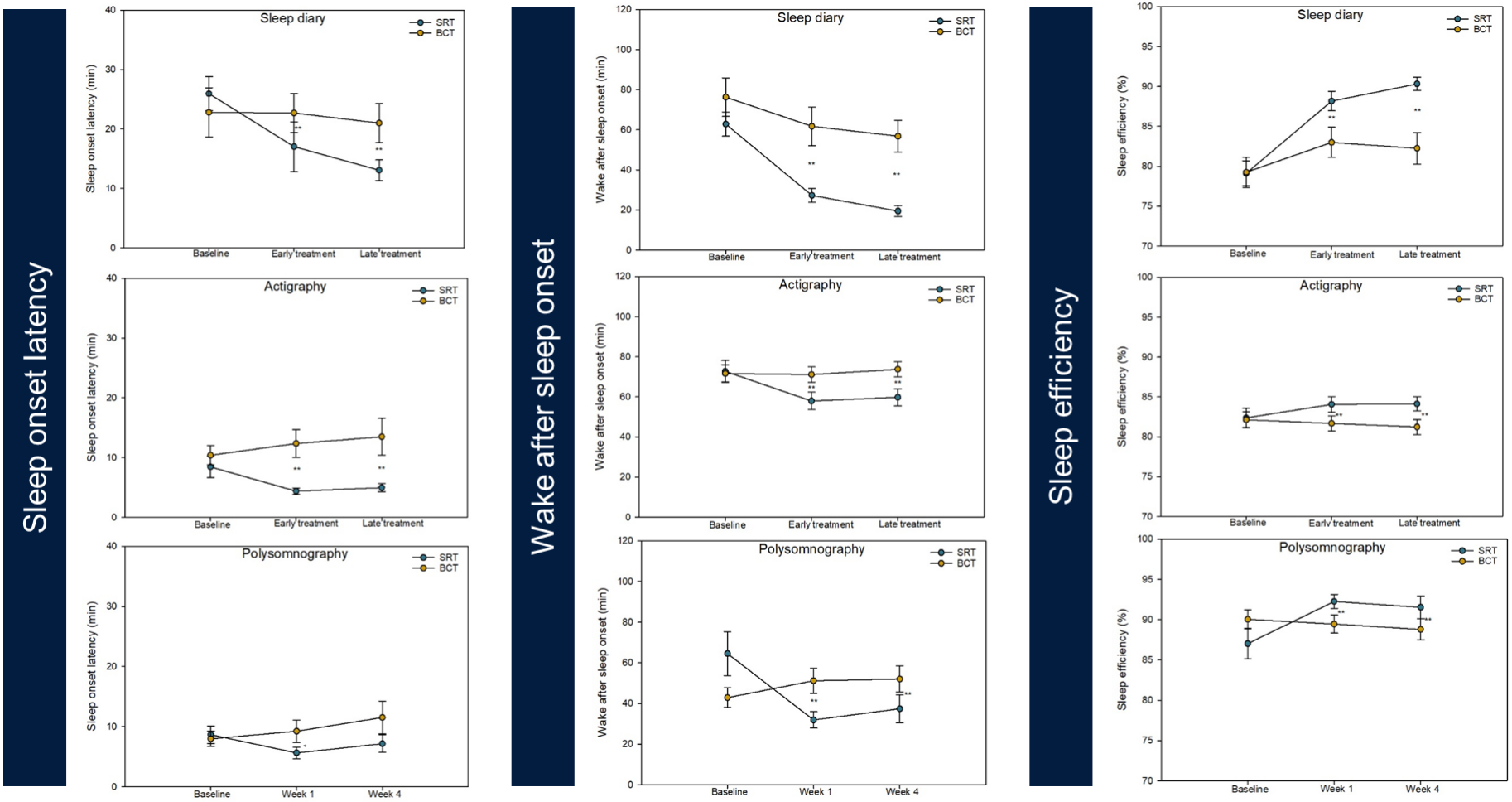


Figure 14. Overview of changes in sleep continuity variables across measurements. From top to bottom: sleep diary, actigraphy, polysomnography. From left to right: sleep onset latency, wake after sleep onset, sleep efficiency. SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy. Raw means (+/- 1 SE) are presented for both groups at each time point. Statistical group differences are derived from linear mixed models and represented by a single or double asterisk (*=p<.05, **=p<.01).

5.3.2.3 Subjective and objective measures of sleepiness

It was proposed that SRT increases subjective and objective measures of sleepiness during treatment phase relative to BCT. Results of all sleepiness measurements are summarised in Table 20. Daily monitored sleepiness will be considered first, followed self-reported daytime sleepiness and objective vigilance measures.

Daily monitored sleepiness. Analysis from daily self-reported sleepiness measurements revealed significant group differences for sleepiness in the morning and in the evening, indicating that the SRT group was sleepier during the acute phase of the treatment when compared to BCT. The treatment effects showed moderate to large effect sizes during early treatment for both, sleepiness in the morning and evening ($p_{\text{morning}} = .003$, $d = .46$; $p_{\text{evening}} < .001$, $d = 1.05$). During late treatment, there were no significant differences for sleepiness in the morning ($p = .129$), yet sleepiness in the evening was still elevated in the SRT group ($p = .002$, $d = .81$; see Figure 15 below).

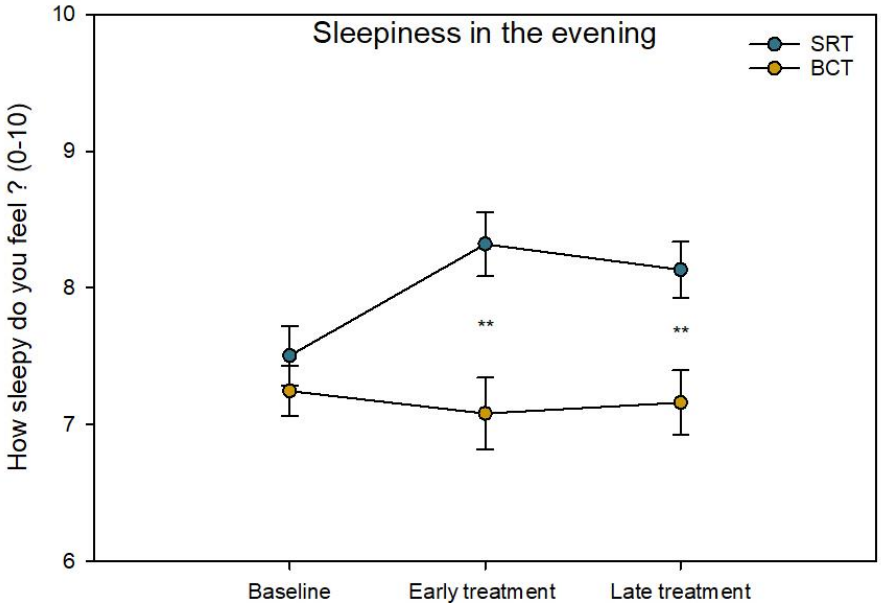


Figure 15. Sleepiness in the evening by group and time point. SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy. Raw means (+/- 1 SE) are presented for both groups at each time point. Statistical group differences are derived from linear mixed models and represented by a double asterisk (**=p<.01).

Daytime sleepiness. We also measured daytime sleepiness with the ESS on a weekly basis at baseline, during the acute treatment phase and at 12-weeks follow-up (see Figure 16). In line with the results from daily measurements of sleepiness in the morning, we found significant group differences during the early, but not during the late phase of the intervention, indicating that participants in the SRT group experienced more daytime sleepiness in the beginning of the treatment ($p_{\text{week 1}} = .006$, $d = .56$; $p_{\text{week 2}} = .021$, $d = .47$). Between-group comparisons at follow-up revealed effects in the opposite direction, suggesting that participants in the SRT group experienced less daytime sleepiness on completion of the intervention ($p = .050$, $d = -.40$).

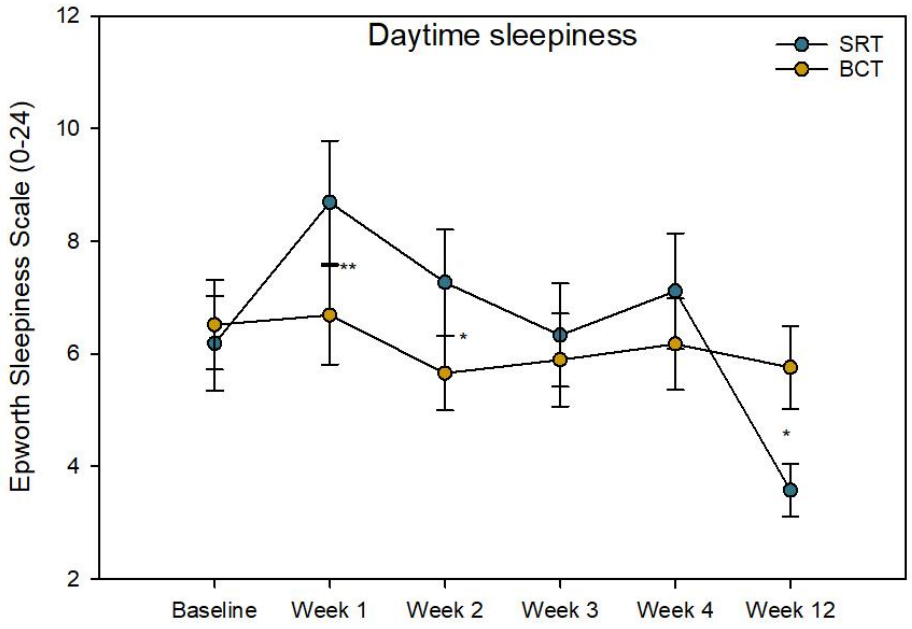


Figure 16. Daytime sleepiness by group and time point. SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy. Raw means (+/- 1 SE) are presented for both groups at each time point. Statistical group differences are derived from linear mixed models and represented by a single or double asterisk (*=p<.05, **=p<.01).

Objective sleepiness. Objective sleepiness was obtained by RTs and attentional lapses derived from the PVT at baseline, week one and week four. Due to task failure (*Eprime* record was empty/ did not save the results) 9% of all PVT measurements were lost, leaving 151 out of 166 records for analysis. While baseline recordings were complete (100%), six

records were missing at week one (SRT = 2, BCT = 4), and nine records were missing at week four (SRT = 3, BCT = 6).

Between-group comparisons of RTs revealed slower RTs for participants in the SRT group at week one (p = .032, d = .33) and week four (p = .026, d = .35) when compared to RTs of participants in the BCT group (see Figure 17).

No significant group-differences were found for attentional lapses at week one (p = .272) or week four (p = .062; see Table 20).

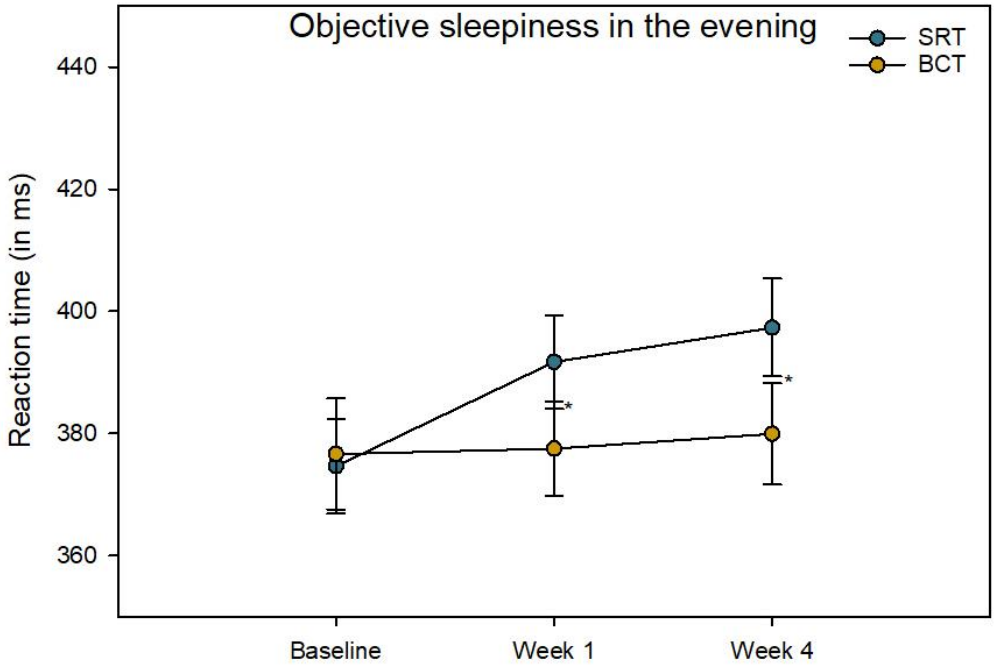


Figure 17. Reaction times measured by the psychomotor vigilance task by group and time point. SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy. Raw means (+/- 1 SE) are presented for both groups at each time point. Statistical group differences are derived from linear mixed models and represented by a single asterisk (*=p<.05).

Table 20. Overview of changes in measurements of daytime sleepiness

		SRT (26)		BCT (29)						
		M	SD	*M*	SD	$Diff_{adj}$	95% CI		*p*	ES
Sleepiness	Baseline	5.88	1.43	5.87	1.62					
morning	Early treatment	7.01	1.91	6.22	1.64	0.71	0.25	1.17	**0.003**	0.46
	Late treatment	6.53	2.15	6.09	1.91	0.36	-0.11	0.82	0.129	0.23
Sleepiness	Baseline	7.50	1.14	7.73	1.10					
evening	Early treatment	8.32	1.20	7.47	1.72	1.17	0.61	1.72	**<.001**	1.05
	Late treatment	8.13	1.05	7.24	0.98	0.90	0.34	1.46	**0.002**	0.81
ESS	Baseline	6.19	4.39	6.52	4.29					
	Week 1	8.69	5.60	6.69	4.73	2.44	0.70	4.18	**0.006**	0.56
	Week 2	7.27	4.81	5.66	3.55	2.01	0.31	3.79	**0.021**	0.47
	Week 3	6.33	4.51	5.89	4.37	0.59	-1.19	2.37	0.513	0.14
	Week 4	7.12	5.26	6.17	4.38	1.38	-0.36	3.12	0.119	0.32
	Week 12	3.58	2.39	5.76	3.95	-1.74	-3.48	-0.03	**0.050**	-0.40
RT	Baseline	374.61	40.18	376.62	48.95					
	Week 1	391.70	37.62	377.49	38.90	14.55	1.26	27.84	**0.032**	0.33
	Week 4	397.34	38.43	379.92	39.74	15.53	1.86	29.21	**0.026**	0.35
Lapses	Baseline	9.04	7.20	8.38	8.72					
	Week 1	10.04	7.75	7.72	6.11	1.68	-1.33	4.69	0.272	0.21
	Week 4	12.48	8.16	8.57	7.27	2.95	-0.15	6.04	0.062	0.37

Notes: ESS=Epworth sleepiness scale; RT=Reaction time; SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy; $Diff_{adj}$=Mean difference adjusted for baseline; 95% CI=95% confidence interval of the adjusted mean difference; ES=Effect size (Cohen's d). Significant p-values are displayed in bold.

5.3.2.4 Subjective-objective sleep discrepancy.

Subjective-objective sleep discrepancy was analysed to test if SRT has an effect on misperception of sleep when compared to BCT. We conducted between-group comparisons of the MI for actigraphy and polysomnography. The MI describes the direction of misperception, being positive when objective TST > subjective TST (underestimation) and negative when objective TST < subjective TST (overestimation).

Actigraphy. For actigraphy, we found a higher negative MI for TST in the SRT group during the late treatment phase (p = .011, d = -.031), indicating higher overestimation of sleep time. No effects were found during the early treatment phase (p = .345)

Polysomnography. No group effects were found for the MI derived from PSG at week one (p = .555) or week four (p = .128). Results are summarised in Table 21.

Table 21. Overview of changes in subjective-objective sleep discrepancy

TST	SRT (26)		BCT (29)						
	mean Diff in min(SD)	mean MI (SD)	mean Diff in min(SD)	mean MI (SD)	$Diff_{adj}$	95% CI		*p*	ES
Actiwatch - Sleep diary									
BL	8.55(51.8)	0.02(0.13)	11.17(62.2)	0.02(0.15)					
ET	-17.00(35.3)	-0.05(0.11)	-8.65(56.6)	-0.03(0.15)	-0.02	-0.05	0.02	0.345	-0.11
LT	-26.17(31.6)	-0.07(0.09)	-7.92(53.7)	-0.02(0.14)	-0.04	-0.08	-0.01	**0.011**	-0.31
Polysomnography - Sleep diary									
BL	37.56(52.3)	0.09(0.13)	33.26(55.1)	0.07(0.12)					
W1	23.00(53.0)	0.06(0.15)	29.18(64.2)	0.06(0.14)	-0.02	-0.09	0.05	0.555	-0.17
W4	7.45(30.6)	0.02(0.08)	29.27(87.7)	0.06(0.20)	-0.06	-0.13	0.02	0.128	-0.45

Notes: SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy; Mean differences (mean Diff) were calculated by subtracting subjective estimates from objectively derived estimates in minutes; Statistics were calculated on the misperception index (MI); BL=Baseline, ET=Early treatment (week 1-2); LT=Late treatment (week 2-3); W1=Week 1; W4=Week 4; $Diff_{adj}$=Mean difference adjusted for baseline; 95% CI=95% confidence interval of the adjusted mean difference, ES=Effect size (Cohen's d). Significant p-values are displayed in bold.

5.3.2.5 Night-to-night sleep variability

We hypothesised that SRT reduces night-to-night sleep variability for TST, SOL and WASO relative to BCT. To compare night-to-night sleep variability between both treatment arms, we extracted RMSSDs for each participant and for each of the three sleep variables derived from sleep diaries and actigraphy recordings (see Table 22).

Table 22. Night-to-night sleep variability

		SRT (26)		**BCT (29)**						
Sleep diary RMSSD		*M*	SD	*M*	SD	$Diff_{adj}$	95% CI		*p*	ES
TST	Baseline	95.19	39.07	91.59	37.36					
	Early treatment	58.46	31.14	77.10	36.06	-21.42	-34.14	-8.70	**0.001**	-0.56
	Late treatment	57.16	21.21	68.23	32.04	-13.85	-26.57	-1.13	**0.033**	-0.36
SOL	Baseline	26.52	18.98	22.72	27.56					
	Early treatment	19.44	29.90	20.19	13.95	-3.36	-14.30	7.58	0.545	-0.14
	Late treatment	13.13	13.43	23.77	33.55	-13.26	-24.20	-2.32	**0.018**	-0.57
WASO	Baseline	68.84	33.87	74.58	44.70					
	Early treatment	30.66	18.40	56.98	29.47	-24.14	-36.05	-12.22	**<.001**	-0.61
	Late treatment	25.50	16.95	49.74	31.82	-22.06	-33.97	-10.14	**<.001**	-0.56
Actigraphy RMSSD										
TST	Baseline	72.83	29.45	66.61	29.33					
	Early treatment	45.00	25.30	53.77	28.23	-12.49	-24.96	-0.01	**0.050**	-0.42
	Late treatment	53.70	29.70	53.91	24.06	-3.03	-15.51	9.44	0.632	-0.10
SOL	Baseline	12.63	9.21	20.01	16.48					
	Early treatment	9.02	5.11	18.01	17.41	-5.54	-11.31	0.24	0.060	-0.43
	Late treatment	8.61	5.55	18.79	14.61	-6.64	-12.42	-0.87	**0.024**	-0.52
WASO	Baseline	30.91	16.71	29.70	14.94					
	Early treatment	20.72	10.12	26.95	17.18	-7.43	-12.76	-2.10	**0.007**	-0.47
	Late treatment	18.54	8.47	26.56	12.26	-9.19	-14.52	-3.86	**0.001**	-0.58

Notes: RMSSD=Root mean squared successive difference; TST=Total sleep time; SOL=Sleep onset latency; WASO=Wake after sleep onset; SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy; $Diff_{adj}$=Mean difference adjusted for baseline, 95% CI=95% confidence interval of the adjusted mean difference, ES=Effect size (Cohen's d). Significant p-values are displayed in bold.

Sleep diary. Comparisons of RMSSDs for sleep diary variables revealed moderate effect sizes for TST and WASO at early and late treatment indicating less sleep variability in the SRT group (*d range* = -.36 to -.61) . Moderate effect sizes were also found for SOL (p = .018, d = -.57) during the late treatment phase. However, no effects were found for variability in SOL during the early treatment phase (p = .545).

Actigraphy. Comparisons for actigraphy-derived RMSSDs revealed moderate effect sizes for TST during early treatment (p = .050, d = -.42); for SOL during late treatment (p = .024, d = -.52); and for WASO during early (p = .007, d = -.47) and late treatment (p = .001, d = -.58). No effects were found for variability in SOL during the early treatment phase (p = .060) and for TST during the late treatment phase (p = .632).

5.3.2.6 Attentional bias to sleep stimuli.

We analysed reaction times of the sleep related dot-probe task to inform about attentional bias to sleep stimuli across intervention groups, whereby a greater negative index implies a greater bias towards sleep stimuli. Results revealed that there was no group difference in attention bias at early (p = .342) or late treatment (p = .873), indicating that the allocation to SRT or BCT did not have an effect on attentional bias towards sleep related stimuli (see Table 23).

Table 23. Attentional bias to sleep stimuli

Attentional bias score	**SRT (26)**		**BCT (29)**						
	M	SD	*M*	SD	$Diff_{adj}$	95% CI		*p*	ES
Baseline	-4.11	27.42	3.30	25.72					
Early treatment	-8.00	21.56	-0.15	19.10	-5.28	-16.23	5.67	0.342	-0.20
Late treatment	1.07	20.71	2.75	18.95	0.89	-10.06	11.83	0.873	0.03

Notes: Attentional bias score=mean (RT (neutral)) - mean (RT (sleep)) with a greater negative index implying a greater bias towards sleep stimuli. SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy; $Diff_{adj}$=Mean difference adjusted for baseline; 95% CI=95% confidence interval of the adjusted mean difference; ES=Effect size (Cohen's d).

5.3.2.7 Self-reported pre-sleep arousal and sleep-related mentation

It was proposed that SRT decreases self-reported pre-sleep arousal and sleep-related mentation. Self-reported pre-sleep arousal was measured 1) daily via five items of the PSAS that were included in the sleep diary and 2) at baseline, post-treatment and follow-up via the full version of the PSAS. Sleep-related mentation before sleep was obtained at the same time points via questions from the GCTI. Results from all analyses are summarised in Table 24.

Daily measured pre-sleep arousal. When compared between groups, we found medium effect sizes during early (p = .005, d = -.55) and late treatment (p = .035, d = -.41) in favour of SRT, suggesting that participants in the SRT group experienced less pre-sleep arousal.

PSAS. We analysed the full scale as well as the cognitive and somatic subscales of the PSAS at week four and week 12. Results of the full scale are summarised in Figure 18 below. Between-group comparisons of cognitive arousal and overall arousal scores showed medium effect sizes at both time points (d range = -.44 to -.63). Between-group comparisons of the somatic subscale showed medium effect sizes at week 12 and in favour of the SRT group (p = .048, d = -.33). No effects were found at week four (p = .363).

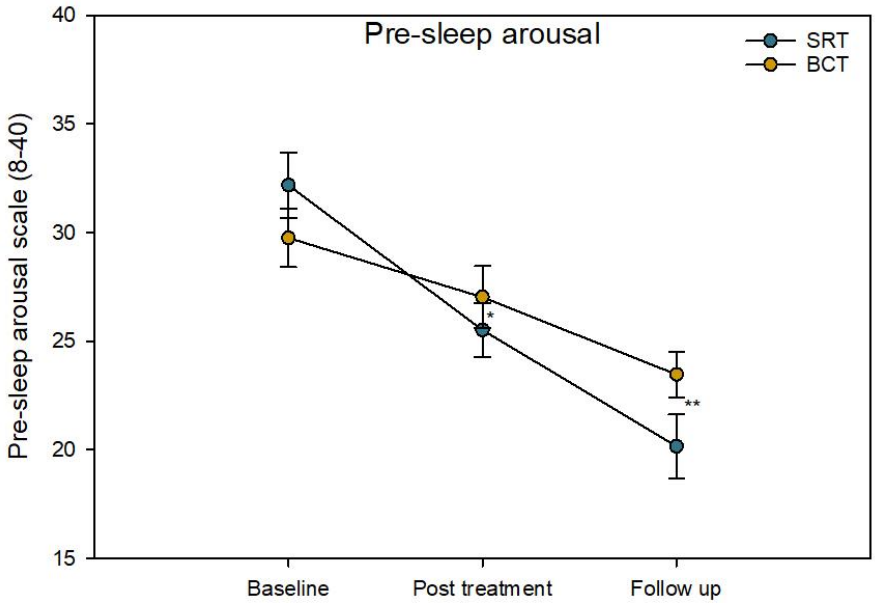


Figure 18. Pre-sleep arousal by group and time point. SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy. Raw means (+/- 1 SE) are presented for both groups at each time point. Statistical group differences are derived from linear mixed models and represented by a single or double asterisk (*=p<.05, **=p<.01).

Sleep-related mentation. Analysis of sleep-related thoughts, obtained by the GCTI, revealed significant group differences at post-treatment (p = .023, d = -.43) and follow-up (p = .037, d = -.39), indicating that participants in the SRT group experienced less sleep-related and sleep-interfering thoughts. Results from the GCTI are also summarised in Table 24 below.

Table 24. Pre-sleep arousal and sleep-related thoughts

	SRT (26)		**BCT (29)**						
	M	SD	*M*	SD	$Diff_{adj}$	95% CI		*p*	ES
Sum score of daily cognitive arousal measurement									
Baseline	5.73	1.92	5.25	2.85					
Early treatment	4.11	2.38	4.99	2.96	-1.31	-2.21	-0.41	**0.005**	-0.55
Late treatment	4.10	2.67	4.65	2.97	-0.97	-1.88	-0.07	**0.035**	-0.41
Somatic arousal (PSAS-S)									
Baseline	13.74	4.18	12.38	3.10					
Week 4	12.16	2.78	11.90	2.74	-0.54	-0.63	1.72	0.363	-0.15
Week 12	10.48	3.94	11.07	2.39	-1.20	-2.38	-0.01	**0.048**	-0.33
Cognitive arousal (PSAS-C)									
Baseline	18.44	5.24	17.38	5.78					
Week 4	13.35	4.37	15.14	5.90	-2.43	-4.26	-0.60	**0.010**	-0.44
Week 12	9.58	3.85	12.39	3.74	-3.42	-5.29	-1.59	**<.001**	-0.62
Overall arousal (PSAS-Sum)									
Baseline	32.19	7.82	29.76	7.25					
Week 4	25.52	6.20	27.03	7.68	-3.31	-5.83	-0.78	**0.011**	-0.44
Week 12	20.16	7.35	23.46	5.54	-4.48	-7.02	-1.93	**0.001**	-0.59
Sleep related thought (GCTI-Sum)									
Baseline	23.58	9.81	28.00	12.87					
Week 4	12.00	8.49	19.07	10.12	-4.87	-9.06	-0.69	**0.023**	-0.43
Week 12	11.32	10.51	19.48	11.52	-4.46	-8.66	-0.27	**0.037**	-0.39

Notes: SRT=Sleep restriction therapy; BCT=Bedtime consistency therapy; PSAS-S=Somatic subscale of the pre-sleep arousal scale; PSAS-C=Cognitive subscale of the pre-sleep arousal scale; GCTI=Glasgow content of thought inventory; $Diff_{adj}$=Mean difference adjusted for baseline; 95% CI=95% confidence interval of the adjusted mean difference; ES=effect size (Cohen's d). Significant p-values are displayed in bold.

6 Discussion

This study was based on the principles of a dismantling trial design, whereby one or more aspects of the original treatment that are thought to be an active change agent (here the restriction of TIB) are isolated. All other aspects of the study design and implementation were held as constant as possible across intervention groups, and attempts were made to ensure equivalence across other aspects of care delivery such as therapist time, attention, and monitoring/review of sleep pattern, with the aim of standardising participant expectation across both arms. Our primary aim was to examine if a restricted sleep opportunity, as prescribed by SRT, is sufficient to bring about improvements in insomnia. Our secondary aim was to conduct a mechanistic evaluation of SRT.

First, consistent with TIB prescription, we demonstrated a reduction in TIB for the SRT group, while participants in the BCT group did not report changes in TIB. These results were also reflected in actigraphy and polysomnography recordings, strongly supporting adherence to the sleep window, validating the interventions and demonstrating that, in the SRT group, sleep was indeed restricted and titrated.

6.1 Superiority of restricting time in bed

We compared treatment effects between the two groups and revealed superiority for the full SRT intervention. The superiority of SRT was demonstrated by large group differences in our primary outcome, insomnia severity, at 4- and 12-weeks post-randomisation. In support of our hypotheses, the SRT arm displayed reduced sleep diary reported WASO and SOL, which manifested in an increase in SE during treatment and relative to BCT. Our data also revealed that SRT improved sleep-related quality of life relative to BCT at 12-, but not at 4-weeks post-randomisation. These results are potentially indicative of a lag between improvements in sleep and daytime functions, whereby the experience of side-effects and restricted sleep time may hinder beneficial treatment effects during the acute phase (see Triple-R model)[99,162]. In contrast, we found no group differences for self-reported cognitive complaints, anxiety or depression. These null findings may reflect true effects or could be

due to our strict exclusion criteria for comorbid caseness of anxiety and depression, limiting the potential for change. Moreover, given the sample size, this study was not powered to detect small to medium effect sizes which are commonly reported for self-reported cognitive complaints[219], anxiety[220] and low depression[221]. Indeed, we note that effect sizes for depressive symptoms and cognitive complaints were medium in strength and in favour of SRT (12 weeks), with corresponding p values <.1.

6.2 Mechanistic evaluation of SRT

It was previously proposed that the improvement in sleep continuity is of significant importance to reduce insomnia symptoms when following the treatment guidelines of SRT[103,162]. While subjective sleep reports, as described above, are indicative for changes in sleep and are relevant to the patient, a multidimensional assessment perspective including actigraphy and polysomnography is recommended[184,222]. For polysomnographic recordings, results from this study confirmed our hypotheses and revealed group effects for SOL, WASO and SE at week one and for WASO and SE at week four in favour of SRT (*d* range = -.56 to -.79). These results were also confirmed by actigraphy, showing improvements in the SRT group for WASO, SOL and SE across the four weeks of treatment (*d* range = .40 to -.87). While these effects are slightly larger than those commonly reported in CBT-I trials[223], the effects for polysomnography-derived SOL at week four were non-significant. This may be because SOL was already low at baseline (< 9 minutes in each group). Interestingly, objective measures also confirmed that the restriction of TIB, as prescribed by SRT, reduced TST during the acute phase of the treatment (PSG derived between-group differences at week 1 = -48 minutes; actigraphy week 1-2 = -51 minutes), and indeed, induced a mild sleep deprivation which persisted during the late treatment phase as indicated by actigraphy (between-group differences at week 3-4 = -39 minutes).

To test if the induced sleep deprivation lead to changes in the macrostructure of sleep, we conducted exploratory analysis of sleep stages and SWS-L. Changes in sleep structure were mainly observed at week one. Consistent with sleep restriction effects in good sleepers, we

found that light sleep stages, such as stage 1 and stage 2, were substantially reduced while stage 3 sleep seemed to be preserved[14]. In contrast to previous literature, we did not observe reductions in REM sleep[14]. The lack of finding could be explained by differences in the study population or in the amount or length of restriction. Furthermore, results revealed a shortening of SWS-L in the SRT group at week one, indicating a higher pressure of stage 3 sleep. However, it has to be noted that although SWS-L has previously shown to differ between people with insomnia and heathy controls, it is not a commonly used indicator of the homeostatic sleep process[64]. The effects of mild sleep deprivation are also commonly experienced by an increase in sleepiness[14]. Here, subjective and objective measures confirmed that participants in the SRT group were indeed sleepier in the morning (early treatment), during the day (early treatment) and in the evening (early and late treatment). Intriguingly, results from daytime sleepiness were reversed at week 12, when the SRT group reported less sleepiness as indicated by the ESS. This supports the idea of a lag between improvements in sleep and daytime functions.

Moreover, we hypothesised that an improvement in sleep consolidation, as described above, could lead to changes in subjective-objective sleep discrepancies which are commonly reported in the insomnia population[224]. Here, indices from actigraphy indicated that participants in the SRT group overestimated TST more during late treatment when compared to BCT. Medium effect sizes from PSG-derived indices at week four pointed in the same direction (sleep seemed to be less underestimated, d = -0.45) but did not reach significance. An overestimation of TST is commonly reported in good sleepers[225], especially when undergoing sleep restriction[226].

Another feature that has been observed in the insomnia population is greater night-to-night sleep variability[227]. Here, both treatment arms aimed to stabilise bedtimes, however, we expected a higher reduction in night-to-night sleep variability in the SRT group because of its direct effects on sleep parameters[88] (e.g. changes in SOL, WASO, and SE). Our analysis supported the hypothesis and revealed moderate group effects in favour of SRT for

variability estimates of WASO and TST at early and late treatment phases as derived from sleep diary and actigraphy (*d range* = -.36 to -.61).

Furthermore, we analysed reaction times towards sleep related stimuli to test our hypothesis that SRT reduces attentional bias. While this measurement could be used as an indicator for the bed-sleep association, our results did not reveal any group differences at early or late treatment indicating that the restriction of TIB does not affect attentional bias towards sleep related stimuli, at least using the dot-probe task. This is in line with a previous study showing that attentional bias did not change with intervention, even though bias was directly targeted by attentional bias modification training[228]. The authors concluded that the absence of the effect could either be explained by the absence of attentional bias at baseline or the non-effectiveness of the treatment on attentional bias. Here, both explanations are plausible. Additionally, it has to be noted that the attentional bias score was derived from reaction times, which in turn have been shown to be affected by the restriction of sleep time as reported by the PVT analysis of this study. Consequently, deteriorations in objective vigilance may have masked potential treatment effects of SRT on attentional bias. Furthermore, we cannot exclude the possibility of learning effects as participants were exposed to the same stimuli across repeated measures.

Lastly, we expected pre-sleep arousal to diminish. Indeed, our results showed that cognitive arousal and sleep related thoughts before sleep were diminished in the SRT group during the acute phase of the treatment (week 1- 4, *d range* = -.43 to -.55). Interestingly, those results persisted at 12-weeks follow-up (*d range* = -.39 to -.63), when we also found small group effects on somatic arousal (*d* = -.33). These results are in line with previous reported effects of SRT on arousal as obtained by the PSAS[229]. As SRT does not comprise a cognitive component, we hypothesise that cognitive pre-sleep arousal could diminish as a result of induced sleepiness (i.e. participants are too tired/sleepy at bedtime to worry about sleep). However, changes in cognitive and somatic pre-sleep arousal at follow-up could be a result of lagged improvements in daytime functioning or a result of the reconditioning of bed with sleep, whereby bed/bedroom are predominantly related to sleep instead of worries and

frustration. Similar changes were also observed for sleep related content of thoughts which were substantially reduced in the SRT group at post-treatment and follow-up, potentially contributing to reductions in arousal. In line with the triple-R model, we expected sleep interfering thoughts to be reduced during SRT in the short term because of induced sleepiness in the evening and in the long term as a result of behavioural experiment effects[162]. The latter refers to the hypothesis that SRT helps to test out and challenge beliefs presumed to underlie insomnia and related distress, such as the conviction that one is a bad sleeper who will be awake all night. By experiencing short sleep onset latencies and less time awake, these beliefs are challenged, leading to reductions in sleep-related thoughts.

Overall, our mechanistic evaluation illustrated several potential modes of action through which SRT improves insomnia complaints. The results could show that sleep pressure increased during the acute phase of the treatment, potentially driving changes in sleep consolidation and reducing insomnia symptoms such as pre-sleep arousal and misperception of sleep. Furthermore, the reduction of symptoms seemed to persist at 12-weeks follow-up, when we also observed improvements in daytime functions. This study was not designed for mediation analysis; however, we could depict evidence for changes in potential mechanisms as a result of the allocation to SRT versus BCT.

6.3 Benefits of bedtime consistency

While the study was designed to isolate TIB restriction this chapter should comment on the changes observed within the BCT arm. Visual inspection of within-group change scores indicates improvements on the ISI from baseline to post-treatment (*mean difference* = 3.0) and from baseline to follow-up (*mean difference* = 4.3), as well as decreases in other questionnaire variables (e.g. BC-CCI and GSII), but not in objective measures of sleep (see Table 9-11). While the effects at follow-up are slightly higher than improvements in typical control groups (e.g. sleep hygiene[105]), they are similar to other controls arms, which were matched for unspecific effects (e.g. information control with telephone support[230]). Research evidence supports the view that regularising bedtimes could confer some therapeutic benefit

by improving sleep and daytime functioning[165]. However, to test these effects, comparisons with a third arm receiving sleep hygiene or treatment as usual would be needed to test the efficacy of BCT.

6.4 Strengths and limitations

The main strength of this work lies in the study design. Choosing a control group that is matched for key therapeutic factors is consistent with recent calls for investigators to carefully select and justify control conditions in psychotherapy research[167,231] and allows to draw strong conclusions about the specificity of TIB reduction. We note also that high-resolution measurement of sleep via sleep diary, actigraphy and polysomnography – with convergent findings across methods – lends support to the robustness of our conclusions. Additionally, this study was the first to systematically assess side-effects in a randomised-controlled trial of SRT and report on its treatment expectations and fidelity.

Limitations of this work should be considered. Our sample was recruited in the restricted area of Oxford, UK and had to undergo a thorough screening process where we excluded for comorbid mental health problems and use of medication. Participants in this study were between the age of 25 and 55, highly educated (29% with doctoral degree), and hence, likely to have a high socio-economic status. Additionally, the average ISI score at baseline seemed to be relatively low (ISI = 14.9) compared to other study samples (e.g. studies of ISI validation ranged from 15.4-19.7)[168]. Consequently, the sample we recruited might not be representative of the general insomnia population in the UK[28]. It is important to note however, that this study did not seek to test effectiveness (or generalisability) but instead aimed to test the role of TIB restriction.

Testing the role of TIB restriction also involved the analysis of multiple potential mechanistic variables and consequently, led to a high number of statistical comparisons. By conducting multiple tests, the potential to find false positives (type 1 error) increased. At the same time, our sample size was only powered to detect large effects in the primary outcome, yet we measured variables that previously revealed small to medium effect sizes.

Consequently, our statistical analysis also had an increased risk of false negatives (type 2 error)[133]. To allow the reader to judge the reported effects, exact p values and effect sizes were reported, consistent with recommended practice guidelines[232].

Furthermore, research visits also served as therapy sessions and the primary researcher acted as both therapist and researcher. Hence, the researcher was not blinded and was aware of the differences between the interventions. To minimise bias, particularly in relation to therapy allegiance, we (1) carefully positioned the study in the participant information sheet (see Appendix B); (2) monitored fidelity and obtained independent appraisal; (3) had standardised procedures for all visits for both arms; (4) objectively verified the implementation of treatment instructions – giving confidence this accounts for group differences; (5) blind scored objective outcomes where possible (e.g. PSG); and (6) collected long-term follow-up outcomes via an online questionnaire (limiting researcher involvement in the collection of clinical outcomes). Although both groups rated treatment credibility in the moderate range, we note that participants in the SRT group gave slightly higher ratings. These differences, however, did not seem to affect treatment participation (all participants attended all treatment sessions), attendance of study procedures, or completion of treatment outcomes (only one participant in the SRT arm withdraw during the first week of treatment).

While the nature of face to face therapy limits the possibility of a double-blind experiment, future studies implementing digital techniques could eliminate therapist allegiance effects completely. Moreover, we aimed to investigate the mechanisms of SRT, but the study sample was not adequately powered and designed to determine mediating effects on clinical outcomes. As stated earlier (see chapter 2), the following conditions should be tested and satisfied for mechanistic evaluation: (1) SRT must be related to therapeutic change (e.g. improvement in insomnia severity); (2) SRT must be related to the proposed mediator (e.g. homeostatic sleep drive); (3) the proposed mediator must be related to therapeutic change; and (4) the relationship between SRT and therapeutic change must be reduced after controlling statistically for the proposed mediator. Here, we were only able to demonstrate condition (1) and (2) and hence cannot determine any mediating effects. In a first step, the

MARTINI study elucidated a number of potential mediators. Future studies should focus on specific variables, such as cognitive arousal or sleep consolidation, and test their effects within the proposed mechanistic framework (see triple R model).

6.5 Conclusion

This is the first study to investigate if a restricted sleep opportunity, as prescribed by sleep restriction therapy, is required to bring about improvements in insomnia. To dismantle the restriction component, we specifically designed a novel intervention, called bedtime consistency therapy, which involves prescription and monitoring of a regular – but not restricted – time in bed. While both arms reported fewer insomnia symptoms at the end of treatment, sleep restriction therapy demonstrated superiority at both 4- and 12-weeks post-randomisation. In conclusion, our study supports and reinforces systematic review evidence that SRT is effective as a standalone therapy and identifies restricted time in bed as central to clinical gains. Similar future manipulation studies are needed to elucidate whether clinical benefit varies in relation to timing, dose and titration of the sleep window. While our study demonstrated effects of the allocation to SRT on several proposed mechanistic variables, a larger study sample is required to perform mediation analysis and determine putative treatment mediators.

CHAPTER 4:

THE EFFECTS OF SLEEP RESTRICTION THERAPY ON CIRCADIAN TIMING

1 Preface

The previous chapters have illustrated the efficacy of SRT and the importance of investigating its modes of action in the treatment of insomnia. Yet, an under-appreciated pathway of SRT may be via changes to circadian timing[233,234]. This chapter is reporting on the ESPRIT study, which investigated the acute effects of SRT on sleep, phase angle and circadian phase.

2 Abstract

Sleep restriction therapy has been shown to effectively reduce insomnia symptoms by prescribing a restricted sleep opportunity. Yet, curtailing the sleep window not only affects sleep duration, it also leads to delayed bedtimes and/or advanced rise times - which in turn has been shown to impact the circadian rhythm. Recent work suggests that the timing of sleep in relation to the timing of the circadian rhythm may be abnormal in insomnia patients. However, no study has yet investigated if SRT affects this relationship in its acute phase. Here, we conducted an exploratory pilot study that examines the relationship between circadian phase and sleep-wake behavior as indicated by phase angle, before and after two weeks of SRT.

Participants followed standard treatment guidelines and selected bed and rise times according to preference and feasibility. Phase angle was derived from the difference between the decimal clock time of dim light melatonin onset (DLMO) and attempted sleep time. Secondary outcomes included DLMO, sleep continuity, insomnia severity, daytime functioning and repeated measures of vigilance.

Eighteen participants meeting insomnia criteria (mean age = 37.06±8.99) were included in the analysis. In line with previous research, results showed improvements in subjective and objective sleep continuity variables after two weeks of SRT (*d* range = .82-2.35) and reductions in insomnia severity (*d* = 1.68). Phase angle was determined in 15 participants and results revealed an increase of 35 minutes from baseline to post-treatment (2.27±0.94 hrs vs 2.85±1.25 hrs, *d* = .56). While DLMO stayed relatively stable (20:49 vs 21:01),

attempted sleep was approximately 47 minutes later (23:13 vs 23:52, *d* = 1.16). Repeated subjective and objective measurements of vigilance indicated medium to large deteriorations after two weeks of SRT (*d* range = .48-1.42). No effects were found on self-reported daytime sleepiness and cognitive complaints.

For the first time, this study has illustrated that SRT increases phase angle in its acute phase. Future studies are needed to experimentally test if an increase in phase angle is linked to therapeutic benefits for insomnia.

3 Introduction

In humans, the circadian rhythm determines our ability and our desire to fall asleep[235,236]. Indeed, research has shown that the circadian propensity for sleepiness is highest before habitual wake time, at ~3:00-6:00am and lowest just before habitual sleep time, ~7:00 to 10:00pm[141]. In contrast, the homeostatic sleep pressure has been shown to be lowest after waking up and highest just before going to sleep[9]. Both processes have to be uniquely timed in order to maintain consolidated sleep throughout the night[10,141,237]. That is, one should attempt sleep when homeostatic sleep drive is high and circadian propensity for wakefulness is low[9,10,237,238]. The alignment between sleep behaviour and circadian phase is commonly determined by phase angle, a composite score derived from the time difference between bedtimes and circadian phase markers[233,239]. The standard marker for circadian phase is typically obtained by the onset of melatonin production which occurs in dim light (dim light melatonin onset = DLMO)[240,241,242]. In individuals with *normal* alignment, DLMO occurs two to three hours before habitual bedtime[242]. In contrast, circadian misalignment, that is attempting sleep too early or too late in the circadian cycle, can result in difficulty falling asleep, maintaining sleep or lead to early morning awakenings[141,243].

3.1 Circadian alterations in insomnia

Although insomnia is not considered a circadian rhythm disorder[20], previous studies have shown that insomnia can be associated with abnormalities in circadian phase and phase angle. For example, the correlation between DLMO and midpoint of sleep time seems to be

weaker in people with insomnia, indicating a less robust relationship between the timing of sleep and circadian phase[244]. Additionally, Flynn-Evans et al. compared circadian phase between good sleepers and people with insomnia[233]. The authors reported that, unlike control participants, sleep among patients with insomnia was not correlated with their diurnal preference. Their results also revealed that patients tended to initiate sleep, on average, at the same clock time but melatonin rise occurred about one hour later compared to good sleeper controls[233]. Consequently, people with insomnia attempted sleep at an earlier circadian phase. While good sleepers initiated sleep around 3.17 $\pm$ 1.14 hrs after their DLMO, people with insomnia went to sleep 2.63 $\pm$ 1.28 hrs after their DLMO, indicating a shorter phase angle. The authors suggested that a short phase angle could indicate a mismatch in the timing of sleep relative to the melatonin rhythm and increase the likelihood that the sleep episode overlaps with the wake maintenance zone (WMZ).

3.2 SRT and its potential impact on circadian timing

Data from the previous chapter illustrated that SRT can lead to a large reduction in TIB (on average 72 minutes). Yet, curtailing the sleep window not only affects sleep duration, it also leads to delayed bedtimes and/or advanced rise times[98]. Indeed, retrospective data analysis from the MARTINI study showed that initial bedtimes were scheduled about one hour later (BCT= 22:48 vs SRT = 23:45), while rise times were scheduled about half an hour earlier when compared to the control arm (BCT = 7:02 vs SRT = 6:28). However, the positioning of the sleep window varies across studies. While most studies seem to tailor sleep opportunity to patient preference (e.g. the MARTINI study), some delay habitual bedtime and advance habitual rise time by equal amounts, and others report delaying bedtimes by a consistent amount across all patients[98]. Importantly, those alterations are linked to changes in morning and evening light exposure, which in turn has been shown to affect the underlying circadian rhythm[245-247].

To our knowledge, only one pilot study has reported on the effect of SRT on circadian phase in people with insomnia. The study by Miller and colleagues analysed overnight measures

of temperature and cortisol in six participants before and after five weeks of SRT[119]. However, analysis of sinusoidal curves for both measurements did not reveal any effect of SRT on circadian phase or periodicity. Yet, studies in good sleepers report that experimental sleep restriction (SR) does indeed affect the circadian system. For example, a research study by Rodgers and Dinges showed that DLMO was delayed by about 1.2 hours during SR even though bed- and rise times were shifted by the same amount (8.2 hours -> 4.2 hours)[248]. Another study by Agostini and colleagues in adolescents showed that DLMO was shifted by approximately three hours during SR when bedtime was delayed only (10 hours -> 5 hours)[249]. Similarly, Gordijn and colleagues showed that the displacement of a whole sleep period by three hours delayed DLMO by approximately 65 minutes, comparable to the effects of three hours of evening bright light exposure[250]. While these results highlight that a shift in bedtime is linked to changes in the circadian phase marker, they also indicate differences in their magnitude of change. Based on the here described studies, it seems that the temporary delay in bedtime is two to three times larger than the associated shift in DLMO.

The previous passages have focused on the effects of sleep restriction on the relation between circadian phase and sleep. However, sleep restriction also has effects on vigilance and alertness during the day, which in turn have been shown to fluctuate as a result of the constant interaction between circadian rhythm and sleep homeostasis[251]. While previous studies, including the MARTINI study, have reported marked effects of SRT on vigilance and alertness, they typically only assessed one specific time point in the evening[99,118,123]. Taking into account that those measures vary with time of day[118], the true effects of SRT might be masked by wake promoting factors of the circadian rhythm[252]. Ultimately, the effects of SRT on alertness and vigilance can only be fully understood if obtained by more sensitive repeated measures.

4 Methods

4.1 Study design

The ESPRIT (Effects of SleeP Restriction therapy for Insomnia on circadian Timing) study was a within-subjects assessment of changes in sleep and circadian phase during acute therapeutic implementation of SRT in people with persistent insomnia. Participants meeting inclusion/exclusion criteria commenced the baseline phase for one week and were invited to the laboratory for their first assessments of circadian phase (DLMO) and vigilance. Following baseline, participants implemented SRT over a two-week treatment period. After these two weeks, participants were invited for a second (post-treatment) assessment at the laboratory. The study was conducted in Oxfordshire, UK and approved by the Central University Research Ethics Committee of the University of Oxford (CUREC R60730/RE002). The study was prospectively registered at ISRCTN (ISRCTN 18006597).

4.2 Objectives

4.2.1 Primary objective

The primary objective of the ESPRIT study was to show that SRT increases phase angle during its acute phase. Phase angle was derived from the difference of the decimal clock times of DLMO and self-reported attempted sleep for the previous seven days as derived from sleep diary. Both clock times were obtained at baseline and following two weeks of treatment (post-treatment).

4.2.2 Secondary objectives

The ESPRIT study aimed to investigate the following secondary hypotheses:

1. SRT improves sleep continuity in its acute phase. Sleep continuity was derived from SE, SOL and WASO obtained by sleep diary and actigraphy during one week of baseline and during two weeks of treatment.

2. SRT reduces self-reported insomnia severity. Insomnia severity was obtained by the ISI[168] at baseline and after two weeks of treatment (post-treatment).
3. SRT delays the circadian phase. The circadian phase was measured by DLMO at baseline and after two weeks of treatment (post-treatment).
4. SRT impairs vigilance in the evening. Vigilance was measured by repeated hourly assessment of subjective sleepiness and PVTs that were obtained at the laboratory sessions at baseline and after two weeks of treatment (post-treatment).
5. SRT acutely reduces subjectively reported daytime functioning. Daytime functioning was assessed by the ESS[127] and the BC-CCI[171] at baseline and after the second week of treatment (post-treatment).

4.3 Study population

4.3.1 Strategies for recruitment and retention

The study aimed to recruit a sample size of N = 22. Based on previously reported between-group effects for phase angle differences in people with insomnia versus good sleeper controls (Cohen's d = 0.65)[233], the study was powered to detect a minimum standardised effect size of 0.65 at a 5% level of significance with 80% power. Accounting for 10% attrition, we sought to recruit 22 participants.

The study recruited through several channels. These included online and print advertisements, as well as the use of contact lists where adults who had previously volunteered to be involved in research were re-contacted. If potential participants were interested in taking part in the study, they were contacted by e-mail and received the participant information sheet (see Appendix G). If recruited via social media, they accessed the participant information sheet online and were then referred to the screening questionnaire. Participants were enrolled in the study between March 2019 and July 2019. All laboratory assessments took place during British summer time.

4.3.2 Screening and eligibility assessment

Before entering the study protocol, participants completed an online screening questionnaire using the 'Qualtrics survey tool' (Qualtrics, Provo, UT) to assess age, consent, insomnia, sleep efficiency, BMI, compliance, anxiety, depression, additional sleep disorders, chronotype, medication, shift work, menopause, pregnancy, drug misuse and travel criteria. Participants who screened 'positively' online were followed up by a brief, structured telephone interview to confirm age, medication and additional sleep disorders criteria, and to address other psychiatric diagnoses, extreme alcohol, nicotine and caffeine consumption, sleep-disruptive medical comorbidities and current prescriptions of current psychotherapy for sleep. Once deemed eligible, participants were invited for their study induction at the SCNi to discuss study procedures, obtain written consent and commence baseline assessments. An overview of inclusion/exclusion criteria and can be found below:

4.3.2.1 Participant inclusion criteria

1. Participant is willing and able to give informed consent for participation in the study
2. Aged 25-55 years
3. Screen positive for persistent insomnia (chronicity > 3 months) as indicated by the SCI[179] and meet DSM-5 criteria for insomnia disorder (see chapter 3)
4. Sleep efficiency < 85%
5. Intermediate chronotype as indicated by the Morningness-Eveningness questionnaire[253] (score between 31 and 69)
6. Participant can comply with study procedures

4.3.2.2 Participant exclusion criteria

1. Clinically significant anxiety or depressive symptoms (subscales of the Hospital anxiety and depression scale = HADS[170], excluded if score > 10)
2. Psychiatric diagnoses other than insomnia
3. Previous or current engagement with psychological treatment for insomnia (by healthcare professional or online)
4. Additional sleep disorder diagnosis or positive screen (e.g. narcolepsy, circadian rhythm disorder)

5. Sleep-disruptive medical comorbidity or conditions contraindicated for SRT (e.g. epilepsy)
6. Current prescription of CNS or hormonal medication
7. Overnight, early morning, evening, or rotating shift work in the last three months
8. Pregnancy, lactation, perimenopausal or menopausal
9. Travelled across more than two time zones in the prior three months
10. Smoked more than five cigarettes/week in the previous three months
11. Consumed more than 300mg of caffeine per day on average
12. Extreme alcohol consumption (decisions were made based on a telephone interview using items from the AUDIT[181])
13. History of drug misuse in the past 12 months

4.4 Study assessments and procedures

All assessments and procedures of the ESPRIT study are summarised below and can be found in the schematic exemplary study protocol (see Figure 21).

4.4.1 Baseline assessments

Eligible participants came to a first visit at the SCNi for their study induction. Printed versions of the participant information sheet (see Appendix G) and the consent form were presented to participants. On signing consent, participants were given a Pro-Diary watch. The Pro-Diary watch is a compact wrist–worn electronic diary with integrated activity monitor designed to collect patient reported outcomes (Camntech Ltd.). Participants were briefed on how to use the device. The Pro-Diary watch was selected because of its user-interface and the possibility to prompt sleep-diary questions and messages at a specific time in combination with the collection of actigraphy data. Participants were asked to keep their habitual sleep-wake patterns, answer sleep diary questions by accessing the Pro-Diary monitor every morning after awakening and every evening before going to bed and wear the Pro-Diary for 24 hours a day except for wet activities (e.g. shower, bath, swimming). For the duration of the baseline phase, participants were instructed not to modify their caffeine, nicotine, or alcohol intake from the levels reported at screening except for 48 hours prior to

their laboratory visit, when participants were instructed to abstain from caffeine and nicotine. Participants were also advised to refrain from eating bananas, chocolate, turkey and tomatoes for the entire day before the laboratory visit because of their acute effects on melatonin levels[254-257]. On the day of the laboratory assessment, participants were asked to refrain from taking aspirin or medicines that contain ibuprofen (Algiofor, Brufen, Dysmenol, Dolocyl, Ecoprofen). These instructions were required to enable the reliable collection of saliva and melatonin.

One week after the study induction, the baseline laboratory assessment was carried out. Laboratory events were scheduled relative to the onset of each participant's mean habitual sleep time (the time they reported to attempt sleep at their study induction), and participants were admitted to the laboratory approximately 5.5 hours before that time.

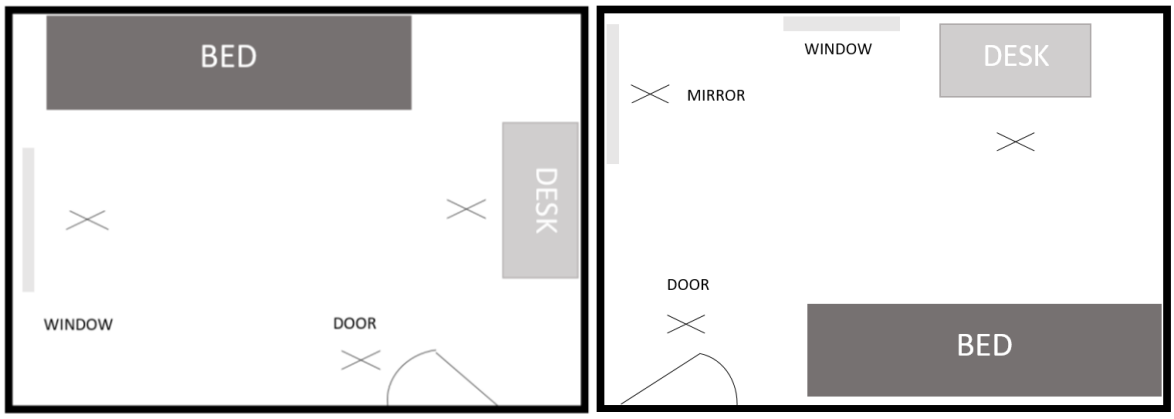


Figure 19. Room set up for the laboratory assessment. Marked crosses indicate the locations where light measurements were taken. Participants were mainly seated in front of the desk and were instructed not to sit or lay on the bed. Windows were covered with black out blinds.

The laboratory assessment ended two hours following habitual sleep time, and participants were provided with a taxi following completion of the study procedures. Participants remained awake for all procedures and consequently, were kept awake two hours past their typical bedtime. Upon arrival, participants remained in a light-controlled room (see Figure 19) at the Warneford clinical research facility (Oxford, UK) and were asked to complete demographic and baseline questionnaires. Ambient light levels remained at a maximum of 10 lux when measured at the eye in the vertical plane. Light levels were measured at various locations in the room (see crosses in Figure 19) with a lux meter (540 Light Meter, Testo SE

& Co. KGaA, Germany) before the arrival of the participant and before the last computer task was scheduled. Beclouded goggles were used when the participant left the room to use the bathroom. The goggles were beclouded with neutral density filters (0.6 neutral density, LEE Filters, UK) and ensured that light exposure was <10 lux in the hallway and in the bathroom of the facilities (see Figure 20).



Figure 20. Beclouded goggles.

Saliva samples were collected hourly with the first saliva sample being collected five hours before habitual sleep time and the last one two hours after habitual sleep time, resulting in a total of eight samples[258]. A modified constant posture protocol was imposed. Participants were seated at least 20 minutes prior to each saliva sample, during which the PVT was performed (~10 minutes). The PVT started and ended with a question about the current sleepiness state of the participant. Food was provided and intake was standardised for timing and content (sandwich after the third saliva sample). Participants were not permitted to eat or drink in the 20 minutes before the saliva sample was taken in order to reduce food particles in the sample and dilution of saliva. Wakefulness was monitored by direct observation from research staff members throughout the laboratory visit. Participants were free to engage in sedentary activities (e.g. listening to the radio, watching movies) at times when they were not required to undertake study procedures.

4.4.2 Study intervention

After a minimum of one day following the baseline laboratory assessment, participants were invited to the SCNi for the treatment session. This was to ensure that participants had at least one recovery night after the laboratory assessment and before commencing SRT. The therapist (LM) followed the same structure for the treatment session as described in chapter three. This included sleep hygiene advice, SRT rationales, reviewing average sleep times, setting a sleep window and discussing an individual action plan. Treatment material was similar to the MARTINI study and included a treatment manual, worksheets and sleep efficiency grids. After the initial session (~60 minutes), participants received two further sessions (each ~15 minutes), one after the first week of treatment (phone call) and one after the second week of treatment (during the second laboratory visit).

4.4.3 Treatment phase

For the duration of the treatment phase (two weeks), participants wore the Pro-Diary watch. They were asked to adhere to their scheduled sleep-wake pattern. To support adherence, the pro-diary watch was pre-programmed to remind participants of their agreed sleep schedule one hour before bedtime and to prompt sleep diary questions before scheduled bedtime and after scheduled rise time. The reminder was personalised and read as follows: *'Dear XXX, please remember to follow your agreed sleep schedule to establish a new improved sleep pattern. Keep going!'*. After the first week of treatment, participants received a phone call in order to review sleep efficiency, adapt the sleep window and check on data collection (session two).

Two weeks after the first laboratory visit (see Figure 21), participants returned for their post-treatment laboratory assessment. The laboratory event was scheduled relative to the first assessment night, and participants were admitted to the laboratory at the same clock time as before. Upon arrival, participants completed the same outcome questionnaires collected at baseline. For DLMO assessments, the same protocol as at baseline was applied; finishing the assessment two hours after the reported sleep time at baseline. In case the bedtime of the

participant was delayed by more than 30 minutes relative to baseline, we asked participants to stay one hour longer and thus, provide one more saliva sample. This was to ensure enough saliva samples were collected to capture melatonin levels. Saliva samples, PVT performance and sleepiness were obtained at the same clock time as the first laboratory assessment, resulting in eight or nine measurements of each. Participants were provided with standardised instructions on how to continue to self-implement SRT beyond the acute treatment phase.

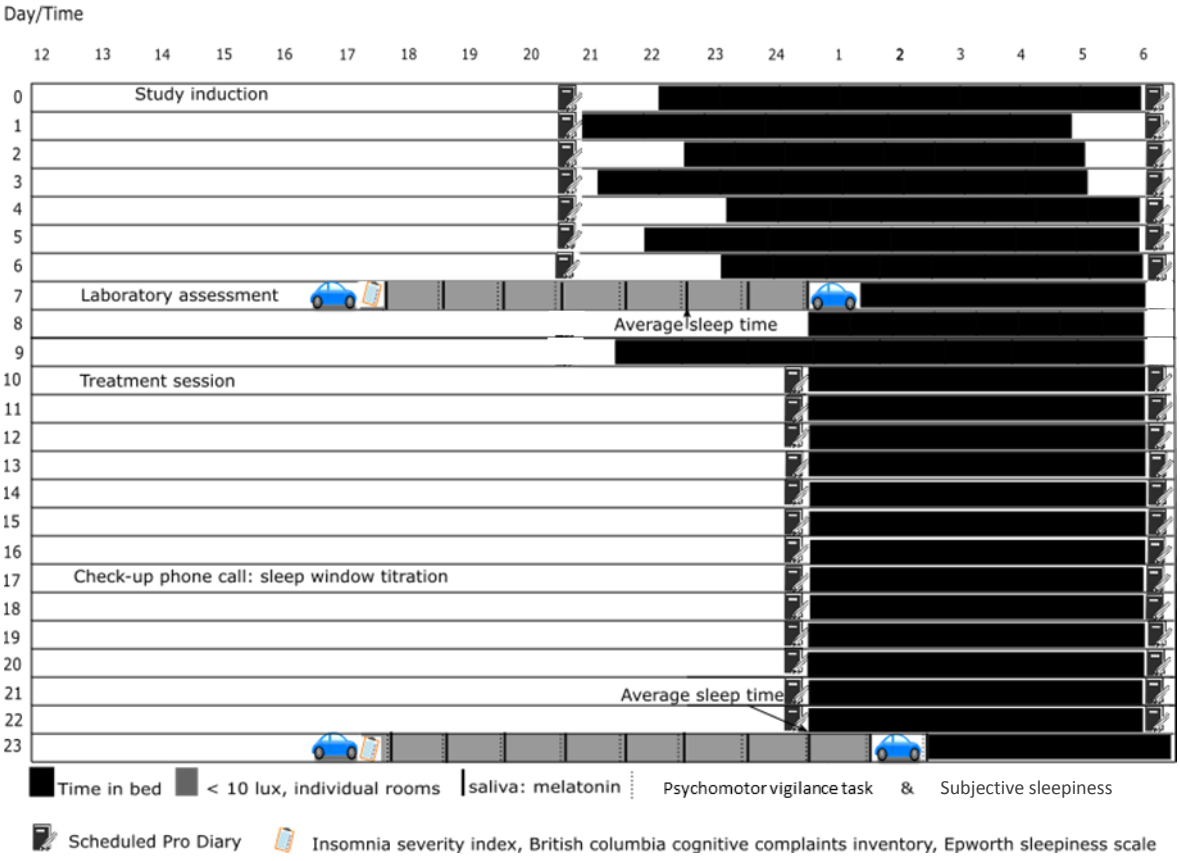


Figure 21. Schematic exemplary study protocol of the ESPRIT study. The axis on the left illustrates the number of days (0-23). The axis on the top represents the time of day (12:00pm to 6:00am). Days 1-7 show the baseline phase and days 10-23 illustrate the treatment phase. The treatment session and the check-up phone call were scheduled according to participant preference and availability of the therapist. In this example bedtime was delayed by two hours and the laboratory assessment at post-treatment was extended by one hour to ensure enough saliva samples were collected to capture melatonin levels. The sleep window was kept constant across both weeks.

4.5 Measures

4.5.1 Sleep continuity

4.5.1.1 Sleep diary

Participants were instructed to complete a sleep diary that was based on the consensus sleep diary[200] in the morning (just after waking up) and in the evening (just before switching off the light) for seven days during the baseline (accessed by the participants) and 14 days during the treatment phase (prompted by the Pro-diary) using the monitoring system of the Pro-diary (see Figure 22). Similar to the MARTINI study, participants provided subjective estimates for the following sleep continuity variables: (1) SOL - time from initial lights out until sleep onset; (2) WASO - time spent awake after initial sleep onset until last awakening and attempted sleep after; and (3) TST – total time spent in bed asleep. To compare sleep variables across a similar number of days, the treatment period (14 days) was split into two seven-day time points, reflecting week one and week two of treatment. Self-reported sleep continuity outcomes of interest were SOL, WASO and SE, which were averaged across the seven-day periods (baseline, week one and week two). We also performed analysis on TST to evaluate the extent of sleep restriction during the acute period of the treatment. During the baseline phase, sleep-diary questions could be accessed up to three hours after habitual rise time and up to three hours before habitual bedtime to avoid data loss due to sleep variability. During the treatment phase, sleep diary questions were prompted by audible tone and by the appearance of a question (*Can you answer some questions now?)* 30 minutes after scheduled rise time and 30 minutes before scheduled bedtime. Data extraction and analysis followed the same procedures as described in chapter three (see chapter three, section 4.7.2)

4.5.1.2 Actigraphy

Participants were provided with a Pro-diary watch (Pro-diary, Camntech Ltd., see Figure 22) for three weeks (one-week baseline, two weeks treatment). The Pro-diary watch was set to record activity in *mode 1* in 30 second epochs, comparable to recording settings in other

sleep studies[202]. Recorded actigraphy data were analysed using MotionWare Software 1.1.26 (see chapter 3, section 4.7.3 for a detailed description).

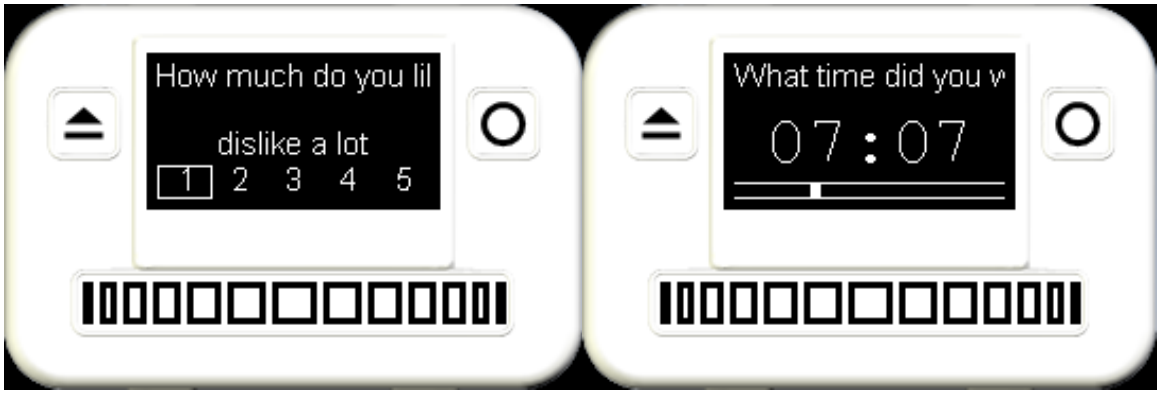


Figure 22. Examples of a general Pro-diary watch display.

4.5.2 Insomnia severity

Insomnia severity was measured by the ISI[187] at baseline and after two weeks of treatment (post-treatment). A detailed description can be found in chapter three.

4.5.3 Dim light melatonin onset and phase angle

To detect the DLMO, we obtained hourly saliva samples in dim light. Saliva samples were collected with the passive drool method (see Appendix H) and were immediately stored at -20^{0}C. The first saliva sample was collected five hours before habitual sleep time and the last one two to three hours after habitual sleep time, resulting in eight samples at baseline and eight to nine samples at post-treatment. Participants were instructed to tilt their head forward and allow saliva to pool in the mouth before directing saliva into the specialised cryotube for collection of passive drools (3.5ml cryovials, Stratech Scientific Ltd.). Participants were asked to collect a minimum of 2.5 mL at each sample time point within a given time frame of five minutes. All samples were shipped to the ARU Biomarker Laboratory (Cambridge, UK), where salivary melatonin concentration was determined using ELISA assays (Bühlmann Direct Saliva Melatonin ELISA, distributed by ALPCO Diagnostics, Windham, NH, USA) and following a standardised protocol (Salimetrics, LLC)[258]. Each assay was run in duplicate and mean average concentration was extracted for analysis. The sensitivity of

the assay was 1.37 pg/ml. The times of DLMO (DLMO-fixed) were calculated for each participant as the time at which the concentration of saliva melatonin continuously exceeded 3.5pg/mL, using linear interpolation between the samples immediately prior to and after the threshold. The threshold of 3.5 pg/ml was decided upon following visual inspection of the raw data to ensure a maximum number of participants could be included in the analysis. This threshold has also been applied in previous studies[259]. If DLMO could not be calculated at one time point, the set of paired data was excluded from related analysis (e.g. phase angle). Each participant's phase angle at baseline and post-treatment was calculated by subtracting the decimal clock time of the DLMO from the average decimal clock time of attempted sleep over the past seven days (phase angle = attempted sleep time – clock time of the DLMO). Average attempted sleep time was derived from sleep diary.

4.5.4 Psychomotor vigilance task and alertness

We performed hourly psychomotor vigilance tasks using the PC-PVT 2.0 software (BHSAI)[260]. The task was conducted on a Dell laptop computer set up on a desk in the laboratory room of the participant. The viewing distance was kept constant at about 45cm. The size of the screen was 32cm (diagonally). Upon starting the task, a pre-trial sleepiness question appeared asking *How sleepy are you?.* The answer scale ranged from one to ten (1 = not at all, 10 = extremely). Upon selecting an answer, the PVT task started. All participants were instructed to press the left mouse button on a computer mouse when perceiving the appearance of a millisecond counter in the centre of the screen (red numbers, see Figure 23). The millisecond counter on the screen started by showing five digits ("00000") and stopped upon mouse button press, reflecting the reaction time, and hence, giving feedback to the participant. Total trial time was set to 600s and inter stimulus interval varied from two to 10 seconds. At the end of the task, the dialog box appeared once again, and participants were asked to rate their sleepiness level for a second time. Reaction times < 100 milliseconds and > 3000 milliseconds were excluded from analysis. Values > 500 milliseconds were considered minor attentional lapses and values > 1000 milliseconds were considered major attentional lapses[260].



Figure 23. Illustration of the psychomotor vigilance task appearance.

4.5.5 Daytime functioning

Daytime functioning was measured by self-reported cognitive complaints and daytime sleepiness. The respective questionnaires are described below.

4.5.5.1 British-Columbia cognitive complaints inventory

Self-reported cognitive complaints were obtained by the BC-CCI[171] at baseline and after two weeks of treatment. A detailed description can be found in chapter three.

4.5.5.2 Epworth sleepiness scale

The Epworth sleepiness scale is a self-administered questionnaire to obtain daytime sleepiness[127]. The scale was administered at baseline and after two weeks of treatment. A detailed description can be found in chapter three.

4.5.6 Adherence and adverse events

To investigate if participants followed their new sleep schedule as prescribed, we compared self-reported and actigraphy-derived TIB during the two weeks of intervention to baseline.

Serious adverse events were defined as: (1) death, (2) suicide attempt, (3) admission to hospital, and (4) formal complaints about the behavioural intervention. Serious adverse events were recorded when a member of the research team was made aware of their occurrence.

4.6 Statistical analysis

Summary statistics (means and standard deviations for continuous variables, frequencies and percentages for binary and categorical variables) are presented for demographics and outcomes at baseline. All analyses were conducted in SPSS.25 (IBM). Graphs were generated using GraphPad Prism version 8.2.1 for Windows (GraphPad Software, La Jolla, California, USA). Data were tested for normality and homogeneity of variances. Since this is a pilot study, no adjustments were made for multiple testing, however effect sizes and confidence intervals are presented for all outcomes. To assess the efficacy of SRT over two weeks, we first analysed sleep continuity. Linear-mixed effect models were fitted for continuous sleep diary and actigraphy data with fixed effects for time point (baseline, week one, week two). Outcomes at week one and week two were included as the response and a participant specific random intercept was embedded to account for repeated measures and their non-independence. The covariance structure for random effects, here participant, was set to variance components (VC) as this is the default for mixed models with one random effect[217]. The primary mechanistic outcome, phase angle, was then considered. Two-sided paired t-tests were applied to test the null hypothesis that there is no difference between baseline and post-treatment. Secondary outcomes, such as insomnia severity, DLMO, and daytime functioning were analysed in the same way. T and p-values are presented. For non-normally distributed data, the Wilcoxon signed-rank test was applied, and Z and p-value are presented. For repeated measurements of sleepiness and vigilance data, linear mixed models were fitted with fixed effects for time point (baseline, week two) session number (one to eight) and time point x session number interaction. Between-time point (baseline vs post-treatment) comparisons were also conducted for each session number to investigate the magnitude of effects specific to the time of day in relation to habitual/scheduled bedtime. Cohen's d statistics were calculated as the treatment effect divided by the standard deviation of the change score derived from T-statistics[261]. However, as linear mixed models do not provide an accurate estimate for the standard deviation of the change score, effect sizes for those statistics were calculated with ES = Diff/SD at baseline[218].

5 Results

5.1 Participant characteristics

Participants were recruited between March and July 2019. Three-hundred-thirty individuals were screened online, out of whom 24 were deemed eligible. The main reason for exclusion was a mixture of not meeting age/consent/shift-work/travel/medication or menopause criteria. Eighteen participants completed baseline assessments and accessed SRT. All participants completed all post-treatment assessments. See Figure 24 for the CONSORT flow diagram. Table 25 provides all baseline characteristics and outcomes at baseline.

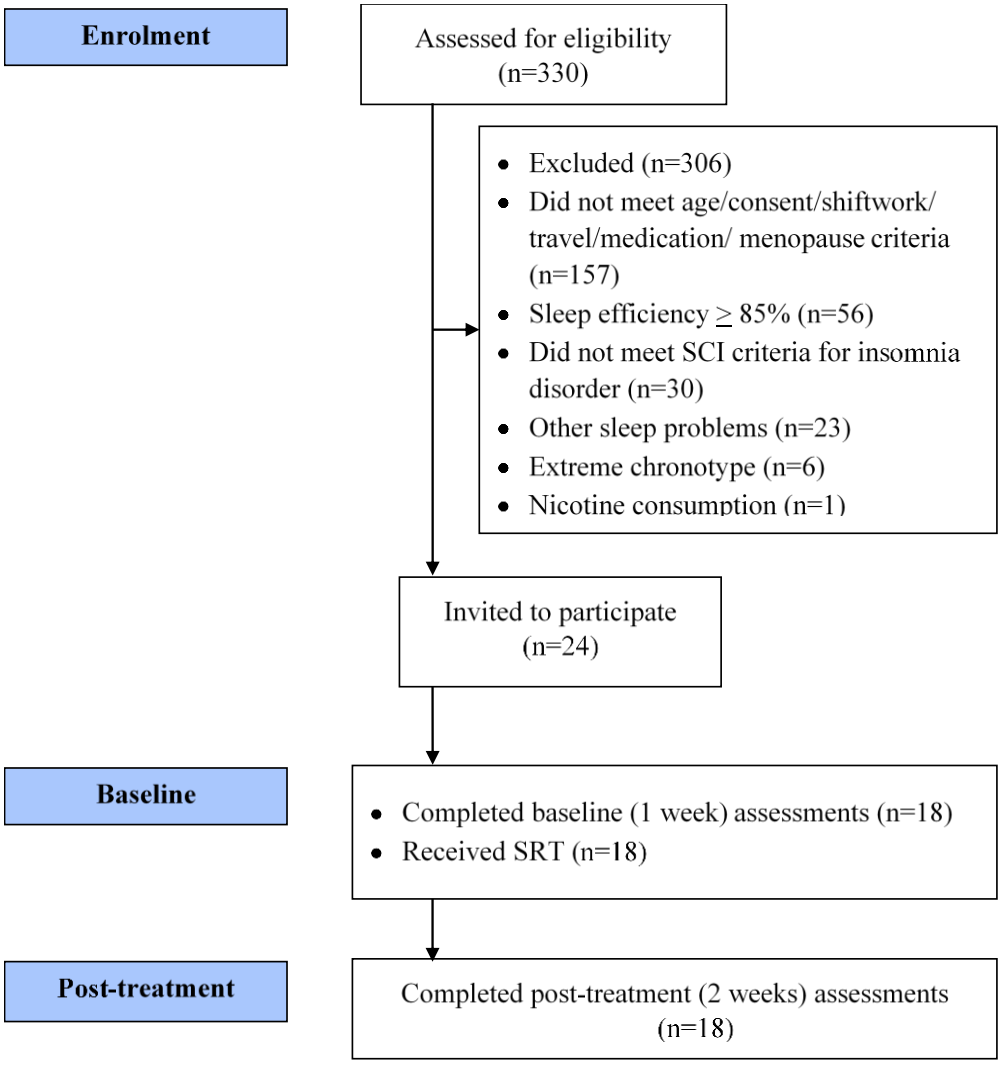


Figure 24. Participant recruitment CONSORT-style flow diagram of the ESPRIT study. *Abbreviations:* SCI=Sleep condition indicator, SRT=Sleep restriction therapy

Table 25. Baseline characteristics

Baseline characteristics	N=18	
Demographics		
Age, years; M (SD)	37.06	8.9
Male (n; %)	11	61.1
Marital status (n;%)		
Married/domestic partnership	10	55.6
Single	8	44.4
Employment status (n;%)		
Employed for wages	15	83.3
Student	3	16.7
Highest level of qualification (n;%)		
A-Levels, diploma or the equivalent	1	5.6
Some college credit, no degree	1	5.6
Trade/technical/vocational training	1	5.6
Bachelor's degree	3	16.7
Master's degree	6	33.3
Professional degree	3	16.7
Doctoral degree	3	16.7
Health characteristics		
BMI, M (SD)	26.01	3.94
Sleep problem duration, years, M (SD)	9.21	7.08
Outcomes at baseline		
Phase angle, M (SD)	2.27	0.94
Dim light melatonin onset, M (decimal clock time; SD)	20.82	1.33
Attempted sleep time M (decimal clock time; SD)	23.08	0.67
Insomnia severity index (ISI), M (SD)	17.78	2.76
Daytime sleepiness (ESS), M (SD)	7.61	4.90
Cognitive complaints (BC-CCI), M (SD)	6.89	4.50
Sleep diary variables		
Sleep onset latency, min, M (SD)	33.09	37.42
Wake after sleep onset, min, M (SD)	79.72	79.71
Sleep efficiency, %, M (SD)	75.76	13.33
Time in bed, min, M (SD)	517.28	88.10
Total sleep time, min, M (SD)	393.84	67.65
Actigraphy variables		
Wake after sleep onset, min, M (SD)	57.62	29.31
Sleep onset latency, min, M (SD)	10.82	17.13
Sleep efficiency, %, M (SD)	85.92	6.25
Total sleep time, min, M (SD)	429.70	60.34

Notes: Dim light melatonin onset at baseline was detected in 15/18 participants, hence phase angle is also only reported for those 15; ISI= Insomnia severity index, ESS= Epworth sleepiness scale; BC-CCI=British Columbia cognitive complaints inventory

The sample was predominantly middle-aged (mean = 37.06 ± 8.99; range 25-54 years), comprised of males (61.1%), reported a BMI of 26.01 (± 3.94), was in a domestic partnership (55.6%), employed for wages (83.3%) and university-educated (88.9%). Consistent with inclusion criteria, ISI scores were in the clinical range (mean = 17.78 ± 2.76) and self-reported SE was below 85% as indicated by sleep diary (mean = 75.76 ± 13.33).

5.2 Sleep continuity

Sleep continuity variables were derived from sleep diary and actigraphy. They were considered first in order to determine the acute treatment effects of SRT. Results from linear mixed models are summarised in Table 26 and revealed small to large effect sizes across all variables (all $p \leq .001$, d range = 0.35 to 1.00) indicating improvements in sleep continuity after two weeks of SRT.

Sleep diary. On average, self-reported SOL decreased by 13 minutes at week one ($p < .001$, $d = -.35$) and by 22 minutes at week two ($p < .001$, $d = -0.59$). Similarly, self-reported WASO was decreased by 34 minutes at week one ($p < .001$, $d = -.43$) and by 44 minutes at week two ($p < .001$, $d = -.55$). These changes were also reflected in an increase of subjective SE by 10% and 13% for week one ($p < .001$, $d = 0.75$) and week two ($p < .001$, $d = 1.00$) respectively. To assess the extent to which sleep time was restricted, we further analysed the impact of SRT on TST. Results showed that participants reported spending on average 34 minutes less asleep during week one ($p < .001$, $d = -.51$) and 30 minutes less during week two ($p < .001$, $d = -.44$).

Actigraphy. Actigraphy derived change scores were smaller in magnitude (SOL decrease = 5-6 minutes, WASO decrease = 18-19 minutes, SE increase = 2%). Effect sizes were in the small to medium range at both time points (d range = 0.29 to 0.65). In support of subjective estimates of TST reduction, actigraphy derived TST estimates indicated an even larger decrease of 75 minutes at both time points ($p < .001$, ds ≥ 1.24).

Table 26. Overview of sleep diary and actigraphy derived sleep variables

Sleep diary		***M***	**SD**	**Diff$_{adj}$**	**95% CI**		**p**	**ES**
SOL	Baseline	33.09	37.42					
	Week 1	20.48	31.74	-12.98	-19.73	-6.23	**<.001**	-0.35
	Week 2	11.88	10.83	-21.96	-28.41	-15.17	**<.001**	-0.59
WASO	Baseline	76.62	79.71					
	Week 1	42.22	57.53	-34.15	-46.33	-21.96	**<.001**	-0.43
	Week 2	35.03	48.84	-43.72	-55.97	-31.47	**<.001**	-0.55
SE	Baseline	75.76	13.33					
	Week 1	86.00	8.84	9.98	6.82	13.15	**<.001**	0.75
	Week 2	89.35	7.81	13.40	10.12	16.67	**<.001**	1.00
TST	Baseline	393.84	67.65					
	Week 1	359.70	40.91	-34.34	-48.78	-19.89	**<.001**	-0.51
	Week 2	364.79	40.41	-29.67	-44.61	-14.74	**<.001**	-0.44
Actigraphy								
SOL	Baseline	10.82	17.13					
	Week 1	5.32	7.29	-4.91	-7.67	-2.15	**0.001**	-0.29
	Week 2	4.50	7.07	-5.93	-8.71	-3.14	**<.001**	-0.35
WASO	Baseline	57.62	29.31					
	Week 1	39.62	18.65	-19.10	-22.86	-15.33	**<.001**	-0.65
	Week 2	39.92	18.72	-18.33	-22.63	-15.02	**<.001**	-0.63
SE	Baseline	85.92	6.25					
	Week 1	87.82	5.85	2.07	1.18	2.97	**<.001**	0.33
	Week 2	88.17	5.62	2.49	1.59	3.40	**<.001**	0.40
TST	Baseline	429.70	60.34					
	Week 1	351.16	50.13	-74.94	-85.47	-64.40	**<.001**	-1.24
	Week 2	352.54	49.80	-74.57	-85.22	-63.93	**<.001**	-1.24

Notes: SOL=sleep onset latency; WASO=Wake after sleep onset; SE=Sleep efficiency, TST=Total sleep time; Diff$_{adj}$=Mean difference adjusted for missing values; 95%CI=95% confidence interval of the mean difference; ES=effect size (Cohen's d). Significant p-values are displayed in bold.

5.3 Insomnia severity

We then considered insomnia severity to investigate if participants experienced less insomnia symptoms after two weeks of SRT. Results from paired t-tests revealed large effect sizes on the ISI between baseline and post-treatment (d = -1.68) which were reflected in an average decrease of 6.6 points from 17.78 $\pm$ 2.67 to 11.17 $\pm$ 4.27 ($t_{1,17}$ = -7.14; p < .001; see Table 29). In support of the hypothesis, these results suggest that after two weeks of SRT less insomnia symptoms were experienced by the participants when compared to baseline.

5.4 Phase angle

Next, analysis of the primary outcome, phase angle, was conducted. Three participants were excluded from the analysis because DLMO could not be detected for both time points. Pairwise comparisons of the remaining 15 participants indicated a medium effect size for the change in phase angle ($t_{1,14}$ = 2.17, p = .048, d = .56) and support the hypothesis that participants attempted sleep at a later circadian phase following SRT. The average increase in phase angle was 0.58 ± 1.04 hrs (34.8 minutes) from baseline and post-treatment (see Figure 25 and Table 28).

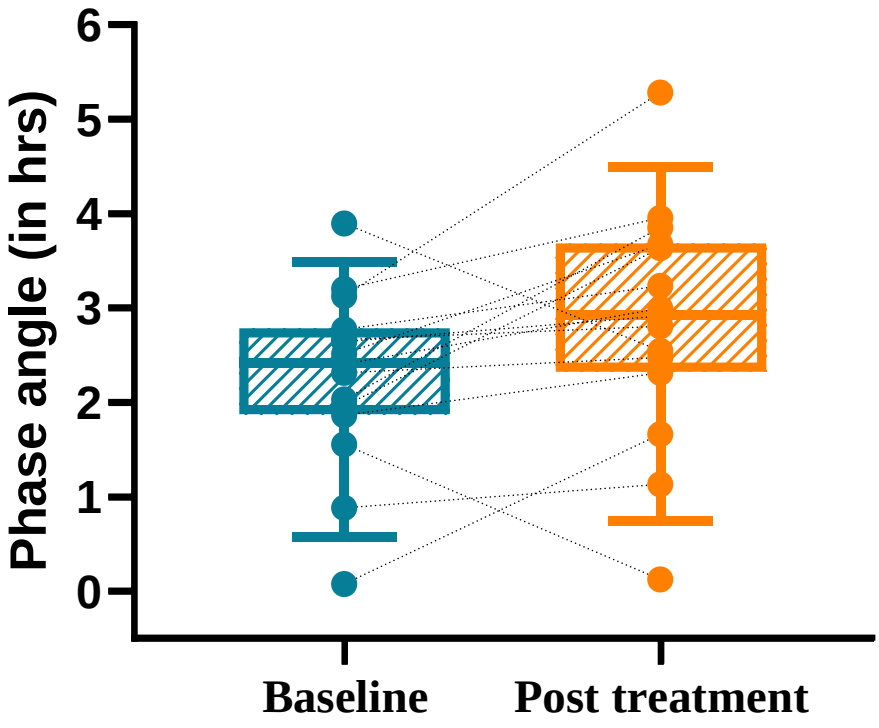


Figure 25. Changes in phase angle from baseline to post-treatment. Dots represent individual measurements at baseline (blue) and post-treatment (orange). Solid lines present the median with the box extending from the 25th to the 75th percentile and whiskers from the 10th to the 90th percentile. Dotted lines represent the individual phase angle change from baseline to post-treatment.

5.5 Dim light melatonin onset and timing of sleep

To further elucidate the effects of SRT on phase angle, we performed analysis on its composite components, DLMO and attempted sleep. Pairwise comparisons of DLMO will be considered first, followed by analysis of attempted sleep and related bed- and rise times.

Dim light melatonin onset. We compared the decimal clock time of DLMO between baseline and post-treatment measurements in the same 15 participants. Against our hypothesis, results from paired t-tests revealed no effect for time point ($t_{1,14} = 0.62$, $p = .543$), indicating that the average rise of melatonin did not change from baseline to post-treatment (see Figure 26 and Table 27).

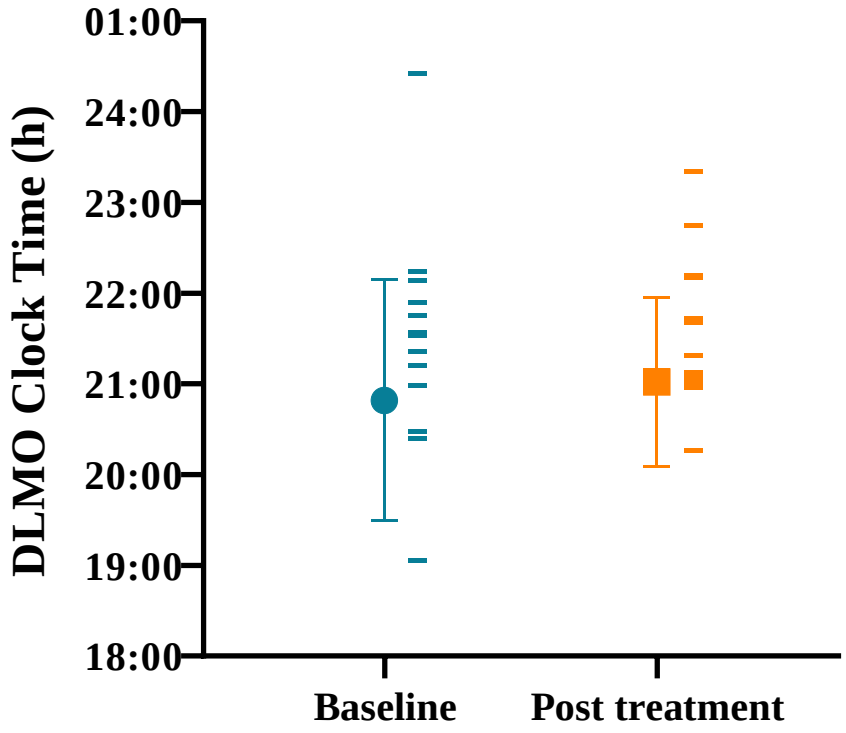


Figure 26. Dim light melatonin onset (DLMO) before and after sleep restriction therapy Individual dashes represent individual participants and filled circles with whisker bars represent the mean and standard deviation for each time point at baseline (blue) and post-treatment (orange).

Timing of bedtime and sleep attempt. To further elucidate the relationship between the newly prescribed sleep window and the circadian phase measurements, we compared sleep diary reported time of attempted sleep between baseline and post-treatment in the same 15 participants. Paired t-tests revealed large effect sizes ($t_{1,14} = 4.51$, $p < .001$, $d = 1.16$) showing that after two weeks of SRT, participants attempted sleep on average 46.8 $\pm$ 40.2 minutes later (baseline: 23.09 $\pm$ 0.67 vs post-treatment: 23.87 $\pm$ 0.60; see Table 27).

Following on from the above, additional exploratory analysis of the positioning of the sleep window for the same 15 participants also revealed large effects of SRT for both bed- ($t_{1,14}$ = 4.78, p< .001, d = 1.57) and rise times ($t_{1,14}$ = 5.96, p < .001, d = 1.54). Consistent with delayed sleep attempt, participants went to bed 58.2 ± 37.2 minutes later, but also got out of bed 57.0 ± 46.8 minutes earlier relative to baseline. In relation to the prescribed sleep window, 12/18 (67%) participants choose to curtail their sleep window from both sides (delaying bedtime and advancing rise time), five (23%) delayed their bedtime only, and one (5.5%) advanced rise time only.

Table 27. Overview of changes in phase angle, DLMO and timing of sleep

N=15		***M***	**SD**	**Diff**	**95% CI**		***t***	***p***	**ES**
Phase angle	Baseline	2.27	0.94						
	Week 2	2.85	1.25	0.58	0.01	1.15	2.17	**0.048**	0.56
DLMO	Baseline	20.82	1.33						
	Week 2	21.02	0.93	0.20	-0.49	0.90	0.62	0.543	0.16
Attempted sleep time	Baseline	23.09	0.67						
	Week 2	23.87	0.60	0.78	0.41	1.15	4.51	**<.001**	1.16
Bedtime	Baseline	22.70	0.67						
	Week 2	23.67	0.71	0.97	0.54	1.40	4.78	**<.001**	1.57
Rise time	Baseline	7.41	1.00						
	Week 2	6.45	0.69	0.95	0.61	1.29	5.96	**<.001**	1.54

Notes: DLMO=Dim light melatonin onset determined at the average decimal clock time of melatonin levels crossing the threshold of 3.5pg/ml; Diff= Mean difference. Attempted sleep time, bedtime and rise time were derived from sleep diaries and are presented in decimal clock time. Significant p-values are displayed in bold.

Overall, results from this and the previous section demonstrate that participants attempted sleep at a later circadian phase while melatonin onset stayed relatively stable from pre-to-post-treatment. Consequently, phase angle (the time difference between DLMO and attempted sleep) increased. Figure 27 shows this relationship for each participant before and

after SRT by plotting melatonin rise and sleep-diary derived sleep times within one graph and at both time points (see below).

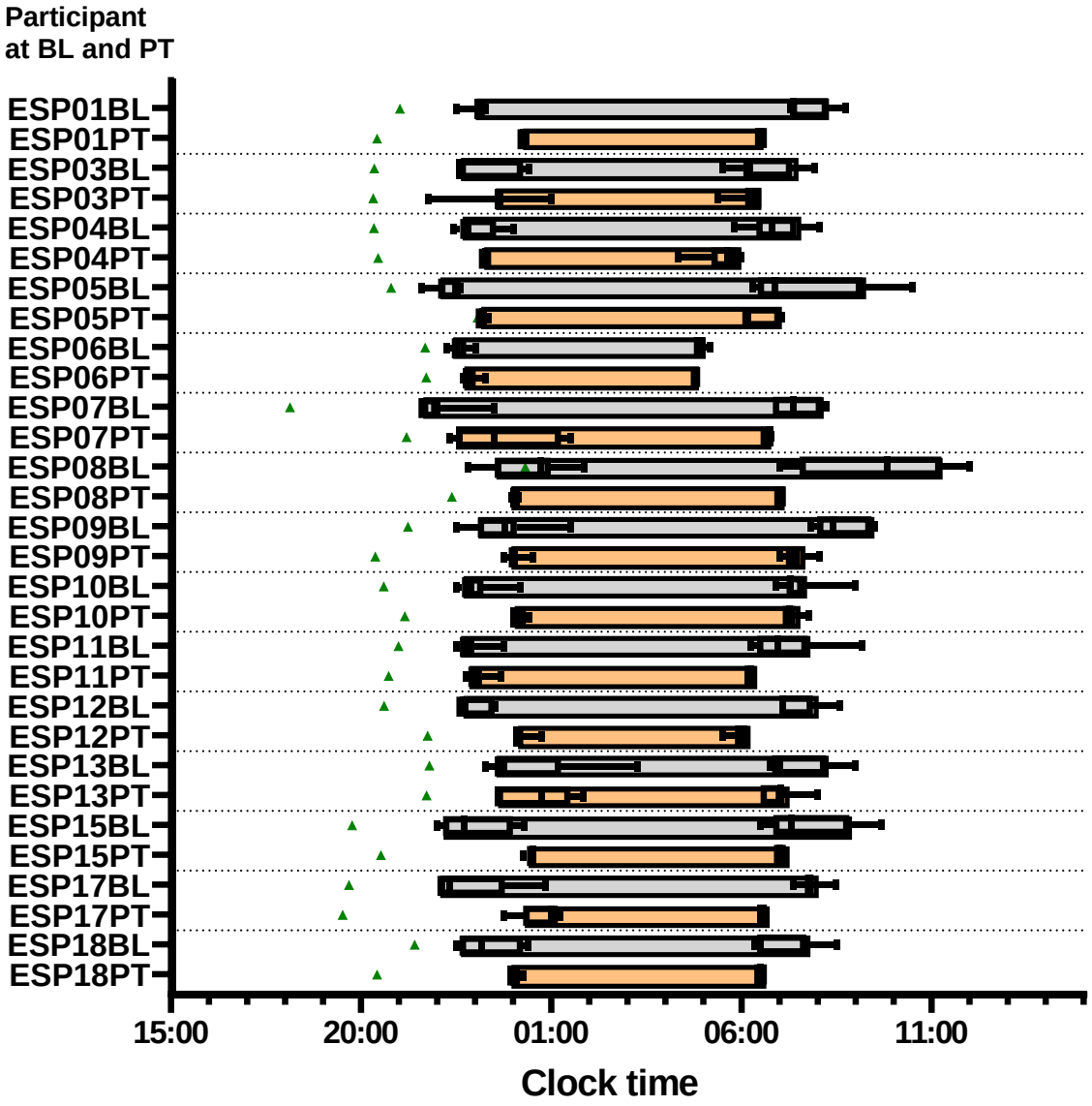


Figure 27. Sleep and circadian phase shift between baseline and post-treatment assessments. Each row represents the data of a single participant at baseline or post-treatment. The green triangles represent DLMO. Grey shaded bars represent sleep time (attempted sleep to rise time) at baseline and orange shaded bars represent sleep time at post-treatment. Boxplots are positioned for attempted sleep time and rise time with whiskers ranging from minimum to maximum values. All sleep values are derived from sleep diary at baseline (ESPXXBL) and post-treatment (ESPXXPT).

5.6 Vigilance and subjective sleepiness

We next considered the potential effect of SRT-related sleep loss on vigilance and sleepiness measured repeatedly over eight hours during the laboratory protocol. Objective data from the PVT will be considered first, followed by self-reported sleepiness.

Reaction time. Results from linear mixed models revealed significant main effects for time point (baseline vs post-treatment, $F_{1,17} = 17.13$; $p < .001$;) and session number (1-8, $F_{7,17} = 2.43$; $p = .02$;), indicating that (1) vigilance was impaired with SRT, and (2) overall, vigilance varied with session number. Pairwise comparisons of time points revealed that participants responded on average 46.42 milliseconds slower to the stimulus at post-treatment when compared to baseline ($d = .46$, see Table 28). However, there was no significant time point x session number interaction ($F_{7,17} = 1.22$; $p = .29$). Figure 28 summarises PVT reaction times across sessions.

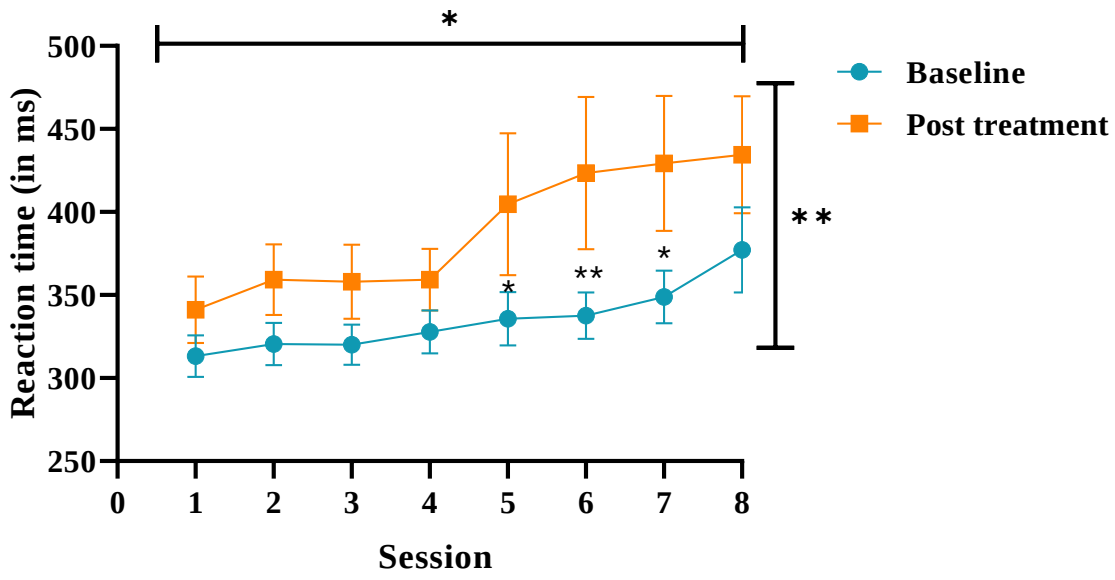


Figure 28. Reaction times measured by the psychomotor vigilance task (PVT) at baseline and after two weeks of SRT. Raw means (+/- 1 SE) are presented for both groups at each time point. Here, session six refers to the time participants reported switching off the light for sleeping at their study induction. PVTs were scheduled relative to that time, starting the first task ~5 hrs before (=session 1). Statistical differences are derived from linear mixed models and represented by a single or double asterisk (*=p<.05; **=p<.01).

Following up the main effect of session, exploratory pairwise comparisons comparing RTs for each session between baseline and post-treatment revealed that RT was significantly slower at sessions five (p = .030, d = 1.01), six (p = .007, d = 1.44) and seven (p = .012, d = 1.19). Differences for other sessions were not statistically significant (session 1: p = .476, d = -.10; session 2: p = .319, d = .61; session 3: p = .232, d = .74, session 4: p = .320, d = .58, session 8: p = .071, d = .38).

Attentional Lapses. Table 28 summarises all vigilance data. We computed linear mixed models to detect changes in attentional lapses between baseline and post-treatment assessments. Minor attentional lapses are considered first, followed by major attentional lapses.

Table 28. Overview of main effects on vigilance

Vigilance		***M***	**SD**	**Diff$_{adj}$**	**95% CI**		***p***	**ES**
Reaction time	Baseline	341.58	100.03					
	Week 2	388.70	139.96	46.42	24.33	68.52	**<.001**	0.46
Minor lapses	Baseline	5.44	7.82					
(500-1000ms)	Week 2	10.34	13.09	4.74	3.28	6.21	**<.001**	0.61
Major lapses	Baseline	0.35	1.44					
(≥1000ms)	Week 2	1.45	3.88	1.08	0.52	1.66	**<.001**	0.75
Subjective sleepiness								
Sleepiness	Baseline	5.79	2.20					
(1-10)	Week 2	6.08	2.08	0.31	0.01	0.61	**0.042**	0.14

Notes: Diff$_{adj}$= Mean difference adjusted for missing values; 95%CI= 95% confidence interval of the mean difference; ES= Effect size (Cohen's d). Significant p-values are displayed in bold.

For minor attentional lapses, analysis revealed significant main effects between baseline and post-treatment assessments ($F_{1,17}$ = 40.7; p<.001) that were also observed per session one through eight ($F_{7,17}$ = 6.671; p < .001). Pairwise comparisons revealed that participants had on average 4.74 more minor lapses after two weeks of SRT when compared to baseline (d =

0.61). There was no significant time point x session number interaction ($F_{7,17}$ = 0.63; p = .73). Following up the main effect of session, exploratory pairwise comparisons comparing minor lapses for each session between baseline and post-treatment revealed more lapses at session three (p = .013, d = 1.31), five (p = .035, d =.46) six (p = .001, d = .98) seven (p = .001, d=.95) and eight (p = .048, d = .33). No effects were found for session one (p = .162, d = .67), two (p = .126, d = .57) and four (p = .097, d = .59).

Similar results were found for major attentional lapses ($\geq$ 1000ms), indicating significant main effects for time point (baseline vs post-treatment, $F_{1,17}$ = 14.15; p < .001) and session number (1-8, $F_{7,17}$ = 2.18; p = .037). Analysis revealed that on average, participants had 1.34 more major attentional lapses after two weeks of SRT (d = .75). Again, there was no significant time point x session number interaction ($F_{7,17}$ = 1.054; p = .394). No exploratory pairwise comparisons were conducted for each session between baseline and post-treatment as major lapses did not occur at each session and consequently, statistical variance could not be analysed.

Subjective sleepiness. Figure 29 summarises subjective sleepiness ratings relative to session number. Results from linear mixed model analysis revealed significant main effects for time point (baseline vs post-treatment, $F_{1,17}$ = 4.20; p =.042) and session number (1-8, $F_{7,17}$ = 47.37; p < .001), indicating that (1) participants experienced more sleepiness with SRT and (2) sleepiness ratings varied with session number. Pairwise comparisons revealed that participants rated their sleepiness on average 0.31 points higher after two weeks of SRT when compared to baseline (d = 0.14). Similar to the reported results for objective vigilance data, there was no significant time point x session interaction ($F_{7,17}$ = .202; p = .985). Following up the main effect of session, exploratory pairwise comparisons comparing sleepiness rating for each session between baseline and post-treatment revealed no significant effects specific for a certain session (range of p's = 0.139-0.792; range of d's = 0.07-0.34).

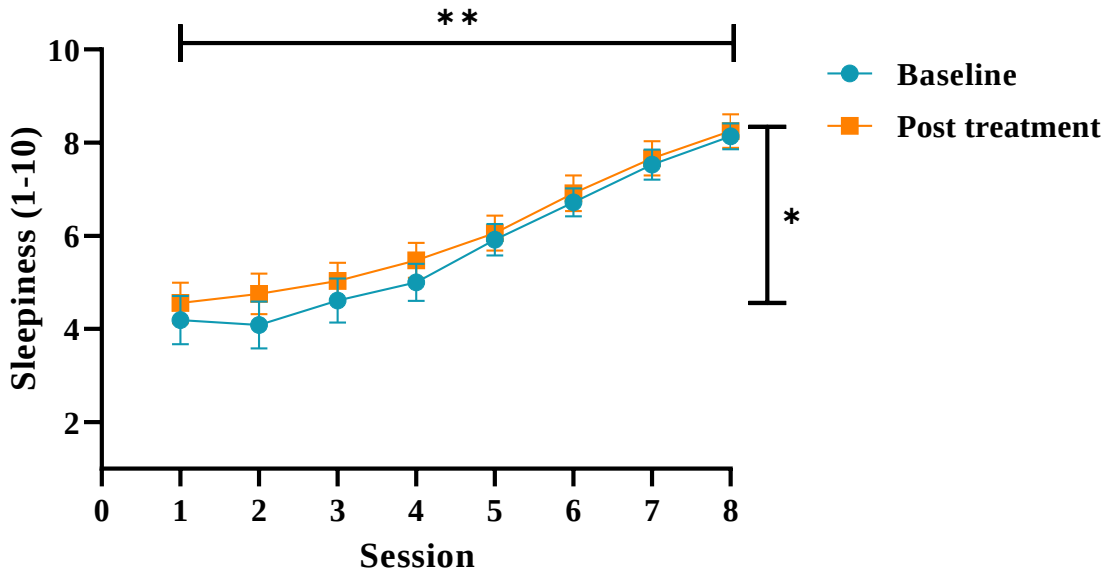


Figure 29. Subjective sleepiness measured hourly at baseline and after two weeks of SRT. Raw means (+/- 1 SE) are presented for both groups at each time point. Here, session 6 refers to the time participants reported switching off the light for sleeping at their study induction. Measurements were scheduled relative to that time, starting the first question ~5 hrs before (= session 1). Statistical differences are derived from linear mixed models and represented by a single or double asterisk (*=p<.05; **=p<.01).

5.7 Daytime functioning

We further assessed whether implementation of SRT is associated with increased daytime sleepiness (ESS) and cognitive complaints (BC-CCI) relative to baseline.

Table 29. Changes in insomnia symptoms and daytime impairments

		M	**SD**	**Diff**	**95% CI**		**t/Z**	**p**	**ES**
ISI	Baseline	17.78	2.76						
	Week 2	11.17	4.27	-6.61	-8.56	-4.66	-7.14	**<.001**	-1.68
ESS	Baseline	7.61	4.90						
	Week 2	6.67	3.97	-0.94	-2.54	0.65	-1.25	0.229	-0.29
BC-CCI*	Baseline	6.89	4.97						
	Week 2	5.67	4.12	-1.22	0.86	-3.04	-1.24	0.216	-0.29

Notes: ISI=Insomnia severity index; ESS=Epworth sleepiness scale; BC-CCI=British-Columbia cognitive complaints inventory. Difference scores (Diff) from the BC-CCI were non-normally distributed and the Wilcoxon Signed Rank test was applied and effect size (ES) was calculated with ES=Z/√n. Significant p-values are displayed in bold.

However, no effects were found for changes on the ESS (p = .229) or on the BC-CCI (p = .216) from baseline to post-treatment. Results are summarised in Table 29 above.

5.8 Adherence and adverse events

Adherence. To investigate if participants followed their new sleep schedule as prescribed, we compared self-reported and actigraphy derived TIB during baseline and during the two weeks of SRT. Results from linear mixed models revealed large effect sizes at week one (sleep diary: $p < .001$, $d = -1.16$; actigraphy: $p < .001$, $d = -1.36$) and week two (sleep diary: $p < .001$, $d = -1.28$; actigraphy: $p < .001$, $d = -1.38$) relative to baseline. Self-reported mean TIB decreased by 102 minutes from baseline to week one and by 112 minutes from baseline to week two. This was also reflected in actigraphy, showing a TIB reduction of 99 minutes at week one and 101 minutes at week two. Together, these results suggest that participants followed their prescribed sleep window and indeed, spent a restricted amount of time in bed.

Adverse events. No serious adverse events were reported.

6 Discussion

The here presented ESPRIT study was designed to elucidate the acute effects of SRT on the relationship between circadian phase and sleep-wake behaviour in people with insomnia. In line with previous research, we hypothesised that SRT would improve sleep continuity and reduce insomnia severity. Additionally, it was assumed that the restriction of TIB, as prescribed by SRT, would increase the primary mechanistic outcome, phase angle. We also sought to assess the effects of SRT on the timing of DLMO, vigilance and daytime impairments.

6.1 Effects on sleep and insomnia severity

Confirming our hypothesis, we found improvements across subjectively and objectively derived sleep continuity variables by demonstrating small to large effect sizes for SOL, WASO and SE. We previously (see chapter two and chapter three) hypothesised that improvements in sleep consolidation would be further linked to improvements in insomnia

severity. Indeed, we found large effect sizes reflecting an average reduction of -6.6 scale points on the ISI. In a clinical sample, a slightly higher change score of -8.4 is associated with moderate improvements in insomnia at post-treatment[188]. Yet, we observed these differences after just two weeks of SRT, when participants still experienced large reductions of TST (sleep diary~34 minutes, acitgraphy~75 minutes). Consequently, we would expect further improvements on completion of the treatment (e.g. after four to six weeks[98]).

6.2 Shifting circadian phase – a potential mechanism of SRT?

To test if SRT increases the phase angle between DLMO and attempted sleep, we compared the difference between decimal clock time of attempted sleep and DLMO before and after two weeks of SRT. Our results demonstrated an average phase angle increase of 35 minutes. Further analysis revealed that this change was mainly explained by a delay of attempted sleep time, which was approximately 47 minutes later during the second week of treatment when compared to baseline. In contrast, the average DLMO was detected approximately 12 minutes later and hence, was similar to baseline. This finding is in line with results from Miller and colleagues who reported no change in the phase of core body temperature after five weeks of SRT[119]. The relative stability of DLMO between baseline and post-treatment may be explained by the shift in rise time that was observed alongside the reported shift in bedtime. After two weeks of SRT, participants got up approximately 57 minutes earlier than at baseline. Hence, sleep onset and sleep offset were curtailed by a comparable amount (47 minutes and 57 minutes, respectively), potentially leading to more light exposure in the evening and morning – and consequently - not affecting average melatonin levels.

In our sample, the average phase angle at baseline was 2:16 hrs, which is comparable to the phase angle duration of 2:13 hrs that was reported for people with insomnia in the study by Flynn-Evans and colleagues[233]. Intriguingly, after two weeks of SRT, our results demonstrated an average phase angle of 2:51 hrs, which is more in line with the phase angle of 3:10 hrs in healthy controls[233]. While this suggests that an increase in phase angle could be associated with therapeutic benefits, it must be noted that there is currently no

recommendation for an optimal phase angle in people with insomnia or indeed, healthy controls. We did not conduct correlational analysis to investigate the association between phase angle and clinical outcomes since the study was neither powered nor designed with this question in mind. However, future studies with larger sample sizes, could assess whether change in phase angle mediates clinical benefit.

6.3 The effects of acute sleep restriction on vigilance and daytime functioning

Analysis of TIB revealed that participants reduced their TIB by more than 1.5 hours, which also came with a significant decrease of TST. To test associated effects of increased sleepiness and impaired vigilance, we conducted repeated measurements at baseline and post-treatment. In line with previous research, including the MARTINI study from this thesis, overall reaction time was significantly slower at post-treatment. Further analysis revealed that these differences were especially pronounced in the hours around the reported habitual sleep time of the participant at baseline (session five, six and seven). Participants also rated their average sleepiness higher across the whole assessment period; however no effects were found for specific sessions. While our results revealed strong main effects for time point, no time x session interactions were observed. These may represent true null findings, or such analyses were under-powered (given the small sample size) to detect significant effects[262].

Overall, our results support the previously reported deteriorations of vigilance measurements (see chapter three). Yet, the higher sensitivity of the here conducted repeated measurements revealed more pronounced effects for reaction times and attentional lapses. While results from the MARTINI study revealed that reaction times were ~14 milliseconds slower after one week of SRT when compared to BCT (391.70 vs 377.49 milliseconds), the here presented analysis showed a deterioration of ~46 milliseconds after two weeks of SRT when compared to baseline (388.70 vs 341.58 milliseconds). Considering the limited comparability of the studies (different time points, comparisons, tasks and testing environments), both highlight the importance of measuring vigilance during the acute

implementation of SRT. The finding that increases in reaction times (and attentional lapses) were especially pronounced in the later part of the evening (around and after reported habitual bedtime at baseline) may be relevant for clinical practice and has implications for safety instructions and adherence. That is, based on the here presented results, patients should be advised to participate in safe activities that prevent them from falling asleep unintentionally, especially if staying awake beyond their habitual bedtime. Knowing about the effects of SRT on vigilance is important to prevent accidents and support adherence. The absence of distinct time effects on subjective sleepiness may indicate that participants are not aware of the extent to which their vigilance deteriorates at a specific time in the evening and highlights the importance of such advice. Studies investigating sleep loss in healthy controls similarly reported that deterioration of reaction time was more pronounced than deterioration of subjective sleepiness ratings[263,264].

We further hypothesised, that the acute effects of sleep restriction would lead to increased reported daytime sleepiness and cognitive complaints. However, we did not find reliable differences in scores derived from the ESS or the BC-CCI. In comparison, the MARTINI study also revealed no effects of SRT on cognitive complaints as measured by the BC-CCI. Together, those results suggest that SRT may not affect complaints about cognitive impairments in its acute phase. Regarding daytime sleepiness, the results of the ESPRIT study are not in line with previous results. In comparison to the ESPRIT study, the MARTINI study reported small to medium effects on increased daytime sleepiness (ESS) at two-week post randomisation. Considering that after two weeks of SRT participants in both studies experienced comparable sleep loss (actigraphy: MARTINI = -59 minutes vs ESPRIT = -75 minutes), we would expect similar effects on daytime sleepiness. However, comparability is limited by several factors. First, it has to be considered that participants in the ESPRIT study experienced more daytime sleepiness at baseline when compared to participants in the SRT group in the MARTINI study (ESPRIT = 7.61 vs MARTINI = 6.19). In fact, the ESS score at baseline was already higher than the ESS score from participants in the MARTINI study after two weeks of SRT (ESS = 7.27). Second, participants in the ESPRIT study were aware

that the 2nd week of treatment was considered a post-treatment assessment, while participants in the MARTINI study answered questions related to the ESS on the phone and in awareness of another two weeks of treatment to come. Third, study samples differed in main characteristics, such as gender (ESPRIT: 61% male vs MARTINI: 30% male), age (ESPRIT: 37 years vs MARTINI: 41 years) and baseline insomnia severity (ESPRIT: 18 vs MARTINI: 15 on the ISI).

6.4 Strengths and limitations

The present study provides the first preliminary evidence that SRT influences the alignment of circadian phase and sleep-wake behaviour. The main strength of the study lies in the highly standardised and controlled measurement of salivary melatonin and repeated measurements of vigilance. Furthermore, the use of Pro-Diary watches allowed us to support adherence to the individual restriction protocol which was considered of central importance.

Yet, the results of the ESPRIT study must be considered as preliminary as we only recruited a small sample size (N=18) and did not include a control group. Although our primary outcome was based on objective measures, results, especially subjective ratings at the laboratory assessments, could have been confounded by an un-blinded design, whereby the main researcher also acted as the therapist. To minimise bias, standardised protocols that separated treatment related discussions and assessments were applied. Furthermore, we did not correct for multiple testing and were only powered for the detection of medium to large effects. Consequently, the risk for both type I and type II error are evident[133]. However, we reported exact values and effect sizes to allow the reader to judge[232]. Similar to the MARTINI study, our sample was recruited in the restricted area of Oxford, UK and had to undergo a thorough screening process where we excluded for comorbid mental health problems, use of medication and menopause. Though, these criteria are highly prevalent in the insomnia population[265,266] and consequently, participants in this study might not be representative of the general insomnia population in the UK[28] (e.g. predominantly male).

By measuring the effects of a new sleep schedule on DLMO we also faced several challenges. Typically, studies investigating the effects of sleep restriction on circadian phase in healthy participants implement highly standardised sleep protocols and control for the effects of light exposure[249,267]. Yet, SRT does not typically prescribe the same sleep window at the same time of day for each participant[98]. Instead, each sleep window is fitted to individual sleep times contingent on lifestyle factors such as work schedule, sleep schedule of the partner, chronotype and feasibility. Consequently, some participants went to bed much later, while others decided to get up earlier. While this ensured adherence to SRT, it also introduced variability in sleep times and by extension, light exposure. Light exposure has previously been shown to have effects on melatonin levels, including DLMO[241]. However, this study did not assess or control for light exposure outside of the laboratory environment. Including a light sensor was originally considered, but not feasible due to the lack of available devices that reliably measure light at eye level, such as sensors that are worn around the neck or sensors that can be attached to clothing. Actigraphy watches with light sensors were deemed to lack reliability as it was assumed that participants might not wear the watch 24 hours as instructed or might accidentally cover the sensor by sleeves or blankets. Instead, it was decided to use pro-diary watches, which had the advantage of prompting sleep diary questions and reminders to support adherence. Future studies should measure light in order to answer the question how light exposure impacts the ability to move into a potentially more optimal phase angle window. This may play an important role in the delivery of SRT as we currently do not know if dim light during the restriction phase should be recommended to keep the circadian phase at the same point - or if the restriction should be based on individual timing of phase, comparable to chronotherapy[268]. Consequently, more research studies are needed to understand the link between circadian phase and SRT.

Overall, the interpretation of our findings is limited by the lack of a clear understanding of the relationship between circadian phase and sleep behaviour, especially in the treatment of insomnia. In order to enhance our current knowledge, future studies are needed to identify what an optimal phase angle is. That is, when, in relation to melatonin rise, one should

attempt sleep. Additionally, studies implementing SRT should consider circadian phase measurements in their study designs, report on changes in bed and rise times and give details about the implementation of SRT (i.e. if the sleep window was set according to circadian preference). Furthermore, phase angle increase could be targeted in experimental settings, for example by delaying bedtimes only or by advancing DLMO with light exposure in the morning. However, it must be considered that patients with specific insomnia symptomatology (e.g. only sleep onset latency versus only early morning awakenings) might benefit from different strategies. Previous literature has shown improvement in insomnia for light induced phase advancement in participants with long SOL[269]. In contrast, participants with early morning awakenings showed improvements after light induced phase delay[270].

6.5 Conclusion

For the first time, this study assessed effects of SRT on circadian phase as indexed by melatonin onset and elucidated a potential mechanism in the alignment of circadian phase and sleep-wake behaviour. It is surprising that after 30 years of systematically delaying and advancing bedtimes in the treatment of insomnia, no study has tested its effects on circadian phase. The present study's findings suggest that SRT, in its acute phase, increases phase angle and reduces vigilance in the evening hours, particularly after DLMO. Yet, future investigations are needed to reveal the optimal length of phase angle for sleep and unveil the link between changes in phase angle and treatment outcomes.

CHAPTER 5:

GENERAL DISCUSSION

1 Key findings

Previous research has primarily focused on the *effectiveness* of SRT but has neglected *how* it improves sleep. This is surprising because hypotheses were generated in the 1980s when SRT was introduced to the field[94]. Understanding the processes that account for therapeutic change is essential to improve interventions and potentially, tailor it to the individual[101]. The aim of this thesis was to investigate the mechanisms of SRT for insomnia disorder. Chapters two, three and four brought together various theoretical and empirical approaches to elucidate the mode of actions through which SRT exerts its effects. An overview of findings from all relevant chapters can be found in Table 30 below:

Table 30. Overview of key findings from the thesis

Chapter	Key findings
2	▪ First systematic review of SRT mechanisms. ▪ Results: Found strong evidence for reported reductions in perpetuating practices, some evidence for increased sleep pressure and very limited evidence for diminished arousal and stabilised circadian sleep-wake cycle. ▪ A new testable model (Triple-R) was introduced which proposes that SRT primarily exerts its effects by regularising, restricting and re-conditioning TIB, followed by subsequent changes in physiological and cognitive-behavioural pathways.
3	▪ First randomised-controlled trial to investigate the mechanisms of SRT and the centrality of the restriction component. ▪ Results: Compared to a regular TIB, SRT revealed superiority across measurements of sleep, insomnia severity and daytime functioning. ▪ In support of the Triple-R model, we found evidence for increased sleep pressure, diminished cognitive arousal, reduced sleep-related mentation and normalised subjective-objective sleep discrepancy. No effects were found for attentional bias.
4	▪ First use of DLMO as circadian phase marker before and after two weeks of SRT. ▪ Results: Acute SRT increased the phase angle by delaying attempted sleep but not by shifting DLMO. ▪ Beneficial effects were found on insomnia severity and sleep consolidation. ▪ Repeated measurements of subjective and objective vigilance before and after treatment revealed medium to large impairments.

1.1 Results from the systematic literature review

In order to examine the mechanisms of SRT this thesis first reviewed Arthur Spielman's proposed mechanisms and evaluated their evidence across the published literature. These included perpetuating practices, circadian sleep-wake cycle, homeostatic sleep drive and hyperarousal/conditioned arousal. The qualitative synthesis of 15 SRT studies revealed mixed results and several challenges. The studies were not designed for mechanistic evaluation, applied heterogeneous measurements of proposed mechanistic variables, and included secondary analysis and uncontrolled designs. Bearing these limitations in mind, we found consistent evidence for reduced TIB, indicating a reduction in putative perpetuating practices and most importantly, accordance with treatment instructions. The review proposed and reported that the curtailment of TIB is commonly accompanied by sleep reductions and hence, could lead to an increase in sleep pressure. While a temporal pathway could not be determined, decreases in SOL and elevation of subjective sleepiness pointed towards sleep pressure enhancement during the acute phase of SRT. There was only limited evidence for reductions in cognitive (alert cognition, sleep effort) and physiological (high frequency EEG, body temperature) arousal, which was hypothesised to result from an increased sleep drive. Lastly, it was proposed that SRT stabilises the circadian sleep-wake cycle. Yet, only two uncontrolled studies reported on it, both of which demonstrated less variability in subjective sleep parameters at the end of treatment. The absence of rigorously conducted mechanistic studies and the conceptual challenges led to the development of the Triple-R model and the subsequent empirical studies.

The final search date of the systematic review was February 2018. Since then, five studies meeting initial inclusion criteria were published. None of those studies focused on mechanistic research. However, in support of the previous findings, three studies reported reduced SOL[229,271,272], two reported on decreased arousal (cognitive and somatic)[229,273], one study showed increased tiredness when going to bed[274], and one revealed reduced napping[271]. It was beyond the scope of this thesis to contemplate research studies outside the human literature. However, one recent publication has to be considered when addressing the

mechanisms of SRT. The article of interest was based on the principles of SRT and presented a *Drosophila* model for behavioural sleep modification[275]. The authors showed first that sleep opportunity extension in wild-type flies led to sleep fragmentation - including increased SOL and WASO; and second, that a variety of *insomnia mutants* responded to sleep opportunity restriction with enhanced sleep efficiency, decreased arousal threshold and improvements across multiple sleep parameters. Based on those results, the authors suggest that the same physiological (and cellular) endpoint could underlay several subtypes of insomnia (*distinct drosophila sleep mutants*).

1.2 The Triple-R model – a new conceptualisation of the mechanistic pathways

When SRT was first developed, it was principally based on the 3-P account of insomnia development and maintenance[69,94]. The model has provided a generic approach to understanding insomnia chronicity and the factors that require modification to achieve therapeutic success. We reasoned that the field was ripe for a more fine-grained model to fully articulate its mechanisms. Based on Spielman's key observations, we outlined a new testable model, specific to SRT, which introduced new hypotheses that were based on our contemporary understanding of insomnia and the principles of basic sleep wake regulation[162]. The newly presented Triple-R model states that SRT exerts its treatment effects by undertaking three key things: restricting time in bed, regularising timing of sleep-wake behaviour, and reconditioning the association between bedroom factors and sleep. The alteration of these key processes is assumed to subsequently drive a cascade of changes in associated physiological and cognitive-behavioural factors, which in turn are presumed to improve sleep consolidation. Potentially, these improvements reduce subjective-objective sleep discrepancy, facilitate positive sleep experiences and enhance sleep self-efficacy. Lastly, the model proposed that with the continued experience of predictable and restorative sleep, the insomnia identity would be challenged and in the long run revised.

1.3 Evidence for the Triple-R model

In order to provide empirically grounded evidence for the mechanisms proposed by the Triple-R model, the MARTINI study was designed. The study compared treatment effects between two groups, SRT and BCT, on multidimensional assessments of physiological, cognitive and behavioural factors that are assumed to contribute to the maintenance of insomnia. Compared to the control group, SRT demonstrated superior treatment effects on the primary outcome, insomnia severity, at post-treatment and follow-up. While this is in accordance with previous effectiveness trials[88], the results are of special interest as our control group, BCT, was matched for both non-specific (e.g. therapist time) and specific treatment effects (e.g. stabilising bed- and rise times) by prescribing a regular but not a restricted time in bed. The MARTINI trial highlighted the centrality of the restriction component in the non-pharmacological treatment of insomnia but also supported the underlying assumption of the Triple-R model, stating that the curtailment of TIB is central to subsequent changes in secondary maintenance factors. Compared to BCT, we illustrated that SRT (1) regularises the circadian sleep-wake cycle as demonstrated by reduced nigh-to-night sleep variability; (2) creates a mild sleep deprivation as indicated by decreased TST; (3) potentiates sleep pressure in the evening as determined by subjective and objective sleepiness measurements and reductions in SOL; (4) diminishes cognitive arousal as revealed by daily and weekly subjective estimates of pre-sleep arousal and reductions in sleep-related mentation; (5) improves sleep consolidation as obtained by sleep diary, actigraphy and polysomnography; (6) normalises sleep-state misperception by reducing underestimation/increasing overestimation of TST; and (7) improves daytime functioning as ascertained by beneficial effects on quality of life and daytime sleepiness at follow-up. While no temporal order has been determined within the cascade, the comparison to BCT suggests that the restriction element is central. The figure below summarises the results of the MARTINI study in respect to the Triple-R model. However, it must be noted that while not every conceptual contributor has a direct and established representation (e.g. bed-sleep association), some variables are indicative of more than one concept (e.g. SOL, see below).

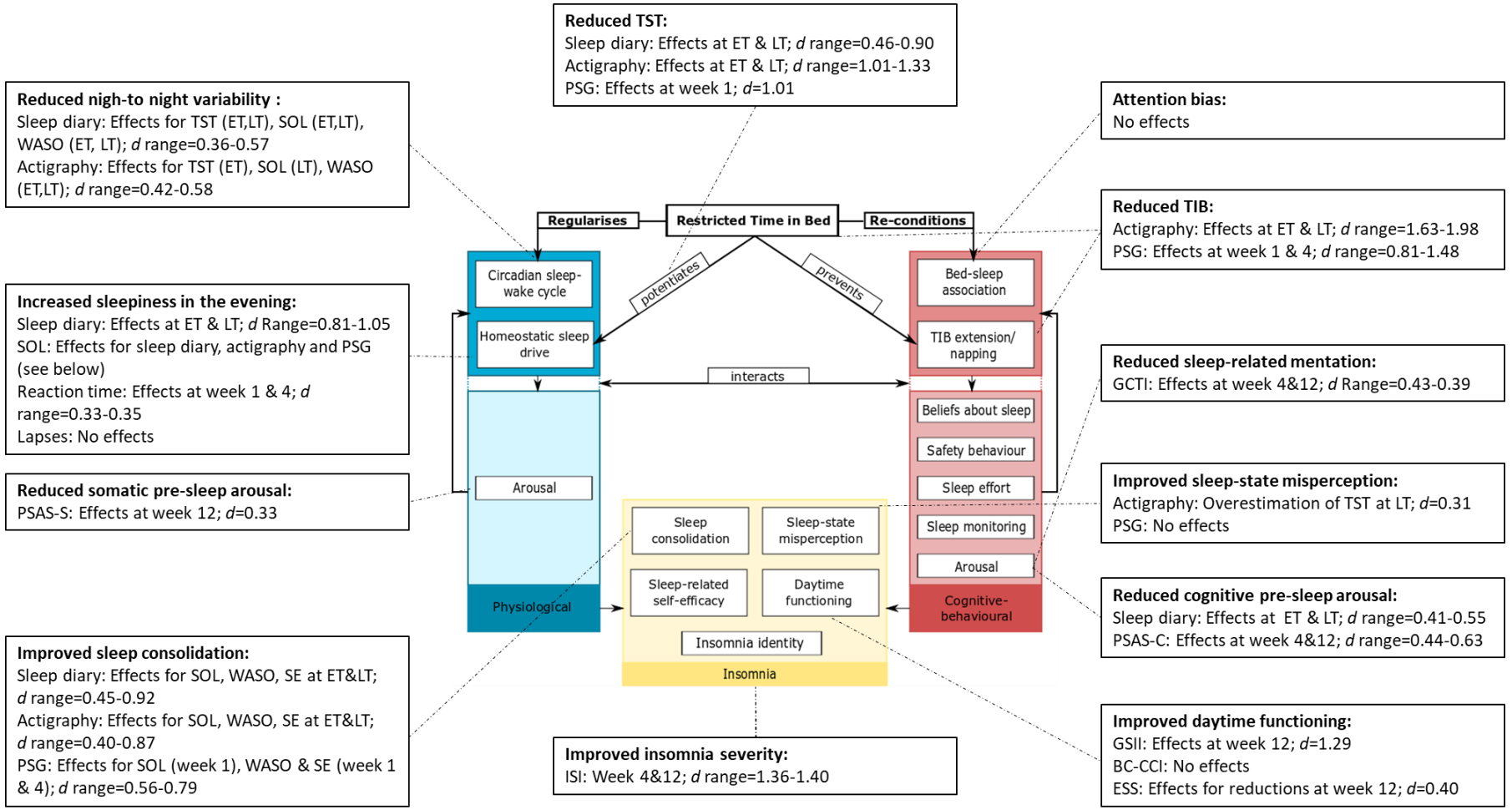


Figure 30. Evidence for the Triple-R model. This figure displays the Triple-R model in the middle, linked to research findings from the MARTINI study. *Abbreviations:* TST=Total sleep time; SOL=Sleep onset latency; WASO=Wake after sleep onset; ET=Early treatment (week 1-2); LT=Late treatment (week 3-4); PSAS-S=Somatic subscale of the Pre-sleep arousal scale; PSAS-C=Cognitive subscale of the PSAS; PSG=Polysomnography; GSII=Glasgow sleep impact index; BC-CCI=British-Columbia cognitive complaints inventory; ESS=Epworth sleepiness scale; GCTI=Glasgow content of thought inventory; d=Effect size derived from Cohen' s *d*.

1.4 The effects of SRT on the circadian sleep-wake cycle

Based on previous literature, it was assumed that phase angle, the time between the circadian marker of sleep induction (melatonin rise) and attempted sleep, would be increased by a narrower sleep window. It was hypothesised that the lengthening of phase angle could be beneficial for sleep as previous reports suggested a shorter phase angle for people with insomnia when compared to good sleeper controls[233]. Indeed, results from the ESPRIT study revealed that phase angle was increased by 35 minutes after two weeks of SRT. While the circadian phase marker (DLMO) stayed relatively stable, attempted sleep was approximately 47 minutes later and consequently, contributed to the increase in phase angle. Full interpretation of this finding is hindered by a current lack of established recommendations for the optimal phase angle. However, it was noted that the phase angle after two weeks of SRT was closer to the phase angle of good sleeper controls reported elsewhere[233]. Additionally, we observed improvements of SRT on insomnia severity and sleep consolidation in the acute phase. Theories support the hypothesis that phase angle increase could be linked to beneficial effects for sleep by potentially aligning the circadian rhythm and the sleep homeostat[9,141,235,236]. As a secondary outcome, the ESPRIT study obtained repeated measurements of subjective and objective vigilance, revealing medium to large impairments after two weeks of SRT and localised to the night-time. This provides further support that SRT harnesses sleep pressure in order to consolidate sleep.

2 Methodological considerations

2.1 Study designs

The principal strength of the MARTINI study was the application of a dismantled trial design, whereby an effective and established behavioural treatment, SRT, was compared to a control group that was matched for most therapy effects but did not involve a restriction component. To date, very few studies in the CBT-I literature have dismantled the multi-component treatment in order to test its underlying effects. The first dismantling trial design in the CBT-I literature was published by Epstein and colleagues in 2012[110]. The authors

compared the behavioural components of CBT-I, revealing that stimulus control, SRT, and the combination of both were equally efficacious in the treatment of insomnia. Two years later, Harvey and colleagues designed a study that compared the behavioural components (BT = stimulus control + SRT) with cognitive therapy (CT') and full CBT-I. The authors reported that full CBT-I led to the greatest overall improvements, while improvements linked to BT were faster but not as sustained and the improvements linked to CT' were slower but sustained. They further suggested that these observed changes may have occurred via faster behavioural processes in the BT group or via a slower cognitive route in the CT' group, potentially explaining the rapid effects for BT and the slower effects for CT'[276]. The same research group conducted a mediator analysis on the same data set and showed that indeed, only outcomes in the BT group were mediated by behavioural processes. However outcomes for both, CT' and BT were mediated by cognitive processes[91]. These studies highlight the importance of dismantling trial designs and their potential to elucidate mechanisms. In chapter three, the idea of comparing dismantled treatment components was further refined by dismantling the dismantled treatment component (SRT) to test its mechanisms of action.

The design of an adequate control group is not just essential for mechanistic research, it is also of crucial importance to minimise the risk of bias in trials of behavioural (and cognitive-behavioural) treatments[277]. Previous CBT literature has emphasised that the failure to blind participant and therapist minimises the quality of evidence for any behavioural intervention[278]. In order to overcome effects of treatment expectations and the lack of participant blinding, guidelines recommend to compare the same therapy with one or more components added or removed[167,277]. The design of the MARTINI trial followed these guidelines by removing the restriction component and creating a control group that followed a regular time in bed.

Despite these strengths, the applied research design cannot inform whether BCT is an effective treatment on its own, or if observed within-group improvements (e.g. ISI decrease of 3.0/4.3) occurred because of specific (e.g. stabilisation of bed- and rise times) or non-specific (e.g. therapist time) treatment effects. Knowing about the effects of BCT is relevant

for clinical practice as regular bedtimes are commonly implemented as part of CBT-I[68,105]. While no studies have determined beneficial effects in the insomnia population, research evidence from studies with students support the view that indeed, regularising bedtimes could confer some therapeutic benefit for sleep and daytime functioning[135,165]. Regarding the MARTINI study, an additional control arm would have been required to test if BCT is efficacious in improving insomnia symptoms. To address therapeutic effects of BCT in future studies, a control arm that is matched for unspecific effects could be included. A potential *candidate intervention* for this control arm could be a combination of imagery relief therapy[279]/quasi-desensitisation treatment[280] with instruction for continuous sleep monitoring. Based on theoretical and empirical support for beneficial effects of stabilised sleep-wake behaviour on daytime functioning and sleep[135,141,165], superiority of BCT compared to imagery relief therapy/quasi-desensitisation would be expected.

An additional control group would have also enhanced the methodological strength of the ESPRIT study. However, the ESPRIT study was based on an exploratory research design and as such, did not aim to provide conclusive answers to the research question, but instead, to provide preliminary information that will help define problems and suggest hypotheses in the field[281]. Consequently, a repeated measures design and a small sample size, informed by power calculations, was deemed appropriate for the research question of interest.

Another limitation of both study designs is the relative short treatment and follow-up period at two, four and 12 weeks. Despite evidence for superiority of SRT at all time points, questions about persistent long-term improvements remain. Indeed, results from a recent meta-analysis[282] indicated that although CBT-I treatment effects were sustained over time, they steadily declined from 3- to 12-months follow-up. In order to determine if the here reported treatment effects are persistent, especially in comparison to BCT, an additional study with outcomes at 6- and 12-months would be required.

2.2 Interventions

Multiple strategies were implemented to ensure participants would follow their sleep schedule (e.g. weekly treatment sessions and supporting text messages). Adherence was considered of special importance to the investigation of the mechanisms of the treatment. If participants would not have adhered to the treatment protocol, no conclusions could have been drawn on the processes that happened during the first weeks of SRT. Yet, the implementation of sleep hygiene advice may have confounded the testing of the *pure* sleep restriction component. Sleep hygiene advice is not considered to be effective as a standalone intervention[93,185] and was added to both groups because of its role in usual care. If one experiences sleep difficulties in the UK, the first point of contact is typically the GP, who in turn commonly prescribes sleep hygiene[183]. Consequently, including sleep hygiene advice is consistent with previous literature[110,276] and helped to ensure that all participants commenced the intervention with a similar knowledge about sleep hygiene practices.

An additional limitation of the treatment implementation in both studies was the interaction between research visits and treatment sessions and that the primary researcher acted as both therapist and researcher. While this is a common limitation in clinical research studies, it can be avoided. For example, future studies should schedule research visits and therapy sessions separately, have different persons acting as therapist and researcher or even implement digital techniques and eliminate therapist allegiance effects completely.

2.3 Study population

For the mechanistic purposes of both studies, we recruited a highly selective study population meeting multiple inclusion/exclusion criteria. Strict criteria were considered necessary to remove confounding variables that could have potentially affected primary or secondary outcome measures, such as melatonin measurements and PSG-recordings. However, it must be noted that the study sample might not be representative of the general insomnia population. Across both studies, participants were highly educated, generally healthy, free from medication and very motivated. Additionally, both studies recruited the

sample size that was required to detect changes in the primary outcomes. However, larger sample sizes would have been required to detect changes in some secondary outcomes, which revealed small to medium effect sizes. Given the study aims and restriction on resource and time, we focused on the rigorous implementation of objective and high-resolution measurements. Yet, replication from future studies with larger and more representative samples would support the reliability and generalisability of the here presented findings.

2.4 Measurements

The applied measures had several strengths: For the first time, we tracked effects of SRT on sleep continuity with PSG, implemented computerised tasks, systematically measured adverse events and provided high-resolution data for daily sleepiness and pre-sleep arousal in a randomised-controlled trial. Furthermore, the ESPRIT study was the first to apply an established measurement of circadian phase to assess the effects of SRT on the circadian rhythm, and the first to conduct repeated measurements of vigilance before and after two weeks of SRT.

The planning and conduct of both studies provided several methodological challenges. In regards to the mechanistic variables in the MARTINI study, not every variable that was deemed to be important in our conceptualisation[162] had a clear-cut direct or proxy measurement. For example, we have a clear understanding of sleep consolidation and can measure it subjectively and objectively with sleep variables. Yet, measuring a construct like the bed-sleep association is difficult to quantify in a definitive manner. Here, we linked attentional bias to the concept of bed-sleep association as measured by the sleep-related dot-probe task.

Additionally, it was not feasible – and indeed is not deemed good practice - to include every variable that potentially could indicate a mechanism of SRT. The measurement of all variables would have been problematic as underlying concepts are overlapping (e.g. content of thoughts in the evening, dysfunctional beliefs about sleep and sleep self-efficacy), and

because more measurements might have exceeded the capacity of the study and more importantly, the burden of the participants. However, future analysis of the MARTINI trial is planned. For example, we will conduct quantitative EEG analysis in order to extract slow and high frequency signals from the obtained PSG recordings and perform non-parametric circadian rhythm analysis of continuously recorded actigraphy measurements (see https://doi.org/10.1186/ISRCTN10974094). Results from this analysis will inform if SWA, the key indicator of homeostatic sleep drive, is elevated during the acute phase of SRT. Furthermore, a reduction in the frequency of brain waves during sleep is expected for the high-frequency range, potentially indicative of reduced physiological arousal. Lastly, non-parametric circadian rhythm analysis will test if the variability of the rest-activity cycle decreases during SRT.

To account for other, especially cognitive mechanisms proposed by the Triple-R model, future studies should implement measurements of changes in sleep- and insomnia related cognition. The investigation of the cognitive pathway is particularly important as changes in cognition have been linked to slow but sustained treatment effects and may explain long term improvements[276]. Typical measurements comprise beliefs about sleep (e.g. Dysfunctional beliefs and attitudes about sleep; DBAS[283]), sleep-related self-efficacy (e.g. Self-Efficacy Scale[284]) and insomnia identity[160].

Furthermore, napping behaviour was described as a perpetuating practice and measured in both studies. However, the measurements of napping behaviour were not included in the here presented analysis. In the MARTINI study, both groups, SRT and BCT, were instructed not to nap, and consequently, we did not expect or test for any group differences.

Additionally, it must be considered that the tracking of changes in mechanistic variables during SRT was hindered by the adjustable treatment implementation of SRT. Sleep restriction therapy is individualised and hence, does not prescribe the same sleep window at the same time of day for each participant. Instead, each sleep window is fitted to individual preferences and reported sleep times. Furthermore, symptomatology also varies from person

to person and subtypes of insomnia are present[285]. As a result, the mechanisms of the treatment might vary between individuals as proposed in chapter two.

The variability of treatment implementation also challenged the measurements of the newly prescribed sleep schedule on DLMO. In good sleepers, studies investigating the effects of experimental sleep restriction on DLMO typically implement highly standardised in-lab sleep protocols and control for the effects of light exposure[267,286]. In contrast, SRT typically prescribes individual TIB reductions for the home environment[98]. The ESPRIT study did not aim to systematically sleep restrict participants in a light-controlled laboratory environment. Instead, variability in sleep schedules and consequently light exposure were part of the implementation of SRT. Here, light exposure was not taken into account as the study did not facilitate the measurement of light. Actigraphy watches with light sensors were initially considered but deemed as not suitable as the sensors are easily covered by sleeves or blankets. Future studies investigating effects of SRT on circadian phase could control for variability of light exposure by using light sensors that can be attached to clothing and reliably measure light exposure close to eye levels[287].

2.5 Statistical analysis

The implementation of linear mixed models for most analysis in the MARTINI study and some results in the ESPRIT study had several advantages. We assumed that only a small percentage of data would be missing and if so, would be missing at random. The mixed model approach takes missing data into account and additionally, includes individual's pattern of change when a subject variable is added as random factor[288]. However, in both studies we conducted multiple statistical comparisons without adjustment and therefore there is a clear risk of false positives (type one error). Moreover, our sample sizes were only powered to detect large effect sizes. Consequently, our statistical analysis had an increased risk of false negatives (type two error)[133]. However, hypotheses were pre-defined and to

allow the reader to judge magnitude and reliability of effects, exact p values, confidence intervals and effect sizes were reported, consistent with recommended practice guidelines[232].

Moreover, the thesis aimed to investigate the mechanisms of SRT, but did not conduct mediator analysis on clinical outcomes. For example, the MARTINI study revealed that PSG-defined sleep continuity differed between groups at post-treatment. Mediator analysis could now determine if improvements in PSG-defined sleep continuity are in relation to reduced insomnia complaints. This hypothesis is supported by the Triple-R model and by evidence from cross-sectional studies in good sleepers that showed that sleep efficiency/continuity is a significant determinant of self-reported sleep quality and the feeling of being refreshed upon awakening[238,289]. Previous mediator analysis has been conducted in the CBT-I literature with a specific focus on cognitive mediators[290]. For example, Lancee and colleagues have shown that changes in dysfunctional beliefs and safety behaviours mediate the effects of CBT-I on insomnia severity and sleep efficiency[291]. The analysis was conducted with results from a randomised-controlled trial revealing a comparable sample size as reported in the MARTINI trial and applying bootstrapping methods[292]. A similar method could be used for the here presented data to investigate if improvements in PSG-defined sleep continuity mediate the effects of SRT on insomnia severity as it was proposed in chapter two. However, future studies should include mediation analysis in their study designs to rigorously test those relationships.

3 Implications and future research

This thesis highlights the explanatory power of mechanistic research focussing on specific components of treatment with comprehensive measurements. The here presented results illustrate the significance of the restriction component in SRT and its underlying processes such as improving sleep consolidation and changes in circadian phase. However, many

questions are yet to be answered. Queries that are relevant to clinical practice and our understanding of insomnia treatment are summarised below.

3.1 Clinical practice

One of the most central questions in regard to clinical practice is addressing the degree of TIB curtailment that is required to experience the most beneficial treatment effects. We know now that consistent bedtimes are not as effective as restricted bedtimes (see chapter three). Yet, we still do not know how short this restriction ought to be and if subjective sleep duration at baseline is the best criteria. To test the effects of dose of TIB curtailment, follow-up studies are required that compare variable restriction protocols and investigate their effects on PSG-defined sleep consolidation and insomnia symptoms across different time points. For example, sleep windows could be selected based on objectively or subjectively defined sleep duration and be compared within one randomised-controlled trial. As people with insomnia tend to underestimate their sleep duration[209], it can be assumed that the group following a subjectively defined sleep schedule would experience more restriction. Results from such studies would also inform about the mediating role of sleep consolidation on the relationship between TIB restriction and insomnia symptom reduction. That is, testing if a shorter TIB leads to better sleep continuity, and consequently to less reported insomnia symptoms.

This thesis has also shown that the restriction of TIB comes with enhanced sleepiness (chapter three and four), impaired vigilance (chapter three and four) and enhanced reporting of side-effects (chapter three). These results confirmed evidence provided by other uncontrolled studies[118,123], but also indicated that impairments may be localised to the night-time (chapter four). In clinical practice, these findings can help deliver treatment rationales and prepare the patient for potential side effects. We know that many patients struggle with the implementation of SRT and often sleep windows are *weakened* in order to help adherence[293]. Yet, results from chapter three state that a consistent TIB is not as effective as a restricted TIB. Future research is needed to determine if, when, and how SRT should be

mitigated. First approaches could be taken by investigating when participants struggle the most with SRT and what kind of support they would benefit from. Study designs that implement adaptive treatment strategies have already been conducted for internet-based CBT-I[294] and could also be applied for SRT on its own, for example by offering more support (e.g. more frequent therapist contact) to those participants who struggle adhering in the first week. Another example was described by Whittall and colleagues[295], who adjusted the sleep window in consideration of experienced daytime sleepiness, i.e. if ESS scores were >10, then this allowed extending TIB by 30 minutes. Consequently, measurements of side-effects could be used to mitigate the sleep restriction in order to keep the participant engaged and potentially, reduce adverse events.

The other aspect to consider is that we currently do not know how long SRT must be implemented by the patient in order to experience optimal treatment outcomes. In this thesis, the therapist facilitated the implementation for two and four weeks respectively. Additionally, chapter three illustrated that treatment effects were even larger at 3-months follow-up. Yet, we do not know if participants were still implementing SRT at that time. Previous research has shown that that the change in TIB from the end of treatment to follow-up was positively correlated with change in total wake time and sleep latency, suggesting that the degree to which TIB is increased following treatment is related to the degree to which sleep deteriorates[94]. These results raise the question if the adherence to SRT after its initial implementation with the therapist is central to its long-term treatment effects. While previous studies have shown that adherence during the acute phase of SRT is associated with treatment outcomes in the short-term[296], no studies have looked at adherence beyond the acute phase of implementation and its treatment outcomes in the long-term. Future studies that apply therapist guided SRT for a specific time period (e.g. 4-6 weeks), could follow-up sleep window implementation on a regular basis (e.g. every month) by using sleep diaries for one week or asking retrospectively if a specific sleep window has been implemented. This research could inform if there is a need for more support after the initial treatment phase to enhance long-term treatment effects.

3.2 Enhancing our understanding of treatment mechanisms

In line with these thoughts, this thesis also encourages future research to consider other mechanisms that persist in the long term. Chapter three and four only observed changes of mechanistic variables during the acute phase of SRT and detected insomnia reductions at week two, four and 12. While it still has to be determined if changes in underlying processes are in fact mediating the effects of reductions in insomnia symptoms, it also remains an unanswered question if changes in mechanistic variables are persistent over time. One mechanism that was proposed to be crucial to the effects of SRT is the improvement in sleep continuity as defined by PSG. Chapter three has demonstrated large effects on PSG-defined sleep continuity variables after one and four weeks. Despite these promising results, questions remain if these changes are persistent or if deteriorations are associated with relapses. To develop a full picture of this relationship, additional studies are needed. For example, a study with a similar design as implemented in the MARTINI trial but with additional measurements of PSG-defined sleep variables at follow-up (e.g. after three and six months) could be conducted. Results from such a study could answer the question if improvements in sleep consolidation are persistent or dependent on the acute restriction during the first weeks of treatment. If sleep improvements are persistent, this would point towards a long-term physiological mechanism of SRT.

Chapter four has illustrated that the implementation of SRT varied from participant to participant, with some delaying their bedtime and some advancing their rise time. Yet, data from all but two participants revealed that phase angle was increased. Importantly, this effect is assumed to be beneficial for sleep, especially if circadian phase and sleep behaviour are misaligned[141,269]. Considering these results, the question emerges how the sleep window should be positioned in the treatment of insomnia with SRT. Several points have to be considered:

First, more experimental studies are needed that systematically modify the phase angle between DLMO and bedtime and investigate its association with treatment outcomes. For

example, larger randomised controlled studies could focus on a circadian treatment for insomnia, whereby phase angle is increased by advancing DLMO with light exposure in the morning or by delaying bedtimes in the evening and compare these conditions to a consistent TIB. Analysis of such a study could then inform if the extent of phase angle increase, or the phase angle at post-treatment, is associated with treatment outcomes such as sleep consolidation and improved insomnia symptoms. These results could give answers to the question how the new therapeutic sleep window should be positioned.

Second, future study designs could incorporate various implementation strategies, for example by comparing an adjustment for bedtime versus an adjustment for rise time versus an adjustment for both, bed- and rise time. Results from this study could show if there is a benefit of one over the other options for the treatment of insomnia.

Third, it must be taken into account that patients with specific symptomatology (e.g. only sleep onset latency versus only early morning awakenings) might benefit from different strategies. Previous literature has shown beneficial effects of light induced phase advancement for sleep onset latency insomnia[269], while patients with early morning awakenings seem to show improvements with light induced phase delay[270]. For example, the study conducted by Lack, Wright and Paynter showed that after one week of treatment, morning bright-light exposure lead to a phase advance of 1:21 hrs as determined by urinary DLMO - which in turn was linked to beneficial effects on sleep outcomes[269]. Consequently, this raises the question if the symptomatology of the participant should be taken into account when prescribing the sleep window. For example, by choosing a later bedtime for participants with early morning awakenings, an earlier rise time for participants with sleep onset latency and potentially both for participants who experience mixed symptomatology.

4 Conclusion

To date, well over 100 randomised controlled trials support that CBT-I is efficacious and effective. However, rigorous methodological approaches that test and manipulate the underlying processes of the treatment are still rare and limited by the composition of multiple

components that are simultaneously implemented with CBT-I. Based on the state of the science and previous literature, this thesis introduced a new-testable model of the mechanisms of SRT. The idea of *fine-tuning* insomnia research was then reconsidered by dismantling a dismantled treatment component to systematically test the assumptions the treatment is based upon. Indeed, the MARTINI study has shown for the first time that TIB restriction is central to SRT for insomnia. Results from this study also support evidence for findings of increased sleep pressure during the acute phase of SRT, a mechanism that potentially drives improvements in sleep consolidation and reductions in insomnia symptoms, pre-sleep arousal and misperception of sleep. Yet, it was also confirmed that the rise in sleep pressure is experienced as increased sleepiness and related to side effects in the acute phase of SRT. A finding that should be addressed in clinical practice. This thesis was also the first to illustrate the effects of SRT on circadian phase and elucidated a potential mechanism for the alignment of circadian phase and sleep-wake behaviour by increasing the phase angle between melatonin rise and attempted sleep. Given that in up to 20% of insomnia patients the timing of sleep relative to melatonin rhythm was found to be abnormal[233], results from this thesis highlight the importance of considering circadian phase in the treatment and in the pathophysiology of insomnia. The emergent findings described within this body of work have significant implications for clinical practice and insomnia research, but also stimulate future mechanistic investigations in order to enhance our current understanding of underlying therapeutic processes and the pathophysiology of insomnia.

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SUPPLEMENTARY

Appendix A: Black and Dawns Study Quality Rating

Question	Epstein 2012	Taylor 2010	Friedman 2000	Miller 2015	Miller 2013	Falloon 2015	Vallieres 2014	Friedman 1991	Whittall 2017	Spielman 1987	Kyle 2011	Kyle 2014	Wang 2015	Brooks 1993	Fernando 2013	Bliwise 1995
1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3	1	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1
4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1
5	2	1	2	1	1	2	1	1	1	1	2	2	2	1	2	1
6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
7	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
8	0	0	0	0	1	1	0	0	1	0	1	1	0	0	0	0
9	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0
10	1	1	0	0	0	1	0	0	1	0	1	1	1	1	1	1
11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
13	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
15	0	0	0	0	0	1	0	0	0	0	0	0	1	0	1	0
16	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
17	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
18	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
19	1	0	0	1	1	0	1	0	0	0	1	1	1	0	0	0
20	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1
21	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
22	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
23	1	1	1	0	0	1	0	1	0	0	0	0	1	0	1	1
24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	1	0	0	1	0	0	0	0	1	0	1	0	1	0
26	0	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1
27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
26	18	17	18	16	16	21	16	14	18	13	20	19	21	15	19	17

Questions of the Black and Dawns Study Quality Rating:

Reporting

1.) Is the hypothesis/aim/objective of the study clearly described? (yes=1; no=0)

2.) Are the main outcomes to be measured clearly described in the Introduction or Methods section? (yes=1; no=0)

3.) Are the characteristics of the patients included in the study clearly described? (yes=1; no=0)

4.) Are the interventions of interest clearly described? (yes=1; no=0)

5.) Are the distributions of principal confounders in each group of subjects to be compared clearly described? (yes=2; partially=1; no=0)

6.) Are the main findings of the study clearly described? (yes=1; no=0)

7.) Does the study provide estimates of the random variability in the data for the main outcomes? (yes=1; no=0)

8.) Have all important adverse events that may be a consequence of the intervention been reported? (yes=1; no=0)

9.) Have the characteristics of patients lost to follow-up been described? (yes=1; no=0)

10.) Have actual probability values been reported (e.g.0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001? (yes=1; no=0)

External validity

11.) Were the subjects asked to participate in the study representative of the entire population from which they were recruited? (yes=1; no=0; unable to determine=0)

12.) Were those subjects who were prepared to participate representative of the entire population from which they were recruited? (yes=1; no=0; unable to determine=0)

13.) Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? (yes=1; no=0; unable to determine=0)

Internal validity – bias

14.) Was an attempt made to blind study subjects to the intervention they have received? (this item was removed due to the nature of behavioural interventions)

15.) Was an attempt made to blind those measuring the main outcomes of the intervention? (yes=1; no=0; unable to determine=0)

16.) If any of the results of the study were based on "data dredging", was this made clear? (yes=1; no=0; unable to determine=0)

17.) In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? (yes=1; no=0; unable to determine=0)

18.) Were the statistical tests used to assess the main outcomes appropriate? (yes=1; no=0; unable to determine=0)

19.) Was compliance with the intervention/s reliable? (yes=1; no=0; unable to determine=0)

20.) Were the main outcome measures used accurate (valid and reliable)? (yes=1; no=0; unable to determine=0)

Internal validity - confounding (selection bias)

21.) Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? (yes=1; no=0; unable to determine=0)

22.) Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? (yes=1; no=0; unable to determine=0)

23.) Were study subjects randomised to intervention groups? (yes=1; no=0; unable to determine=0)

24.) Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? (yes=1; no=0; unable to determine=0)

25.) Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? (yes=1; no=0; unable to determine=0)

26.) Were losses of patients to follow-up taken into account? (yes=1; no=0; unable to determine=0)

Power

27.) Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? (size of smallest intervention group <n_1=0; n_1-n_2=1; n3-n4=2; n_5-n_6=3; n_7-n_8=4; n_8+=5)

Appendix B: Participant information sheet - MARTINI

Sleep and Circadian Neurosciences Institute (SCNi),
Nuffield Department of Clinical Neurosciences,
Sir William Dunn School of Pathology, University of Oxford, South Parks Road, Oxford, OX1 3RE

Leonie Maurer
01865 618656
leonie.maurer@ndcn.ox.ac.uk

Mechanisms of Sleep Restriction Therapy in Insomnia (MARTINI): A randomised, controlled evaluation comparing bedtime consistency therapy with sleep restriction therapy

PARTICIPANT INFORMATION SHEET
Ethics Approval Reference: R51331/RE004

We would like to invite you to take part in a research project. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, family or your GP if you wish. If there is anything that you do not understand, or if you would like more information, please ask us. Please take time to consider whether you wish to take part. Thank you for reading this.

What is the purpose of the research?

In this study we want to compare two common treatments for insomnia, Sleep Restriction Therapy (SRT) and Bedtime Consistency Therapy (BCT). Both interventions have been shown to improve sleep quality in those with poor sleep, however they have not been directly compared in a single study. We want to determine what the most effective treatment is (SRT or BCT) and investigate how the treatments may be working to change sleep and daytime functioning. We will recruit participants who are poor sleepers and who do not currently take medication for their sleep or mental health. We will randomly allocate you to one of the two treatment groups.

Why have I been invited?

You have been invited to take part because you may have a sleep problem and may be interested in an insomnia treatment study. It could be that you have seen a notice, news story or advertisement about our research. We are looking to recruit around 56 participants. Participants must be aged 25-55.

Do I have to take part?

No. It is up to you to decide if you want to take part in this study. This information sheet outlines what the study involves and if you have any further questions please contact Leonie Maurer, leonie.maurer@ndcn.ox.ac.uk. If you agree to take part, we will ask you to give

consent. However, you would still be free to withdraw from the study at any time, without needing to give a reason and without penalty.

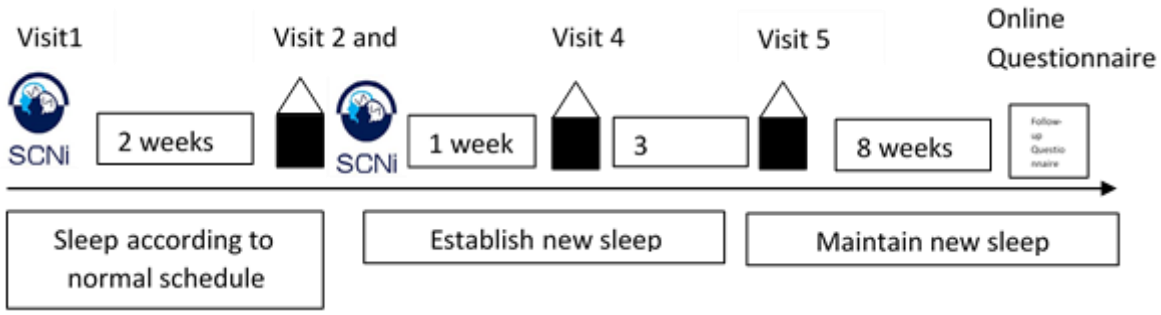
What will happen if I want to take part?

If you decide to take part, you will be asked to complete a brief set of online questionnaires. This will take approximately 10-15 minutes to complete and will ask you about your sleep and emotional wellbeing. If you do not meet the criteria for participation in the study, you will be thanked for your time and your information will not be used in the study.

If you do meet criteria, you will be asked to provide a telephone number and email address. You will be contacted by the research team within 24-28 hours and undergo a brief telephone interview about your sleep and health and to assess your eligibility for the study in more detail. This should take approximately 10 minutes.

What will happen if I take part?

Taking part will involve a total of 14 weeks, during which you will have your sleep carefully assessed and you will be expected to implement a behavioural sleep treatment programme. We will ask you to visit the Sleep and Circadian Neuroscience Institute (SCNi) twice during the whole study. Furthermore, you will be visited three times at home for an overnight recording of your sleep and be asked to fill out questionnaires and perform brief computerised tasks measuring reaction time and accuracy. All visits are explained in detail below.



Visit 1 (at the SCNi)

If you are eligible for the study, we will invite you to visit the Sleep and Circadian Neuroscience Institute (SCNi), Nuffield Department of Clinical Neurosciences, Sir William Dunn School of Pathology, University of Oxford, South Parks Road, Oxford, OX1 3RE. When you arrive (visit 1), you will be given a study induction, provide written consent to participate in the study, and confirm dates of the next visit at your home. You will take home a participant checklist, a sleep diary (questions about your sleep) and an actiwatch (a watch-like device which assess sleep at home). This visit should take around 30 minutes.

Week one and two

The next part of the study will require you to go to bed and rise from bed as you normally do. However, we ask you to monitor your sleep by filling out a daily sleep diary in the morning and evening and wearing the actiwatch.

Visit 2 (at home)

Two weeks after the study has started, we will record your sleep at your home, approximately between the hours of 8pm – 8am. The recording of sleep – called polysomnography - is a standard way of measuring sleep objectively. Polysomnography [PSG - sleep study] will be recorded during the night to assess your sleep at home. This allows to measure exactly how long you were asleep and what time you spent in the various stages of sleep. Polysomnography will include an EEG with additional leads and sensors that are placed on your chin, and forehead for the duration of the night. EEG stands for Electroencephalogram. It is a common and safe form of measuring electrical activity of the brain. These are small sensors placed on your scalp. To establish electrical contact between the scalp and the sensors, gel containing salts that conduct electricity are placed under each metal contact. It is often necessary to prepare the area of the scalp under the sensor by cleaning it with rubbing alcohol and massaging an abrasive substance using a cotton swab, or by scratching the surface of the scalp with a blunt wooden stick. We would ask you to let the researcher know if at any time the procedure becomes uncomfortable. In such a case, we would terminate the study procedure, without this having any negative consequences for you. The gel used to make the electrical contact is water based and washes away easily. Before going to bed you will be asked to fill out some short questionnaires and complete two brief computerised tasks which assesses reaction time (about 20 minutes) afterwards the researcher will leave. In the morning the researcher will come and remove the sensors and you will be asked to complete two short questionnaires.

Visit 3 (at SCNi)

After the overnight recording you will be randomly allocated (akin to tossing a coin) to one of the two treatments (SRT or BCT). You will be asked to visit the Sleep and Circadian Neuroscience institute for the second time, where we will discuss the treatment with you (about 1 hour). Both treatments involve implementing a prescribed bed and rise time based on knowledge gained from sleep science and tailored to your individual sleep pattern. You will learn about the regulation of sleep and about environmental and lifestyle factors that may influence sleep. Before the session, we will ask you for your consent to record (audio) the treatment session. The audio recording is needed for treatment evaluation, which will be conducted by a researcher not involved in the treatment. The recording will be deleted afterwards.

Week three

In this week you will put the treatment into practice. The treatment will involve implementing a new sleep schedule each day under the guidance of the lead researcher (LM). In the first week of your treatment you will receive daily text messages to support you with the adaption of your new sleep schedule.

Visit 4 (at home)

At the end of your first treatment week, we will obtain a second PSG/EEG measurement during the night including questionnaires and two computerised tasks in the evening as well as two short questionnaires in the morning.

Week four to six

The next part of the study requires you to continue with the implementation of your sleep schedule under the guidance of LM and to continue wearing the actiwatch and filling out the sleep diaries for three treatment weeks. You will receive weekly check-up calls from the researcher to review your progress.

Visit 5 (at home)

At the end of treatment week 4, the researcher will visit you at home for your last overnight recording. The researcher will again come to your home in the evening to set up the EEG measurement and you will be asked to fill out questionnaires and complete two short computerised tests. The researcher will come again in the morning to remove the electrodes and to ask you to answer two questionnaires. Afterwards your sleep diary and your actiwatch will be collected.

Week seven to fourteen

We will ask you to continue to implement your tailored sleep schedule. Eight weeks after the last visit we will ask you to complete some questionnaires using an online survey. This will ask you about your sleep so that we can assess any long-term effects of the treatments. This will take you about 30 minutes. Afterwards you will be thanked for your participation.

Are there any risks in taking part in this study?

The sensors and electrodes for the PSG recordings are commonly used in sleep research and are non-invasive and only temporary attached to the skin of the subject. EEG is a procedure for measuring brain waves. It is harmless and painless and carries no significant risk to participants. EEG recording has been used safely for many years, and we are aware of no cases of adverse events. EEG equipment comes from certified suppliers of medical equipment, who are obliged by law to adhere to published guidelines on electrical and mechanical safety (IEC-601). If you feel any discomfort, then please let the researcher know and they will stop the procedure. Slight irritation and abrasion of the skin can occur due to the cleaning and preparation of the skin. Otherwise, no further risks are expected.

Are there any benefits from taking part in this study?

Participants will receive free access to evidence-based treatment. There may be a benefit, therefore, of improved sleep when following the sleep programme. Furthermore, all participants who are interested in receiving a summary of the study findings will also be sent a copy of this at the end of the study. On completion of the study all participants regardless of group or treatment response will be offered a code (value of £46) for an online insomnia treatment programme to further support sleep improvement.

Will my time/travel costs be reimbursed?

Participants will be reimbursed £20 for each completed trial phases (Baseline, Treatment phase 1, Treatment phase 2 and Follow-up). Thus, the payment for completing the study in full is £80. Travel costs will be reimbursed up to £60 per participant.

Who has reviewed this study?

All research studies are checked by an ethics committee to ensure the research is conducted safely and to the best standards. This research has been reviewed by, and received favourable opinion through, the University of Oxford Central University Research Ethics Committee (CUREC)

Who is organising and funding the research?

This study is conducted as part of the doctoral thesis of the researcher Leonie Maurer, supervised by Dr Simon Kyle and Professor Colin Espie and research funding is provided by the Dr Mortimer & Theresa Sackler Foundation.

What will happen to the results of the research?

All the information and data we collect is kept strictly confidential. Data and test results will be identified by a code number only and are kept in a locked filing cabinet or on password-protected computers. The research will be written up as part of a doctoral thesis and submitted to peer-reviewed journals for consideration for publication. The results may be shared at relevant conferences. On completion of full data analysis and manuscript submission we will make study data available to the public and research community via Oxford Research Archive (http://ox.libguides.com/ora-data/about-ora-data). Participants who have indicated that they would like to hear the results of the study will be sent a lay summary of the research. Audio recordings of the treatment will be used for evaluation of treatment delivery only and will be deleted afterwards.

Who will know that I am taking part in this research?

Any information collected about you during this study would be kept strictly confidential. Any electronic data will be anonymised with a code. All such data are kept on firewall and password-protected computers and any paper information (such as your contact details and any research questionnaires) would be stored safely in lockable cabinets in a swipe-card secured building and would only be accessed by the research team. Collected data will be retained for 10 years and then destroyed, in line with Oxford University policy on the management of research data and records. Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure we are complying with guidelines. With your consent, we will keep your personal information on a secure database in order to contact you for future studies.

What if there is a problem?

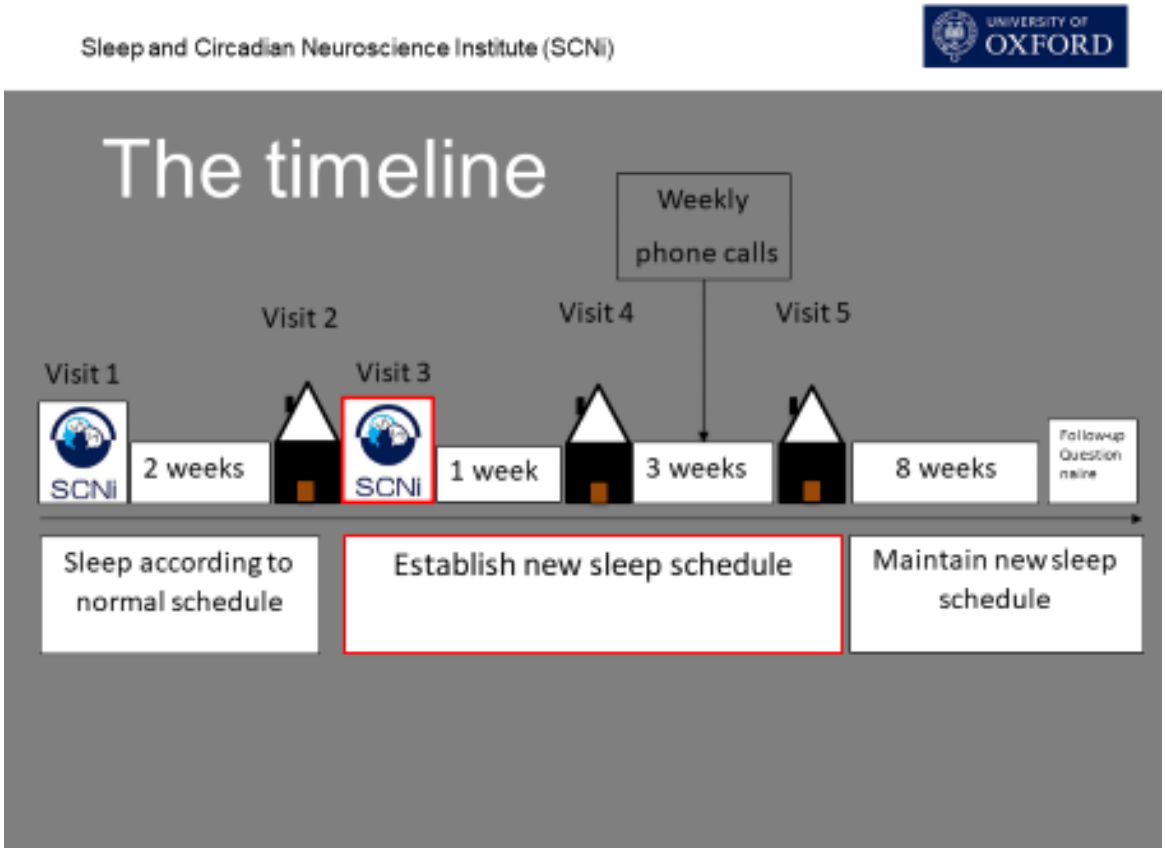
If you have concerns about any aspect of this project, please speak to the relevant researcher Leonie Maurer, leonie.maurer@ndcn.ox.ac.uk, 08165 18656 or primary investigator, Dr Simon Kyle, simon.kyle@ndcn.ox.ac.uk, 01865 618675 who will do their best to answer your query. The researcher should acknowledge your concern within 10 working days and give you an indication of how they intend to deal with it. If you remain unhappy or wish to make a formal complaint, please contact the chair of the Research Ethics Committee at the University of Oxford (using the contact details below) who will seek to resolve the matter in a reasonably expeditious manner:

Chair, Medical Sciences Inter-Divisional Research Ethics Committee
Email: ethics@medsci.ox.ac.uk;
Address: Research Services, University of Oxford, Wellington Square, Oxford OX1 2JD
If you would like to discuss the research with someone beforehand (or if you have questions afterwards), please contact:

Leonie Maurer
Leonie.maurer@ndcn.ox.ac.uk
01865 618656
Sleep and Circadian Neurosciences Institute (SCNi),
Nuffield Department of Clinical Neurosciences,
Sir William Dunn School of Pathology,
University of Oxford,
South Parks Road,
Oxford, OX1 3RE

Appendix C: Treatment slides

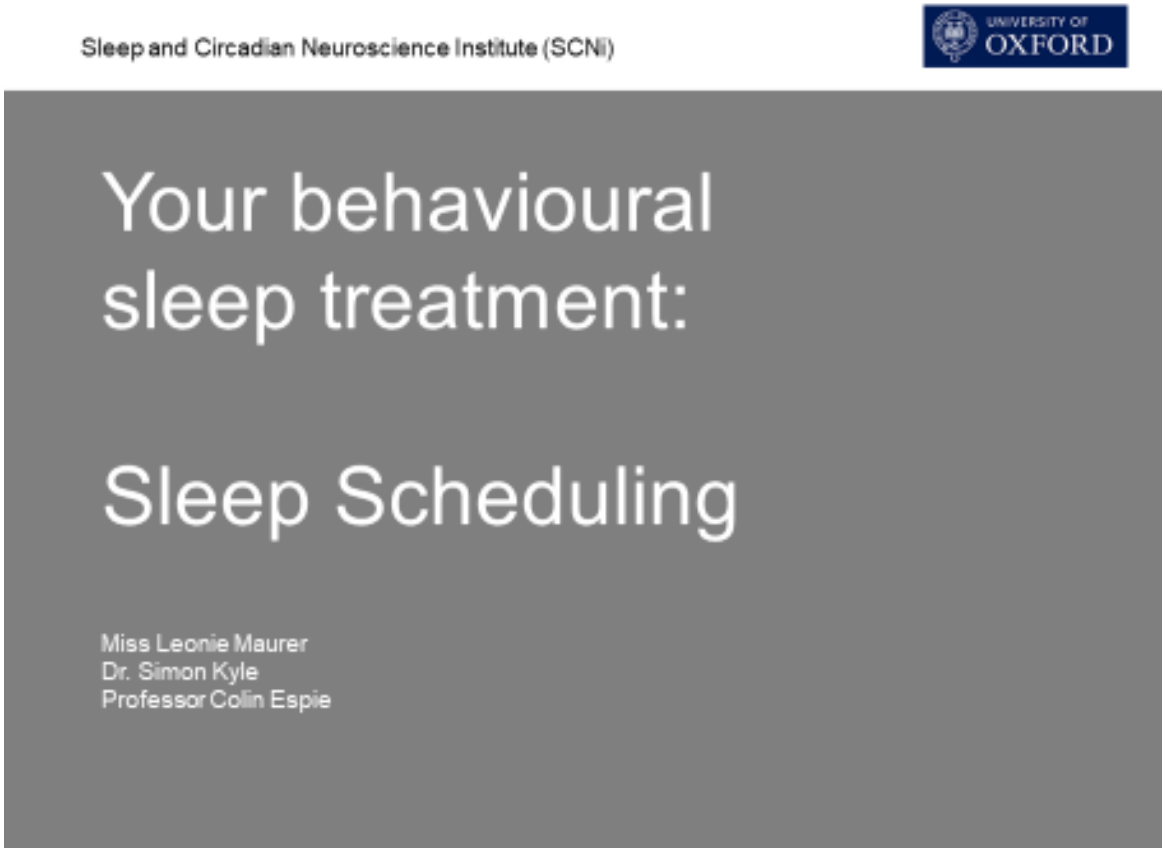
Sleep Restriction Therapy



Slide 1:

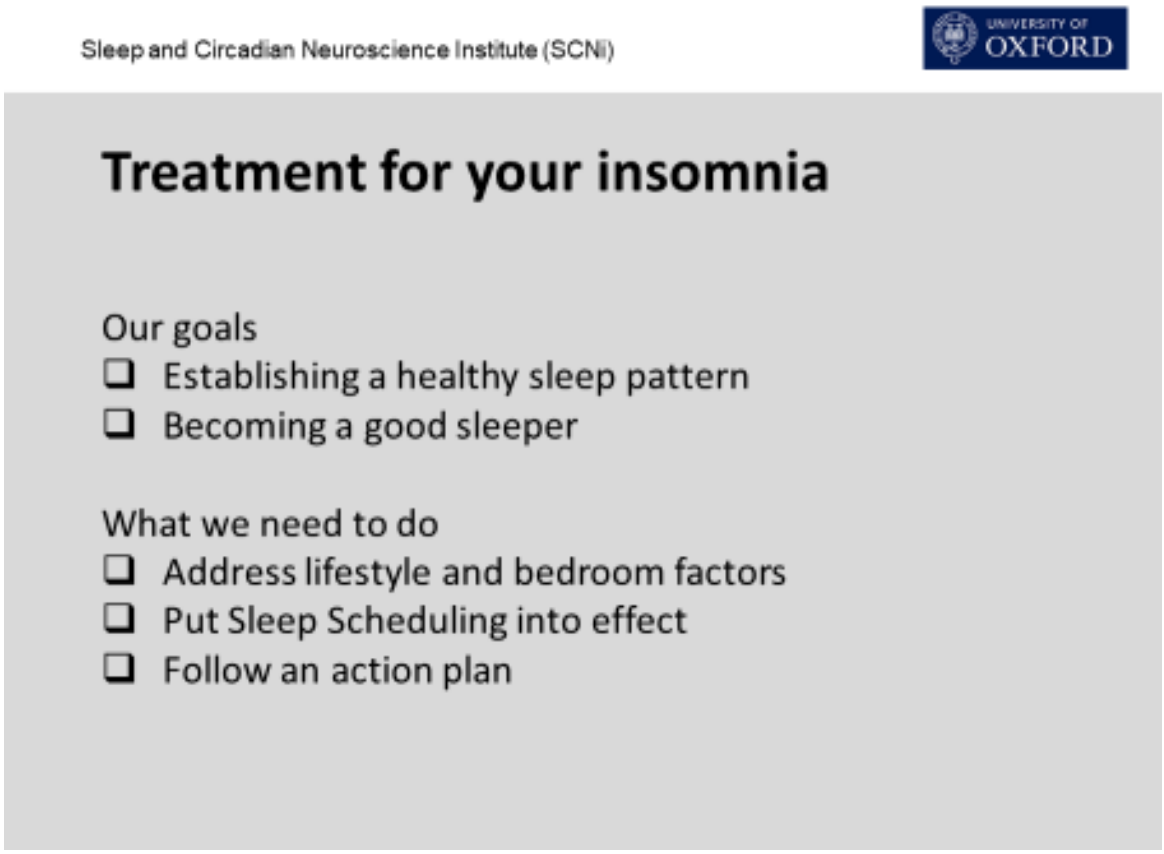
Preamble/Expert team

So here we have a picture that shows the timeline. This was when we first met, and since then you have been following your usual sleep routine or schedule and keeping some records for me. At this point today, we are here, your third visit, and we are going to introduce your new treatment shortly. Today's session will last around 45 minutes, so you should be away by [time]. Then, these points here and here mark our further contact points, which will be by at your home or on the phone. This is to check how you are getting on and to make any necessary adjustments to your treatment. As you know it is important that, as well as doing your best to put the treatment plan into action, you wear the actigraph and complete your diaries each night. I will arrange to visit you at home here and here to set you up for your overnight sleep assessments.



Slide 2:

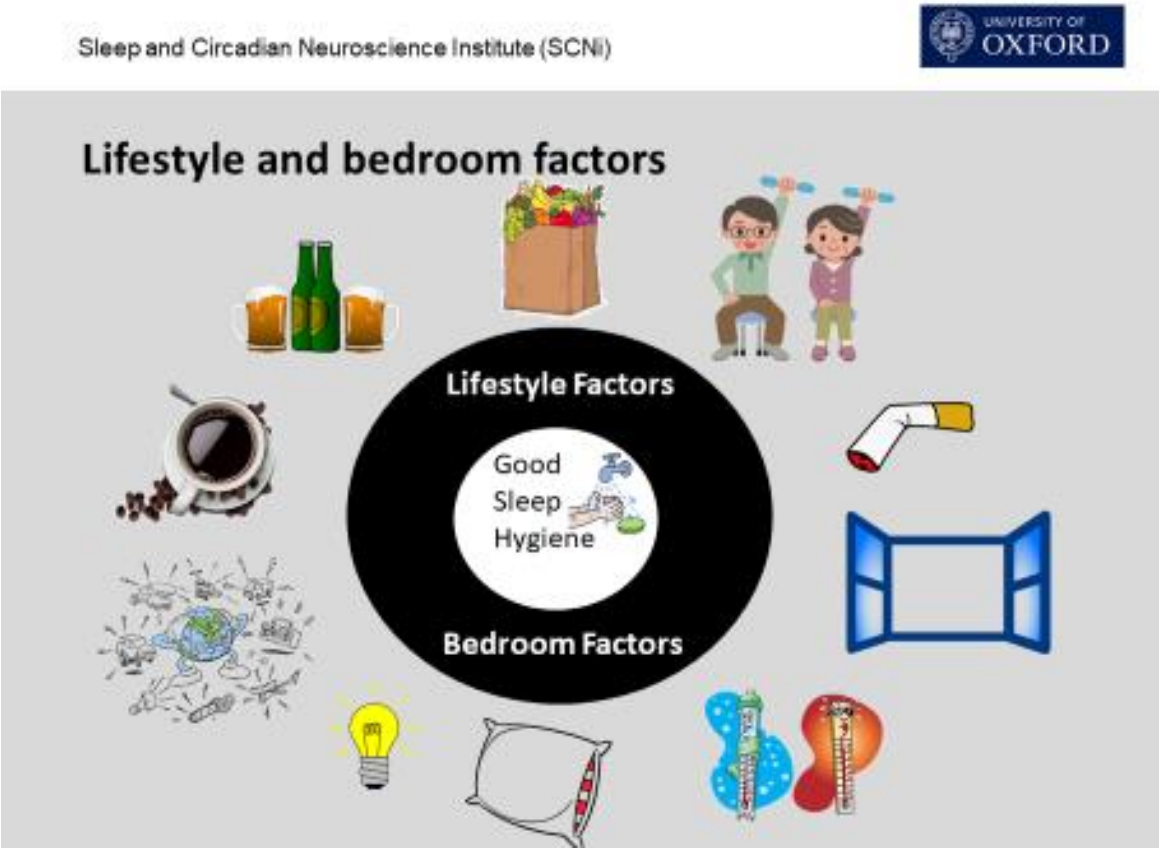
So, let's move on now to talk about how to improve your sleep. You were randomised to something called 'Sleep Restriction Therapy', this is a well-established treatment for insomnia and essentially what it involves is establishing a healthy new sleep schedule, so I'm just going to call it 'sleep scheduling' from now on. This treatment will hopefully help you to become a good sleeper. Let's look at what's involved.



Slide 3:

Establishing a healthy sleep schedule or sleep pattern probably sounds appealing! It would be great to be a good sleeper I imagine. These certainly are our goals. But what do we need to do to get there? During this treatment, I will try first to give you a bigger picture of lifestyle and bedroom factors that might affect your sleep, so that you can improve those. After that we will look closely at your sleep pattern, understand it properly, and develop a strategy to reset it so it begins to follow a healthy schedule. This is the sleep scheduling part and will be the main focus of the treatment. Based upon all of this, we will work together on a clear action plan, so that you know exactly what to do, … how to do it … and when to do it.

I will support you of course because I think this treatment is very suitable for you, so whenever you have a question just ask.



Slide 4:

So, let's think about some practices that can help us sleep. Some of this you will probably know, but it's always good to cover ground even if it is familiar. There may be one or two things that you pick up that could be useful. You can see here that what is sometimes called 'sleep hygiene' can be divided into two components – lifestyle factors and bedroom factors. Let's see if any of them are important for you. First the lifestyle factors; see them here in the top half of the diagram. The advice on lifestyle is that it's best not to drink caffeinated (tea/coffee) or alcoholic drinks, or to have a main meal, within four hours of going to bed. A small snack at suppertime shouldn't be a problem. Likewise, although exercise is good for our physical and mental health, it's best not to exercise immediately before going to bed because that would tend to be stimulating and might keep you awake. The best advice of all is to get fit and stay fit because healthy people generally sleep better! Smoking, of course, is bad for our health, but if you must smoke, then you should cut down before bedtime and try not to smoke during the night. Not only is nicotine a stimulant drug (like caffeine), your body may also wake you up craving a cigarette. Is there anything so far that is relevant for you? What would you try to work on? (Write them down in worksheet). Then in the lower half of the diagram, you'll see there are bedroom factors. These also can be important. How can you make your bedroom more suitable for sleep? Well, limiting noise (but that does not mean that you need complete silence), making it dark (but not necessarily pitch-black), and making sure that you have a comfortable mattress and pillows may help. Temperature is also important. The ideal room temperature is around 18C (64F) – not too hot and not too cold. If anything, sleep prefers the cool, so you shouldn't be too warm in bed. It's also a good idea to keep the room well aired – maybe leave a window a little bit open. Does anything here seem important to change in your bedroom? (Write them down in worksheet).

Sleep and Circadian Neuroscience Institute (SCNi)

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Sleep scheduling: How much sleep am I getting?

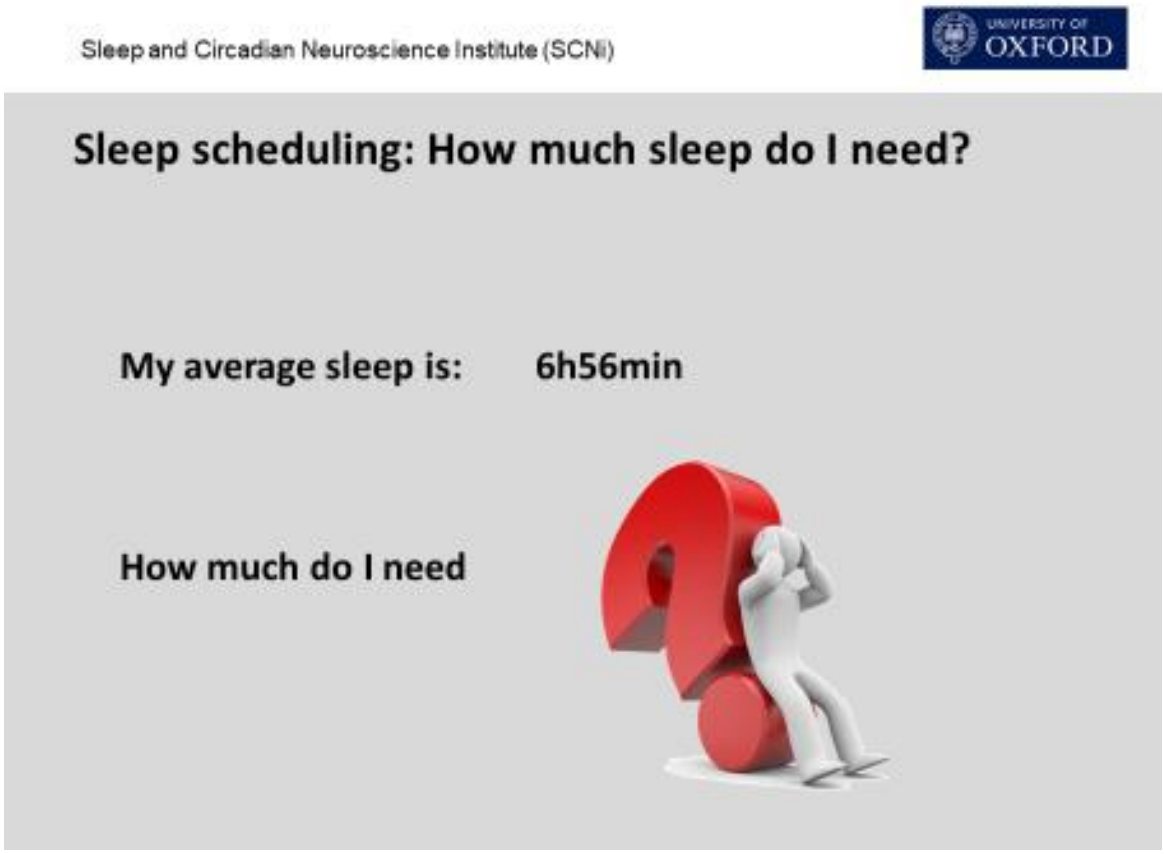
Night	Amount of time I slept (hours)	Amount of time I slept (min)
1	8:00	420
2	6:30	360
3	7:15	450
4	6:00	420
5	7:00	300
6	7:00	480
7	7:00	390
8	7:00	390
9	7:00	420
10	7:30	420
11	6:00	450
12	7:00	420
13	7:00	390
14	7:00	390



Total amount of sleep over all days = **97.25h / 5835** min
My average sleep time = **97.25h / 5835 min**/ number of days = **6.94h/416** min ~ **6h 56** min

Slide 5:

OK, so now that we have covered lifestyle and bedroom factors, the next thing is to take a good look at your sleep pattern itself and see how we can improve it. Once we understand your sleep pattern we can then develop a strategy to re-set it, so that it quickly begins to follow a more healthy schedule. The purpose of sleep scheduling is to reshape your sleep so that it meets your personal needs and develops into a strong pattern that will last. The obvious place to start then is to ask the questions 'how much sleep am I getting just now?' and 'how much sleep do I actually need?'. The best way to find out how much sleep you are getting at the moment is to have a look at the information we already have in your sleep diary. You will see here that I have taken the information on the amount of time that you feel that you slept each night and put it into this table. It varies of course from night to night. With some poor nights and some relatively better nights! Can you see? Next I added up the total time you have slept across all these nights. That's this figure. If we then divide that total by the number of nights that we have here, we get the average length of your night's sleep. So now you can see how much you slept each night and the average amount you slept over the past while. Does that make sense? I'm sure that you are thinking that this isn't enough … but it seems to be where you are right now!



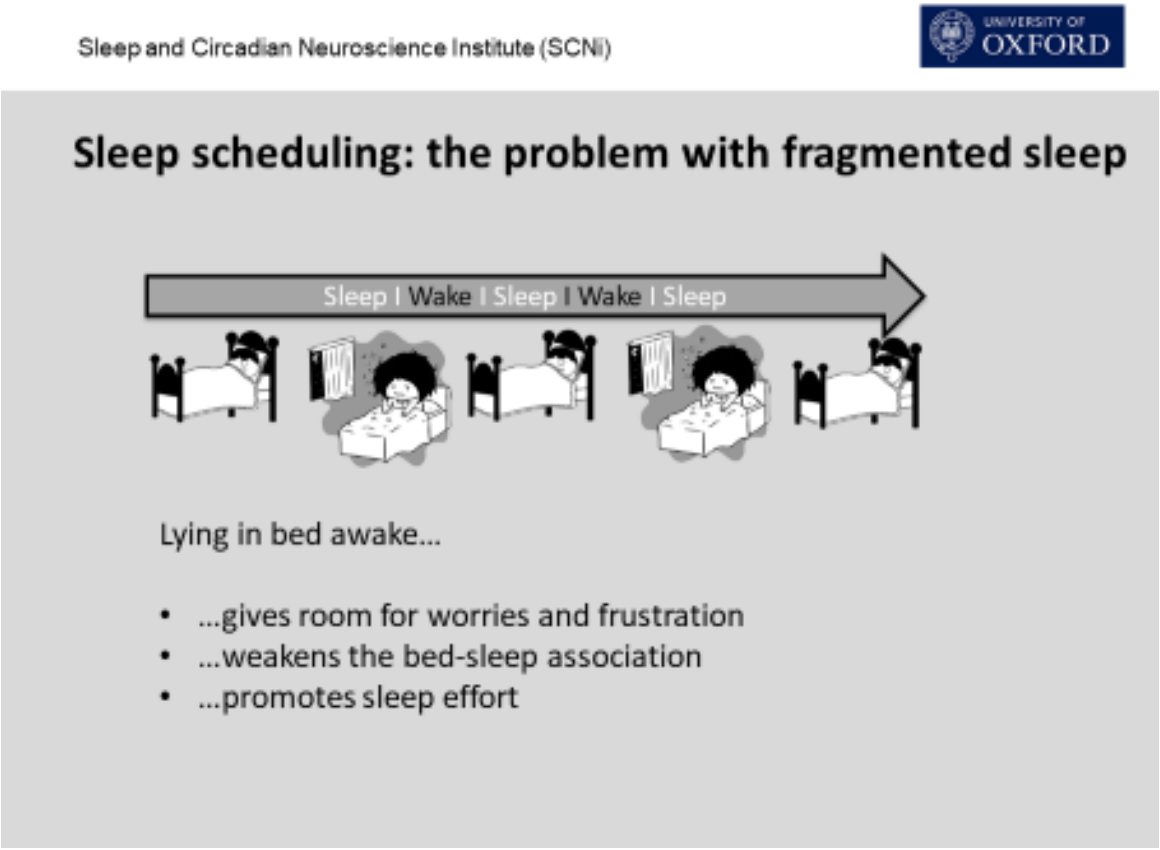
Slide 6:

So, we turn to that other question. - How much sleep do I need?

It's often said that we need 8 hours of sleep, or something like that, but It's not the case that there is an exact amount that is the same for everyone.
The truth is that everyone's sleep needs differ, just like not everyone is the same height or has the same shoe size … and the other thing is that the amount of sleep you need can change over the course of your life. This variability in sleep need from person to person, and the fact that sleep need can change for any given person over their lifetime can make it quite hard even for a good sleeper to figure out exactly how much sleep they need. When it comes to people like yourself, who have insomnia, it's even harder to figure out, for two reasons:

1. Your sleep is different from night to night and so your sleep has become very unpredictable
2. We can see that from your own sleep diary information – can't we?

A good sleeper on the other hand tends to have a more stable and consistent sleep from night to night. The sleep that you do get is broken up into bits and pieces. Unlike the good sleeper who more likely than not sleeps right through the night. Does this make sense so far? The great thing is that sleep scheduling treatment sorts all this out



Slide 7:

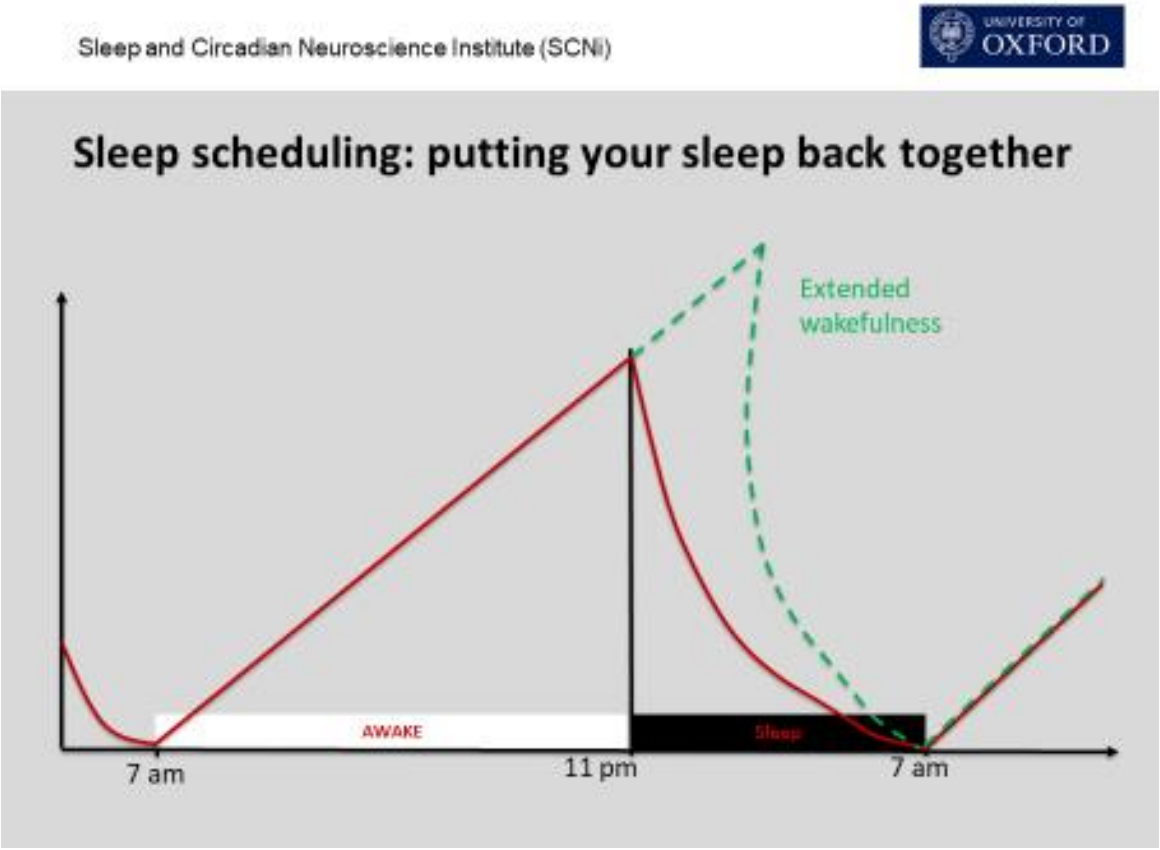
Let's consider this last point about broken sleep a little bit further – it's what we sometimes call 'sleep fragmentation'. If you have a fragmented sleep this normally means that you are spending more time in bed awake. Lying in bed awake can also happen to good, healthy sleepers as researchers have shown that their sleep gets really fragmented if you ask them to spend more time in bed as normal. They also report more daytime sleepiness even though they were able to get more sleep during the long nights. Unfortunately, compensating for sleep loss by spending a longer time in bed is a frequently encountered factor that maintains chronic insomnia. This is problematic as it gives you time to worry about your sleep and other things that are in your mind. It also weakens your bed-sleep association, as you may start connecting your bed with tossing and turning. A lot of people might also start to put effort into trying to fall asleep while they are lying in bed awake. Unfortunately, this makes them even more alert and lowers the chances for sleep to come naturally.



Slide 8:

I wonder if you can see where I am going with this.

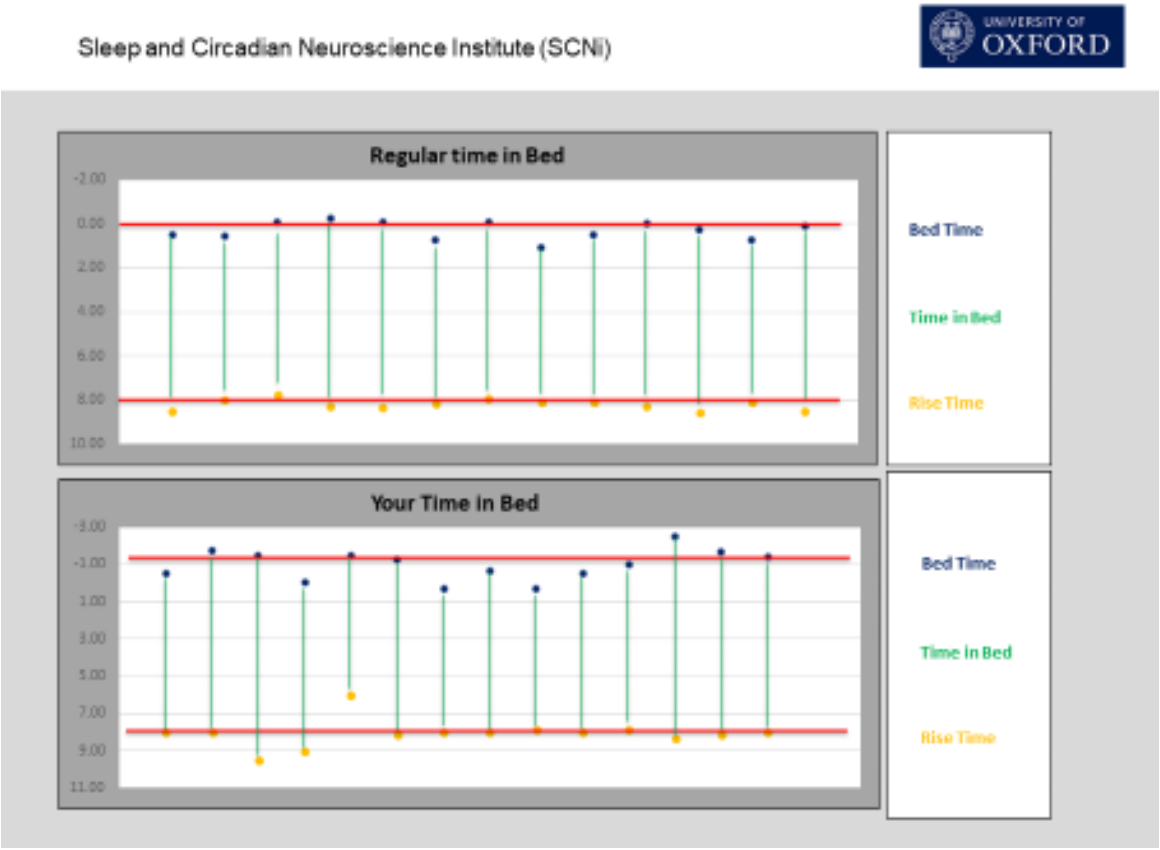
I'm suggesting that getting started on sorting your insomnia problem could be about taking the raw material that you have – all the bits of sleep that at the moment add up to xxx – and shaping them into a single block of xxx – like creating a picture rather than being frustrated by a broken jigsaw. We call this picture your "sleep window". It's the size of the frame that we need to fit all the pieces in tightly, snugly … Now I know that xxxx is probably not the answer to the question about how much sleep you need … but we do know how much sleep you are getting on average at the moment … and it seems to be xxx. This is our starting point for your sleep window. It's a way of leaving no space for your difficulties getting to sleep and your difficulties staying asleep – all that wakeful time gets squeezed out - because your sleep gets knitted back together again and is held tightly in the sleep window frame. Now you may be getting a bit worried, but let me quickly reassure you that we will be in a much stronger position to build up your total sleep time – to increase it, to the amount of sleep you actually need, if we start with your sleep in a block like this rather than fragmented into bits and pieces. These fragments of sleep are not going to knit themselves back together, we are going to have to push them into place … but once we have done that there is the best chance of growth.



Slide 9:

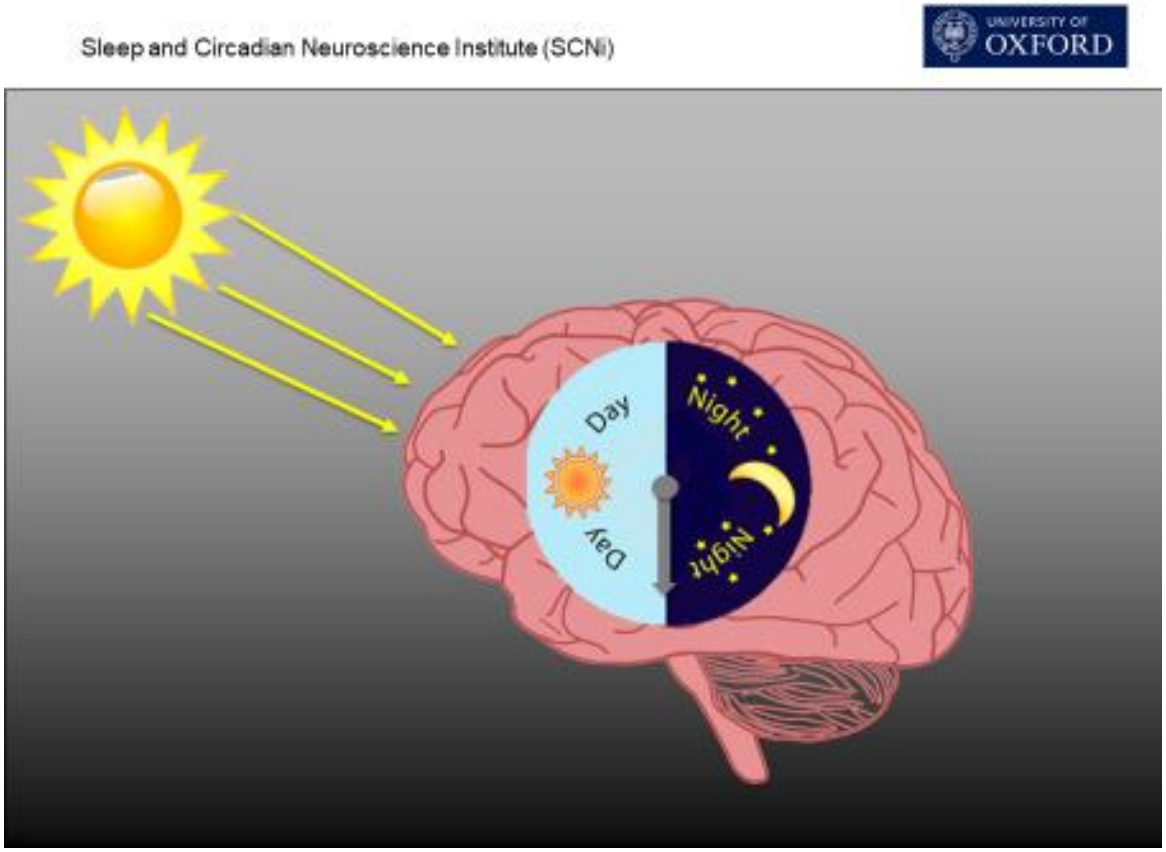
This is why a shorter time-in-bed option can give you a better sleep quality.

The quality of your sleep will get better because of something we call "sleep drive". Sleep drive is a homeostatic process that we build up during the day, as soon as we wake up in the morning. The process is simple, the longer we are awake, the more sleep drive we have, and the more sleep drive we have, the deeper our sleep will be once we go to bed. Once we fall asleep our sleep drive declines and the whole process starts again once we've woken up. Now, if I ask you to stay up longer than normally, your sleep drive will continue to rise even higher and therefore promote good, solid and deep sleep. It might seem odd that you have to sleep less to solve your sleep problems, and it might also seem really hard to suffer from even more sleep loss. But if you think about muscle training, you need weights that are hard to lift to build up your muscles. Or if you want to build immunity, you expose your body to certain germs, rather than obsessively keeping it clean. So, it figures that by reducing your "sleep time", you're raising the stakes, giving your powers of sleep a real challenge, which brings out the best in them. (By contrast, responding to insomnia by increasing time in bed lowers the stakes: it becomes less important that you're asleep for any given hour you're trying). What do you think, what happens to the sleep pressure if you take a daytime nap?



Slide 10:

A second problem that comes with insomnia is that sleep is likely to be upset in a way that makes each night different. In this graph here on the top you can see a regular sleep pattern. The blue dots show the time the person went to bed every day and the yellow dots indicate when the person was getting out of bed. The green line in between gives information about how much time was spent in bed. You can see that this pattern is regular as the blue dots are aligned around midnight and the yellow dots around 8AM. This means the person got about 8 hours of sleep for the 13 days that where recorded. The graph on the bottom shows your sleep pattern, I plotted the data that you reported in your sleep diary for the last XX days. As you see there is a lot of day-to-day variability, neither the blue dots, nor the yellow dots are aligned and the green connection lines show different length. In the top graph, all the dots are nicely aligned close to the red line at 8am in the morning and at midnight. If I compare your bed and rise time, you can see, that some of the blue and yellow dots are quite distant from the red line. This is where you have room for improvement. If we can reduce the variability of your bedtimes you will have the chance to see improvements in your sleep problems.



Slide 11:

An irregular sleep schedule is problematic as it challenges our internal clock to align with the local clock. Our internal clock is in our brain and receives information about the local clock through light receptors in our eyes. This means, as soon as our eyes detect light, our brain knows it's time to wake up and a number of alerting processes are getting promoted. When the light level decreases at the start of the night, the clock in our brain is signalling that it's night-time. If we are exposed to light at different times every day, say because some days we stay up really late and other days, we sleep-in really long, this confuses the system and our internal clock cannot reliably promote sleep and wakefulness. Unfortunately, compensating for sleep loss by sleeping in or going to bed early is a frequently encountered factor that maintains chronic insomnia. As a result, we might lay in bed awake at night trying to sleep while our internal clock think that it's time to be awake.

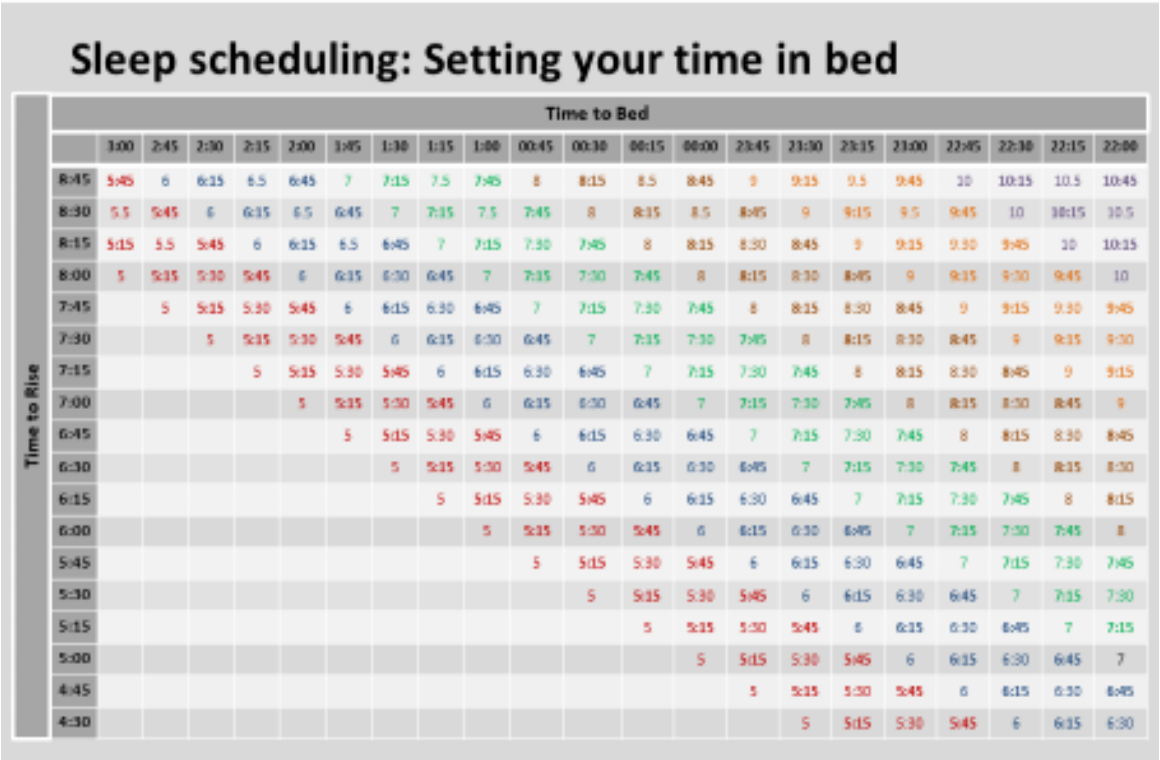


Slide 12:

Now the other thing, that we have already mentioned is that as well as having unbroken sleep, good sleepers have a consistent sleep from night to night. If we establish your starting off sleep window as xxxx, we can plan to make this the same every night – just like these septuplets, pretty … and pretty much the same!! Although this might be quite a challenging idea - It is best to have a set pattern, seven nights a week, until you get your sleep problem sorted. Let's think then about how that can be achieved in practice.

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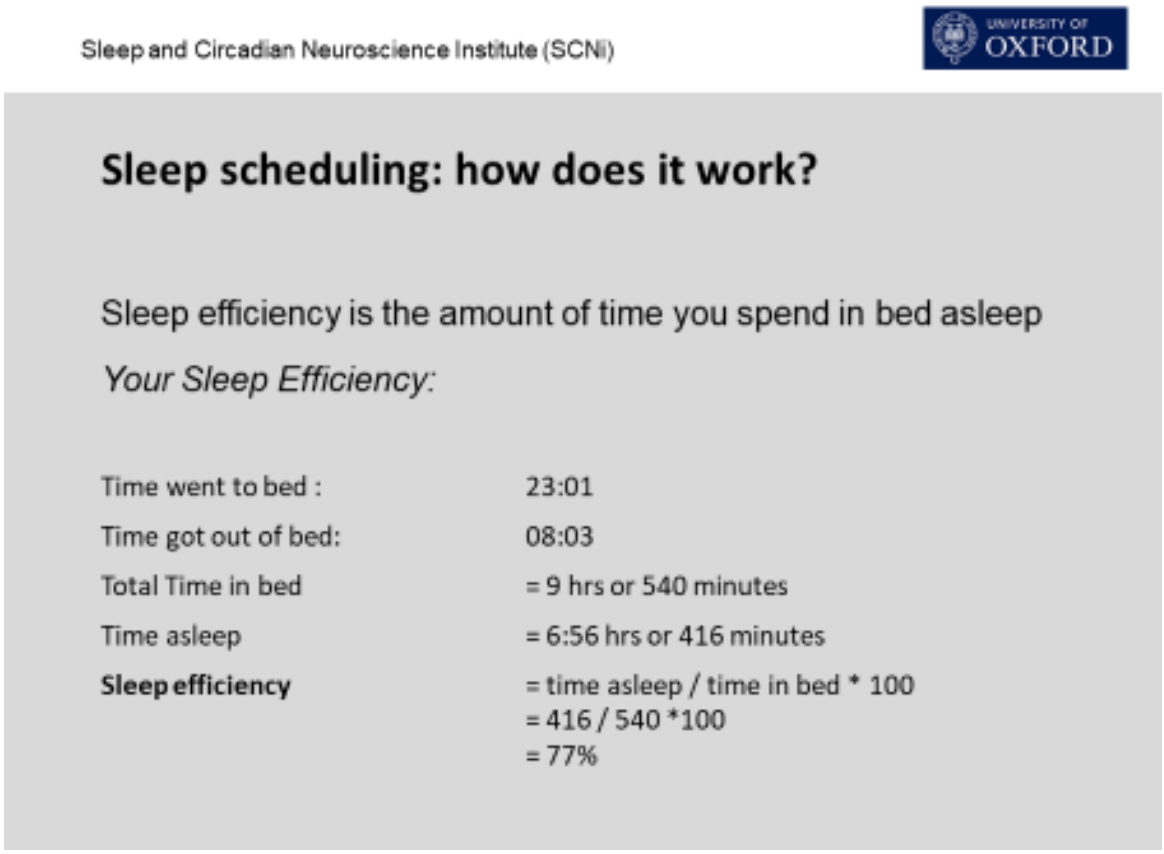


Sleep scheduling: Setting your time in bed

Time to Rise	Time to Bed																			
	3:00	2:45	2:30	2:15	2:00	1:45	1:30	1:15	1:00	00:45	00:30	00:15	00:00	23:45	23:30	23:15	23:00	22:45	22:30	22:15	22:00
8:45	5:45	6	6:15	6:5	6:45	7	7:15	7:5	7:45	8	8:15	8:5	8:45	9	9:15	9:5	9:45	10	10:15	10:5	10:45
8:30	5:5	5:45	6	6:15	6:5	6:45	7	7:15	7:5	7:45	8	8:15	8:5	8:45	9	9:15	9:5	9:45	10	10:15	10:5
8:15	5:15	5:5	5:45	6	6:15	6:5	6:45	7	7:15	7:30	7:45	8	8:15	8:30	8:45	9	9:15	9:30	9:45	10	10:15
8:00	5	5:15	5:30	5:45	6	6:15	6:30	6:45	7	7:15	7:30	7:45	8	8:15	8:30	8:45	9	9:15	9:30	9:45	10
7:45		5	5:15	5:30	5:45	6	6:15	6:30	6:45	7	7:15	7:30	7:45	8	8:15	8:30	8:45	9	9:15	9:30	9:45
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6:45						5	5:15	5:30	5:45	6	6:15	6:30	6:45	7	7:15	7:30	7:45	8	8:15	8:30	8:45
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4:45														5	5:15	5:30	5:45	6	6:15	6:30	6:45
4:30															5	5:15	5:30	5:45	6	6:15	6:30

Slide 13:

So, let's try to find out more about what your sleep window could look. We want to work out a way of achieving the same amount of sleep every night. Remember we should be aiming for a sleep pattern that you can rely upon – that is, one that is stable and does not vary much from night to night, and one that allows you to sleep right through. To set your new, regular time in bed we should anchor your sleep around a fixed morning rising time. This anchoring is to stop your sleep from drifting and to help it to settle down to a reliable pattern. To do this, you should now choose a time in the morning that you will rise from bed. The time you choose is up to you, but it should be a time that you are comfortable with and that allows you to do all the things you need to do during the day. Can you pick a time you would be willing to set your alarm 7 days per week? Here are your options to the nearest 15 minutes. Now we have both, your average sleep time (of xxxx) and your fixed morning rising time that you just selected (xxxx), but when should you go to bed? You can work this out from the table by reading across from your fixed rising time and reaching the value of your total sleep. Reading up will show you what we call your 'threshold time' for going to bed. This is to mark the point at which you can cross the threshold from waking to sleeping. It is - as you can see - worked out by subtracting your average sleep time from your fixed morning rising time. Your threshold time is not your actual bedtime. Your time for going to bed must always be at, or after, the threshold time. Your threshold time is the earliest you can go to bed, but you should always wait until you feel 'sleepy tired'. In other words, once you reach that threshold time, you can go to bed as long as you feel sleepy, and not just because it's a certain time. You will see that the table gives you a bit of flexibility. If you stick to the same average sleep time you can adjust your rising time to earlier or later and this affects when your threshold time would be. Ok have you established the best threshold time for you. Great. I'm going to write down the times you have decided on right here – your fixed rising time and your threshold time.



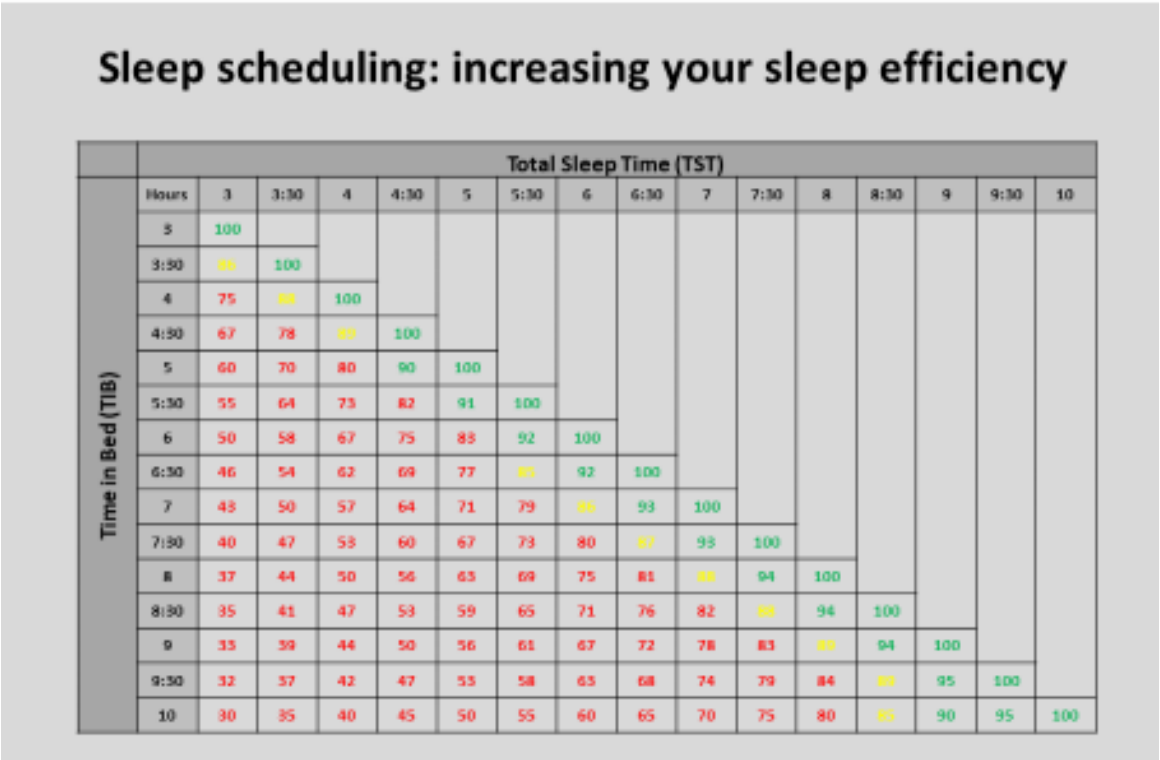
Slide 14:

It is important that you understand what lies behind sleep scheduling as well as what to do, so I will do my best to explain as we go along. Don't worry if you find that some of this is quite complex. Most people do. Let me explain a bit about sleep efficiency. Sleep efficiency is simply the percentage of time you spend in bed sleeping. If you slept right through from the moment your head hits the pillow until the moment your clock went off you would be sleeping 100% of the night.

In your example it looks like this: You are going to bed at XX:XX p.m. and waking up at XX:XX am. You spend about XX hours in bed but you are only sleeping for XX hours because you might struggle to fall asleep or you are waking up during the night. To calculate your sleep efficiency we divide the time asleep by the time in bed and multiply it by 100. This gives you a sleep efficiency of only XX%. The sleep scheduling programme that we have now agreed will give you the chance to get towards 100%, at least some nights. So sleep scheduling works by making your sleep efficient, just like a good sleeper. Let's try the example in your worksheet by using information from a day of your sleep diary.

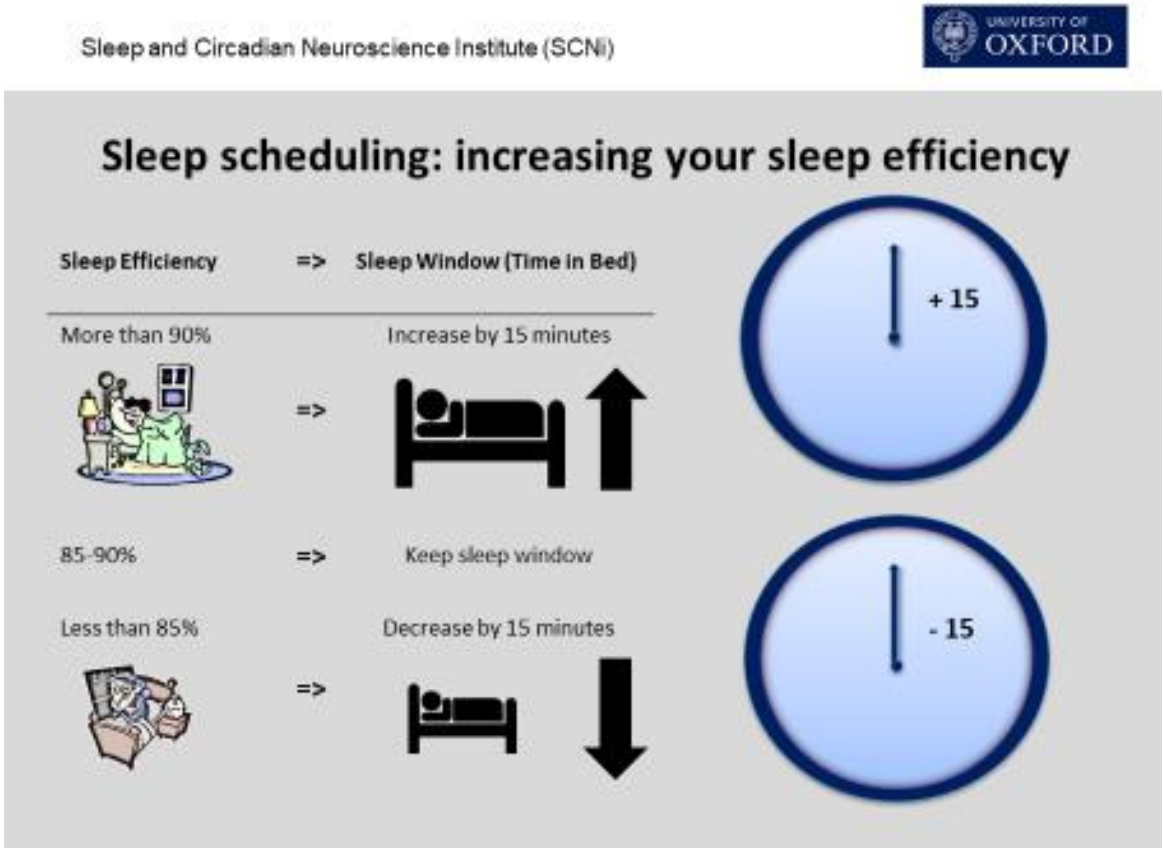
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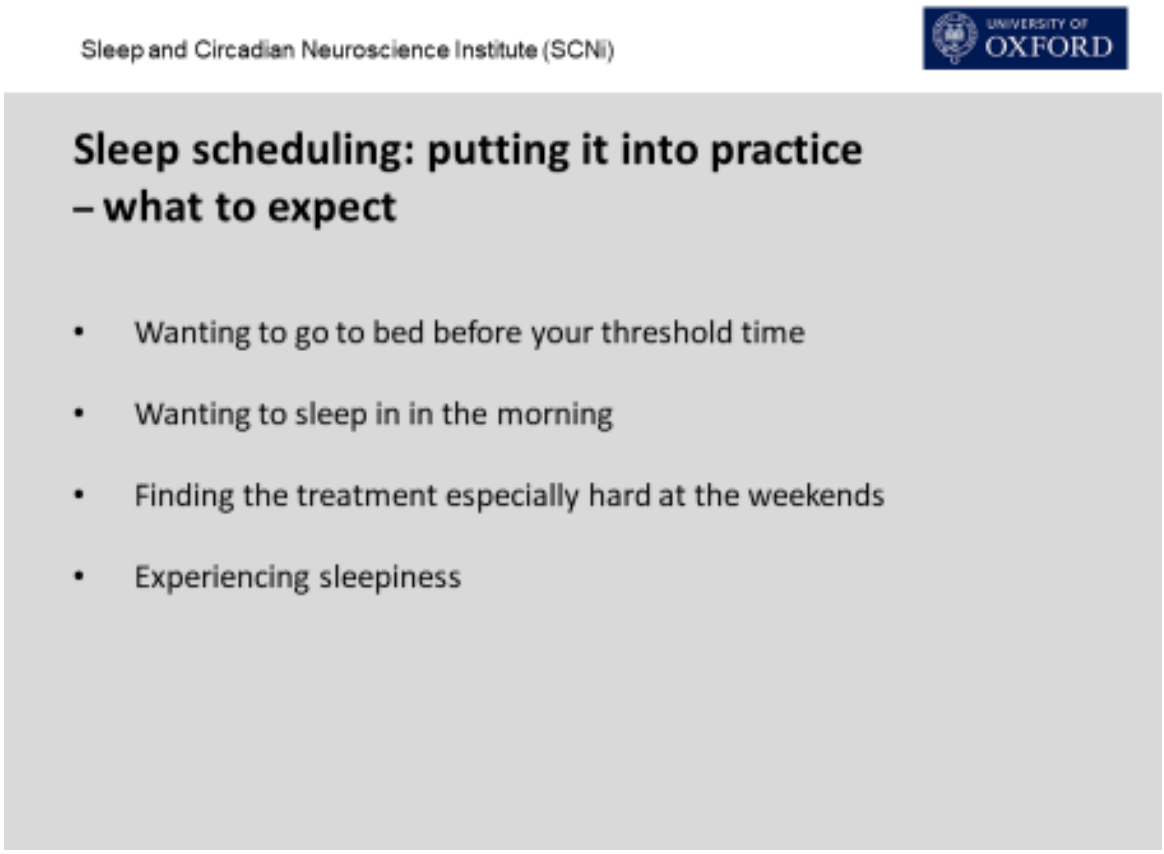
Slide 15:

In practice, I want to help you to increase your sleep efficiency to more than 90%. We can check in this table here what your sleep efficiency looks like for your last two weeks. You have been spending this amount of time in bed and getting this amount of sleep, so that equals xx% as we have just worked out, and you are in the red/ yellow zone – so that is not so good. For the upcoming week the plan is for you to keep your sleep window as we have discussed, with a rising time here and a threshold time here. This will help you to sleep right through and take you into the green zone. Instead of having bits and pieces of sleep, we will see it all squashed together and then we can let it grow bigger, hopefully to the amount you would like, or at least to the amount you need.



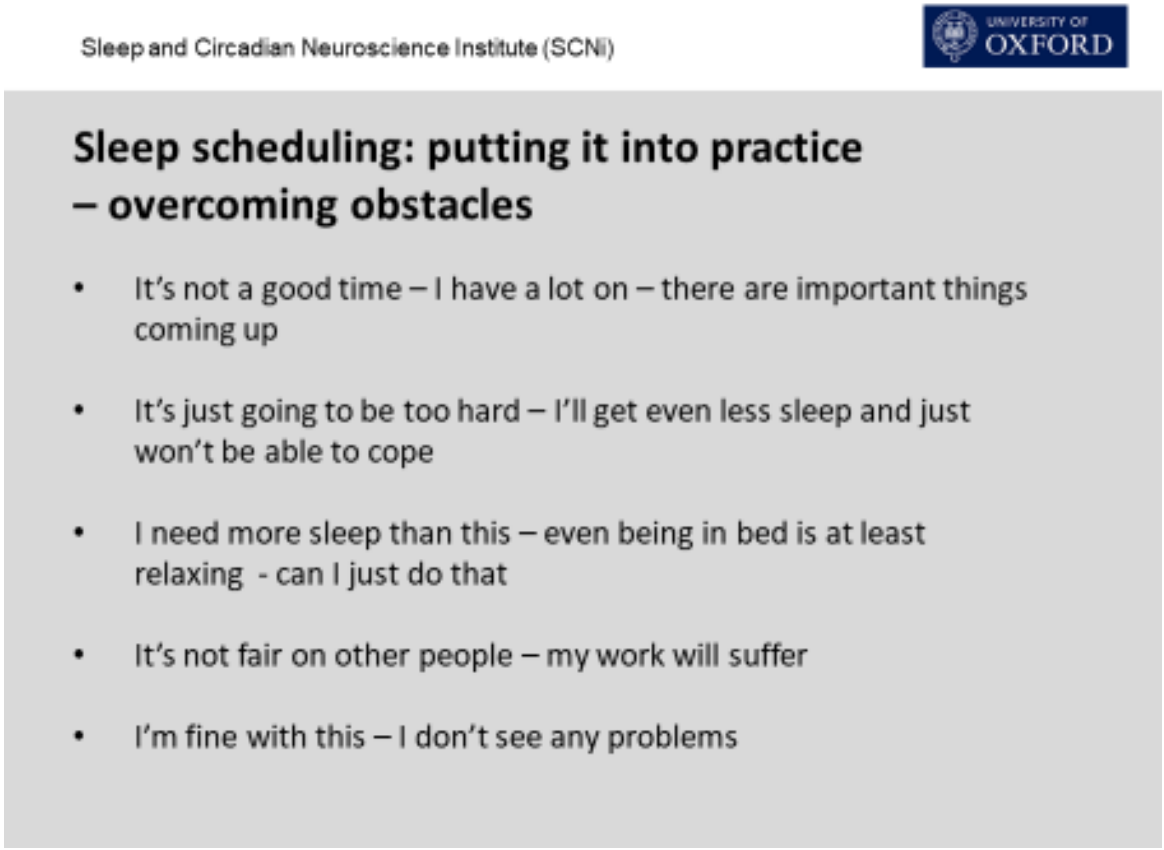
Slide 16:

In the next weeks our guide here, again, is your sleep efficiency. Once you are sleeping 90% of the time you are in bed (threshold time to time you rise) for one full week, we will increase your sleep window by 15 minutes for the next week, by either going to bed 15 minutes earlier or staying in bed 15 minutes later in the morning. If your sleep efficiency is in between 85 and 90% we will keep your sleep window from the previous week. If your sleep efficiency has not reached 90 percent but you are already restricted to 5 hours in bed, we will also keep your sleep window. We will use our telephone calls to make these changes and to discuss how you are getting on putting the program into practice. So, each time we check in, we will see if you have made it to 90% and we can keep adjusting the sleep window. After trying that out for another week, we will check again to see if you still make it to 90%. All the while as your sleep is improving we want to keep you in that healthy green zone. Does all this make sense?



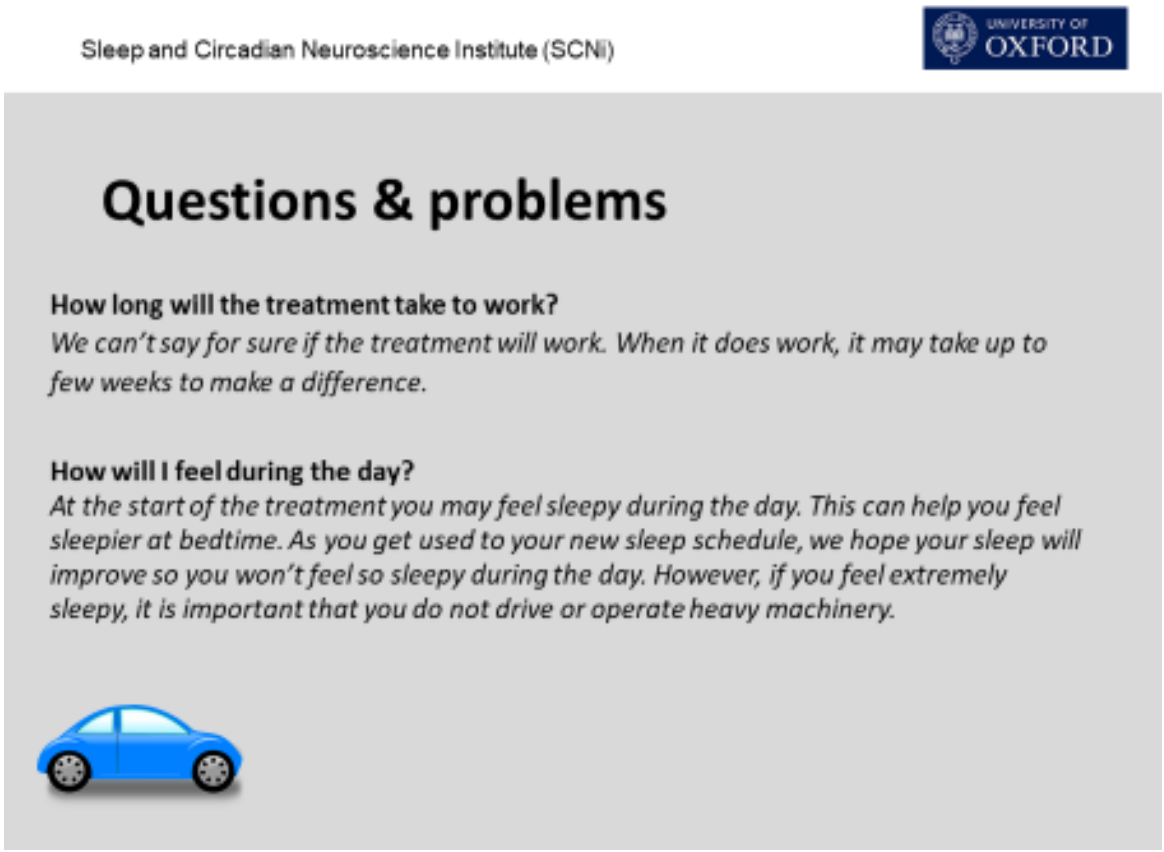
Slide 17:

To get your schedule settled I want you to stick to the bed and rise time we decided on for the next week. It is likely that during this week you will feel that it is very early to get up in the morning, or that it seems very late to stay up until your threshold time. Especially on the weekend it might be tempting to sleep in. You're facing quite a challenge getting your sleep pattern sorted out, and it's going to take a seven-nights-a-week treatment to do it. Your threshold time and your rising time are meant for every day of the week. You may also have some side-effects from the treatment, especially feeling sleepy. Most people find that experience comforting – because they are desperate for more sleep and begin to feel that they can sleep.



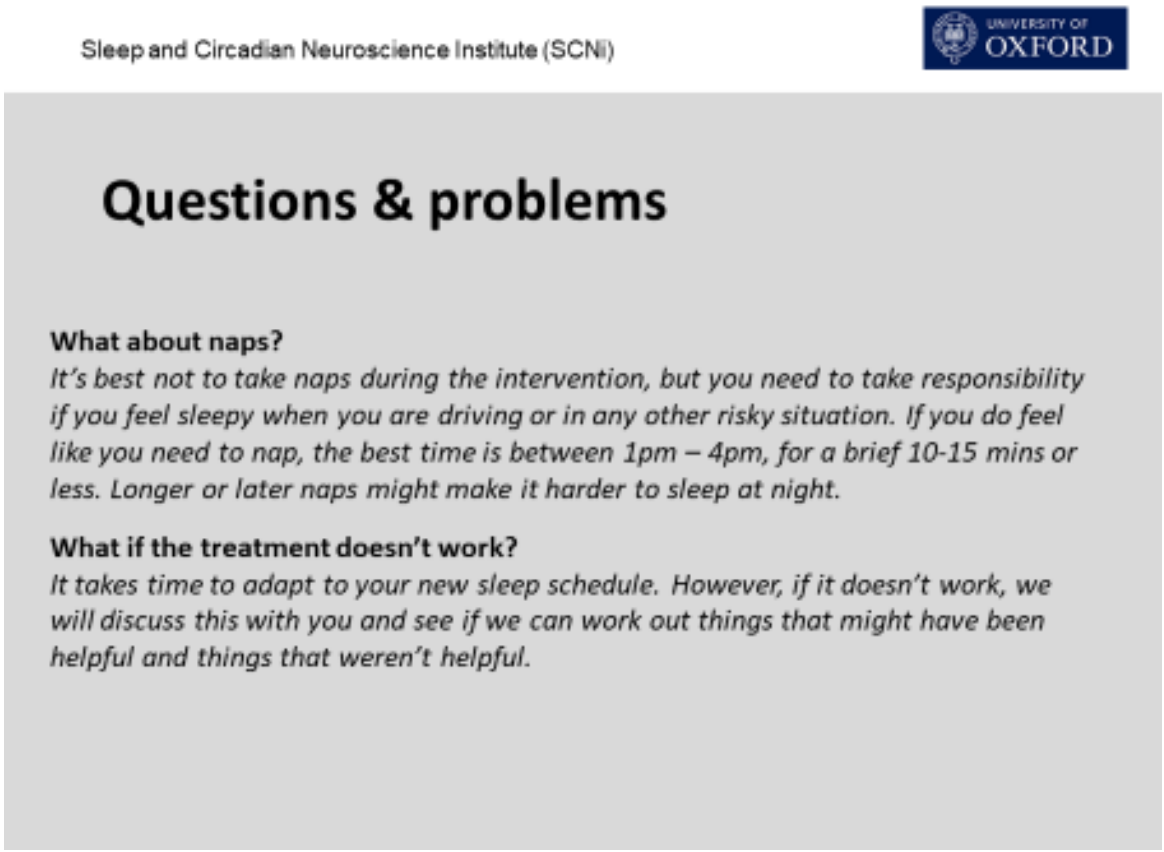
Slide 18:

Do you think the sleep scheduling treatment is something you could commit to for the next week? Most people say that they are willing to give it a go, even if they are apprehensive or unsure it will work for them. In our experience though it works best if people are well prepared. I have mentioned things to expect, but here are some common barriers to putting sleep scheduling into practice. Let's think about these and how to overcome them. It's not a good time – I have a lot on – there are important things coming up. This can just be procrastination. You might never have a better opportunity to sort your sleep. Besides your insomnia is badly affecting you and that's why you are here. Often people make a very quick response to sleep scheduling. You won't know until you have tried it. In my experience, when people put things off until later they never get them done. It's just going to be too hard – I'll get even less sleep and just won't be able to cope. This is a very common concern and sometimes leads to people not putting the programme into practice. They cut the corners and then it doesn't work so well. If I could give you a pill that would sort your insomnia for good and you only had to use it for a few weeks would you take it if it had some side effects? Or if I said there's a minor surgical operation that would work, would you elect for surgery. Think of it like this – it isn't easy, but you've had this problem quite a while, and this treatment works for most people. I need more sleep than this – even being in bed is at least relaxing - can I just do that. Of course, that is the plan, to get you more sleep. Lying awake in bed is part of the problem and it hasn't worked so far. The initial curtailment of your time in bed is a crucial first step in a gradual, multistep process. Your sleep window will be expanded slowly as sleep becomes more consolidated and we find out how much sleep you need. It's not fair on other people – my work will suffer. Most people with insomnia complain that their poor sleep is having negative consequences on their energy, their mood, their concentration, productivity and relationships. All good reasons to overcome the insomnia and not very good reasons to walk away from treatment. Even if there is short term pain the gains will be there sooner than you might imagine. I'm fine with this – I don't see any problems. Great! But often when people are super-positive it's because they haven't thought through some of the challenges that they might face. It's important to anticipate and be ready for what those might be. Do you have any other concerns that we should discuss?



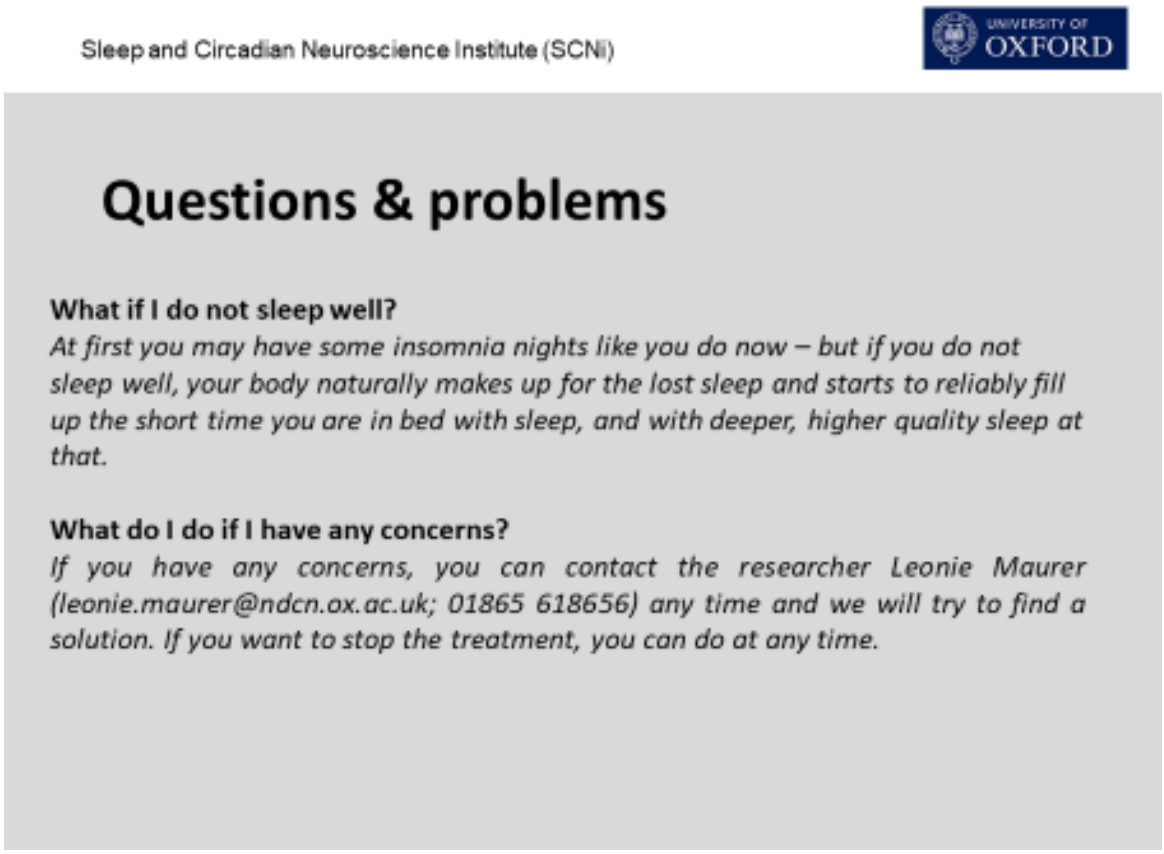
Slide 19:

OK. Establishing these new routines is not going to be easy. So, before we round off I just want to take a bit more time to think over some other common questions that crop up. How long will the treatment take to work? We can't say for sure if the treatment will work. When it does work, it may take up too few weeks to make a difference. How will I feel during the day? At the start of the treatment you may feel sleepy during the day. This can help you feel sleepier at bedtime. As you get used to your new sleep schedule, we hope your sleep will improve so you won't feel so sleepy during the day.



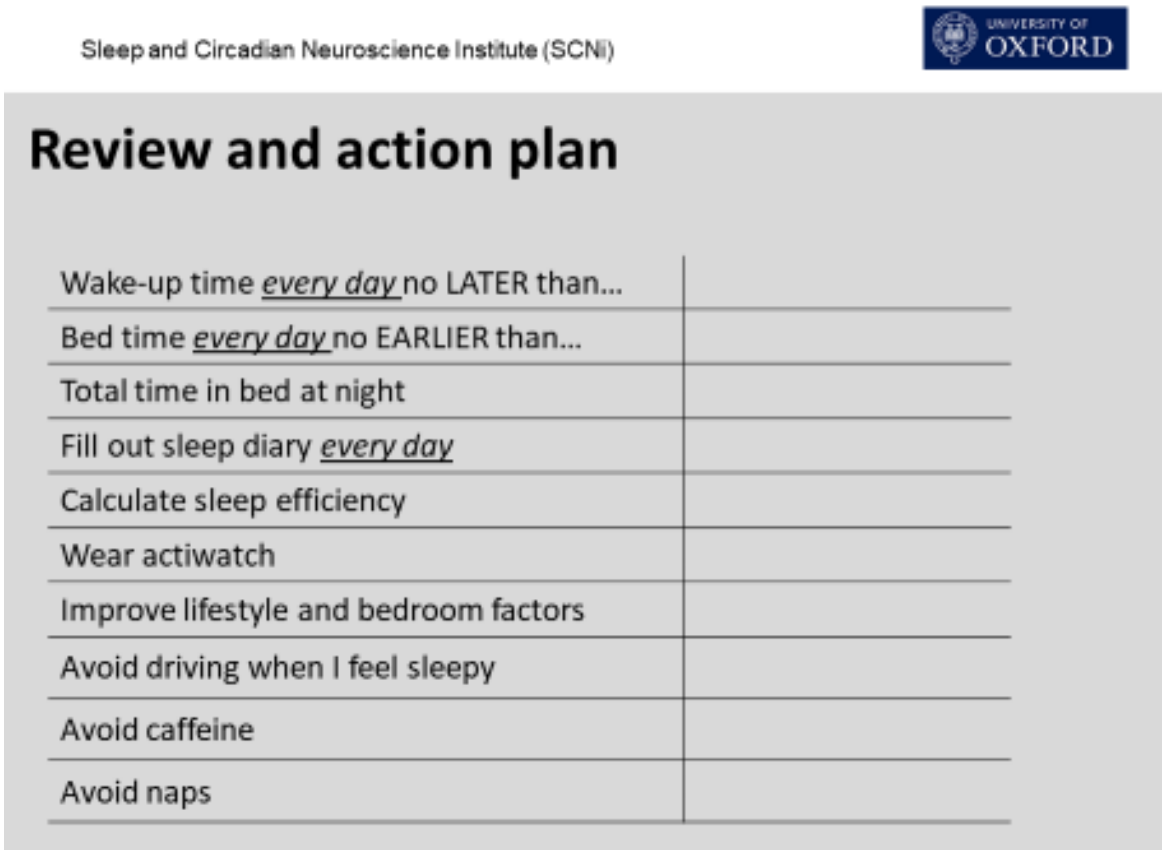
Slide 20:

What about naps? It's best not to take naps during the intervention, but you need to take responsibility if you feel sleepy when you are driving or in any other risky situation. If you do feel like you need to nap, the best time is between 1pm – 4pm, for a brief 10-15 mins or less. Longer or later naps might make it harder to sleep at night. What if the treatment doesn't work? It takes time to adapt to your new sleep schedule. However, if it doesn't work, we will discuss this with you and see if we can work out things that might have been helpful and things that weren't helpful.



Slide 21:

What if the treatment doesn't work? It takes time to adapt to your new sleep schedule. However, if it doesn't work, we will discuss this with you and see if we can work out things that might have been helpful and things that weren't helpful. What if I do not sleep well? At first you may have some insomnia nights like you do know – but if you do not sleep well, your body naturally makes up for the lost sleep and starts to reliably fill up the short time you are in bed with sleep, and with deeper, higher quality sleep at that. What do I do if I want to stop the treatment? If you have any concerns, you can contact me any time and we will try to find a solution. If you want to stop the treatment, you can do at any time.



Slide22:

OK so let's summarise what your personal plan of action is for the next week: You can find this plan on page 10 of your workbook. Let's fill it in and check all the factors you're going to address.

Go to bed every day no earlier than your threshold time of ….

Wake-up every day no later than …

Follow this schedule every night

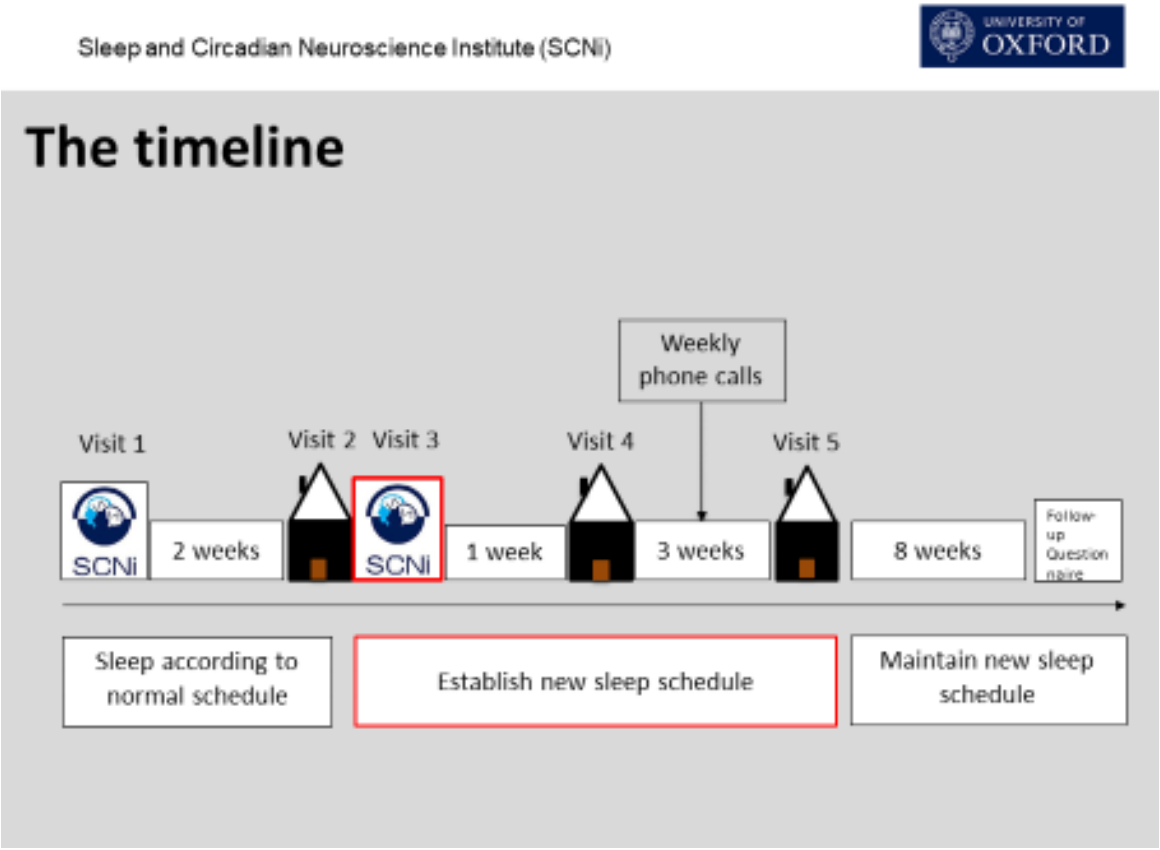
Remember what to expect in terms of experiences and symptoms

Work to overcome any obstacles to putting the programme into action

Address any lifestyle or bedroom factors that are important

And of course, continue to fill out your sleep diary each morning, and your bedtime consistency checklist and continue to wear your actiwatch.

Let me know if there are any problems



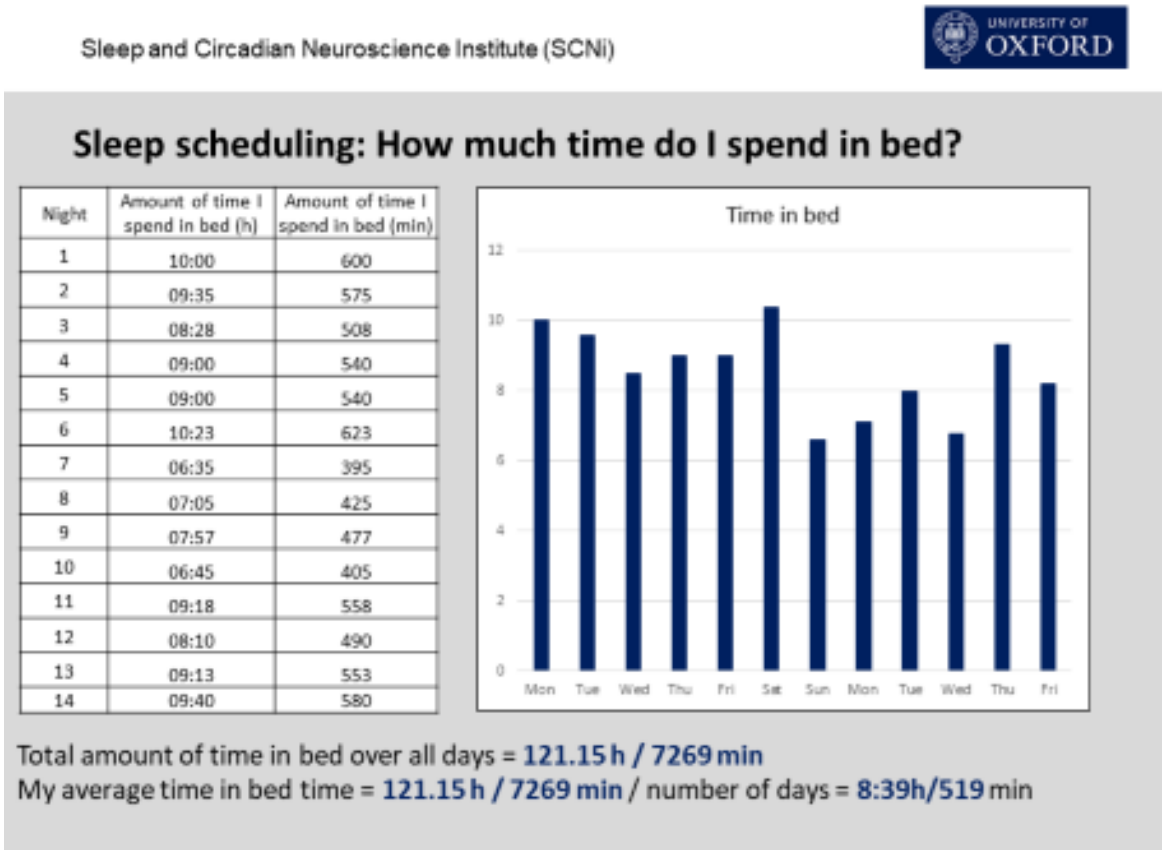
Slide 23:

This is our timeline again. We will check your sleep efficiency in one week, at our second overnight sleep recording and go together through your sleep diary. In the following 3 weeks after the sleep recording, we will have weekly phone calls to see how you are getting on with your new sleep schedule. We will then go through you checklist and your sleep diary on the phone.

Do you have any questions?

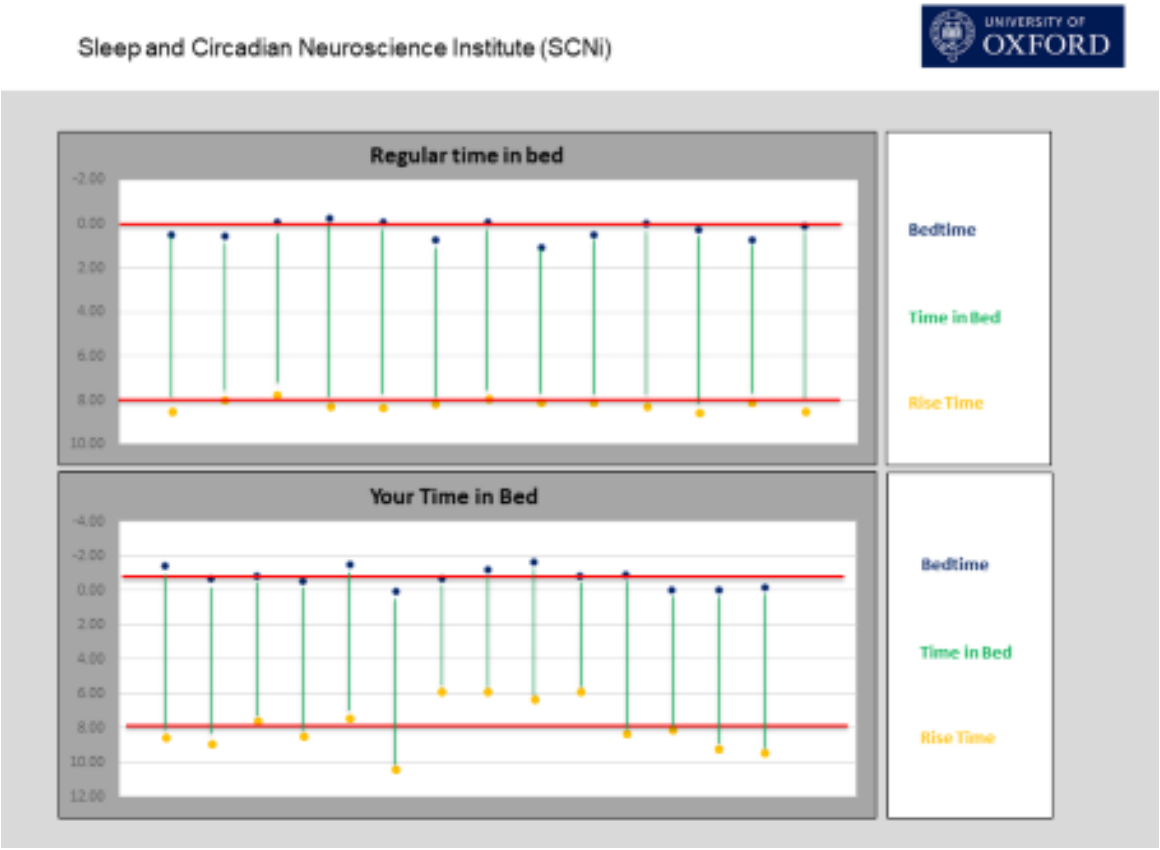
Bedtime consistency therapy

Bedtime consistency therapy applied the same slides for the beginning and the end of the treatment session. This means that slides 1-4 and slides 17-23 (here 13-19), with slight modifications for slide 2 and 22, were duplicated. The 'core' slides of BCT are summarised below. Note that some of those slides are also duplicates of slides used for SRT but were applied in a different order or focused on a different aspect.



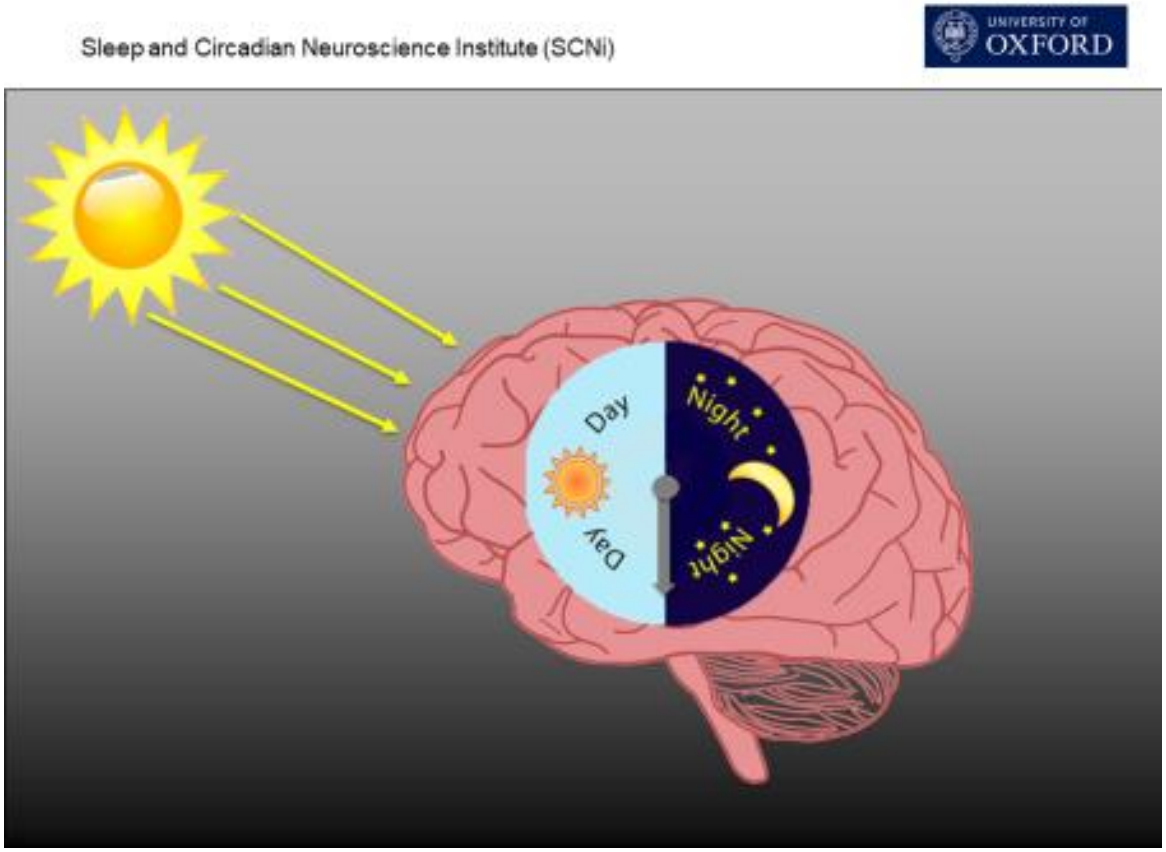
Slide 5:

OK, so now that we have covered lifestyle and bedroom factors, the next thing is to take a good look at your sleep pattern itself and see how we can improve it. Once we understand your sleep pattern we can then develop a strategy to re-set it, so that it quickly begins to follow a healthier schedule. The purpose of sleep scheduling is to reshape your sleep into a strong pattern that will last. The obvious place to start then is to ask the questions … how does you sleep pattern look like right now? The best way to find out is to have a look at the information we already have in your sleep diary. You will see here that I have taken the information on the amount of time that you have spent in bed each night and put it into this table. As you can see it varies from night to night. I have also calculated your average time in bed, if I add all the time in bed together and divide it by the number of days, it comes to XXX.



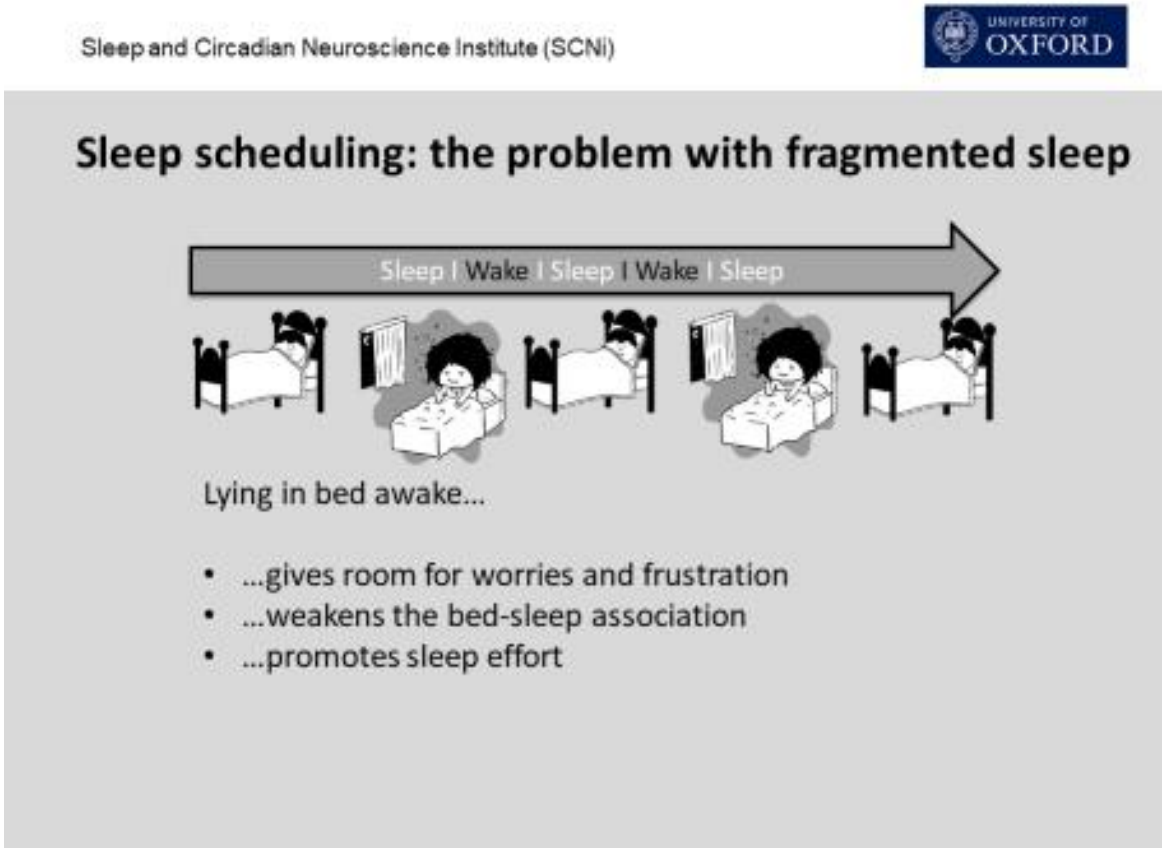
Slide 6:

A particular problem with insomnia is that sleep is likely to be upset in a way that makes each night different. In this graph here on the top you can see a regular sleep pattern. The blue dots show the time the person went to bed every day and the yellow dots indicate when the person was getting out of bed. The green line in between gives information about how much time was spent in bed. You can see that this pattern is regular as the blue dots are aligned around midnight and the yellow dots around 8AM. This means the person got about 8 hours of sleep for the 13 days that where recorded. The graph on the bottom shows your sleep pattern, I plotted the data that you reported in your sleep diary for the last XX days. As you see there is a lot of day-to-day variability, neither the blue dots, nor the yellow dots are aligned, and the green connection lines show different length. In the top graph, all the dots are nicely aligned close to the red line at 8am in the morning and at midnight. If I compare your bed and rise time, you can see, that some of the blue and yellow dots are quite distant from the red line. This is where you have room for improvement. If we can reduce the variability of your bedtimes you will have the chance to see improvements in your sleep problems.



Slide 7:

An irregular sleep schedule is problematic as it challenges our internal clock to align with the local clock. Our internal clock is in our brain and receives information about the local clock through light receptors in our eyes. This means, as soon as our eyes detect light, our brain knows it's time to wake up and a number of alerting processes are getting promoted. When the light level decreases at the start of the night, the clock in our brain is signalling that it's night-time. If we are exposed to light at different times every day, say because some days we stay up really late and other days we sleep-in really long, this confuses the system and our internal clock cannot reliably promote sleep and wakefulness. Unfortunately, compensating for sleep loss by sleeping in or going to bed early is a frequently encountered factor that maintains chronic insomnia. As a result we might lay in bed awake at night trying to sleep while our internal clock think that it's time to be awake.



Slide 8:

Spending time awake in bed is problematic as it gives you time to worry about your sleep and other things that are in your mind. It also weakens your bed-sleep association, as you may start connecting your bed with tossing and turning. A lot of people might also start to put effort into trying to fall asleep while they are lying in bed awake. Unfortunately, this makes them even more alert and lowers the chances for sleep to come naturally. This is why a regular time-in-bed option can give you a better sleep quality. If your body clock strengthened your sleep will feel more substantial. Let's try to find out how we can you strengthen your body clock.



Slide 9:

For your internal clock it is really important to get a regular sleep as it comes with regular light inputs. I therefore suggest that we establish now a new sleep window for you that we can plan to make you get the same sleep every night – just like these septuplets, pretty … and pretty much the same!! Although this might be quite a challenging idea - It is best to have a set pattern, seven nights a week, until you get your sleep problem sorted. Let's think then about how that can be achieved in practice.

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Getting started: What are your daily bed times?

Night	Bedtime	Rise time	Time in Bed
1	22:35	08:35	10:00
2	23:20	08:55	09:35
3	23:10	07:38	08:28
4	23:30	08:30	09:00
5	22:30	07:30	09:00
6	00:05	10:28	10:23
7	23:20	05:55	06:35
8	22:50	05:55	07:05
9	22:23	06:20	07:57
10	23:10	05:55	06:45
11	23:05	08:23	09:18
12	00:00	08:10	08:10
13	00:00	09:13	09:13
14	23:50	09:30	09:40
Average	23:16	07:55	08:39

Slide 10:

Anchoring wake time is the foundation of a good sleep. The plan is to keep a fixed wake time in the morning and a fixed bedtime in the evening to strengthen the signal from the circadian pacemaker.

Let's look together at a summary of your sleep diary. You can see the times when you get out of bed and when you went to bed. On average you went to bed at around ……pm and you were getting out of bed at around ….am.

As we have discussed earlier, you can also see how much time you spend in bed each night and the average amount of time in bed for the last week. On average you go to bed at …. And you rise from bed at….. On average……hours and ……minutes.

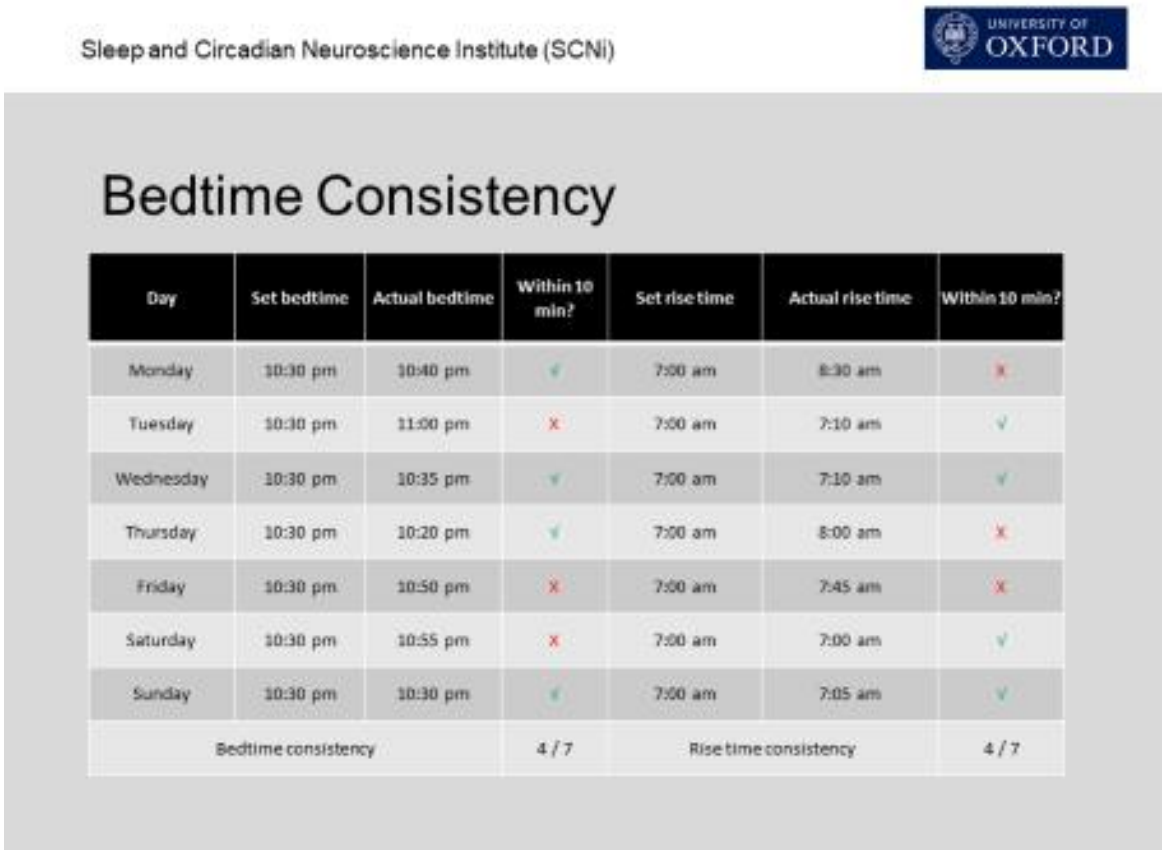
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Slide 11:

To set your new, regular time in bed we should anchor your sleep around a fixed morning rising time. This anchoring is to stop your sleep from drifting and to help it to settle down to a reliable pattern. To do this, you should now choose a time in the morning that you will rise from bed. The time you choose is up to you, but it should be a time that you are comfortable with and that allows you to do all the things you need to do during the day. Can you pick a time you would be willing to set your alarm 7 days per week? Now we have both your average time in bed and your fixed morning rising time, but when should you go to bed? It is worked out by subtracting your average time in bed from your morning rising time. We can use the table here to find out your bedtime.



Slide 12:

A good bedtime consistency can be achieved if you try to not deviate more than 10 minutes from your bed and rise time, however this can be variable even in a good sleeper. A checklist can help you to keep track of your bedtime consistency like you can see in the following example. The person's bedtime in this example here was set to 10:30 pm and the set rise time was set to 7 am. You can find this checklist in your workbook on page XXX. We can go through it together and fill in your set bedtime and rise time for the next week. In the following week I want you to fill in your actual bedtime and rise time for every day. You can do this in the morning after you filled in your sleep diary and check if you managed your times within 10 minutes.

Let's have a look again at the bed and rise times that you reported for the last week and fill out the example you have in your treatment manual. If we compare it to the bed and rise times you just set, you can see that your bedtime consistency is not good right now, only XX out of 7 for rise time and XX out of 7 for bedtime. For the next four weeks your goal should be to reach a 7/7 for both, your bedtime and your rise time consistency.

Appendix D: Treatment leaflet

1. Sleep Restriction Therapy

Maintaining an un-fragmented sleep pattern (weeks 5-12)

You have had sleep problems for a long time now and, although it can take some time for things to begin to get better, we hope that you may already have seen some improvement in your sleep! At the moment though it is more important to get encouragement from your success in following the treatment, than from your success in sleeping. That will come if you persevere!! So far, we have established a new sleep schedule that fits your sleep needs. Now it is up to you to maintain your schedule and make lasting changes to your sleep.

You will get most benefit if you put the next three steps into action and continue to follow advice that we have discussed during our previous sessions.

Step 1: Continue to stick to your set sleep schedule as closely as possible, **7 days a week.**

Review your sleep each week and remember the following rules: If your sleep efficiency (see manual) is 90% or above increase your Time in Bed by 15 minutes. If your sleep efficiency is below 85%, your sleep window should be decreased by 15 minutes. If your sleep efficiency falls between 85 and 90% then we recommend that you maintain your current Time in Bed. We will provide you with sheets to help with these weekly calculations.

You should continue to adjust your time in bed until you are sleeping better at night and feeling better during the day. But remember that these adjustments should be gradual so that your new pattern becomes ingrained (a bit like a habit) over time. You may find that, after a point, increasing your time in bed does not lead to any additional sleep during the night, and when this happens can vary from individual to individual. Keeping a consistent bed and rise-time and your desired time in bed will lead to a strong and stable sleep pattern.

Step 2: Avoid napping. This will decrease night-time sleep drive, making it harder to fall asleep and stay asleep throughout the night.

Step 3: Practice good sleep hygiene. Do not drink too much coffee or tea and only have a light snack for supper. Do not drink alcohol to aid your sleep – it usually upsets sleep. Make sure your bed and bedroom are comfortable – not too cold, not too warm, and not too noisy or bright. Keep the room well aired.

A Cautionary Note: It is suggested that you do not spend less than 5 hours in bed, regardless of how long you think you sleep, to limit the impact on your daytime functioning.

GOOD LUCK!

2. Bedtime Consistency Therapy

Maintaining a regular sleep pattern (weeks 5-12)

You have had sleep problems for a long time now and, although it can take some time for things to begin to get better, we hope that you may already have seen some improvement in your sleep! At the moment though it is more important to get encouragement from your success in following the treatment, than from your success in sleeping. That will come if you persevere!! So far, we have established a new sleep schedule that helps your sleep to come reliably. Now it is up to you to maintain your schedule and make lasting changes to your sleep.

You will get most benefit if you put the next three steps into action and continue to follow advice that we have discussed during our previous sessions.

Step 1: Stick to your regular sleep schedule as closely as possible and follow your schedule **7 days a week**.

Occasionally giving in to the temptation to sleep in beyond your risetime or going to bed earlier than your planned bedtime can weaken the body clock signal and offset the benefits that you may have experienced thus far. A good bedtime consistency can be achieved if you try to not deviate more than 10 minutes from your bed and rise time. A checklist for each day during a week can help you to keep track of your bedtime consistency. Your aim should be to get a 7 out of 7 for both bedtime and rise time consistency.

Step 2: Avoid napping.

Step 3: Practice good sleep hygiene. Do not drink too much coffee or tea and only have a light snack for supper. Do not drink alcohol to aid your sleep - it usually upsets sleep. Make sure your bed and bedroom are comfortable - not too cold, not too warm, and not too noisy or bright. Keep the room well aired.

GOOD LUCK

Appendix E: Treatment fidelity checklists

Checklist SRT

Give two points for each bullet point that was covered. Give one point for a point that was mentioned but not covered. Give zero points if neither mentioned nor covered.

Participant ID:		Date:	
Slide	Topic	Score:	Comments
1	The Timeline: - Overnight assessments - Follow sleep schedule for four weeks - Telephone calls - Daily messages - Follow-up questionnaire	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/10	
2	Sleep Scheduling: - Randomised to SRT - Well established treatment - Involves sleep scheduling	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/6	
3	- Goals (healthy sleep schedule & become good sleeper) - What we need to do (lifestyle & bedroom, sleep scheduling, action plan)	 0 / 1 / 2 0 / 1 / 2 ___/4	
4	Lifestyle and bedroom factors: - Caffeine - Alcohol - Diet - Exercise - Nicotine - Noise - Light - Mattress/pillow/duvet - Temperature - Air quality	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/20	
5	Sleep scheduling: - Discuss total sleep time - Variability - Average	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/6	
6	How much sleep do I need: - Average - Not enough	 0 / 1 / 2 0 / 1 / 2	

		___/4	
7	Fragmented sleep: - worries/frustration - bed-sleep association - sleep effort	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/6	
8	Sleep Scheduling: - squeeze out wakefulness - compressed sleep window - extends when consolidated	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/6	
9	Sleep drive: - increases during the day - decreases while sleeping and makes us have a good sleep - extends with wakefulness - what happens with naps?	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/8	
10	Sleep efficiency: - calculation - your sleep efficiency	 0 / 1 / 2 0 / 1 / 2 ___/4	
11	Variability: - Bedtime - Rise time - Comparison to regular sleeper - Comparison to individual average	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/8	
12	Master clock: - regular clock - irregular clock	 0 / 1 / 2 0 / 1 / 2 ___/4	
13	- regular sleep pattern every night	0 / 1 / 2 ___/2	
14	Setting time in bed: - pick rise time - pick bedtime - 7 days a week	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/6	
15	Sleep efficiency - your sleep efficiency - goal is 100%	 0 / 1 / 2 0 / 1 / 2 ___/4	
16	Sleep efficiency - 90% -> increase	 0 / 1 / 2	

	- 85-90% -> keep window - Less than 85% -> decrease	0 / 1 / 2 0 / 1 / 2 ___/6	
17	What to expect: - Wanting to go to bed before bed time - Wanting to sleep in - Problems at the weekend - Experiencing sleepiness	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/8	
18	Overcoming obstacles: - Not a good time - Too hard - Need more - Not fair - I'm fine	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/10	
19	Questions and problems: - How long will it take to work? - Feel during the day? - Driving	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/6	
20	- Naps - What if it is not working?	0 / 1 / 2 0 / 1 / 2 ___/4	
21	- If I do not sleep well? - Concerns?	0 / 1 / 2 0 / 1 / 2 ___/4	
18	Review and action plan: - Wake-up time - Bed time - Total time - Sleep diary - efficiency - Actiwatch - Lifestyle & bedroom - Driving - Caffeine - naps	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/18	
19	Timeline: - next assessment	 0 / 1 / 2 ___/2	
TOTAL SCORE:		___/156	

Checklist BCT

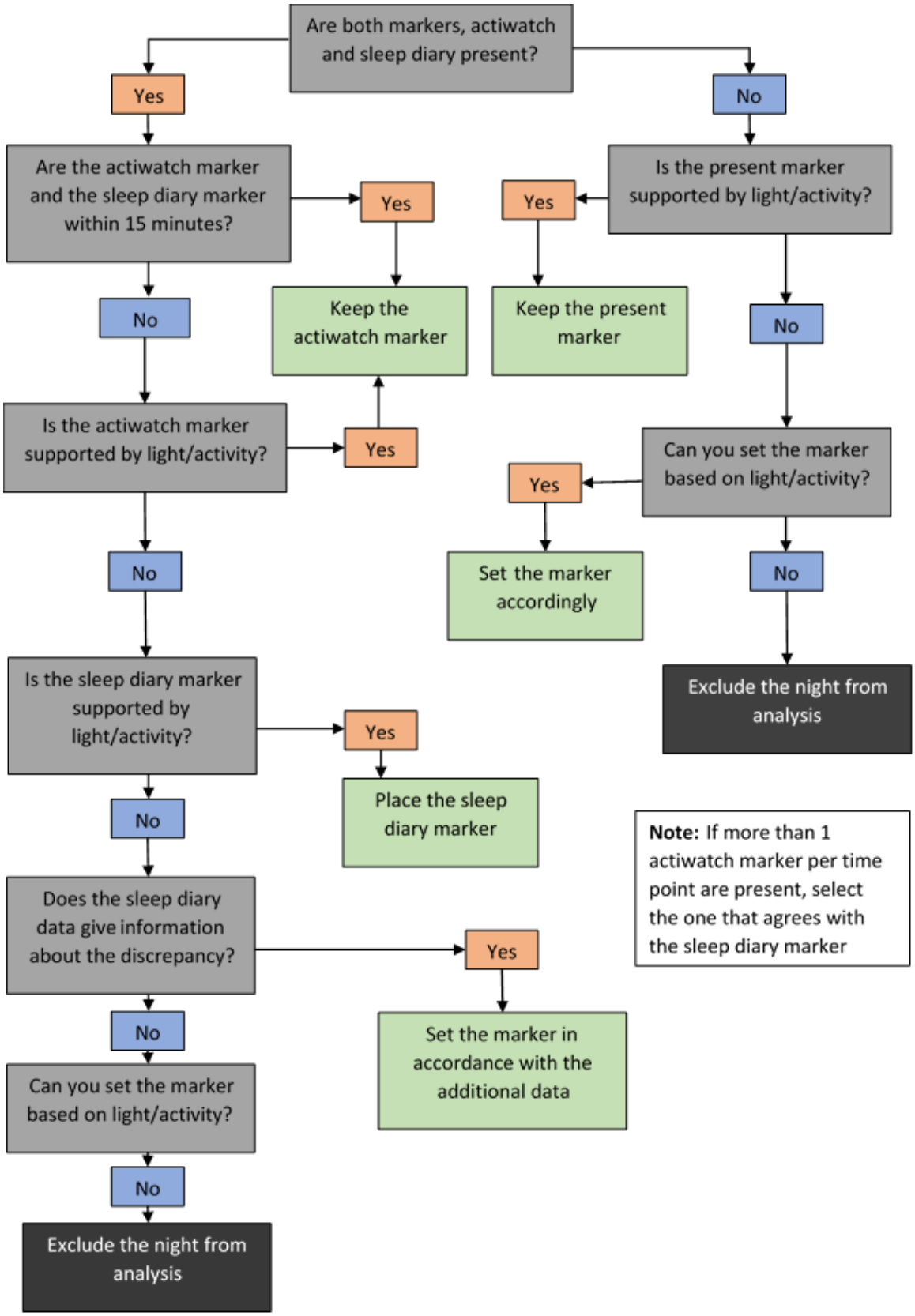
Give two points for each bullet point that was covered. Give one point for a point that was mentioned but not covered. Give zero points if neither mentioned nor covered.

Participant ID:		Date:	
Slide	Topic	Score	Comments
1	The Timeline: - Overnight assessments - Follow sleep schedule for four weeks - Telephone calls - Daily messages - Follow-up questionnaire	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/10	
2	Sleep Scheduling: - Randomised to BCT - Well established treatment - Involves sleep scheduling	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/6	
3	- Goals (healthy sleep schedule & become good sleeper) - What we need to do (lifestyle & bedroom, sleep scheduling, action plan)	 0 / 1 / 2 0 / 1 / 2 ___/4	
4	Lifestyle and bedroom factors: - Caffeine - Alcohol - Diet - Exercise - Nicotine - Noise - Light - Mattress/pillow/duvet - Temperature - Air quality	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/20	
5	Sleep scheduling: - Discuss time spent in bed - Variability - Average	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/6	
6	Variability: - Bedtime - Rise time - Comparison to regular sleeper - Comparison to individual average	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/8	

7	Master clock: - regular clock - irregular clock	 0 / 1 / 2 0 / 1 / 2 ___/4	
8	Fragmented sleep: - worries/frustration - bed-sleep association - sleep effort	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/6	
9	- regular sleep pattern every day	0 / 1 / 2 ___/2	
10	Daily bedtimes - bedtime: - rise time - time in bed	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/6	
11	Setting time in bed: - pick rise time - pick bedtime - 7 days a week	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/6	
12	Bedtime Consistency: - 10 minutes rule - Example for bedtime - Example for rise time - Calculation in session for last week	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/8	
13	What to expect: - Wanting to go to bed before bed time - Wanting to sleep in - Problems at the weekend - Experiencing sleepiness	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/8	
14	Overcoming obstacles: - Not a good time - Too hard - Not fair - I’m fine	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/8	
15	Questions and problems: - How long will it take to work? - Feel during the day? - Driving	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/6	

16	- Caffeine - Naps	0 / 1 / 2 0 / 1 / 2 ___/4	
17	- What if it is not working? - If I do not sleep well? - Concerns?	0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/6	
18	Review and action plan: - Wake-up time - Bedtime - Total time - Sleep diary & consistency - Actiwatch - Lifestyle & bedroom - Driving - Caffeine - naps	 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 0 / 1 / 2 ___/18	
19	Timeline: - next assessment	 0 / 1 / 2 ___/2	
TOTAL SCORE:		 ___/138	

Appendix F: Actiwatch analysis flowchart



Appendix G: Participant information sheet – ESPRIT

Investigating the Effects of Sleep Restriction Therapy for Insomnia on Circadian Timing (ESPRIT)

PARTICIPANT INFORMATION SHEET

Ethics Approval Reference: R60730/RE002

Date of approval: 09.01.2019

What is the purpose of this research?

Sleep restriction therapy (SRT) is an effective treatment for insomnia and has been used in practice for over 30 years. It prescribes a new bed and rise time that aims to improve sleep quality, but also has an impact on the body clock, a circadian system that's designed to regulate feelings of sleepiness and wakefulness over a 24-hour period. To date, no study has investigated how the new sleep schedule affects the body clock in people experiencing sleep problems. We therefore want to investigate how physiological markers (e.g. melatonin concentration of saliva) of the body clock change in response to SRT.

Why have I been invited to take part?

You have been invited to take part because you may have a sleep problem and may be interested in an insomnia treatment study. It could be that you have seen a notice, news story or advertisement about our research. We are looking to recruit around 22 participants. Participants must be aged 25-55.

Do I have to take part?

No. You can ask questions about the research before deciding whether or not to participate. If you do agree to participate, you may withdraw yourself from the study at any time, without giving a reason, by advising the researchers of this decision.

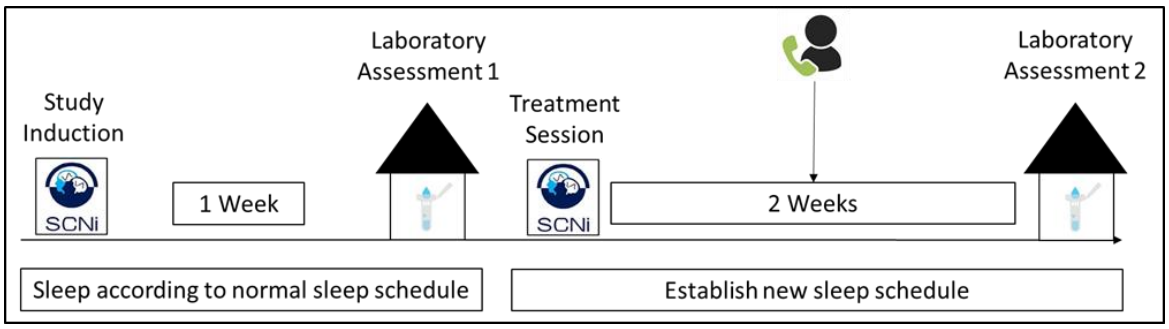
What will happen if I take part in the research?

If you decide to take part, you will be asked to complete a brief set of online questionnaires. This will take approximately 10-15 minutes to complete and will ask you about your sleep and health. If you do not meet the criteria for participation in the study, you will be thanked for your time and your information will not be used in the study.

If you do meet criteria, you will be asked to provide a telephone number and email address. You will be contacted by the research team within 48 hours and undergo a brief telephone interview about your sleep and health, to further assess your eligibility for the study in more detail. This should take approximately 10 minutes.

Taking part will involve a total of 3 weeks, during which you will have your sleep carefully assessed and you will be asked to implement a behavioural sleep treatment programme. We will ask you to visit the Sleep and Circadian Neuroscience Institute (SCNi) twice during the whole study and to visit our research facility at the Warneford hospital also twice during the study. All visits are explained in detail below.

Study Protocol:



Visit 1: Study Induction at the SCNi

If you are eligible for the study, we will invite you to visit the Sleep and Circadian Neuroscience Institute (SCNi), Nuffield Department of Clinical Neurosciences, Sir William Dunn School of Pathology, University of Oxford, South Parks Road, Oxford, OX1 3RE. When you arrive, you will be given a study induction, provide written consent to participate in the study, and confirm dates of the next visit at the Warneford hospital for laboratory assessments. You will take home a watch-like device, which assesses sleep at home and prompts questions about your daily sleep that is called 'pro Diary'. We will ask you to wear the pro diary for the baseline phase (1 week) and the treatment phase (2 weeks). This visit should take around 30 minutes.

Baseline phase: Week 1

The next part of the study will require you to go to bed and rise from bed as you normally do. However, we ask you to monitor your sleep and mood by answering sleep and mood related questions that are prompted by your pro diary watch.

Visit 2: Laboratory Assessment 1 at the Warneford Hospital

One week after your study induction, we will invite you for your first laboratory assessment (this can take place on the weekend). The visit is scheduled relative to the time you normally try to go to sleep and takes about 8 hours. You will be admitted to the laboratory approximately 5.5 hrs before this time. So, if you normally try to go to sleep around 22:30, we would ask you to come at 5pm to our research facilities. Upon arrival, you will remain in a bedroom with dim light at the Warneford research facility (Oxford, UK). In the beginning we ask you to complete a few questionnaires about your sleep. Afterwards we will start to collect hourly saliva samples, resulting in 8 samples in total. The saliva is collected in order to determine your melatonin concentration (an important marker of your body clock). You will be asked to sit 20 minutes prior to each saliva sample, during which we will conduct a short computerised task and ask you about your alertness. You are free to engage in sedentary activities (reading, watching movies, listening to the radio, engage with research

staff) at times when you are not required to undertake study procedures. We will provide a few entertaining activities, but you can also bring your preferred choice of entertainment (upon approval by the researcher). We will provide a selection of meals that you can choose from, however you can also bring your own food, which will be discussed at the study induction. The laboratory assessment ends 2 hours following your habitual sleep time (so at 00:30 in the example) and you will be provided with a taxi home following completion of the study procedures.

Visit 3: Treatment Session

A few days after your first laboratory assessment, you will be asked to visit the Sleep and Circadian Neuroscience institute for the second time, where we will go through your treatment plan with you (about 1 hour). The treatment involves implementing a prescribed bed and rise time based on knowledge gained from sleep science and tailored to your individual sleep pattern. You will learn about the regulation of sleep and about environmental and lifestyle factors that may influence sleep.

Treatment phase: Week 2 and 3

During weeks 2 and 3 you will put the treatment into practice, following a new tailored sleep schedule. You will continue wearing the pro diary to track your sleep patterns during the treatment phase. After the first week, you'll receive a check-up call from the researcher to review your progress.

Visit 4: Laboratory Assessment 2 at the Warneford Hospital

Two weeks after your treatment session, you'll be invited for your second laboratory assessment at the research facilities of the Warneford hospital (again, this can take place on the weekend). The same schedule as visit 1 will be followed. So, if your first laboratory assessment started at 5pm, the second assessment will start at 5pm too. Upon arrival we will ask to fill out questionnaires and hourly saliva as well as computer tasks will be obtained as before. Here, again the assessment finishes 2 hours after your average sleep time of the previous week and you will be provided with a taxi home following completion of the study procedures. Afterwards you will be thanked for your participation.

Are there any potential risks in taking part?

The laboratory assessments require you to stay up longer in the night and you'll go to bed significantly later on both nights. It is therefore not safe to drive or cycle home after the assessments or operate heavy machinery, which is why taxis will be provided. Otherwise, no further risks are expected.

Are there any benefits in taking part?

You will receive access to an evidence-based treatment. There may be a benefit, therefore, of improved sleep when following the sleep programme. On study completion, each participant will receive individual feedback about your body clock (melatonin concentration at baseline). This includes explaining how the underlying circadian timing system works. Furthermore, all participants who are interested in receiving a summary of the study findings will also be sent a copy at the end of the study.

Expenses and payments

Participants will be reimbursed £40 for each completed study phases (Baseline and Treatment phase). Thus, the payment for completing the study in full is £80.

What happens to the data provided?

The information you provide as part of the study is the **research data**. Any research data from which you can be identified (e.g. your name, date of birth), is known as **personal data**. It does not include data where the identity has been removed (anonymous data). We will minimise our use of personal data in the study as much as possible. The **research data** will be stored confidentially without name or address and assigned a study ID. A linking file will enable identification by matching the study ID to the participant name; this file will be stored securely and separately from the coded research data. In case there are names on paper forms, other than the consent form, they will be crossed out, so they are not readable anymore and the paper forms will be stored in lockable filing cabinets. Data will be held on a secure database on a passwordprotected University of Oxford computer. **Personal data** will be collected in consent forms only in the SCNi, where they will be transferred to a password protected University of Oxford computer in a password protected excel-file, a backup will be stored on a password-protected external hard drive. Paper records will be locked in lockable cabinets in a swipe-card secured building and would only be accessed by the research team. Within 7 days after collection all provided saliva samples will be send to ARU Biomarker lab (Cambridge) where the saliva will be decellularised in order to extract the melatonin concentration.

All research data and records will be stored for at least 10 years after publication or public release of the work of the research. Personal data and the linkage file will be destroyed/deleted upon completion of the research study (when the last participant has finished the last laboratory assessment). We may retain and store your contact details (e.g. e-mail address) for an additional period of time as necessary for the purposes of the study (e.g. to send you a summary of the research), and for further research (if you indicate that you would like to be contacted for future research). The paper version of the consent forms will be stored for a minimum of 3 years after publication or public release of the work of the research. If you agree, the research data collected in this study can be given to other researchers, including those working outside of the EU, to be used in other research studies. In that case any data that leaves the research group will be fully anonymised so that you cannot be identified.

Will the research be published?

The research may be submitted to peer-reviewed journals for consideration for publication. The results may be shared at relevant conferences.

The University of Oxford is committed to the dissemination of its research for the benefit of society and the economy and, in support of this commitment, has established an online archive of research materials. This archive includes digital copies of student theses successfully submitted as part of a University of Oxford postgraduate degree programme. Holding the archive online gives easy access for researchers to the full text of freely available theses, thereby increasing the likely impact and use of that research.

The research will be written up as a thesis. On successful submission of the thesis, it will be deposited both in print and online in the University archives, to facilitate its use in future research. The thesis will be openly accessible.

Who is organising and funding the research?

This study is conducted as part of the doctoral thesis of the researcher Leonie Maurer, supervised by Dr Simon Kyle, Dr Suzanne Ftouni and Professor Colin Espie and research funding is provided by the Dr Mortimer & Theresa Sackler Foundation.

Who has reviewed this study?

This study has been reviewed by, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee (Reference number: R60730/RE002).

Who do I contact if I have a concern about the study or I wish to complain?

If you have a concern about any aspect of this study, please speak to the relevant researcher, Leonie Maurer [01865 618656] or their supervisor, Dr Simon Kyle [01865 618675], who will do their best to answer your query. The researcher should acknowledge your concern within 10 working days and give you an indication of how they intend to deal with it. If you remain unhappy or wish to make a formal complaint, please contact the relevant chair of the Research Ethics Committee at the University of Oxford who will seek to resolve the matter in a reasonably expeditious manner:

Chair, **Medical Sciences Inter-Divisional Research Ethics Committee**; Email: ethics@medsci.ox.ac.uk; Address: Research Services, University of Oxford, Wellington Square, Oxford OX1 2JD

Data Protection

The University of Oxford is the data controller with respect to your personal data, and as such will determine how your personal data is used in the study.

The University will process your personal data for the purpose of the research outlined above. Research is a task that we perform in the public interest.

Further information about your rights with respect to your personal data is available from http://www.admin.ox.ac.uk/councilsec/compliance/gdpr/individualrights/.

Further Information and Contact Details

If you would like to discuss the research with someone beforehand (or if you have questions afterwards), please contact:

Leonie F. Maurer
Sleep and Circadian Neurosciences Institute (SCNi)
Leonie.maurer@ndcn.ox.ac.uk

Appendix H: Saliva collection



1. Rinse your mouth thoroughly with water 15-20 minutes before you collect each



2. Open foil pouch and remove the Saliva Collection Aid (SCA).



3. Place ribbed end of the SCA securely into a collection vial.



4. Allow saliva to pool in mouth. Then, with head tilted forward, gently guide saliva through the
SCA into the vial. Fill to the required



5. Remove and discard SCA. Attach cap to collection vial and tighten.