CHANGE ACROSS COGNITIVE BEHAVIOURAL THERAPY FOR INSOMNIA

INVESTIGATING CHANGE IN COGNITIVE AND PSYCHOSOCIAL FUNCTIONING, SUBJECTIVE-OBJECTIVE SLEEP DISCREPANCY AND AN OXIDATIVE STRESS MARKER AFTER GROUP COGNITIVE BEHAVIOURAL THERAPY FOR INSOMNIA

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TITLE: Investigating change in cognitive and psychosocial functioning, subjective-objective sleep discrepancy, and an oxidative stress marker after group cognitive behavioural therapy for insomnia

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LAY ABSTRACT

Insomnia disorder is a sleep disorder that negatively affects day-to-day-functioning and is associated with poorer mental and health outcomes. Cognitive Behavioural Therapy for insomnia (CBT-I) is an established psychological treatment that focuses on changing sleep behaviours and thinking patterns for improving sleep. This thesis aimed to examine factors that may be related to how CBT-I works to improve sleep with both self-reported and objective measures. We investigated whether cognition (e.g., memory and attention), different measures of sleep, clinical symptoms, and biological factors associated with sleep changed across treatment with CBT-I. Results indicated that several self-reported measures of cognition and sleep improved across CBT-I. Our findings suggest that these variables were related to improvements in sleep following CBT-I. By understanding what factors may be contributing to sleep difficulties and change across CBT-I, we can improve treatment outcomes and better adapt treatment strategies to those struggling with insomnia disorder.

ABSTRACT

Insomnia disorder is a debilitating sleep disorder that impacts nearly 10% of Canadian adults. Cognitive Behavioural Therapy for insomnia (CBT-I) is a psychological treatment that targets cognitions and behaviours to improve sleep outcomes. CBT-I has been shown to be an effective treatment for insomnia symptoms; however, little is known about the cognitive and physiological underpinnings of the treatment response. This thesis examines correlates of cognitive, clinical, and biological markers of change across group CBT-I treatment. Specifically, we evaluated: (1) objective and subjective cognitive and psychosocial functioning, (2) discrepancies between objective and subjective measures of sleep, and (3) the relationship between a biological marker of stress and sleep parameters. The first study in this thesis investigated how objective and self-report measures of cognitive functioning, and psychosocial functioning changed across CBT-I. Findings illustrated that changes in self-report cognitive ability and psychosocial functioning were related to the improvements in insomnia symptom severity across treatment. The second study investigated the discrepancy between objectively measured sleep with actigraphy and self-reported sleep variables. Findings showed that the mismatch between objective and subjective sleep parameters decreased early on during the implementation of CBT-I. Additionally, improvement of clinical symptoms was related to a decrease in sleep discrepancies across treatment. In the third study, we examined if there was a relationship between a biological marker of oxidative stress across CBT-I. Results showed that following CBT-I, the biological marker was related to both objective sleep parameters and self-reported symptom improvement. Overall, this thesis demonstrates that in our well-characterized sample of adults with insomnia disorder, group CBT-I was associated with significant post-group changes in cognitive, clinical, and biological factors. This has important implications for the

factors that may influence an individual's treatment response to CBT-I, and thus lead to improvements in tailoring treatments to optimize outcomes for treatment of insomnia disorder.

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ABBREVIATIONS

AASM	American Academy of Sleep Medicine
CBT–I	Cognitive Behavioural Therapy for Insomnia
CSD–M	Consensus Sleep Diary morning version
CVLT–II	California Verbal Learning Test – Second Edition
CPT–II	Connor's Continuous Performance Test – Second Edition
DBAS	Dysfunctional Beliefs About Sleep
DSISD	Duke Structured Interview for Sleep Disorders
DSM–5	Diagnostic and Statistical Manual of Mental Disorders
FAST	Functioning Assessment Short Test
FDR	False Discovery Rate
FSS	Fatigue Severity Index
ISI	Insomnia Severity Index
LMM	Linear mixed-effects models
LM–I	Logical Memory immediate recall
LM–II	Logical Memory delayed recall
MDA	Malondialdehyde
MINI	Mini-International Neuropsychiatric Interview
PDQ–D	Perceived Deficits Questionnaire – Depression
PHQ–9	Patient Health Questionnaire–9
PSG	Polysomnography
REDCap	Research Electronic Data Capture

RCI_{PE}	Reliable change index for practice effects
RMC	Repeated measures correlation
ROS	Reactive oxygen species
SD	Standard deviation
SE	Sleep efficiency
$SED_{Iverson}$	Standard Error of Difference
SOL	Sleep onset latency
STICSA	State-Trait Index for Somatic and Cognitive Anxiety
TBARS	Thiobarbituric acid reactive substances
TIB	Time in bed
TOL	Tower of London
TST	Total sleep time
WASO	Wake after sleep onset

DECLARATION OF ACADEMIC ACHIEVEMENTS

This thesis contains five chapters: Chapter 1 provides a general background to the material in the empirical chapters that follow (Chapters 2 through 4), and Chapter 5 discusses the main conclusions, limitations, and future directions.

Chapter 2

L. E. Cudney was the primary contributor of study conceptualization and design, literature review, protocol development, recruitment and data collection, data analysis, and manuscript preparation. S.M. Green was the primary investigator in the study and provided supervision throughout all stages of the project, including protocol development, data analysis, and manuscript preparation. B.N. Frey provided project conceptualization, manuscript preparation and critical review. R.E. McCabe provided supervision throughout the project and aided with input into the study conceptualization and design, along with manuscript preparation. This chapter, in its entirety, is currently *under review* with the *Journal of Clinical and Experimental Neuropsychology*.

Chapter 3

L. E. Cudney was the primary contributor of study conceptualization and design, literature review, protocol development, recruitment and data collection, data analysis, and manuscript preparation. S.M. Green was the primary investigator in the study and provided supervision throughout all stages of the project, including protocol development and manuscript preparation. R.E. McCabe provided supervision throughout the project and aided with input into the study conceptualization and design in data analysis planning and manuscript preparation. B.N. Frey provided project conceptualization, manuscript preparation and critical review. This chapter, in its entirety, is currently *provisionally accepted* in *Trends in Psychiatry and Psychotherapy*.

Chapter 4

L. E. Cudney was the primary contributor of study conceptualization and design, literature review, protocol development, recruitment and data collection, data analysis, and manuscript preparation. B.N. Frey provided protocol development, manuscript preparation and critical review. R.E. McCabe provided input into the study conceptualization and design along with manuscript preparation. S.M. Green was the primary investigator in the study and provided supervision throughout all stages of the project, including protocol development, data analysis, and manuscript preparation. This chapter, in its entirety, is to be submitted to the *Journal of Clinical Medicine.*

CHAPTER 1: GENERAL INTRODUCTION

Sleep is an essential human need for maintaining physical and mental well-being. In the dark silence of recurrent sleepless nights, Cognitive Behavioural Therapy for Insomnia (CBT-I) offers solace for those suffering from insomnia disorder. Insomnia disorder is a pervasive sleep disorder that impairs daily functioning and leads to decreased quality of life (Dai et al., 2019). CBT-I is a gold standard psychological intervention, which has considerable empirical support for improving insomnia symptoms (Edinger et al., 2021a). However, as the journey towards understanding the mechanisms of CBT-I unfolds, questions arise such as: What factors influence the efficacy of CBT-I? How do subjective experiences intertwine with objective measurements in predicting outcomes? An important next step in investigating the etiology of insomnia disorder and nature of CBT-I is to delve into understanding multifaceted correlates that may be associated with the disorder and impacted by the treatment. By employing an array of assessment modalities, this thesis endeavors to understand the cognitive, clinical, and biological factors contributing to the transformative journey of CBT-I, thereby enriching our understanding of insomnia treatment outcomes.

This thesis uses multiple modes of assessment to understand factors associated with treatment response for CBT-I including examination of clinical, cognitive, and biological measures. We studied the various subjective (i.e., self-reported) and objective factors that may contribute to variations in treatment response. The overall goal of this thesis is to investigate mechanisms of change (e.g., cognitive, clinical, and biological) that occur across treatment for insomnia disorder with CBT-I. The following section provides a general introduction to the relevant topics of insomnia disorder and treatments.

What is insomnia disorder?

Insomnia disorder is characterized by chronic impairments in initiating and/or maintaining sleep, and/or early morning wakening, and/or experiencing non-restorative sleep, in addition to significant distress or impairments in daytime functioning. A diagnosis of insomnia disorder, as outlined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), specifies that the sleep difficulty and associated distress must occur despite having adequate opportunity to sleep and occur at least three nights of the week for at least three months (American Psychiatric Association, 2013). The experience of significant distress or daytime impairment include fatigue, decreased energy, mood disturbances or reduced cognitive functioning (Morin et al., 2015). It also must not be attributed to another sleep disorder, mental disorder, substance use, or general medical condition (American Psychiatric Association, 2013). Insomnia symptoms affect nearly 40% of the population (Chaput et al., 2018), with nearly 10% of the population meeting diagnostic criteria (Morin & Jarrin, 2022). In Canada, a population-based study of insomnia incidence estimated that there was a 30.7% rate of insomnia symptoms with 7.4% meeting criteria insomnia disorder (LeBlanc et al., 2009).

Insomnia disorder is commonly comorbid with other mental health conditions, including anxiety disorders, mood disorders, other sleep disorders, and medical conditions (Fernandez-Mendoza & Vgontzas, 2013). Insomnia disorder is associated with impaired quality of life, increased risk of disease and mortality, and significant economic burden related to work absences and reduced productivity (Daley, Morin, LeBlanc, Gregoire, et al., 2009). Insomnia symptoms and their consequences have also been shown to be the main reason for work-related absences in those with insomnia disorder (Daley, Morin, LeBlanc, Grégoire, et al., 2009). Despite the high prevalence of insomnia disorder, the reasons for the significant economic and

financial burden remain poorly understood. Insomnia has also been identified as a significant risk factor for predicting onset of psychiatric disorders, suggesting it is an important target for treatment to mitigate risk of further psychopathology (Hertenstein et al., 2019). In fact, insomnia symptoms may be the most malleable transdiagnostic factor for risk of psychiatric disorders, and as such, there has been a recent call for transdiagnostic attention to insomnia symptoms across the mental healthcare field (Reesen et al., 2024).

Methods of diagnosing insomnia disorder rely primarily on self-reported concerns of sleep difficulties and associated daytime impairment. Insomnia disorder is considered a "subjective disorder", and use of objective measures of sleep such as polysomnography (PSG) or actigraphy is not necessary for evaluation of insomnia disorder as per professional practice guidelines (Davidson, 2012). PSG is the gold-standard physiological measurement of sleep and provides useful information for ruling out other sleep disorders which might account for sleep concerns, such as periodic limb movement disorder, restless leg syndrome, and obstructive sleep apnea (Morin et al., 2015). These sleep disorders are often comorbid with insomnia disorder but require different treatments for management of each (e.g., continuous positive airway pressure [CPAP] for sleep apnea).

Treatment for insomnia disorder

Treatments for insomnia disorder include pharmacological and psychological therapies. Pharmacological therapies of insomnia are the most common treatment offered to patients with insomnia disorder and are amongst the most frequently prescribed medications in the United States (Madari et al., 2021). These hypnotic medications include prescription drugs such as benzodiazepines, non-benzodiazepines, and tricyclic antidepressants and over-the-counter products including melatonin (Zheng et al., 2020). Hypnotic medications are most frequently

used as the first treatment option for insomnia disorder in a primary care setting (Sun et al., 2021). However, the strength of evidence for individual drugs commonly used to treat insomnia disorder is weak based on American Academy of Sleep Medicine (AASM) clinical practice guidelines (Sateia et al., 2017). In addition, the long-term use of benzodiazepine and non-benzodiazepine medications is associated with increased risk of falls, cardiovascular disease, psychiatric disorders, and mortality (Kripke, 2016). Furthermore, there is a significant risk for long-term dependence and relapse of insomnia symptoms after discontinuation of benzodiazepine medications (Riemann & Perlis, 2009). As such, non-pharmacological treatment methods, specifically Cognitive Behavioural Therapy for Insomnia (CBT-I), is recommended as a first-line treatment for chronic insomnia (Edinger et al., 2021a) since is more efficacious in the long-term (Riemann & Perlis, 2009).

CBT-I is a multi-component intervention that targets nighttime sleep behaviours and associated daytime symptoms (Edinger et al., 2021b). The Canadian national strategy for sleep identifies access to CBT-I as an important public health measure for combatting the negative consequences of insomnia disorder (Chaput et al., 2022). However, in the same vein it is discussed how there are several barriers to accessing this specialized treatment, including a lack of healthcare professionals with training and a need to extend research to discover more cost-effective forms of CBT-I treatment. They proposed that research is needed into various cost-saving modes of treatment delivery, including group sessions. In this thesis, we utilized a 6-session group CBT-I program which was developed based on existing evidence for CBT-I reviewed below.

The Cognitive Behavioural Model of Insomnia

Spielman et al. (1987) proposed the cognitive behavioural model of insomnia involved predisposing, precipitating, and perpetuating factors. This is a stress-diathesis model defined as the three-factor model of insomnia. Predisposing factors are factors which make someone more susceptible to insomnia, including genetic, physiological, or psychological factors. Precipitating factors include stressful life events, medical or psychiatric illness, or other psychological or environmental stressors which result in acute sleep disruption. Perpetuating factors include the behavioural, psychological, physiological, and environmental factors which keep an individual from re-establishing healthy sleep (e.g., napping, staying in bed when not sleeping, dysfunctional beliefs about sleep). Often an acute sleep disturbance can resolve when the acute stressors resolve, but in some cases chronic insomnia persists well beyond the initial stressor (Riemann et al., 2010). Therefore, an individual's susceptibility to develop insomnia disorder may stem from inherent traits, while specific triggering events may lead to actual episodes of insomnia (Spielman et al., 1987). This transition from acute to chronic insomnia occurs due to maladaptive behavioural coping strategies and dysfunctional beliefs about sleep (Spielman et al., 1987). Chronic insomnia involves conditioned arousal because of sleep behaviours, and often an attentional bias to daytime consequences of sleep disturbance (Riemann et al., 2010). Perlis et al. (1997) postulated that those with insomnia had enhanced cognitive arousal due to increased cortical arousal. It was proposed that trouble falling or staying asleep was a result of being more responsive to their environment, which is referred to as the "hyperarousal model" for insomnia. Shared cognitive processes have been identified across different models of insomnia (Tang et al., 2023).

Effective interventions primarily target the perpetuating factors to alleviate and reverse chronic insomnia. A recent systematic review and meta-analysis of treatments for insomnia disorder identified that multicomponent CBT-I treatment is supported by a large evidence base from randomized controlled trials (Edinger et al., 2021b). CBT-I consists of psychoeducation and sleep hygiene (i.e., general guidelines about lifestyle factors which may promote or interfere with sleep), cognitive strategies (i.e., targeting dysfunctional beliefs about sleep) and behavioural strategies that target the perpetuating behaviours (Carney & Manber, 2009; Edinger & Means, 2005). The behavioural strategies that are involved in CBT-I include: (1) stimulus control, (2) time in bed restriction, and (3) relaxation training (Edinger et al., 2021a).

(1) Stimulus control operates on the principles of classical conditioning and involves behaviours meant to reassociate the bed with sleep only (and extinguishing associations of bed and wakefulness). This involves instructions to only go to bed when sleepy, rising from bed if unable to fall back to sleep, and establishing a consistent wake time.

(2) Time-in-bed restriction, also known as sleep restriction therapy, acts on the homeostatic sleep system and is designed to consolidate sleep by limiting the time in bed to closer to sleep duration. The time spent in bed is initially restricted based on the average amount of current sleep duration and then gradually increased based on sleep efficiency guidelines.

(3) Relaxation training (also known as counter-arousal training) involves the introduction of exercises for reducing tension (i.e., progressive muscle relaxation, diaphragmatic breathing), as well as cognitive arousal (i.e., guided imagery training).

Evidence suggests that the combination of these critical components of CBT-I (psychoeducation, cognitive, and behavioural strategies) results in optimal treatment outcomes and has strong recommendations for use compared to single-component therapies (Edinger et al., 2021a). CBT-I is a well-received psychological treatment that produces improvements comparable to pharmacological treatment (Sivertsen et al., 2006), and is superior in terms of long-term effectiveness (Morin et al., 2006). CBT-I has also demonstrated effectiveness in reducing depressive and fatigue symptoms (Ballesio et al., 2017), for those with and without psychiatric comorbidities (Belanger et al., 2016; Edinger et al., 2009).

Measuring treatment response to CBT-I

A meta-analysis of RCTs of group CBT-I showed that it had medium-to-large effect sizes for improving subjective experiences of sleep quality, as well as sleep diary reported measures (Koffel et al., 2015). Several decades of efficacy and effectiveness research have shown CBT-I improves symptoms long-term (Okajima et al., 2011). As such, it has been highlighted that continuing to study efficacy of CBT-I is no longer a research priority (Vitiello et al., 2013), but instead researching the underpinnings of treatment and identifying factors which lead to increased effectiveness in "real-world' samples. Although CBT-I is an effective treatment for insomnia symptoms, little is known of the cognitive and neurobiological underpinnings of the treatment response. Identifying and understanding the mechanisms of CBT-I and the mediators that lead to greatest sleep improvement is currently lacking in the literature (Schwartz & Carney, 2012). Further, a recent meta-analysis identified a significant need for CBT-I clinical trials to incorporate assessment of daytime functional impairments and identify factors that influence treatment response based on clinical characteristics (Edinger et al., 2021b). Given the high

degree of comorbid medical and psychiatric disorders with insomnia, it is important to further investigate the impact of comorbidity on treatment outcome.

Cognitive and psychosocial functioning in insomnia disorder

Insomnia has been associated with clinically significant deficits in attention and episodic memory (Fortier-Brochu & Morin, 2014). A meta-analysis of cognitive performance in insomnia patients revealed working memory, episodic memory and executive function are particularly impaired (Fortier-Brochu et al., 2012). A large cohort study showed that individuals with insomnia that reported seeking treatment for sleep problems had greater cognitive deficits than those who did not seek treatment (Goldman-Mellor et al., 2015). These studies suggest a significant link between daytime cognitive performance and degree of insomnia severity, as measured with objective cognitive tests; however, results are mixed and often the impairments have small to moderate effect sizes across studies (Fortier-Brochu et al., 2012). A recent meta-analysis revealed that a significant cause for discrepant results is related to more than 44% of studies failing to use diagnostic criteria when characterizing insomnia (Wardle-Pinkston et al., 2019). These findings highlight the need for studies of cognitive functioning on well-characterized samples of those with insomnia disorder, rather than those reporting symptoms only. There is a gap in our understanding of the objective and subjective cognitive and psychosocial functioning of individuals with insomnia disorder undergoing CBT-I.

Subjective-objective sleep discrepancy in insomnia disorder

Objective short sleep duration (as measured by actigraphy) has been identified as a predictor of non-response to CBT-I (Bathgate et al., 2016). Sleep questionnaires gather one's retrospective views on sleep, which are susceptible to the influence of one's current mood and anxiety levels (Hartmann et al., 2015). A prospective sleep diary provides a comprehensive

assessment of sleep experiences and self-reported insomnia symptoms. This includes time into and out of bed, amount of time taken to fall asleep (sleep onset latency [SOL]), sleep duration (total sleep time [TST]), length of awakenings after sleep onset (wake after sleep onset [WASO]), and subjective ratings of sleep quality, and is less biased than retrospective questionnaires about sleep (Maich et al., 2018). As a result, subjective sleep parameters may differ based on the method by which they are reported (e.g., sleep diary versus self-report questionnaire). Sleep duration, for example, was significantly longer when reported on a sleep diary compared to questionnaires in a longitudinal cohort of adults. To add to this, the presence of self-reported insomnia symptoms were associated with greater perceived differences between sleep diary and questionnaire data (Mallinson et al., 2019)

Although subjective experiences of sleep are the basis of an insomnia disorder diagnosis, objective measures of sleep, including polysomnography (PSG) and actigraphy, have been investigated to understand the value of physiological data for the diagnosis and understanding of insomnia disorder (Andrillon et al., 2020). Actigraphy is increasingly used in the sleep medicine field as a cost-effective and convenient tool for measuring sleep variables, which can collect objective sleep data in one's own home environment.

Interestingly, individuals with insomnia disorder commonly describe having sleep quantity and quality issues, even when objective sleep measures appear normal (Fernandez-Mendoza et al., 2011). This discrepancy between self-report or subjective experiences of sleep and objectively measured sleep parameters has been referred to in different ways over time including, "subjective insomnia", "paradoxical insomnia" (Castelnovo et al., 2019), or "sleep-state misperception" (Harvey & Tang, 2012). The discrepancy between subjective and objective sleep measures (referred to as the subjective-objective sleep discrepancy within this thesis) may

contribute to the trivialization and under-treatment of insomnia disorder (Harvey & Tang, 2012). The subjective-objective sleep discrepancy has been considered a "prodrome" for development of more serious objective sleep deficits, suggesting it is an important target for treatment (Harvey & Tang, 2012). As such, it is important to understand trajectories of the subjective-objective sleep discrepancy and its associations with treatment response and related clinical factors across CBT-I.

Biological markers in insomnia disorder and across CBT-I

Chronic sleep disturbance is associated with increased systemic inflammation across many populations, including those with insomnia disorder (Irwin et al., 2016). The studies that investigated changes in biological markers in response to CBT-I have focused on inflammation. A randomized-controlled trial of CBT-I treatment measured inflammatory markers in older adults with insomnia (Irwin et al., 2015; Irwin et al., 2014). C-reactive protein (CRP) is considered one of the most stable and commonly measured inflammatory markers. CBT-I treatment was associated with reduced risk of having high CRP at post-treatment and remained reduced at the one-year follow-up compared to the control of sleep hygiene education only (Irwin et al., 2014). These studies suggest that systemic inflammation is targeted with CBT-I in an older adult population. The studies by Irwin et al. (Irwin et al., 2015; Irwin et al., 2014) provide evidence that a multi-component psychological treatment for insomnia such as CBT-I, can improve sleep and change biological markers of inflammation.

There is mounting pre-clinical evidence that chronic sleep deprivation and insomnia negatively impact other biological processes, such as increased oxidative stress (Feng et al., 2016). Oxidative stress is a state of imbalance between the production of reactive oxidant species and the antioxidant defense, which can be measured via multiple markers including lipid

peroxidation. A cross-sectional study found increased markers of lipid peroxidation and decreased antioxidant defense in primary insomnia patients compared to healthy controls (Gulec et al., 2012). To date, there is one small study which has looked at how an oxidative stress marker has changed across CBT-I, which was focused only on participants with kidney disease receiving dialysis. They identified there was a reduction in an oxidative stress marker following improved sleep with CBT-I (Chen et al., 2011). These studies provide evidence that oxidative stress may be associated with the underlying neurobiology of insomnia disorder. To our knowledge, there are no studies to date looking at the impact of response to CBT-I treatment on biological markers of oxidative stress in a broader population of adults with insomnia disorder.

Main Aims

Based on the background research presented in this chapter, we have identified several gaps in the literature related to the multi-modal measurement of markers of change across treatment for insomnia disorder with CBT-I. The overall aim of this thesis is to further elucidate factors which may influence treatment response to CBT-I, using multiple subjective and objective modes of assessment.

The study in Chapter 2 aimed to investigate cognitive functioning in a sample of individuals with insomnia disorder seeking CBT-I. Understanding the impact of insomnia on cognitive functioning in a sample with comorbid symptoms is key for addressing real-world concerns, since insomnia is rarely a concern on its own and CBT-I is effective for many psychiatric and medical conditions that are comorbid with insomnia disorder (Raglan et al., 2019). The first aim of this study was to measure if the objective cognitive functioning of participants is impaired and changes/improves following a 6-session CBT-I group treatment in participants with moderate to severe insomnia disorder, using a broad test battery with an

emphasis on domains previously implicated in the insomnia literature (e.g., attention, working memory, episodic memory, and executive function). The second aim of this study was to investigate whether self-report subjective measures of cognitive and psychosocial functional deficits change across treatment, and whether these domains change in concordance with insomnia symptom severity. We hypothesize that both objectively measured cognitive functioning and self-reported cognition and psychosocial functioning will improve across treatment. We further hypothesize that the self-reported changes will be associated with the severity of insomnia symptoms reported.

Our study in Chapter 3 aimed to understand how undergoing treatment with CBT-I changes the discrepancy between objective and self-reported sleep across a 6-week group CBT-I protocol. The primary objective of this study is to determine how the discrepancy between wrist-worn actigraphy, and sleep diary-derived sleep parameters change across CBT-I. We hypothesized that sleep perception would improve with each subsequent CBT-I session, such that sleep discrepancy decreases across treatment from baseline to post-treatment. A secondary aim of the study was to understand whether clinical variables including depression, anxiety, fatigue, and maladaptive sleep-related cognitions were associated with a change in the subjective-objective sleep discrepancy across CBT-I treatment.

In Chapter 4, we examine whether self-reported or objective sleep measures (assessed with actigraphy) in adults with insomnia are related to a marker of lipid peroxidation. The main objectives of the study are to determine whether: 1) a relationship exists between oxidative stress – as measured by lipid peroxidation – and the severity of insomnia symptoms and measures of sleep disturbance; 2) oxidative stress levels change across treatment for insomnia with CBT-I, and 3) baseline oxidative stress levels could predict response to CBT-I treatment after 8 weeks.

We hypothesized that higher levels of sleep disturbance would be associated with increased lipid peroxidation at baseline, as measured with thiobarbituric acid reactive substances (TBARS), that would normalize following CBT-I treatment. We also hypothesized that those with higher levels of oxidative stress at baseline would show differential response to CBT-I (as shown with greater decrease in insomnia symptoms).

In summary, this thesis aims to address these gaps in the following way:

- First, we were interested in understanding the objectively measured cognitive performance in a well-characterized sample with insomnia disorder undergoing CBT-I, and how objective and self-reported cognitive and psychosocial functioning change across treatment. In Chapter 2, we examine the objective and self-reported cognitive performance and psychosocial functioning of participants with moderate to severe insomnia prior to and following CBT-I. This study contributes to the growing body of research on understanding the functional and cognitive impairments in insomnia disorder, and how these may be addressed by CBT-I.
- Second, we aimed to investigate the impact of cognitive behavioural therapy for insomnia on the discrepancy between objective and subjective measures of sleep, and to assess whether changes in clinical variables such as depression, anxiety, fatigue, and beliefs about sleep, were related to changes in discrepancy. The study in Chapter 3 presents these results and will allow us to gain a better understanding of the relationship between subjective and objective measures of sleep in those with insomnia disorder following CBT-I.
- Third, we investigated whether a potential marker of oxidative stress, specifically lipid peroxidation, may be associated with response to CBT-I, given the mounting evidence for

biological markers of inflammation associated with differential treatment response (Irwin et al., 2015; Irwin et al., 2014). The study presented in Chapter 4 identified how a lipid peroxidation marker is related to insomnia severity, and both subjective and objective measures of sleep across CBT-I. This study aims to identify a novel biomarker that should be further investigated to disentangle how insomnia disorder and CBT-I may impact biological pathways of oxidative stress.

- Finally, in Chapter 5 a general discussion is outlined and ties these findings together. Limitations and future directions for this body of research are discussed.

Taken together, this thesis aims to provide evidence of the clinical, cognitive, and biological variables that influence outcomes of CBT-I. The novel findings of this thesis contribute to the growing body of literature aiming to explore multi-modal mechanisms of change within a psychological treatment for insomnia disorder such as CBT-I. This has implications for improving clinical efficacy for "real-world" implementation of group CBT-I.

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CHAPTER 2

Study 1: Objective and self-reported cognition and psychosocial functioning across cognitive behavioural therapy for insomnia (CBT-I)

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Objective and self-reported cognition and psychosocial functioning across cognitive behavioural therapy for insomnia (CBT-I)

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Abstract

Introduction: Diagnostic criteria for insomnia disorder includes daytime functional impairment, which may include cognitive or psychosocial complaints; however, it remains unclear whether objective or self-reported measures of these impairments change following treatment with Cognitive Behavioural Therapy for insomnia (CBT-I). The present study aimed to examine the objective and self-reported cognitive performance and psychosocial functioning of participants with moderate to severe insomnia prior to and following CBT-I.

Methods: Twenty-nine participants (Mean age= 51.9, SD= 14.2), completed a 6-week group CBT-I intervention consisting of weekly 2-hour sessions. Participants completed baseline and post-treatment cognitive testing to measure domains of attention, memory, executive function, and logical memory, and self-report measures of insomnia symptom severity, cognition and psychosocial functioning.

Results: There were significant within-subject improvements in objective measures of sustained attention, including commissions and detectability ($p < 0.01$). Verbal episodic memory, problem-solving skills, and mental flexibility did not significantly change after controlling for practice effects. Self-reported cognitive and psychosocial functioning deficits significantly decreased across CBT-I, which were related to improvements in insomnia severity and lower age in linear modeling.

Conclusions: Objective cognitive assessments revealed significant improvements in sustained attention, but not in the domains of memory or executive functioning assessed across CBT-I. CBT-I was effective at improving self-reported cognitive complaints and psychosocial functioning following treatment, relative to the severity of insomnia and age. These findings

suggest that CBT-I is associated with broader benefits beyond sleep improvement in a well-characterized sample with insomnia disorder.

Keywords: Insomnia disorder, Cognition, Psychosocial functioning, self-report, Cognitive Behavioural Therapy for insomnia

Introduction

Insomnia is characterized by chronic impairments in initiating or maintaining sleep, or early morning wakening, in addition to significant distress or impairments in daytime functioning. Insomnia symptoms affect nearly 40% of the population (Chaput et al., 2018), with 6-10% of the population meeting diagnostic criteria for insomnia disorder (American Psychiatric Association, 2013). Insomnia disorder is associated with significant economic and financial burden, often attributed to decreased occupational functioning (Chaput et al., 2018). For instance, in a study comparing those with insomnia disorder with good sleepers, those with insomnia disorder were almost five times more at risk for reduced productivity (Daley et al., 2009). Daley et al. (2009) also found that insomnia and its consequences were the main reason for work-related absences in those with insomnia disorder. Despite the high prevalence of insomnia disorder, the reasons for the significant economic and financial burden remain poorly understood.

There has been an emphasis on understanding the cognitive underpinnings of insomnia by primarily measuring the domains of attention, memory and executive functioning (Brownlow et al., 2017) with insomnia being previously associated with clinically significant deficits in attention and episodic memory (Fortier-Brochu & Morin, 2014). A meta-analysis of cognitive performance in individuals with insomnia disorder revealed impairment in working memory, episodic memory and executive function (Fortier-Brochu et al., 2012). A recent cross-sectional study showed that spatial and verbal working memory were significantly impacted as severity of insomnia increased (Aasvik et al., 2018). These studies suggest a significant link between daytime cognitive performance and degree of insomnia severity, as measured with objective cognitive tests; however, results are mixed and often the impairments have small to moderate

effect sizes across studies (Fortier-Brochu et al., 2012). A recent meta-analysis revealed that a significant cause for discrepant results is related to more than 44% of studies failing to use diagnostic criteria when characterizing insomnia (Wardle-Pinkston et al., 2019). This finding highlights the need for studies of cognitive functioning on well-characterized samples of those with insomnia disorder, rather than those reporting symptoms only.

Self-reports of poor concentration and cognitive performance are among the most commonly described complaints by those with insomnia disorder (Ballesio et al., 2019). Daytime functional impairment is part of the diagnostic criteria for insomnia disorder and has been cited as a significant consequence of insomnia (Wardle-Pinkston et al., 2019). Subjective or self-report complaints of cognitive impairments and decreased daytime functioning have been documented across several systematic reviews and meta-analyses (Fortier-Brochu et al., 2012; Wardle-Pinkston et al., 2019). Since the definition and categorization of insomnia has been inconsistent across studies, it remains unclear what the impact of insomnia symptom severity is on self-reported cognitive symptoms and functioning in those with diagnosed insomnia disorder.

Cognitive Behavioural Therapy for insomnia (CBT-I) is the first-line treatment for insomnia disorder with significant evidence for long-term improvement in sleep parameters. A large cohort study showed that individuals with insomnia symptoms who sought treatment for sleep problems had greater cognitive deficits than those who did not seek treatment (Goldman-Mellor et al., 2015). This suggests patients who may seek CBT-I could have significant subjective cognitive impairments. However, it remains unclear whether these cognitive and functional impairments are impacted after treatment for insomnia disorder with CBT-I (Herbert et al., 2018).

The current study aimed to investigate cognitive functioning in a sample of individuals with insomnia disorder seeking CBT-I. Understanding the impact of insomnia on cognitive functioning in a sample with comorbid symptoms is key for addressing real-world concerns, since insomnia is rarely a concern on its own and CBT-I is effective for many psychiatric and medical conditions comorbid with insomnia disorder (Raglan et al., 2019). The first aim of this study was to measure if the objective cognitive functioning of participants changes following a 6-session CBT-I group treatment in participants with moderate to severe insomnia disorder, using a broad test battery with an emphasis on domains previously implicated in the insomnia literature (e.g., attention, working memory, episodic memory, and executive function). Additionally, the second aim of this study was to investigate whether self-report subjective measures of cognitive and functional deficits change across treatment, and whether these domains change in concordance with insomnia symptom severity. We hypothesize that both objectively measured cognitive functioning and self-reported cognition and psychosocial functioning will improve across treatment. We further hypothesize that the self-reported changes will be associated with the severity of insomnia symptoms reported.

Methods

Study Participants

Twenty-nine study participants (Mean Age = 51.93, SD= 14.16, Range 22 - 70), with a Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnosis of insomnia disorder were included in the present study. Participants were screened for eligibility for group CBT-I clinical services after being referred from the Sleep Medicine Program, Firestone Institute for Respiratory Health or the Mood Disorders Outpatient Clinic at St. Joseph's Healthcare, Hamilton. Participants were invited to participate in research if their symptoms met criteria for

insomnia disorder and they were enrolled in group CBT-I. All study participants were informed in detail about the purpose of the investigation and provided their written informed consent prior to the onset of the study. The study was approved by the local ethics committee, the Hamilton Integrated Research Ethics Board.

The presence of insomnia disorder was confirmed based on DSM-5 criteria with the Duke Structured Interview for Sleep Disorders (DSISD; Edinger et al., 2004). Participants were assessed with the DSISD for the presence of other sleep disorders (e.g., sleep apnea, limb movement, and circadian rhythm disorders) and were excluded if the comorbid sleep disorders were considered primary or were untreated/unstable (e.g., those with sleep apnea who were adherent to positive airway pressure therapy were included). The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was conducted to assess participants for comorbid psychiatric disorders. Participants were excluded for disorders that are typically contraindicated for CBT-I, including bipolar disorder and psychotic disorders (e.g., schizophrenia, schizoaffective disorder). Exclusion criteria also included: current shift work, current alcohol or substance abuse or dependence, or history of, in the past six months prior to screening. Participants with other comorbid psychiatric and medical conditions were otherwise included, since CBT-I for insomnia disorder has been shown to be very effective in the context of co-occurring psychiatric conditions (Raglan et al., 2019). Prescription and over-the-counter sleep medications were allowed over the duration of the study provided the participants were on a stable dose throughout (i.e., were using the medication non-contingently from screening to post-treatment).

Study Design

The present study employed a within-subjects design. Participants completed an initial screening visit to determine eligibility for the study. A baseline cognitive assessment was conducted 1-2 weeks prior to initiating group CBT-I along with measures of sleep, and symptoms. This same assessment was administered again at a post-treatment assessment, 1-2 weeks following completion of group CBT-I. Participants were considered completers if they attended four or more of the six group CBT-I sessions. If they missed a session, they were provided with an individual make up session.

Measures

Clinician-Rated Measures

The Duke Structured Interview for Sleep Disorders (DSISD; Edinger et al., 2009) includes criteria for diagnosing sleep disorders. DSISD consists of four modules, including sleep disorders associated with insomnia, excessive daytime sleepiness-hypersomnia, circadian rhythm sleep disorders, and sleep disorders associated with parasomnias. The DSISD has shown high inter-rater reliability (kappa values between 0.71 and 0.86 (Carney et al., 2009)

The Mini International Neuropsychiatric Interview (MINI) is a psychiatric semi-structured diagnostic interview based on the DSM-5 (American Psychiatric Association, 2013). The Cohen's kappa values for inter-rater reliability for the clinician delivered MINI are 0.79 and above, indicating a moderate to strong level of agreement across interviewers (Sheehan et al., 1997).

Self-report Questionnaires

The Insomnia Severity Index (ISI; Bastien et al., 2001) is a 7-item self-report scale used to evaluate the severity of insomnia symptoms. Each item is scored on a 0 to 4 scale with higher values representing greater insomnia severity (Bastien et al., 2001). Scores > 11 are indicative of

clinical insomnia and it has been shown that improvement of ≥ 9 was consistent with marked improvement in symptoms (Morin et al., 2011). The ISI has shown high internal consistency in clinical samples ($\alpha = 0.91$; Morin et al., 2011).

Sleep diaries are the gold-standard for tracking sleep disturbances, and the information derived is used to determine sleep efficiency, initiation, and maintenance (Carney et al., 2012). The Consensus Sleep Diary for Morning (CSD-M) is a sleep diary that requires participants to self-report estimates of sleep patterns and quality daily upon wakening. Information from the CSD is used to calculate total sleep time, sleep onset latency, time in bed, sleep efficiency, and wake after sleep onset. Participants are asked to complete the CSD for two weeks prior to treatment and throughout the duration of the group CBT-I 6-week sessions for both diagnostic purposes and to inform treatment targets and strategies.

The Functioning Assessment Short Test (FAST; Rosa et al., 2007) is a 24-item questionnaire that assesses 6 domains of psychosocial impairment or disability, including: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time (Rosa et al., 2007). The items are rated on a 4-point scale. A recent study has validated the use of the FAST in the general population (Riegler et al., 2020).

The Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001) is a 9-item brief self-report measure of depressive symptoms rated from 0 (“not at all”) to 3 (“nearly every day”; (Kroenke et al., 2001). A total score of greater than 10 has been shown to have sensitivity of 88% and specificity of 88% for major depression in a primary care setting (Kroenke et al., 2001).

The Perceived Deficits Questionnaire- Depression (PDQ-D; Sullivan et al., 1990) is a 20-item self-report measure of cognitive dysfunction. It includes four domains, including: attention/concentration, retrospective memory, prospective memory, and organization/planning.

The items are rated on a 5-point Likert scale. The PDQ was originally developed to measure patient-reported cognitive symptoms as part of a disease-specific instrument for Multiple Sclerosis (Sullivan et al., 1990). The PDQ-D was adapted for use by adults with Major Depressive Disorder and has been validated against other measures of cognitive function and was responsive to changes in depression (Lam et al., 2018; Lam et al., 2013). We have chosen to use this version due to the high comorbidity between major depressive disorder and insomnia disorder in our population. The PDQ-D has high internal consistency with Cronbach's alpha 0.81-0.96 (Lam et al., 2018).

The State-Trait Inventory for Cognitive and Somatic Anxiety (STICSA; Ree et al., 2008) is a 21-item self-report measure of anxiety, which includes subscales for both cognitive and somatic anxiety. Items are rated on a 4-point Likert scale (Ree et al., 2008). It has been validated in clinical and non-clinical samples and the subscales have demonstrated excellent internal consistency (Cronbach's alpha coefficients > 0.87; Grös et al., 2007).

Cognitive Assessment

Participants completed a one-hour battery of standardized and experimental cognitive measures at baseline and post-treatment. The battery consisted of measures of attention, verbal fluency, verbal learning, verbal memory, logical memory, and executive function. An estimate of pre-morbid IQ was measured with the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) at baseline only. The measures utilized in the battery are described below.

The *California Verbal Learning Test-II* (CVLT-II; Delis et al., 2000) was administered to assess verbal and declarative memory (Delis et al., 2000). Participants were asked to learn and remember a list of 16 words within four different semantic categories (original list), presented over the course of the learning trials (Trials 1-5). This was followed by an interference list trial

(List B). The participant was asked to immediately recall (Short-Delay) the original list in both immediate free-recall and cued-recall trials. Following a 20-minute gap (Long-Delay), the participant was asked to recall the original list in delayed free-recall and cued-recall trials. Finally, a Yes/No recognition trial was administered following the Long-Delay recall trials. The number of correct responses, as well as repetitions and intrusions (i.e., new words not in the list) were measured. Analysis of CVLT-II included trial scores from: Total Correct Responses from the learning trials (Trial 1–5 total), Interference Trial score (List B), Short-Delay Cued-Recall (i.e., the semantic category was provided), Short-Delay Free-Recall (i.e., no cues for semantic category was provided), Long-Delay Cued-Recall, and Long-Delay Free-Recall. Total Repetitions and Intrusions were also captured and analyzed. The CVLT-II recognition trial was not analyzed since there was a lack of impairment observed in the recall trials at baseline. The standard form was administered at baseline and the alternate form was administered at post-treatment (Woods et al., 2006).

The *Connor's Continuous Performance Test – Second Edition* (CPT-II; Conners et al., 2003) was administered to assess sustained attention, response inhibition, and executive control of attention with a computerized task. Letters were presented in succession and participants were instructed to press the space bar as fast as possible to each letter except when the letter is "X" for a duration of 14 minutes (Conners et al., 2003). The number of omission errors (i.e., not pressing the bar when a stimulus is not an "X"), commission errors (i.e., pressing the bar when the stimulus is an "X"), perseveration errors (i.e., hits with a reaction time below 100 milliseconds), the detectability index (i.e., an index of the ability to detect targets from other stimuli), and the hit rate block change (i.e., change in reaction time with time-on-task) were analyzed.

The *Tower of London* (TOL; Keith Berg & Byrd, 2002) was administered to assess preparation, planning, and processing, encompassing important aspects of executive functioning and problem-solving. The TOL required participants to arrange three coloured beads on a peg board to match a given pattern in as few moves as possible (Keith Berg & Byrd, 2002). More problems solved correctly and shorter execution time both indicate greater problem-solving skills and mental flexibility, while greater initiation time indicated greater planning and inhibition of impulsivity. Total number of moves, total problem-solving time, total execution time, and the number of correct solutions (i.e., items solved in the minimum number of moves). Time and rule violations (i.e., placing or trying to place more beads on a peg than it will hold, or removing two beads from the peg at the same time) were counted for each trial.

The *Wechsler Memory Scale- Logical Memory Subtest, 3rd Edition* (WMS-III LM; Wechsler 1997) was administered to assess verbal logical memory. The WMS-III LM consisted of three parts, including immediate recall after hearing a short passage (logical memory I; LM-I), delayed recall (logical memory II; LM-II), and a recognition trial after LM-II. The delayed recall occurred between 25 and 35 minutes after the immediate recall had been completed (Wechsler, 1997). Recall total scores for LM-I and LM-II consisted of the number of details in the story that the participant recalls. The inter-rater reliability has previously been shown to be 0.97 (Sullivan, 2005).

Intervention

The CBT-I group protocol was a manual-based intervention that consisted of six two-hour sessions. It was conducted by a licensed doctoral clinical psychologist and trained clinical psychology graduate students. The components of the intervention included psychoeducation and sleep hygiene, stimulus control, time in bed restriction, cognitive restructuring,

relaxation/counter-arousal strategies, and relapse prevention (Carney & Manber, 2009). Participants completed the Consensus Sleep Diary for morning (CSD-M; Carney et al., 2012), throughout the duration of the sessions to track sleep parameters such as time into and out of bed, that guide treatment decisions (i.e., time-in-bed prescriptions). Learning was reinforced with weekly home practice exercises, including stimulus control, time in bed restriction, relaxation strategies, and cognitive strategies. Analysis of the insomnia measures were performed to assess if the treatment was effective, and therefore would allow for further examination of cognitive functioning across treatment.

Statistical Analyses

For the primary objective of the study, paired comparisons were performed on the cognitive battery raw test scores. Analyses with raw scores, as compared to standardized scores, capture more variability within the data. The Shapiro-Wilks test was performed on the difference between baseline and posttreatment pairwise comparisons to determine normality of the sample. Paired t-tests were performed for parametric data and the Wilcoxon paired rank test was performed for non-parametric data. Corrections for multiple comparisons were performed using the false discovery rate (FDR). Assuming a medium effect size of 0.5 in a within-subjects design for 80% power, a sample size of 34 was needed. However, analyses were performed on our sample size of 29 due to the cessation of data collection following the onset of the COVID-19 pandemic. Limitations of a small sample size are considered within the discussion.

The reliable change index for practice effects (RCI_{PE}) was used for the cognitive tests that were more prone to practice effects and did not have different versions available. These included the TOL and WMS-III LM tests. Reliable change determines if there is improvement or deterioration in cognitive functioning beyond probable range of measurement error and

correcting for the average practice effects, which involves the addition of a constant based on group-level average change (Iverson, 2011). The RCI_{PE} was only used for the variables which showed significant change across treatment, in order to determine the breakdown of how many participants reliably changed after accounting for measurement error and practice effects. The RCI_{PE} was performed using the Iverson method, which accounts for variability in the post-treatment scores within the Standard Error of Difference ($SED_{Iverson}$) (Duff, 2012). The standard cut-off for RCI_{PE} that indicates reliable change is ±1.64, which is a z-score on the normal distribution table that 90% of cases would fall within. If the individual's score is above or below this cut-off, it is considered a reliable change. The following formula was used to calculate the RCI_{PE} score (Duff, 2012):

$$SED_{Iverson} = \sqrt{(SD_1\sqrt{1- r_{12}})^2} + \sqrt{(SD_2\sqrt{1- r_{12}})^2}$$

$$RCI_{PE} = (T_2 – T_1) – (M_2 – M_1) / SED_{Iverson}$$

Notes: M_1 = group mean at baseline; M_2 = group mean at post-treatment; r_{12} = correlation between baseline and post-treatment scores; SD_1 = Standard Deviation at baseline; SD_2 = Standard Deviation at post-treatment; T_1 = score at baseline; T_2 = score at post-treatment

For the second objective, self-reported cognitive (PDQ-D), and psychosocial functioning concerns (FAST) scores were measured at baseline and post-treatment. The Shapiro-Wilks test was performed on the difference between baseline and posttreatment pairwise comparisons to determine normality of the sample. Pearson's correlations were used to investigate the relationship between the self-report cognitive and psychosocial functioning deficits and insomnia symptom severity at baseline. Paired t-tests were performed for parametric data and the Wilcoxon paired rank test was performed for non-parametric data. Corrections for multiple comparisons were performed using the FDR. A linear mixed-effects model was used to

understand how the PDQ-D and FAST total scores changed over time (from baseline to post-treatment) while accounting for covariates of insomnia severity (ISI) and age, since both variables may play a role in the self-reported level of cognitive and functional deficit (Navarra-Ventura et al., 2019).

Results

Thirty-one participants were eligible for the study and completed the screening and baseline visits. Of these participants, one completed only two sessions of the CBT-I group treatment and one completed only the screening and baseline visits and did not initiate the CBT-I group within the specified timeline due to the COVID-19 pandemic. As a result, a total of 29 participants who completed the baseline and post-treatment visits were included in this analysis. The average number of days between baseline and post-treatment cognitive testing was 55.8 (8 weeks).

Demographics for the 29 participants are presented in Table 2. The majority of participants were female (72.4%).

Effectiveness of CBT-I Treatment

Participants significantly improved in terms of insomnia symptoms as measured with the ISI (t = -9.95, $p < 0.001$, d = 2.19) across treatment with CBT-I. This was also indicated by improvements in sleep variables on the CSD-M. See Supplementary Table S1 for description and analysis of CSD-M derived sleep variables. The PHQ-9 indicated the sample had mild symptoms of depression at baseline, and that the depression symptoms significantly improved across treatment (W = 27.50, $p < 0.001$, d = 0.91). Anxiety symptoms measured with the STICSA also showed significant improvements across treatment (t = -3.60, p < 0.001, d = 0.43).

Objective Cognitive Measures

The pre-morbid IQ as measured with the WTAR showed that the sample performed within the high average range (mean = 116.17, standard deviation = 9.42), with performance ranging from low average to superior. All baseline mean scores on cognitive tests fell within the average range of performance compared to normative samples (Supplementary figures S1- S4).

Pairwise comparisons revealed several significant changes across CBT-I in the cognitive functioning battery (Table 3). In terms of sustained attention (CPT-II), the number of commissions were significantly decreased ($t = 3.65$, $p < 0.01$), meaning participants were better able to distinguish targets from non-targets. Detectability was also significantly improved ($t = -3.64$, $p < 0.01$) at post-treatment, meaning that the participants had an increased ability to detect targets in the task. Executive function as measured with the TOL showed significant changes with the pairwise group comparisons, including increased total correct ($t = -2.88$, $p < 0.05$), decreased execution time ($t = 5.42$, $p < 0.0001$), decreased total time ($t = 5.09$, $p < 0.0001$), and decreased time violations ($W = 4.00$, $p < 0.05$). No significant changes were revealed in the verbal memory task (CVLT-II). Pairwise comparisons for the logical memory tasks (WMS-III LM) showed significant improvements in a number of LM-I scores including: recall total score ($t = -5.15$, $p < 0.0001$), thematic total score ($t = -4.10$, $p < 0.001$), first recall total score ($t = -5.56$, $p < 0.0001$). Performance on LM-II scores also improved, including: recall total score ($t = -5.41$, $p < 0.0001$) recognition total score ($t = -2.36$, $p < 0.05$) and thematic total score ($W = -5.16$, $p < 0.001$).

Next, the individual levels of change were determined for the TOL and WMS LM-I and LM-II tasks using the RCI_{PE}, which corrects for measurement error and practice effects. RCI_{PE} results indicated that most participants did not show a reliable change across treatment and that

<6.90% reliably improved across CBT-I for each variable, despite showing a group-wise trend (Supplementary Table S2 and S3).

Self-report cognitive and psychosocial functioning measures

Pairwise comparisons of the self-report measures showed that the PDQ-D total score significantly improved across treatment ($t = -9.95$, $p < 0.001$, $d = 0.65$). The subscale scores of the PDQ-D all significantly decreased from baseline to post-treatment, with medium effect sizes for retroactive memory, proactive memory, and planning/organization (Table 4). The FAST total score significantly decreased from baseline to post-treatment ($t = -3.90$, $p < 0.001$, $d = 0.40$; Table 4). Pearson's correlations revealed significant correlations between baseline insomnia severity (ISI) and PDQ-D ($r_P = 0.45$, $p < 0.05$) and FAST ($r_P = 0.46$, $p < 0.05$). Table 5 shows the results of the linear mixed effects models for PDQ-D and FAST. The linear mixed effects models revealed that age and ISI had a significant effect on PDQ-D ($x^2(4) = 39.52$, $p < 0.001$) and FAST ($x^2(4) = 32.83$, $p < 0.001$), while time (across baseline and post-treatment) was not significant.

Discussion

The current study examined the effect of CBT-I on cognitive functioning measured objectively and by participant self-report measures. The first aim of the study was to determine whether objectively measured cognitive domains significantly change in those with insomnia disorder following CBT-I treatment. At baseline, our sample of participants with insomnia disorder performed within normal limits within all objective cognitive domains measured. With respect to objective cognitive functioning across treatment, results revealed several variables that significantly improved based on pair-wise comparisons within the group. Following CBT-I, participants showed significant increased sustained attention and lower response inhibition, due

to fewer mistakes in the CPT-II task. Detectability was also significantly improved, meaning participants showed improved perceptual power or "sharpness" during the task. This is in line with previous studies which showed those with insomnia had less accurate or slower sustained attention which was improved when symptoms improved (Altena et al., 2008). Increased problem-solving skills and mental flexibility were observed based on the improvements in total correct, and decreased execution and total times for the TOL task. In terms of memory, there were no changes in unstructured, non-contextual verbal memory, based on the CVLT-II task. This task had different versions used at baseline and post-treatment, to avoid practice effects. We did see significant improvement in several domains of the structured verbal memory (i.e., ability to verbally learn and recall details of a story), as seen in the WMS-III LM task. Recall and recognition scores were improved from baseline to post-treatment, however, the same stories were used 8-10 weeks apart and therefore practice effects may have influenced performance.

Although structured verbal memory/logical memory showed significant group effects across treatment, the practice effects were not accounted for in the pairwise analysis. The potential practice effects were controlled for with the RCI_{PE}, which involved examining individual levels of change and categorizing whether the cognitive evaluation resulted in reliable improvement, deterioration, or no reliable change. The majority of individuals did not show a reliable change after accounting for practice effects for the TOL and WMS-III LM tasks (shown in Supplementary Tables S2 and S3). This suggests that although there was a significant improvement within the group, it may be best accounted for by practice at the individual level. RCI methods do not account for regression to the mean, which means they are less accurate when applied to participants who scored exceptionally low or high at baseline (Iverson, 2011). There are few participants who scored outside of the low average to high average range on these

tasks, which indicates this is a more accurate method for controlling for practice effects within our sample.

As well, there may have been a ceiling effect since all the mean cognitive domains were within average range. This signifies that the sample were not significantly impaired at baseline compared to the normative sample. Given that years of education and premorbid functioning were relatively high in our sample, it is likely that the self-reported deficits in cognition and functioning describe a subjective relative decrease from a likely high premorbid performance. This is a high functioning group from a cognitive perspective, but interestingly their perceived cognitive deficits did not align with their actual test performance at baseline. This suggests that the subjective experiences of these participants with insomnia were that they were not performing as well as they should be (despite being within normal limits), as reflected in the baseline self-report cognitive complaints.

This study provided evidence for small-to-moderate effects of CBT-I on self-report improvements in cognitive and psychosocial functioning. Self-report measures of cognitive deficits were significantly improved on all subscales (i.e., attention, proactive memory, retroactive memory, planning and organization) following CBT-I. When comparing objective and subjective data, there was a discrepancy at baseline wherein participants perceived their cognitive functioning to be worse than it was. Following CBT-I treatment, there seemed to be improved agreement between objective and subjective cognitive test scores. There was also a significant improvement in self-reported psychosocial functioning as well, which is in line with the few studies which have measured this construct (Maguen et al., 2021). This is notable since many of the domains captured in the FAST are not easily changed within the short time span of 8 weeks when the post-treatment measures were collected (e.g., occupation, financial issues,

interpersonal relationships, etc.). This small effect size may be something that continues to change or improve following a longer period post-treatment.

The second objective of this research was to understand the relationship between self-report cognitive abilities and psychosocial functioning while controlling for improvements in insomnia symptoms and the impact of age. Perceived cognitive ability and functioning deficits were significantly predicted by insomnia symptom severity across treatment and age. This suggests that improvements in insomnia following CBT-I explain the simultaneous improvements in cognitive and functioning deficits, while controlling for age (since age is known to influence cognitive functioning). Time was not a significant predictor for either PDQ-D or FAST, indicating that the covariates accounted for the changes seen across treatment. This means that without the improvement in insomnia symptoms, changes in cognition and functioning may not have occurred. Together, these results suggest that decreased insomnia symptoms may be necessary for improvement in self-reported cognitive and functional abilities.

Cognitive deficits are a common concern amongst those with insomnia (Herbert et al., 2018), so it is encouraging that participants' perceptions of their cognitive abilities improved following treatment with CBT-I. This suggests that although deficits in domains of cognitive ability were not substantiated with the objective cognitive data at baseline or follow-up, their subjective experiences in the areas of attention, memory, and planning and organizing changed with treatment. These domains were not specifically targeted in CBT-I in that cognitive remediation is not provided. However, common beliefs about sleep in insomnia are addressed in sessions 4 and 5 with 'myth busting' unhelpful thoughts related to the impact of sleep on functioning. This brief cognitive intervention draws awareness to thoughts that relate sleep and

cognition/functioning and introduces ideas for cognitive restructuring and questioning how much their abilities are impacted by sleep.

Limitations and Future Directions

A significant limitation of the current study was the lack of control group. We attempted to account for repeated measures of tasks more prone to practice effects with the reliable change index. In the future, the use of a waitlist control group or recruiting a healthy control group would be beneficial for understanding more about the impact of CBT-I on cognitive domains or allow for the interpretation of deficits in comparison to a non-insomnia population. Either of these control conditions would enhance the interpretability of the experiences of cognitive or functional changes across CBT-I. Future studies could also focus on including participants who have poorer objectively measured cognitive scores at baseline, which would eliminate the possibility of ceiling effects seen in our sample.

Further, our sample of participants were somewhat homogenous in terms of ethnicity and there was a higher percentage of female participants, which may be explained by the increased prevalence of insomnia in females (Morin & Jarrin, 2022) and the increased likelihood of females seeking therapy (Drapeau et al., 2009). Recruiting a more diverse population could improve generalizability of these findings.

Another limitation of our study is the relatively small sample size, and confirming these findings with a larger sample size would allow for analysis of subgroups. Our sample included those with comorbidities that can be associated with cognitive impairments (e.g., depression and sleep apnea) that were currently managed/treated. Future studies should investigate whether there are differences between those with these comorbidities in objective and self-reported cognitive and functioning. Previous studies have shown differences in cognitive ability between

participants with insomnia who have objectively short sleep duration compared to those with normal sleep duration (Fan et al., 2019). Investigating whether differences in cognition and functioning exist between objective short or normal sleep duration could further identify those with insomnia at increased risk of cognitive deficits. Another future direction includes examining objective cognitive measures over a longer follow-up period. This would help to understand the long-term trajectories of both objective and self-report cognitive ability and functioning as participants continue to hone the skills learned in CBT-I. Collection of qualitative data to better understand the subjective experiences of cognition and function changes is another important future direction. This could provide helpful insight into the reasons for change in self-reported change, and shed further light into whether these changes translate into differences in their daily lives.

Conclusions

This study contributes to the understanding of how objective and self-report cognitive functioning tell different stories following CBT-I in a well-characterized sample of participants with moderate to severe insomnia. To our knowledge, this is the first study to illustrate that changes in self-report cognitive ability and psychosocial functioning were related to the improvements in insomnia symptom severity across treatment. The effects of CBT-I on objective cognitive performance showed significant improvement in attention and attentional "sharpness". Further research is needed to confirm these findings with a larger sample and compared to a control group. These results indicate that regardless of objective cognitive abilities, addressing reports of distress related to cognitive complaints and decreased psychosocial functioning remain an important component of insomnia treatment. Doing so may improve how those with insomnia

disorder perceive their symptoms and how perceived insomnia-related cognitive impairments change throughout treatment.

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Table 1: Description of group CBT-I session content

Session	**Content**
Session 1	Introduction to CBT, Psychoeducation on insomnia, Sleep drive, Stimulus control, Time-in-bed restriction therapy
Session 2	Review of psychoeducation, Time-in-bed restriction therapy and Adherence difficulties
Session 3	Counter-arousal strategies (e.g., relaxation training, 'worry time')
Session 4	Review of CBT model, Understanding dysfunctional beliefs about sleep, and Cognitive restructuring
Session 5	Continued cognitive restructuring, Identifying current obstacles with sleep difficulties and Maintaining gains
Session 6	Relapse prevention, Individualized recommendations

Table 2: Demographic and clinical characteristics

Demographics (N=29)	**Mean (SD)**	**Range**
Age (years)	51.93 (14.16)	22- 70
Sex: Males (n, %) Females (n, %)	8 (27.6%) 21 (72.4%)	
Education (total years)	15.6 (2.5)	12- 21
Ethnicity (n, %) Middle Eastern Black Caucasian Chinese	 2 (3%) 1 (3%) 26 (89.6%) 1 (3%)	
Employment Status (n, %) Currently working Student Unemployed Long-term disability Retired	 14 (50%) 1 (4%) 2 (7%) 2 (7%) 10 (36%)	
Psychiatric Comorbidities (n, %) Major Depressive Disorder or Episode Generalized Anxiety Disorder Social Anxiety Disorder Agoraphobia Post-Traumatic Stress Disorder	 10 (34%) 3 (10%) 4 (14%) 1 (3%) 1 (3%)	
Duration of insomnia (years)	14 (11)	1.5- 45
Comorbid Sleep Disorders (n, %) Obstructive Sleep Apnea Restless Legs Syndrome Circadian Rhythm Disorder Excessive Daytime Sleepiness Periodic Limb Movement	 9 (31%) 2 (7%) 1 (3%) 1 (3%) 1 (3%)	
Psychotropic Medication Use Antidepressants Antipsychotics Benzodiazepine Hypnotics Non-Benzodiazepine Hypnotics	 13 (45%) 3 (10%) 7 (24%) 4 (14%)	
Premorbid IQ (standard scores, interpretation)	116.17 (9.42) (High Average)	84-126 (Low Average-Superior)

Table 3: Baseline and post-treatment pairwise comparisons of objective neuropsychological variables

Variable	**Baseline Raw Score mean (SD) (n=29)**	**Post-treatment Raw Score Mean (SD) (n=29)**	**Pairwise Comparison (t-test or Wilcoxon, FDR-corrected p-value) ***
CPT-II Task			
Omissions	1.57 (1.35)	0.92 (1.65)	W = 82.50, $p > 0.05$
Commissions	12.39 (7.19)	9.17 (6.46)	**t = 3.65, $p < 0.01$**
Hit Reaction Time	411. 23 (69.40)	420.35 (61.86)	W = 112.00, $p > 0.05$
Variability	5.79 (1.90)	5.50 (1.66)	T = 0.65, $p > 0.05$
Detectability	0.75 (0.42)	0.99 (0.51)	**t = -3.64, $p < 0.01$**
Response Style	0.60 (0.61)	0.70 (0.67)	T = -0.71, $p > 0.05$
Perseverations	0.25 (0.59)	0.07 (0.26)	W = 6.00, $p > 0.05$
CVLT Task			
Trial 1	7.00 (2.43)	7.14 (2.34)	W = 123.00, $p > 0.05$
Trial 5	13.00 (2.17)	13.76 (1.62)	W = 55.00, $p > 0.05$
Trials 1-5 Total	53.48 (10.14)	56.07 (7.75)	t = -1.66, $p > 0.05$
List B	5.86 (1.94)	5.97 (2.32)	t = -0.27, $p > 0.05$
SD Free Recall	11.66 (3.32)	12.17 (2.49)	W = 149.00, $p > 0.05$
SD Cued Recall	12.52 (3.03)	13.55 (2.40)	W = 92.50, $p > 0.05$
LD Free Recall	11.66 (2.53)	12.34 (3.34)	t = -1.46, $p > 0.05$
LD Cued Recall	12.76 (2.50)	13.24 (2.80)	t = -1.12, $p > 0.05$
Total Intrusions	2.52 (2.64)	3.27 (3.69)	t = -1.19, $p > 0.05$
Total Repetitions	6.07 (4.40)	6.07 (5.57)	t = 0, $p > 0.05$
LD Recognition Hits	14.69 (3.16)	15.10 (1.32)	W = 52.00, $p > 0.05$
Discriminability	2.32 (0.49)	2.42 (0.48)	t = -1.22, $p > 0.05$
WMS LM-I and LM-II Tasks			
LM-I Recall Total Score	37.86 (11.20)	45.69 (9.34)	**t = -5.16, $p < 0.0001$**
LM-I Thematic Total Score	16.07 (3.57)	18.82 (2.95)	**t = -4.10, $p < 0.001$**
LM-I 1st Recall Total Score	22.72 (7.27)	28.38 (6.43)	**t = -5.56, $p < 0.0001$**
LM-I Learning Slope	5.37 (3.31)	4.31 (1.85)	t = 1.51, $p > 0.05$
LM-II Recall Total Score	23.10 (9.82)	29.38 (7.66)	**t = -5.41, $p < 0.0001$**

LM-II Recognition Total Score	26.20 (2.57)	27.15 (2.11)	**t = -2.36, $p < 0.05$**
LM-II Thematic Total Score	10.62 (3.27)	12.31 (2.38)	**W = 41.5 $p < 0.01$**
Percent Retention	81.00 (23.24)	89.07 (11.08)	t = -2.36, $p > 0.05$
TOL Task			
Total Correct	4.07 (2.07)	5.46 (2.74)	**t = -2.88, $p < 0.05$**
Total Move Score	33.36 (15.98)	26.00 (20.86)	t = 2.21, $p > 0.05$
Initiation Time	74.00 (42.98)	63.32 (27.30)	t = 1.60, $p > 0.05$
Execution Time	234.50 (90.58)	168.11 (75.26)	**t = 5.42, $p < 0.0001$**
Total Time	308.50 (97.27)	231.43 (83.50)	**t = 5.09, $p < 0.0001$**
Time Violations	0.96 (1.20)	0.32 (0.61)	**W = 4.00, $p < 0.05$**
Rule Violations	0.43 (0.74)	0.14 (0.36)	W = 9.00, $p > 0.05$

Table 4: Self-report baseline and post-treatment pairwise comparison and effect sizes

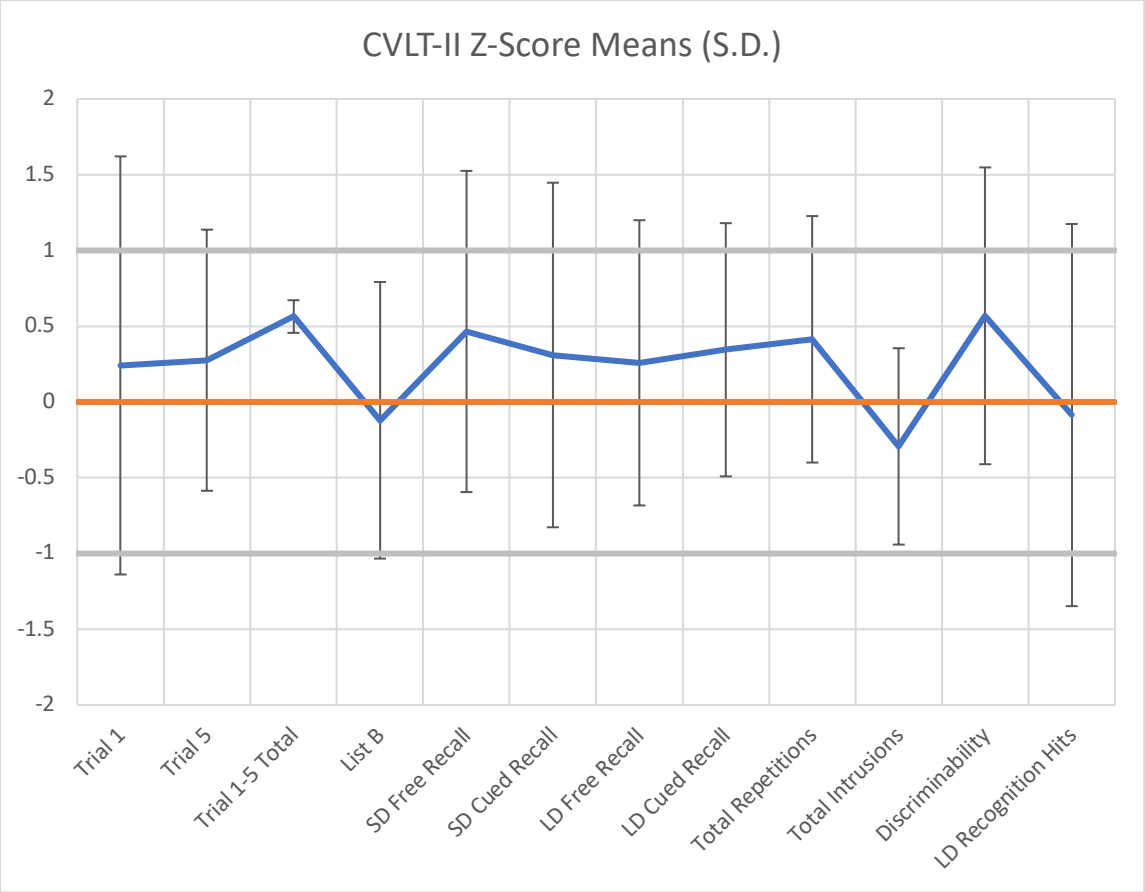
Self-Report Measure	**Baseline Score Mean (SD) (n=29)**	**Post-treatment Score Mean (SD) (n=29)**	**Pairwise Comparison (t-test or Wilcoxon, FDR-corrected p-value)**	**Effect Size (Cohen's d, interpretation)**
ISI	18.24 (4.24)	8.10 (4.97)	t = -9.95, $p < 0.001$	2.19 (large)
PHQ-9	9.24 (5.35)	4.79 (4.03)	W = 27.50, $p < 0.001$	0.91 (large)
STICSA	39.45 (10.42)	35.21 (8.26)	t = -3.60, $p < 0.001$	0.43 (small)
FAST Total	41.31 (13.68)	36.03 (12.09)	t = -3.90, $p < 0.001$	0.40 (small)
PDQ-D Total	28.34 (14.42)	19.62 (11.76)	t = -4.00, $p < 0.001$	0.65 (medium)
PDQ-D Attention	8.76 (4.67)	6.69 (3.68)	t = -3.02, $p < 0.001$	0.48 (small)
PDQ-D Retroactive Memory	7.52 (4.10)	5.52 (3.55)	t = -2.72, $p < 0.05$	0.52 (medium)
PDQ-D Proactive Memory	5.45 (2.77)	3.45 (2.20)	t = -4.25, $p < 0.001$	0.79 (medium)
PDQ-D Planning/Organization	6.62 (4.81)	3.97 (3.64)	W = 22.00, $p < 0.001$	0.60 (medium)

Table 5: Results from the Linear Mixed-Effects Model predicting PDQ-D and FAST

Outcome	**Predictor**	***b***	**t-value (DF)**
PDQ	**ISI**	**1.64**	**3.94 (26),** $p < 0.001$
	Age	**-0.38**	**-3.37 (27),** $p < 0.001$
	Time (post-treatment)	11.80	1.46 (26)
	ISI*Time interaction	-0.48	-0.93 (26)
FAST	**ISI**	**0.98**	**3.18 (26),** $p < 0.001$
	Age	**-0.40**	**-3.23 (27),** $p < 0.001$
	Time (post-treatment)	6.52	1.14 (26)
	ISI*Time interaction	-0.23	-0.64 (26)

Supplementary Figures & Tables

Figure S1: Baseline CVLT-II Z-Score Means



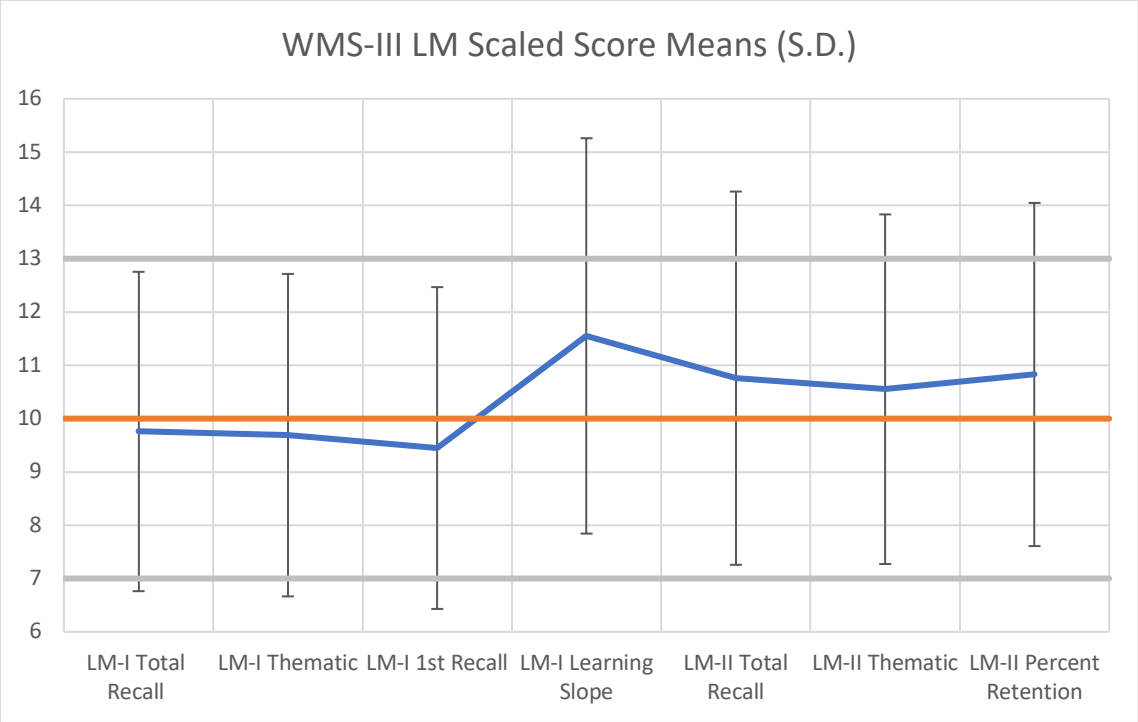
Note:

Blue line: Mean CVLT-II Z-Scores

Orange line: Normative average

Grey lines: Upper and lower limits of Normative scores

Figure S2: Baseline WMS-III Scaled Score Means

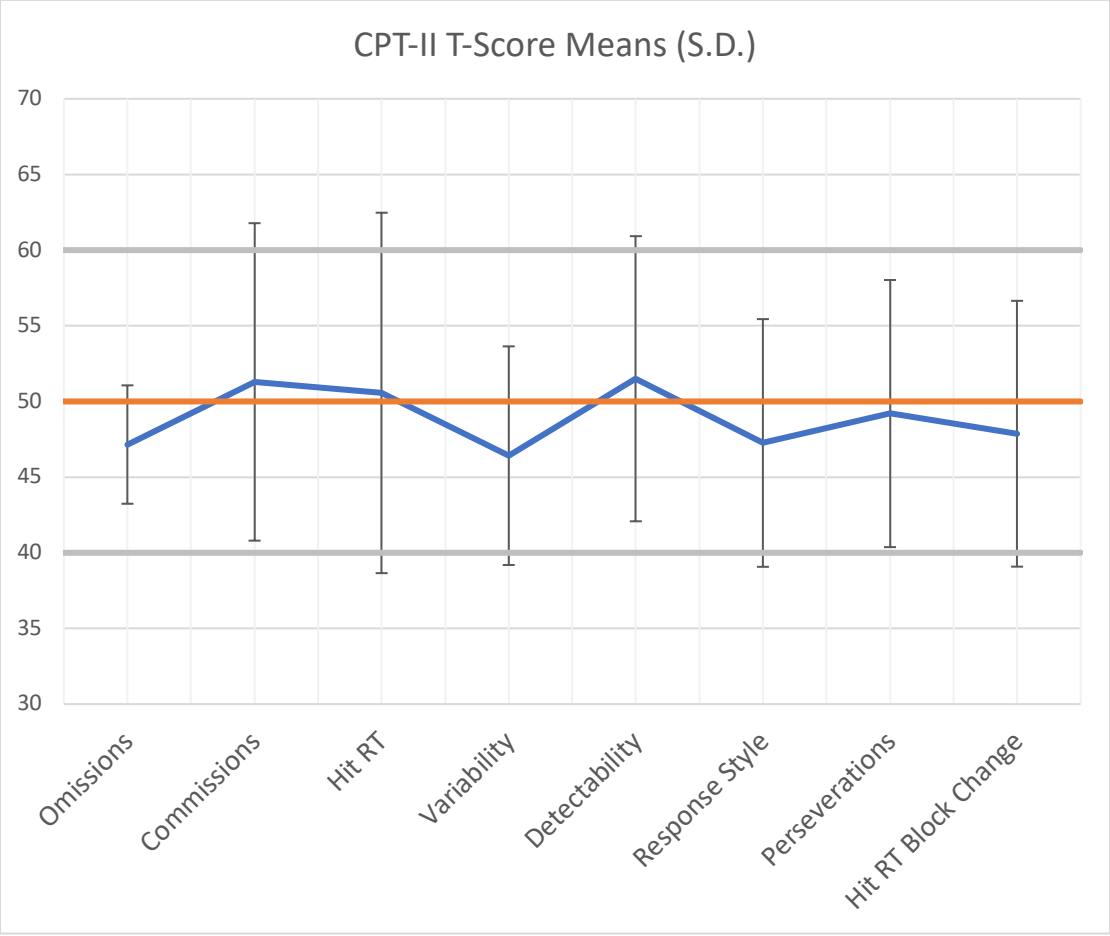


Blue line: Mean WMS-III Scaled Scores

Orange line: Normative average

Grey lines: Upper and lower limits of Normative scores

Figure S3: Baseline CPT-II T-Score Means

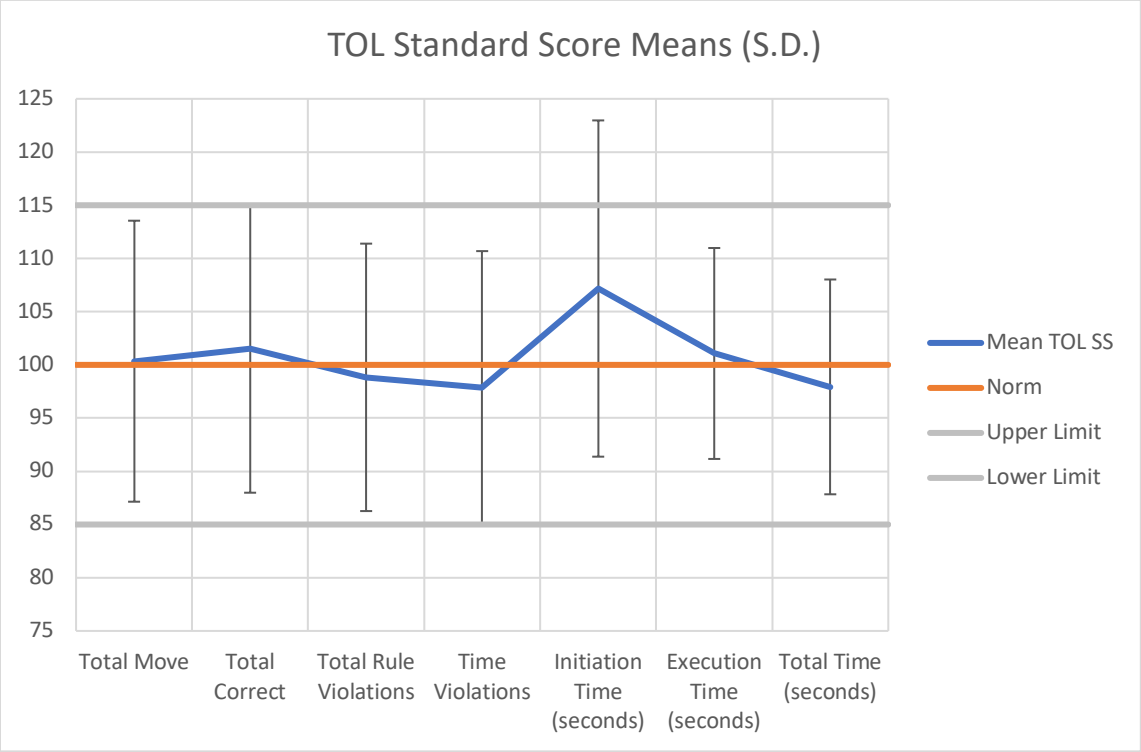


Blue line: Mean CPT-II T-Scores

Orange line: Normative average

Grey lines: Upper and lower limits of Normative scores

Figure S4: Baseline TOL Standard Score Means



Blue line: Mean TOL Standard Scores

Orange line: Normative average

Grey lines: Upper and lower limits of Normative scores

Table S1: Consensus Sleep Diary variables at baseline and post-treatment

Sleep Variable	**Baseline Mean (SD)**	**Post-Treatment Mean (SD)**	**Test Statistic**
Total Sleep Time (minutes)	335.20 (77.22)	358.75 (70.59)	t (25) = -2.27*
Sleep Efficiency (%)	67.46 (14.13)	82.82 (12.56)	t (25) = -6.99**
Sleep Onset Latency (minutes)	56.27 (45.41)	21.75 (25.03)	V = 351**
Wake After Sleep Onset (minutes)	70.71 (50.30)	32.22 (26.06)	t (25) = 5.79**

*p <0.05; ** p <0.01

Table S2: WMS LM-I and LM-II Reliable Change Index for Practice Effects results

WMS Variables	**Reliable Change Interpretation**	**Percentage of Sample**
LM-I Recall Total Score	Improvement: 1/29 No Change: 26/29 Deterioration: 2/29	3.45% 89.66% 6.90%
LM-I Thematic Total Score	Improvement: 1/29 No Change: 27/29 Deterioration: 1/29	3.45% 93.10% 3.45%
LM-I 1st Recall Score	Improvement: 1/29 No Change: 27/29 Deterioration: 2/29	3.45% 93.10% 6.90%
LM-II Recall Total Score	Improvement: 1/29 No Change: 25/29 Deterioration: 3/29	3.45% 86.21% 10.34%
LM-II Recognition Total Score	Improvement: 2/29 No Change: 27/29 Deterioration: 0/29	3.45% 93.10% 0.00%
LM-II Thematic Total Score	Improvement: 3/29 No Change: 25/29 Deterioration: 1/29	10.34% 86.21% 3.45%

Table S3: TOL Reliable Change Index for Practice Effects results

TOL Variables	**Reliable Change Interpretation**	**Percentage of Sample**
Total Correct	Improvement: 1/29 No Change: 27/29 Deterioration: 1/29	3.45% 93.10% 3.45%
Execution Time	Improvement: 1/29 No Change: 28/29 Deterioration: 0/29	3.45% 96.55% 0.00%
Total Time	Improvement: 1/29 No Change: 27/29 Deterioration: 1/29	3.45% 93.10% 3.45%
Time Violations	Improvement: 2/29 No Change: 26/29 Deterioration: 1/29	6.90% 89.66% 3.45%

CHAPTER 3

Study 2: Cognitive Behavioural Therapy for insomnia decreases the discrepancy between objective and subjective measures of sleep

Chapter link: In-press

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Cognitive Behavioural Therapy for insomnia decreases the discrepancy between objective and subjective measures of sleep

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Abstract

Introduction: Individuals with insomnia disorder often exhibit differences between reported experiences of sleep and objectively measured sleep parameters; however, the implications of this subjective-objective sleep discrepancy during treatment remains unclear.

Objective: The aim of this study was to investigate the impact of cognitive behavioural therapy for insomnia (CBT-I) on the discrepancy between objective and subjective measures of sleep, and to assess whether changes in clinical variables such as depression, anxiety, fatigue, and beliefs about sleep, were related to changes in discrepancy.

Methods: Twenty-five participants with insomnia disorder were enrolled in group CBT-I. Sleep measures were continually sampled from baseline until 2 weeks post-treatment with both objective (i.e., actigraphy) and subjective (i.e., sleep diary) methods.

Results: The subjective-objective discrepancy significantly decreased from baseline early on in treatment (following the second session) and were maintained at post-treatment for sleep onset latency, wake after sleep onset (WASO) and sleep efficiency (SE). Total sleep time (TST) discrepancy and misperception decreased from baseline to post-treatment. Improvement in depression symptoms, fatigue symptoms, and negative beliefs about sleep were significantly correlated with the decrease in the discrepancy for WASO and SE.

Conclusion: These findings suggest that CBT-I resolves the mismatch between objective and subjective sleep parameters early in treatment for adults with insomnia. Sleep discrepancy improved from underestimating to accurately estimating TST. Improvement of psychological symptoms were related to decrease in sleep discrepancies across treatment. Future research is

needed to explore how feedback on objective and subjective sleep discrepancy may impact sleep perception across treatment with CBT-I.

Keywords: Insomnia, Cognitive Behavioural Therapy for Insomnia, Actigraphy, Subjective-objective sleep discrepancy

Introduction

Insomnia disorder is characterized by persistent difficulties with falling asleep, maintaining sleep, and/or early morning awakenings accompanied by daytime impairments for at least 3 months (American Psychiatric Association, 2013) and is diagnosed based on subjective reporting of sleep disturbance. Sleep questionnaires gather one's retrospective views on sleep, which are susceptible to the influence of one's mood and anxiety (Hartmann et al., 2020). A prospective sleep diary provides a comprehensive assessment of sleep experiences and self-reported insomnia symptoms. This includes time into and out of bed, amount of time taken to fall asleep (sleep onset latency [SOL]), sleep duration (total sleep time [TST]), length of awakenings after sleep onset (wake after sleep onset [WASO]), and subjective ratings of sleep quality, and is less biased than retrospective questionnaires about sleep (Maich et al., 2018). As a result, subjective sleep parameters may differ based on the method by which they are reported (e.g., sleep diary versus self-report questionnaire; Mallinson et al., 2019). Sleep duration, for example, was significantly longer when reported on a sleep diary compared to questionnaires in a longitudinal cohort of adults. To add to this, self-reported insomnia symptoms were associated with greater perceived differences between sleep diary and questionnaire data (Mallinson et al., 2019).

Although subjective experiences of sleep are the basis of an insomnia disorder diagnosis, objective measures of sleep, including polysomnography (PSG) and actigraphy, have been investigated to understand the value of physiological data to aid in the diagnosis and understanding of insomnia disorder (Andrillon et al., 2020). PSG includes continuous measurement of electrical activity throughout the night, often done in a lab, which can be costly and in conditions that are quite different from at-home sleep. Wrist-worn actigraphy employs

accelerometry to measure movement in order to estimate sleep parameters (Ancoli-Israel et al., 2015). Actigraphy is increasingly used in the sleep medicine field as a cost-effective and convenient tool for measuring sleep variables, which can collect objective sleep data in one's own home environment.

Interestingly, individuals with insomnia disorder commonly describe having sleep quantity and quality issues, even when objective sleep measures appear normal (Fernandez-Mendoza et al., 2011). This discrepancy between self-report or subjective experiences of sleep and objectively measured sleep parameters has been referred to in different ways over time including, "subjective insomnia", "paradoxical insomnia" (Castelnovo et al., 2019), or "sleep-state misperception" (Harvey & Tang, 2012). Paradoxical insomnia was differentiated as a subtype of insomnia in previous versions of the International Classification of Sleep Disorders, but this has been controversial and it is no longer seen as a separate category of insomnia nor conceptualized as being significantly different than those whose sleep disturbance is captured objectively (Rezaie et al., 2018). This subjective-objective discrepancy may occur within a continuum of insomnia disorder, rather than as a separate subcategory of the disorder (Harvey & Tang, 2012). The discrepancy between subjective and objective sleep measures may contribute to the trivialization and under-treatment of insomnia disorder (Harvey & Tang, 2012). Rather, misperception of sleep has been proposed as a "prodrome" for the development of a more serious objective sleep deficit (Harvey & Tang, 2012). The theoretical mechanisms of this transition from misperception of sleep to insomnia disorder that the discrepancy increases distress related to sleep and results in increased arousal. This suggests that sleep misperception itself may be an important target for treatment (Harvey & Tang, 2012).

Cognitive behavioural therapy for insomnia (CBT-I) is the first line treatment for chronic insomnia that targets the cognitive and behavioural factors that contribute to persistent sleep difficulties (Edinger et al., 2021). Important components of CBT-I include psychoeducation, stimulus control, time-in-bed restriction, and cognitive restructuring (Edinger et al., 2009). CBT-I has been shown to be effective at improving self-reported insomnia symptom severity, as well as sleep parameters measured with a sleep diary (Trauer et al., 2015). A recent meta-analysis revealed that PSG sleep measures did not change across CBT-I treatment, whereas objective sleep parameters measured with actigraphy had mixed results including a small improvement in SOL and a reduction in TST with a moderate effect size (Mitchell et al., 2019). There are a number of studies that have investigated subjective and objective measures separately following CBT-I, but relatively few studies that look at the impact of treatment on the discrepancy between objective and subjective sleep parameters (Perrault et al., 2022). One such study by Lovato et al. (Lovato et al., 2021) compared those with insomnia with objective short sleep vs. objective normal sleep duration at baseline. However, a recent study found that actigraphy and PSG identified the "short sleepers" differently, with only 51% consistency between the two objective sleep methods (Galbiati et al., 2021). Interestingly, all participants showed significant improvement in self-report insomnia symptoms and diary-reported sleep parameters following CBT-I regardless of whether they were identified as having short sleep duration or not, which suggests that this is not a reliable or useful distinction (Galbiati et al., 2021).

The studies that have evaluated change in sleep perception across treatment have primarily focused on older adult populations only (Ahn et al., 2022; Dzierzewski et al., 2019; Kay et al., 2015; Lovato et al., 2021; Lund et al., 2013). To date, only one study has investigated subjective-objective sleep discrepancy across treatment with CBT-I in a population that included

young and middle-aged adults as well (Janků et al., 2020). Janků et al. (Janků et al., 2020) looked at session-by-session changes in subjective-objective sleep discrepancies in adults across group CBT-I. They identified that the discrepancies for SOL decreased following CBT-I, but that the discrepancy in WASO did not significantly change (Janků et al., 2020). This study identified that their total population was overall quite accurate with estimating TST at baseline and that there was a shift toward overestimating TST by post-treatment due to a decrease in objective TST and no changes in subjective TST (Janků et al., 2020). Since many with insomnia disorder tend to underestimate TST (as discussed above), this was further investigated in their study by subdividing their population into accurate/overestimators and underestimators, resulting in analysis of relatively small samples. As this is the only study of a adults of a wider age range, further exploration of how sleep perception changes across CBT-I in an adult population with insomnia disorder is warranted.

It has been suggested that those with insomnia disorder may not misperceive sleep only because of poor perception of time, but also because of cognitive and psychological factors (Tang & Harvey, 2005). There is established literature that shows that CBT-I improves psychological symptoms such as depression, anxiety, fatigue, and we were interested in understanding how these changes may or may not correlate with changes in the objective-subjective sleep discrepancy. This may provide additional understanding to how CBT-I works to improve these factors despite the symptoms not being directly targeted by the treatment. In theory, psychological factors such as mood, anxiety, fatigue, or sleep-related cognitions could predispose individuals to altered perception of sleep and serve as a link between how changes in subjective-objective sleep discrepancy may change across treatment. There have been few studies to look at the link between changes in the subjective-objective sleep discrepancy, and

those that have were cross-sectional and focused on mood and anxiety (Dittoni et al., 2013; Herbert et al., 2017). It remains unclear whether psychological variables contribute to the changes in sleep misperception.

Our study aimed to understand how undergoing treatment with CBT-I changes the discrepancy between objective and self-report sleep across a 6-week group CBT-I protocol. The primary objective of this study was to determine how the discrepancy between wrist-worn actigraphy, and sleep diary-derived sleep parameters change across CBT-I. We hypothesized that sleep perception would improve with each subsequent CBT-I session, such that sleep discrepancy decreases across treatment from baseline to post-treatment.

The secondary aim of the study was to understand whether clinical variables including depression, anxiety, fatigue, and maladaptive sleep-related cognitions were associated with a change in the subjective-objective sleep discrepancy across CBT-I treatment. Previous studies have shown that actigraphy is a valid method for measuring sleep parameters in those with comorbid insomnia and depression (McCall & McCall, 2012). Depressive symptoms have been consistently shown to decrease following CBT-I, but there are mixed results for its impact on fatigue symptoms (Ballesio et al., 2017). We hypothesized that depressive and anxiety symptoms will decrease and that this will be related to a decrease in the subjective-objective discrepancy as well. As sleep-related are targeted with CBT-I, we predicted that a decrease in dysfunctional beliefs about sleep and fatigue will also be correlated with a decrease in the subjective-objective sleep parameter discrepancies (Lund et al., 2013).

Methods

Study Participants

Twenty-five participants (Mean Age = 51.93, SD = 14.16, Range 22 - 70), with a diagnosis of insomnia disorder were included in the present study. Participants were screened for eligibility for group CBT-I clinical services after being referred from the Sleep Medicine Program, Firestone Institute for Respiratory Health or the Mood Disorders Outpatient Clinic at St. Joseph's Healthcare, Hamilton. Following the screen, participants were invited to participate in research if their symptoms met criteria for insomnia disorder and they were enrolled in group CBT-I. All study participants were informed in detail about the purpose of the investigation and provided their written informed consent prior to the onset of the study. The study was approved by the local ethics committee, the Hamilton Integrated Research Ethics Board.

To determine the sample size of the study, we used the G*power version 3.1.9.6 (Faul et al., 2009). A total sample size of 23 was needed for repeated measure analysis, with an alpha error of 0.01, a power of 0.8, an expected medium effect size of 0.25 (Crönlein et al., 2019).

Screening

The presence of insomnia disorder was confirmed based on Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria with the Duke Structured Interview for Sleep Disorders (DSISD; Edinger, 2009). Participants were assessed with the DSISD for the presence of other sleep disorders (e.g., sleep apnea, limb movement, and circadian rhythm disorders) and were excluded if the comorbid sleep disorders were considered primary or were untreated/unstable (e.g., those with sleep apnea who were adherent to positive airway pressure therapy were included). The Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) was conducted to assess participants for comorbid psychiatric disorders. Participants were excluded for presence of bipolar disorder and psychotic disorders (e.g., schizophrenia, schizoaffective disorder). It is important to note that CBT-I has been shown to be effective for

those with bipolar or psychotic disorders (Harvey et al., 2015; Waite et al., 2016; Waters et al., 2020); however, we did not these individuals in our study due to provision of manualized group CBT-I. Exclusion criteria also included: current shift work, current or recent history (in the past six months) of alcohol or substance abuse or dependence, unmanaged chronic pain that interfered with sleep, and trauma-related nightmares that disrupted sleep. Participants with other comorbid psychiatric and managed medical conditions were otherwise included, since CBT-I for insomnia disorder has been shown to be effective in the context of a range of co-occurring psychiatric conditions (Raglan et al., 2019). Prescription and over-the-counter sleep medications were allowed over the duration of the study provided participants remained on a stable dose throughout (i.e., were using the medication non-contingently from screening to post-treatment).

Study Design

The present study employed a within-subject repeated-measures design. Participants completed an initial screening visit to determine eligibility for the study. A baseline assessment was conducted within two weeks prior to initiating group CBT-I along with a battery of measures related to sleep and clinical variables. Actigraphy monitoring was initiated at the baseline visit and continued until the post-treatment visit within two weeks after completing CBT-I. This same battery was administered again at a post-treatment assessment, within two weeks following completion of group CBT-I. Participants were considered completers if they attended four or more of the six group CBT-I sessions. If they missed a session, they were provided with an individual make up session.

Study Measures

Daily Measures

Actigraphy

Objective measures of sleep were obtained using the wrist-worn Philips Respironics Actiwatch Spectrum Plus device. The actigraphy data were collected using 1-minute epochs continuously from the baseline visit, throughout CBT-I, until the post-treatment visit which occurred within two weeks after completing the final treatment session. Actigraphy data was extracted using the Philips Respironics Actiware software (version 6.0). Raw actigraphy reports were visually inspected to identify artefacts and remove missing data (i.e., device removed from wrist) according to published guidelines (Ancoli-Israel et al., 2015). Default sleep/wake thresholds from the software were then used to determine periods of sleep and activity periods. The default wake detection method in the Actiware software was used to detect sleep and rest intervals. The automatic wake threshold method was used, which computes an automatic threshold for wake based on activity counts. The threshold uses the sum of activity counts divided by mobile time multiplied by 0.88. Visual inspection of the visualization of activity and light data along with the Actiware-detected intervals was used to verify that the sleep intervals were not non-wear, where intervals were removed if there was, for instance, zero activity throughout the duration sleep interval. The actiware sleep algorithms yields better performance in sleep detection than the Cole-Kripke algorithm, when compared with polysomnography (Gao et al., 2022). The extracted outcomes included the average SOL, WASO, TST, and SE for each period of interest (i.e., baseline, week 1, 2, 3, 4, 5 and post-treatment).

Sleep Diary

Self-reported measures of sleep were obtained using a sleep diary. Sleep diaries are the gold-standard for tracking sleep disturbances, and the information derived is used to determine sleep efficiency, initiation, and maintenance (Carney et al., 2012). The *Consensus Sleep Diary for Morning* (CSD-M) is a standardized prospective sleep assessment tool that requires

participants to self-report daily estimates of sleep patterns and quality upon waking. Information from the CSD-M was used to calculate sleep parameters, including SOL, WASO, TST, and SE (SE percentage = TST/time in bed). Data were averaged across the week for the CSD-M sleep parameters. Averages were the CSD-M sleep parameters were only calculated if ≥ 5 days of data were recorded for that week. Eligible participants were asked to complete the CSD-M for two weeks prior to treatment, which was used to confirm the presence of insomnia (i.e., SE ≤ 85%). They were asked to continue to use the CSD-M throughout the 6-weekly CBT-I sessions until the post-treatment visit, which occurred within 1-2 weeks after the final treatment session.

Clinical Measures

The *Insomnia Severity Index* (ISI) is a 7-item self-report scale used to evaluate the severity of insomnia symptoms (Bastien et al., 2001). Each item is scored on a 0 to 4 scale with higher values representing greater insomnia severity (Bastien et al., 2001). Scores > 11 are indicative of clinical insomnia and an improvement of ≥ 9 was consistent with marked improvement in symptoms (Morin et al., 2011). The ISI has shown high internal consistency in clinical samples (Cronbach's $\alpha = 0.91$; Morin et al., 2011). In this sample, internal consistency for ISI was good (Cronbach's $\alpha = 0.71$). This is in line with the literature, which shows that most studies show Cronbach's $\alpha \geq 0.70$, but with high heterogeneity across studies (Cerri et al., 2023).

The *Dysfunctional Beliefs About Sleep* (DBAS) is a 16-item scale used to assess changes in sleep-related cognitions such as worry, faulty beliefs, and attentional bias across treatment, validated in an insomnia population (Morin et al., 2007). Each item is scored between 0 (strongly disagree) to 10 (strongly agree), and an average score is calculated. Higher scores indicate greater sleep-related dysfunctional cognitions (Morin et al., 2007). The DBAS has strong internal

consistency (Cronbach's α= 0.80), concurrent validity, and sensitivity to change following CBT-I (Chung et al., 2016). In this sample, internal consistency was good (Cronbach's α = 0.81).

The *Fatigue Severity Scale* (FSS) is a 9-item questionnaire that assesses physical tiredness and lack of energy (Krupp et al., 1988). Responses are on a 7-point scale ranging from 1 (strongly disagree) to 7 (strongly agree), with higher scores indicating greater fatigue (Krupp et al., 1988). It has been shown to measure self-reported fatigue with high internal consistency (Cronbach's α= 0.95; Rosti-Otajärvi et al., 2017). In this sample, internal consistency for FSS was high (Cronbach's α = 0.94).

The *Patient Health Questionnaire-9* (PHQ-9) is a 9-item brief self-report measure of depressive symptoms rated from 0 ("not at all") to 3 ("nearly every day") (Kroenke et al., 2001). A total score of greater than 10 has been shown to have sensitivity of 88% and specificity of 88% for major depression in a primary care setting (Kroenke et al., 2001). In this sample, internal consistency was high (Cronbach's α = 0.88).

The *State-Trait Inventory for Cognitive and Somatic Anxiety* (STICSA) is a 21-item self-report measure of anxiety, which includes subscales for both cognitive and somatic anxiety (Ree et al., 2008). Items are rated on a 4-point Likert scale. It has been validated in clinical and non-clinical samples and the subscales have demonstrated excellent internal consistency (Cronbach's α > 0.87; Grös et al., 2007). In this sample, internal consistency was high (Cronbach's α = 0.91).

Intervention

The CBT-I intervention was a manual-based group intervention that consisted of six two-hour sessions. It was conducted by licensed doctoral clinical psychologists and trained clinical psychology graduate students. The groups consisted of a maximum of six participants. The manual was developed to include components of the intervention such as psychoeducation and

sleep hygiene, stimulus control, time in bed restriction, cognitive restructuring, relaxation/counter-arousal strategies, and relapse prevention (Carney & Manber, 2009). Session-by-session content is included in Table 1. Time-in-bed restriction was conducted based on a minimum time-in-bed of 5 hours and was extended when SE reached 85%. The sleep window was extended by 15-30 minutes at a time and the positioning of the sleep window was decided collaboratively between the clinicians and participants based on preferences to ensure highest likelihood of adherence (SD et al., 2015). Stimulus control instructions included the following guidelines (MD et al., 2023): (1) only go to bed when sleepy, but not before earliest bedtime; (2) not engage in wakeful activities in bed; (3) not take naps during the day; (4) wake up at the same time every day; (5) leave the bed or bedroom if unable to fall asleep at the beginning or middle of the night, and only return when sleepy; (6) if unable to fall back to sleep within 30 minutes, leave the bed or bedroom and only return when sleepy. These stimulus control guidelines were introduced at the first session and reinforced at each subsequent session. Learning was reinforced with weekly home practice exercises, including stimulus control, time in bed restriction, relaxation strategies, and cognitive strategies.

Objective and self-report discrepancies

To examine the primary objective of determining how the discrepancy in sleep parameters change across treatment, we first calculated the "discrepancy score" between the actigraphy and sleep diary-derived sleep parameters by subtracting the sleep diary value from the actigraphy value for each sleep parameter (SOL, WASO, TST, and SE). A positive discrepancy score indicated a subjective underestimation of sleep parameters with the sleep diary and a negative score indicated an overestimation with the sleep diary. This is an established measure of sleep discrepancy in the literature (Crönlein et al., 2019; Dzierzewski et al., 2019; Fernandez-

Mendoza et al., 2011; Lovato et al., 2021). The discrepancy score was calculated as the difference between the average subjective and objective sleep parameter value for each week. In addition to this absolute discrepancy score, the misperception index (MI) was calculated for TST as a relative measure of discrepancy (objective TST - subjective TST/objective TST), as this is a formula frequently reported for TST misperception (Manconi et al., 2010). Positive MI indicates underestimation of objective sleep and negative MI indicates overestimation with the sleep diary.

Statistical Analyses

Statistical analyses were performed using *R* (Version 4.2.2). We first determined whether sleep parameters changed across CBT-I using paired analysis between baseline and post-treatment. The changes in the actigraphy sleep parameters, sleep diary-derived parameters, and discrepancy scores from baseline to post-treatment were determined using either the Wilcoxon or paired t-tests, depending on normality of the data, which we determined using the Shapiro-Wilks test for normality. Effect sizes were determined with Cohen's D.

The primary objective of assessing how the discrepancy in sleep parameters changed across all timepoints (baseline compared to each subsequent sessions and post-treatment) was determined using a linear mixed-effects models (LMM). Four separate models were used with the sleep parameter discrepancy scores (for SOL, WASO, TST, and SE) as the dependent variable and time (i.e., the sessions) as the independent variable. LMMs was used because the data does not meet the criteria of independence due to the within-subject design. LMM allows for regression in which observations are correlated, by including a 'random effects' factor to specify that data within each participant is dependent. The Maximum-Likelihood estimation was used. For models with a significant main effect of time, post hoc pairwise comparisons between

baseline and each subsequent session, resulting in 6 contrasts (baseline to session 1, 2, 3, 4, 5 and post-treatment). Multiple comparisons were corrected for using the Bonferroni method.

The secondary objective namely, to understand how clinical variables were associated with the discrepancy in sleep parameters was investigated using repeated measures correlations (RMC). This was performed using the rmcorr package in *R* (Bakdash & Marusich, 2017). This allowed for assessment of how change in each clinical variable was associated with the change of discrepancy between objective and subjective sleep variables from baseline to post-treatment. The RMC takes into account within-participant variation, rather than averaging the repeated measure data from each participant before performing a correlation (which does not meet the assumption of independence). RMC analysis estimates the common regression slope/association between repeated measures that is shared among participants. Non-independence is accounted for by considering each participant as a factor-level variable and therefore removing inter-individual variation. The rho correlation coefficient is bounded by -1 to 1 and represents the strength of the overall or common intra-individual linear relationship between two measures over multiple timepoints (Bakdash & Marusich, 2017). Multiple comparisons were corrected for using the Bonferroni method (5 clinical variables and 4 sleep discrepancy scores were correlated for a total of 20 tests, therefore the adjusted threshold for significance was set to $p < 0.0025$).

Results

Data from 25 participants were included in the final analysis. Two participants completed the final session but stopped recording in their sleep diaries after session 6. For these two participants, the session 5 sleep diary was used to calculate the post-treatment discrepancy (i.e., last observation carried forward [LOCF]). The LOCF approach was used for session 5 since the content of session 6 was relapse prevention and did not include or introduce new content, and

therefore the data are comparable for these two participants. Demographic characteristics are described in Table 2. Changes in sleep parameters and self-report clinical scales across CBT-I are shown in Table 3. Completing CBT-I led to significant reduction in insomnia severity (ISI; t = 10.26, $p < 0.01$, $d = 2.31$), which reflects a clinically significant improvement (i.e., decrease from moderate insomnia to not clinically significant insomnia). There were also significant improvements in dysfunctional beliefs about sleep (DBAS, t = 8.44, $p < 0.01$, $d = 1.75$), depressive symptoms (PHQ-9, t = 5.27, $p < 0.01$, $d = 0.96$), anxiety symptoms (STICSA, t = 3.22, $p < 0.01$, $d = 0.46$), and fatigue (FSS, t = 6.66, $p < 0.01$, $d = 1.08$).

Paired-analyses from baseline to post-treatment of the sleep diary and actigraphy-derived sleep parameters are shown in Table 3. Self-reported sleep variables, derived from sleep diaries, all showed significant improvement across CBT-I. Self-reported SOL was significantly shorter (V = 324, $p < 0.01$, $d = 0.90$), self-reported WASO significantly decreased (V = 313, $p < 0.01$, $d = 1.12$), and the SE was significantly higher (V = 19.5, $p < 0.01$, $d = 1.10$), all with large effect sizes. The self-reported TST did not significantly change (t = -1.42 , $p = 0.17$). Actigraphy-derived objective sleep parameters showed a reduction in WASO with a small effect size (t = 2.21, $p = 0.04$, $d = 0.44$), and TST decreased with a large effect size (V = 4.19, $p < 0.01$, $r = 0.84$). There were no significant changes in objective SOL (V = 163, $p = 0.72$). and SE (V = 176.5, $p = 0.72$) between baseline and post-treatment.

The primary aim was to evaluate how the discrepancy scores between self-reported and actigraphy-derived sleep parameters changed across CBT-I using LMMs. The LMMs revealed significant reduction in the discrepancy scores between baseline and each of the 6 subsequent sessions for the SOL discrepancy scores ($\chi^2(6) = 45.12$, $p < 0.001$) and the WASO discrepancy scores ($\chi^2(6) = 75.94$, $p < 0.0001$). The SE discrepancy scores ($\chi^2(6) = 58.71$, $p < 0.001$)

significantly decreased between baseline and session 2, 3, 4, 5, and post-treatment (i.e., all contrasts except between baseline and session 1). The absolute TST discrepancy scores ($\chi^2(6) = 28.86$, $p < 0.001$) significantly decreased from baseline to post-treatment following correction for multiple comparisons (Bonferroni method). The LMM revealed that the relative TST MI scores significantly decreased between baseline and post-treatment only ($\chi^2(6) = 27.23$, $p < 0.001$) following Bonferroni correction. The mean MI was positive at baseline and negative at post-treatment. These results are illustrated in Figures 1-5.

The secondary analysis of how change in discrepancy scores was related to change in clinical variables are reported in Table 4. The direction of the correlation was related to *how* the discrepancy changed across CBT-I. For example, sleep diary SE and TST values were both lower than the actigraphy values at baseline and increased following treatment; whereas the sleep diary SOL and WASO values were higher than the actigraphy values at baseline and decreased following treatment. The direction of this change is the direction of the RMC results (positive for SE/TST and negative for SOL/WASO). The RMC analyses revealed that there were significant associations between the change in WASO discrepancy and several self-report clinical variables including insomnia severity (ISI r = -0.60), depression (PHQ-9 r = -0.61), and dysfunctional beliefs about sleep (DBAS r = -0.61) after correction for multiple comparisons. It was not significantly correlated with fatigue (FSS r = -0.52) after correction for multiple comparisons, or anxiety (STICSA r = -0.45). The change in SE discrepancy scores were also significantly correlated with insomnia severity (ISI r = 0.72), depression (PHQ r = 0.60), fatigue (FSS r =0.57), and dysfunctional beliefs about sleep (DBAS r = 0.68) after correction for multiple comparisons, but not anxiety (STICSA r = 0.46). The RMC results showed that the change in discrepancy for SOL and TST were not correlated with the specified clinical variables measured.

Discussion

Our study aimed to investigate the change in subjective-objective sleep discrepancy across CBT-I using a sleep diary and wrist-worn actigraphy device. Our analyses revealed a significant decrease in the discrepancy between subjective and objective measures of sleep following CBT-I. This change occurred after a single session for SOL and WASO, and after the second session for TST and SE, and persisted throughout the course of the CBT-I treatment. This outcome could be explained as an improvement in sleep perception that was observed early on in treatment and was maintained by post-treatment. At baseline, our study showed a significant mismatch between sleep-diary and actigraphy. This was expected based on previous cross-sectional studies (Bilterys et al., 2023), which showed that those with insomnia disorder tended to overestimate time to fall asleep, length of awakenings, and underestimate the duration of sleep. Previous studies that investigated the subjective-objective sleep discrepancy with actigraphy as the objective measure also found the discrepancy significantly decreases following CBT-I (Ahn et al., 2022; Dzierzewski et al., 2019; Janků et al., 2020; Perrault et al., 2022). However, many of the studies of the change in subjective-objective sleep discrepancy across CBT-I have focussed on older adults (i.e., over age 55) only (Ahn et al., 2022; Dzierzewski et al., 2019; Kay et al., 2015; Lovato et al., 2021; Lund et al., 2013). Our results extend these findings by showing the decrease in discrepancy occurs in a group of treatment-seeking adults with insomnia disorder with a wide age range (ages 22-70 included), and not only in older adults. This is an important replication of the single study which has also found decreased discrepancy in adults across CBT-I (Janků et al., 2020).

The changes in the discrepancy scores were significant for each of the sleep parameters in our study (SOL, TST, WASO, SE) and could be driven by several factors, including more

awareness of sleep as participants gain more experience with documenting multiple aspects of their sleep experience with the sleep diary over time. Importantly, the initial session of CBT-I introduces critical psychoeducation on insomnia, including the diagnostic criteria, stimulus control, and rationale for time-in-bed restriction. During the first session participants are asked to pay attention to subtle changes within their 24-hour sleep experience and document this on the sleep diary throughout the course of CBT-I. As a result, the decrease in sleep discrepancy may be seen as a 'correction' in sleep perception. However, this alone is unlikely to account for the significant change in discrepancies between baseline and the first session, since participants had already filled out the sleep diary for 1-2 weeks prior to initiating treatment. The sleep diary is a necessary tool for effectively implementing time in bed restriction and stimulus control (Maich et al., 2018), since clinicians base personalized recommendations for time into and out of bed based on the behaviours from the previous week as recorded on the sleep diary. Therefore, sleep diary reported sleep parameters reflect both the behavioural changes and perceptual changes across treatment. In theory, actigraphy should also capture behaviours that encompass stimulus control and time in bed restriction (i.e., movements of getting into/out of bed upon awakenings, with an emphasis on getting out of bed if awake for more than 20 minutes), but not perception. Since psychoeducation occurs alongside behavioural changes of stimulus control and time-in-bed restriction, we are unable to disentangle which components are driving this early change in subjective-objective sleep discrepancy.

Our results showed that the TST discrepancy significantly decreased from baseline to post-treatment. Two recent studies also showed that the discrepancy in TST significantly improved with CBT-I (Janků et al., 2020; Perrault et al., 2022). This trend began in our study following the first session, when time in bed restriction and stimulus control strategies were delivered, with

adjustments to implementing these strategies made in subsequent sessions based on sleep diary analysis and problem solving. A recent meta-analysis analyzed how sleep duration changed across CBT-I measured with PSG, actigraphy, and sleep diary (Chan et al., 2023). TST significantly increased by an average of 30 minutes following CBT-I when measured with sleep diary and PSG. Interestingly, actigraphy-measured TST significantly decreased by an average of 30 minutes following CBT-I. Indeed, this is the trend within our study, as TST measured by the sleep diary increased while TST measured by actigraphy decreased from baseline to post-treatment. The relative change in TST, as measured with the MI, showed a trend from underestimation of TST with sleep diary at baseline to being accurate or overestimating TST across sessions, and was significantly decreased by post-treatment This significant decrease in MI was similar to the results shown by Janku et al. (Janků et al., 2020), except their total sample mean MI was accurate at baseline and were overestimators of TST following CBT-I. This suggests our sample had a greater proportion of participants who underestimated their sleep and that this sleep misperception was corrected across CBT-I.

Another possible explanation for why the subjective-objective sleep discrepancy decreased following CBT-I, is that actigraphy is better able to capture sleep as participants change their behaviours during treatment. Actigraphy has been shown to overestimate total sleep time compared to other objective measures of sleep, such as PSG (Danzig et al., 2020). A drawback of using actigraphy as an objective marker of sleep is that it only provides an indirect measure of sleep based on lack of movement, so a participant who is still in bed may be inaccurately scored as asleep even if they are awake (Sadeh, 2011). This suggests that rather than there being a "misperception" of sleep, participants may be accurately reporting sleep, while actigraphy is overestimating sleep parameters. This may be especially true at baseline, when participants are

more likely to be lying in bed awake, prior to the introduction of stimulus control. A recent study found that the mean amount of misperception of sleep between actigraphy and sleep diary was able to differentiate those with insomnia disorder from healthy controls, which suggests that the difference in these measures is capturable prior to treatment (Te Lindert et al., 2020). In summary, it is possible that actigraphy is better able to capture the "awake time" during and after CBT-I, which may be a driving force of the decreased sleep discrepancy.

The secondary analyses in this study investigated how the changes in subjective-objective sleep discrepancy were related to changes in clinical variables across treatment. The decrease in depression symptoms, dysfunctional beliefs about sleep, fatigue symptoms and insomnia symptom severity overall were significantly correlated with changes in WASO, SE, TST and SOL. These results suggest that there is a correlation in the degree of clinical symptom change alongside the improvement in sleep discrepancy. Depression, fatigue, and negative beliefs about sleep may bias the sleep diary reports at baseline and improvement in these clinical symptoms may help with the 'correction' of the discrepancy by post-treatment. Interestingly, the change in anxiety (as measured with the STICSA) was not correlated with any of the changes in sleep discrepancies, possibly because the degree of change was smaller in this measure compared to the other clinical variables. As these are correlational results, one drawback is that causation of these changes cannot be implied. A future direction of this study is to look at subsets of a larger sample to understand the direction of change (i.e., how sleep discrepancy changes in those with greater depression compared to lower depression scores).

Actigraphy-measured sleep parameters changed less than sleep diary-measured parameters in our study, which is in line with the established literature (Janků et al., 2020). A recent study found that based on at-home actigraphy, most sleep variables did not differentiate insomnia from

controls (Rösler et al., 2023). This study also suggested that the within-subject night-to-night variability in SE and WASO differentiated those with insomnia disorder from healthy controls, but only with small effect sizes (Rösler et al., 2023). A possible future direction of our study is to evaluate whether CBT-I leads to a decrease in the night-to-night variability in sleep parameters rather than the average of each sleep parameter over each week.

There are important implications for how these results could be used therapeutically. For example, Tang and Harvey (Tang & Harvey, 2004) showed that patients who were shown the discrepancy between self-reported sleep estimates and actigraphy recordings had improved anxiety and more accurate SOL estimates. Similarly, use of actigraphy could prove important for showing participant's perceptual differences across treatment. Incorporating feedback from sleep wearables into CBT-I treatment, including the subjective-objective sleep discrepancy, is an important future direction of this work. A recently published study protocol aims to use wrist-worn devices to provide feedback to the participant throughout a randomized controlled trial for CBT-I (Spina et al., 2023). The use of devices has become increasingly popular but current treatments do not routinely use data from objective sleep during treatment. As we have shown in this study, the objective measures of sleep do not match subjective experiences prior to the start of treatment; however, exploring this discrepancy with participants at the start and during treatment has the potential to further improve outcomes within the first few weeks of intervention.

Understanding the neurobiology of insomnia, and in particular, the tendency to underestimate sleep duration/misperceive sleep, is another important future direction of this work. The brain activity of those with insomnia showed there was higher activation with EEG in NREM sleep compared to healthy controls (Lecci et al., 2020). In addition, the density of sleep

spindles appears to differ in those with "paradoxical" insomnia, suggesting a possible neurobiological basis for an increased subjective-objective sleep discrepancy (Benbir Şenel et al., 2021). It is possible that those with insomnia require a greater amount of sleep in order to perceive the state of sleep, which may explain why the objective and subjective experiences of sleep are different for the insomnia population (Hermans et al., 2020). This has been shown for misperception of SOL, since those with insomnia required 34 minutes of undisturbed sleep before recognizing sleep onset, compared to 22 minutes for healthy controls (Hermans et al., 2020). These studies suggest that those with insomnia may be perceiving more "wake-like" brain activity rather than underestimating their sleep (Lecci et al., 2020), and perhaps this is what changes after receiving CBT-I treatment.

There are several limitations of the current study including the lack of a control group to compare our sample to (e.g., those with insomnia undergoing a different treatment, or a wait-list control group). Therefore, we cannot be certain that the changes observed are due to undergoing CBT-I compared to general changes over time. This has been the case with other similar studies (Janků et al., 2020), which suggests that another future direction of treatment should include observing sleep discrepancies across different treatments for insomnia. In addition, our study had a relatively small sample size which limited our ability to look at subsets of our population (e.g., age groups) to further explore factors related to sleep discrepancy. We enrolled participants with other sleep disorders but only if the other sleep disorders were appropriately managed; specifically, if OSA was treated with regular use of CPAP. There is a possibility that those with comorbid insomnia and OSA may respond differently than those with only insomnia (Bensen-Boakes et al., 2022). Our sample captures a "real world" sample from a treatment-seeking population in a tertiary care setting as we aimed to have increased external validity and is in line

with the finding that 30-50% of patients in a sleep clinic have comorbid insomnia and OSA (Zhang et al., 2019). We also included those who were taking sleep medications, and so future studies are needed to investigate how sleep medication use impacts sleep discrepancies across treatment.

To conclude, the present study was the first to assess the impact of CBT-I on the objective and subjective sleep discrepancies outside of older adults and evaluate the associations with change in clinical variables across CBT-I. The subjective-objective sleep discrepancy significantly improved for all sleep parameters in those with insomnia following CBT-I. This change in discrepancy was 'corrected' early on in treatment and was maintained throughout the course of treatment. This suggests that psychoeducation and the early implementation of behavioural components like stimulus control and time in bed restriction, are helpful in changing the mismatch between actigraphy and self-reported sleep. The changes in sleep discrepancy parameters across CBT-I were also associated with the improvement of several clinical variables, such as depression symptoms, fatigue symptoms, dysfunctional beliefs about sleep, and insomnia symptoms in general. Important future directions of this research include using actigraphy as an objective sleep measure to inform participants across treatment, and further exploring the treatment components and clinical factors that influence the sleep discrepancies across CBT-I treatment.

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Table 1: Description of group CBT-I session content

Session	**Content**
Session 1	Introduction to CBT, Psychoeducation on insomnia, Sleep drive, Stimulus control, Time-in-bed restriction therapy
Session 2	Review of psychoeducation, Time-in-bed restriction therapy, Adherence difficulties
Session 3	Counter-arousal strategies (e.g., relaxation training, 'worry time')
Session 4	Review of CBT model, Understanding dysfunctional beliefs about sleep, Cognitive restructuring
Session 5	Continued cognitive restructuring, Identifying current obstacles with sleep difficulties, Maintaining gains
Session 6	Relapse prevention, Individualized recommendations

Table 2: Demographic and clinical characteristics of the sample

Demographics (N=25)	**Mean (SD)**	**Range**
Age (years)	52.92 (14.32)	22-70
Sex: Males (n, %)	7 (28%)	
Females (n, %)	18 (72%)	
Education (total years)	15.44 (2.58)	12- 21
Ethnicity (n, %)		
Arab	2 (8%)	
Caucasian	21 (84%)	
Chinese	1 (4%)	
Black	1 (4%)	
Employment Status (n, %)		
Currently working	11 (44%)	
Unemployed	2 (8%)	
Long-term disability	2 (8%)	
Retired	10 (40%)	
Psychiatric Comorbidities (n, %)		
Major Depressive Disorder or Episode	10 (34%)	
Generalized Anxiety Disorder	3 (10%)	
Social Anxiety Disorder	4 (14%)	
Agoraphobia	1 (3%)	
Post-Traumatic Stress Disorder	1 (3%)	
Duration of insomnia (years)	14 (11)	1.5- 45
Comorbid Sleep Disorders (n, %)		
Obstructive Sleep Apnea	9 (31%)	
Restless Legs Syndrome	2 (7%)	
Circadian Rhythm Disorder	1 (3%)	
Excessive Daytime Sleepiness	1 (3%)	
Periodic Limb Movement	1 (3%)	
Psychotropic Medication Use		
Antidepressants	13 (45%)	
Antipsychotics	3 (10%)	
Benzodiazepine Hypnotics	7 (24%)	
Non-Benzodiazepine Hypnotics	4 (14%)	

Table 3: Baseline to Post-treatment differences in measures

Measure	**Baseline** Mean (SD)	**Post-treatment** Mean (SD)	**Paired analysis** (t-test [t] or Wilcoxon [V])	**Effect Size** (Cohen's D interpretation)
CSD-M Sleep Diary				
SOL (min)	55.27 (50.51)	19.08 (16.93)	V = 324**	0.90 (large)
WASO (min)	147.31 (84.62)	65.86 (38.85)	V = 313**	1.12 (large)
SE (%)	70.44 (14.89)	84.24 (9.22)	V = 19.5**	1.10 (large)
TST (min)	348.26 (88.55)	370.51 (82.25)	t = -1.42	
Actigraphy				
SOL (min)	18.58 (15.30)	16.30 (15.74)	V = 163	
WASO (min)	54.56 (19.64)	45.94 (17.16)	t = 2.21*	0.44 (small)
SE (%)	83.09 (5.80)	82.85 (7.86)	V = 176.5	
TST (min)	413.90 (76.15)	379.34 (88.72)	t = 4.19**	0.84 (large)
Self-Report Measures				
ISI	18.82 (4.26)	7.56 (5.15)	t = 10.26**	2.31 (large)
DBAS	5.98 (1.38)	3.04 (1.93)	t = 8.44**	1.75 (large)
FSS	4.56 (1.50)	3.01 (1.35)	t = 6.66**	1.08 (large)
PHQ-9	9.56 (5.53)	4.84 (4.19)	t = 5.27**	0.96 (large)
STICSA	39.72 (10.70)	35.28 (8.54)	t = 3.22**	0.46 (small)

Notes: N=25; *p<0.05, **p< 0.001; Cohen's d interpretation: 0.2 = small effect size, 0.5 = medium effect size, 0.8 = large effect size

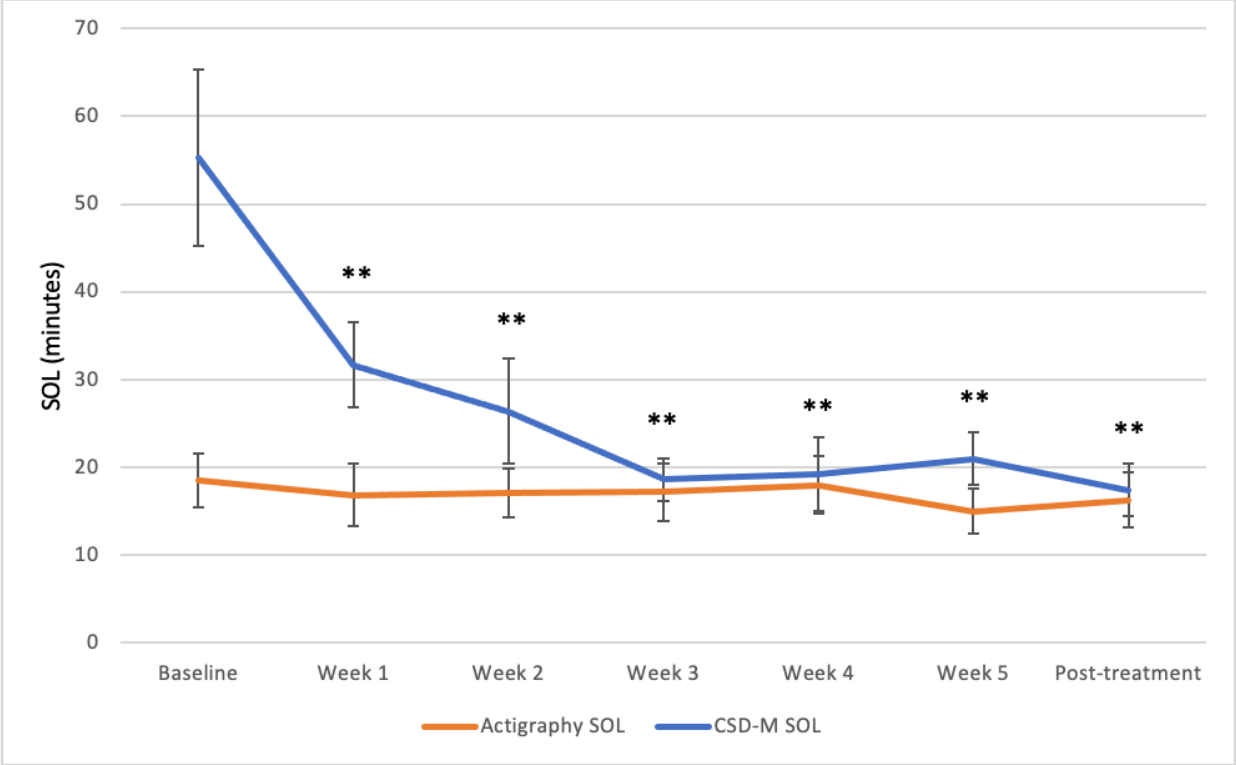
Acronyms: Dysfunctional Beliefs About Sleep (DBAS), Fatigue Severity Scale (FSS), Insomnia Severity Scale (ISI), Patient Health Questionnaire-9 (PHQ-9), Sleep efficiency (SE), Sleep Onset Latency (SOL), State-Trait Inventory for Cognitive and Somatic Anxiety (STICSA), Total Sleep Time (TST), Wake After Sleep Onset (WASO)

Table 4: Repeated measures correlations between baseline and post-treatment sleep discrepancy scores and clinical self-report variables

Correlations (*r*)	**SOL Discrepancy**	**WASO Discrepancy**	**SE Discrepancy**	**TST Discrepancy**
ISI	-0.56*	-0.60**	0.72**	0.47
PHQ-9	-0.44	-0.61**	0.60**	0.45
STICSA	-0.23	-0.45	0.46	0.37
FSS	-0.40	-0.52*	0.57**	0.50*
DBAS	-0.41	-0.61**	0.68**	0.52

*$p < 0.05$, **Bonferroni corrected $p < 0.0025$

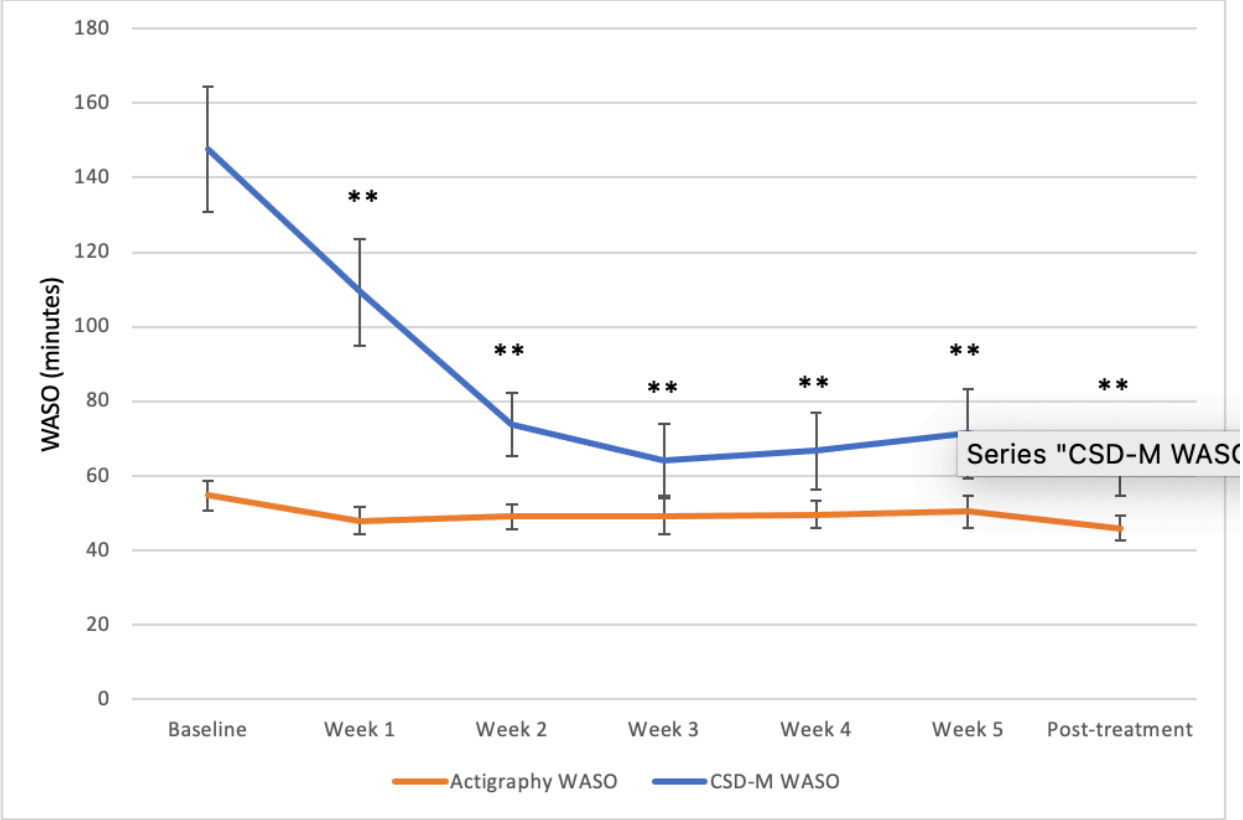
Figure 1: Mean SOL Measured with Actigraphy and Sleep Diary across CBT-I sessions



Note for Figures 1-4: Mean with Standard Error bars. The discrepancy is reflected by the distance between the lines which plot the sleep diary and actigraphy-derived sleep parameters in each graph, such that larger gaps between the lines indicate a greater discrepancy.

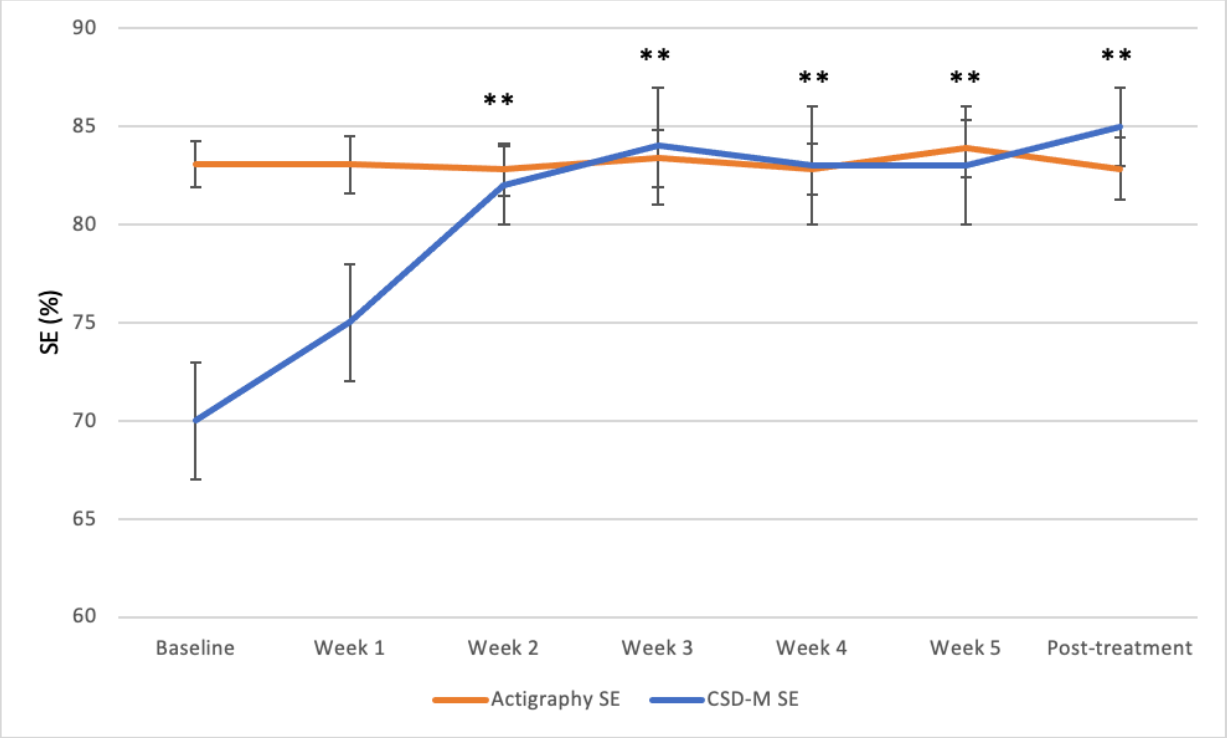
Acronyms: Sleep Onset Latency (SOL), Consensus Sleep Diary- Morning (CSD-M)

Figure 2: WASO Measured with Actigraphy and Sleep Diary across CBT-I sessions



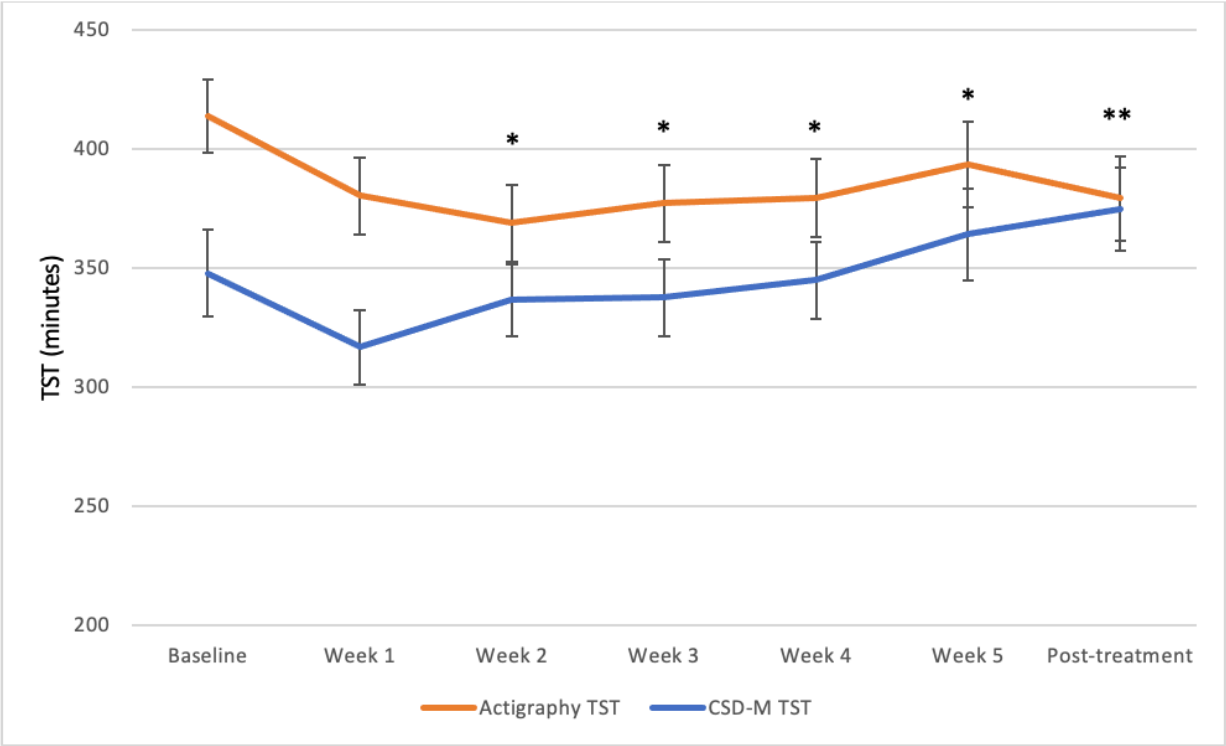
Acronyms: Consensus Sleep Diary- Morning (CSD-M), Wake After Sleep Onset (WASO)

Figure 3: SE Measured with Actigraphy and Sleep Diary across CBT-I sessions



Acronyms: Consensus Sleep Diary- Morning (CSD-M), Sleep Efficiency (SE)

Figure 4: TST Measured with Actigraphy and Sleep Diary across CBT-I sessions



Acronyms: Consensus Sleep Diary- Morning (CSD-M), Total sleep time (TST)

CHAPTER 4

Study 3: Lipid peroxidation is related to objective and subjective sleep parameters following cognitive behavioural therapy for insomnia

Chapter link:

Cudney, L.E., Frey, B.N., McCabe, R.E., Green, S.M. Lipid peroxidation is related to objective and subjective sleep parameters following cognitive behavioural therapy for insomnia. Submitted to *Journal of Clinical Medicine.*

Abstract

Objective: Insomnia and increased oxidative stress and are independently associated with poor health outcomes, but little is known about how they are related. This study examined how a biomarker of oxidative stress (lipid peroxidation) was related to insomnia severity, objective and subjective sleep variables measured across treatment with cognitive behavioural therapy for insomnia (CBT-I).

Methods: Twenty-six adults with insomnia disorder completed a 6-session CBT-I group treatment. Peripheral biomarker levels of lipid peroxidation (measured with thiobarbituric acid reactive substances; TBARS) collected at baseline and post-treatment. Sleep measures included self-report insomnia symptom severity, sleep diary, and wrist-worn actigraphy. Correlations were performed relationship between sleep measures and TBARS at baseline and post-treatment were completed. Paired t-tests across baseline and post-treatment were used to examine mean change across treatment.

Results: Higher levels of TBARS following treatment with CBT-I were significantly correlated with greater improvement in insomnia symptoms (Rho = -0.53, $p < 0.01$) and actigraphy-measured total sleep time at post-treatment (Rho = 0.48, $p < 0.05$). TBARS were not related to sleep measures from the sleep diary. Mean levels of TBARS did not significantly change across CBT-I treatment.

Conclusions: This is the first study to provide evidence that lipid peroxidation levels are related to both objective sleep parameters and self-reported symptom improvement following treatment with CBT-I. These results contribute to understanding potential underlying biological mechanisms involved in insomnia and how treatment with CBT-I may impact biological

pathways, such as oxidative stress. Independent replication and comparison with a control group are important future directions.

Keywords: insomnia, oxidative stress, lipid peroxidation, actigraphy, sleep, cognitive behavioural therapy.

Introduction

Insomnia is characterized by chronic impairments in initiating or maintaining sleep, or early morning wakening's, in addition to significant distress or impairments in daytime functioning. Insomnia symptoms affect nearly 40% of the population based on self-report (Chaput et al., 2018), with between 6-10% of the population meeting diagnostic criteria for insomnia disorder (American Psychiatric Association, 2013). Insomnia is associated with impaired quality of life (Dai et al., 2019), as well as increased risk of chronic disease and mortality (Daley et al., 2009). There are several biological pathways which have been hypothesized to link sleep issues with increased risk of pathology, including inflammation and oxidative stress (Tobaldini et al., 2017).

Chronic sleep disturbance has been associated with increased systemic inflammation (Irwin et al., 2016). Inflammation and oxidative stress are both potential mechanisms for increased morbidity and mortality seen in those with poor sleep. Oxidative stress is a disturbance in the oxidant-antioxidant balance, as a result of an overproduction of reactive oxygen species (ROS) and/or an insufficient antioxidant defense, resulting in cellular damage. ROS and lipid peroxides are produced by free radicals and can be neutralized by primary antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase.

Increased oxidative damage can manifest in several cellular processes, including lipid peroxidation. A common measure of lipid peroxidation is thiobarbituric acid reactive substances (TBARS), much of which consists of malondialdehyde (MDA), which is quite stable within blood serum (Ho et al., 2013). A cross-sectional study found markers of increased lipid peroxidation and decreased antioxidant defense in primary insomnia patients compared to

healthy controls (Gulec et al., 2012); however, the relation between oxidative stress and sleep continues to require investigation.

Multiple mechanisms have been proposed to explain the correlation between sleep and oxidative stress, including sleep-related transcriptional modulation of genes involved in oxidative stress in peripheral tissues (Anafi et al., 2013). A small pilot study of whole blood transcriptomic analysis identified a number of gene networks associated with inflammation and mitochondrial processes related to oxidative stress that differentiated insomnia participants from controls (Mithani et al., 2021). In addition, participants who experienced sleep deprivation showed a reliable decrease in plasma lipid profiles that were associated with increased levels of oxidative stress (Chua et al., 2015). As such, increased time awake – as experienced by individuals with insomnia – may be associated with increased oxidative stress levels measured peripherally.

Cognitive behavioural therapy for insomnia (CBT-I) is the gold standard treatment for insomnia that consists of psychoeducation, cognitive strategies (e.g., targeting dysfunctional beliefs about sleep) and behavioural strategies such as stimulus control, sleep restriction, and relaxation training (Edinger & Means, 2005). Although the clinical efficacy of CBT-I is well-documented in the literature, the biological consequences of CBT-I remain unclear and have important implications for the relationship between sleep disturbance and chronic illness. A randomized-controlled trial of CBT-I treatment measured inflammatory markers in older adults with insomnia (Irwin et al., 2015; Irwin et al., 2014). C-reactive protein (CRP) is considered one of the most stable and commonly measured inflammatory markers. CBT-I treatment was associated with reduced risk of having high CRP at post-treatment and CRP remained at a reduced level at the one-year follow-up compared to the control group who received sleep

hygiene education (Irwin et al., 2014). Following CBT-I treatment, a lower percentage of monocytes producing interleukin-6 (IL-6) and tumor necrosis factor (TNF-α) were seen at two months (mid-treatment) compared to sleep education, but not at post treatment or at one-year follow-up (Irwin et al., 2015). These studies suggest that systemic inflammation is targeted with CBT-I in an older adult population. These findings indicate that treatment for insomnia with CBT-I can improve sleep and change biological markers of inflammation. To our knowledge, there are no studies looking at the impact of response to CBT-I treatment on biological markers of oxidative stress, such as lipid peroxidation.

In the current study, we examine whether self-reported or objective sleep measures (assessed with actigraphy) in adults with insomnia are related to a marker of lipid peroxidation. The main objectives of the study are to determine whether: 1) a relationship exists between oxidative stress – as measured by TBARS – and the severity of insomnia symptoms and measures of sleep disturbance; 2) oxidative stress levels change across treatment for insomnia with CBT-I, and 3) baseline oxidative stress levels can predict response to CBT-I treatment after 8 weeks.

We hypothesized that higher levels of sleep disturbance would be associated with increased lipid peroxidation at baseline, as measured with TBARS, that will normalize following CBT-I treatment. We also hypothesized that those with higher levels of oxidative stress will show differential response to CBT-I (as shown with greater decrease in insomnia symptoms).

Methods

Study Participants

Twenty-six study participants (Mean Age = 52.54, SD= 13.33, Range 30 - 70), with a diagnosis of insomnia disorder were included in the present analysis. Participants were screened

for eligibility for group CBT-I clinical services after referral from the Sleep Medicine Program, Firestone Institute for Respiratory Health or the Mood Disorders Outpatient Clinic at St. Joseph's Healthcare, Hamilton. Participants were invited to participate in research if they were enrolled in group CBT-I. All study participants were informed in detail about the purpose of the investigation and provided their written informed consent prior to the onset of the study. The study was approved by the local ethics committee, the Hamilton Integrated Research Ethics Board.

The presence of criteria for insomnia disorder was confirmed based on Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. Prescription and over-the-counter sleep medications were allowed provided the participants were on a stable dose throughout the study period (i.e., were using the medication non-contingently from screening to post-treatment).

Participants were screened with the Duke Structured Interview for Sleep Disorders (DSISD) (Edinger, 2009) for the presence of other self-reported symptoms of sleep disorders (e.g., sleep apnea, limb movement, and circadian rhythm disorders) and were excluded for any other sleep disorders that were considered primary, or were untreated/unstable (e.g., those with sleep apnea who were adherent to positive airway pressure therapy were included). The Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was conducted to assess participants for comorbid psychiatric disorders. Participants were excluded for disorders that are typically contraindicated for CBT-I, including bipolar disorder and psychotic disorders (e.g., schizophrenia, schizoaffective disorder). Exclusion criteria also included: current shift work, current alcohol or substance abuse or dependence, or history of, in the past six months prior to screening.

Study Design

The present study employed a within-subjects design. Participants completed an initial screening visit to determine eligibility for the study. Measures of sleep, symptoms, and biological samples were collected at a baseline assessment 1-2 weeks prior to initiating group CBT-I, and again at a post-treatment assessment 1-2 weeks following completion of group CBT-I. Participants completed at least four of the six group CBT-I sessions and were provided with individual sessions for any missed group sessions. Participants were given an actigraphy wrist-worn device at the baseline assessment, to be worn throughout treatment and returned the device at the post-treatment session.

Intervention

The CBT-I group protocol is a manual-based intervention that consists of six two-hour sessions. It was conducted by a clinical psychologist and trained clinical psychology graduate students. The components of the intervention included psychoeducation and sleep hygiene instructions, stimulus control, time in bed restriction, cognitive restructuring, relaxation/counter-arousal strategies, and relapse prevention (Carney & Manber, 2009). Participants completed the Consensus Sleep Diary for morning (CSD-M), a validated sleep diary (Carney et al., 2012), throughout the duration of the sessions. Learning was reinforced with weekly home practice exercises.

Measures

The *Mini International Neuropsychiatric Interview* (MINI) is a psychiatric structured diagnostic interview based on the DSM-5 (American Psychiatric Association, 2013). The MINI is similar in reliability and validity to the SCID-P, and is able to be administered in a shorter period of time. The Cohen's kappa values for inter-rater reliability for the clinician delivered

MINI are 0.79 and above, indicating a moderate to strong level of agreement across interviewers (Sheehan et al., 1997).

The *Duke Structured Interview for Sleep Disorders* (DSISD; Edinger et al., 2009) incorporates criteria for diagnosing sleep disorders. DSISD consists of four modules, including sleep disorders associated with insomnia complaints, excessive daytime sleepiness-hypersomnia, circadian rhythm sleep disorders, and sleep disorders associated with parasomnias. The DSISD has shown high inter-rater reliability (kappa values between 0.71 and 0.86) (Carney et al., 2009)

The *Insomnia Severity Index* (ISI) is a 7-item self-report scale used to evaluate the severity of insomnia symptoms. Each item is scored on a 0 to 4 scale with higher values representing greater insomnia severity (Bastien et al., 2001). Scores > 11 are indicative of clinical insomnia and it has been shown that improvement of ≥ 9 was consistent with marked improvement in symptoms (Morin et al., 2011). The ISI has shown high internal consistency in clinical samples ($\alpha = 0.91$; Morin et al., 2011).

Sleep diaries are the gold-standard for tracking sleep disturbances, and the information derived is used to determine sleep efficiency, initiation, and maintenance (Carney et al., 2012). The *Consensus Sleep Diary for Morning* (CSD-M) is a sleep diary that requires participants to self-report estimates of sleep patterns and quality daily upon wakening. Information from the CSD is used to calculate total sleep time, sleep onset latency, time in bed, sleep efficiency, and wake after sleep onset. Participants are asked to complete the CSD for two weeks prior to treatment and throughout the duration of the group CBT-I 6-week sessions for both diagnostic purposes and to inform treatment targets and strategies.

The *Patient Health Questionnaire-9* (PHQ-9) is a 9-item brief self-report measure of depressive symptoms (Kroenke et al., 2001). A total score of >=10 has been shown to have

sensitivity of 88% and specificity of 88% for major depression in a primary care setting (Kroenke et al., 2001).

The *State-Trait Inventory for Cognitive and Somatic Anxiety* (STICSA) is a 21-item self-report measure that is purported to be a more pure measure of anxiety compared to commonly used scales (Grös et al., 2007). There are subscales for both cognitive and somatic anxiety, that have been validated in clinical and non-clinical samples (Van Dam et al., 2013).

Actigraphy

Participants wore an Actiwatch Spectrum Plus wrist actigraph unit on the non-dominant wrist 24-hours per day (Philips Respironics, Inc. Bend, OR). The Actiwatch Spectrum Plus records data on gross motor activity using an accelerometer. The activity counts were downloaded and analyzed with Philips Actiware v.6.0.9 software. Actigraphy data were collected in 1-minute epochs and a wake threshold of 40 and number of epochs of sleep/wake for sleep onset/offset of 10.

Actigraphy-measured sleep measures were included for twenty-three participants (two participants discontinued use of the device after a few nights and one participant's data could not be uploaded). Baseline sleep variables were determined as the average for the nights worn prior to session one, with a minimum of three nights (mean number of nights = 7.85, SD = 5.50, range 3 - 22). Post-treatment sleep variables were determined as the average for the nights worn between the final session (session 6) and the post-treatment assessment (mean number of nights = 5.46, SD = 3.78, range 3-16).

Laboratory analysis

The blood samples were collected via venipuncture by trained personnel. The serum was separated by centrifugation at 3,000 g at a temperature of 4 degrees Celsius for 15 minutes. Aliquots were stored at -80 degrees C until assays were performed.

The thiobarbituric acid reactive substances (TBARS) assay was performed to measure levels of lipid peroxidation (R&D Systems Inc., #KGE013). The assay kit was measured according to the manufacturer's instructions, which quantified the amount of malondialdehyde (MDA) thiobarbituric acid (MDA-TBA) adduct through colorimetric detection. This was measured at an absorbance of 532 nm. The assays were performed in duplicate.

Data Management

Self-report measures were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the St. Joseph's Healthcare Hamilton Research Institute. REDCap is a secure, web-based software platform designed to support data capture for research studies (Harris et al., 2009). Data may be made available upon request.

Statistical Analyses

All analyses were performed with R (Version 4.0.4, 2021). The Shapiro-Wilks test was performed on the difference between baseline and posttreatment pairwise comparisons to determine normality of the sample. The Spearman rank-order correlation was used to assess the relationships between TBARS levels and sleep variables measured with actigraphy and CSD, at both baseline and post-treatment timepoints. Paired t-tests or Wilcoxon paired rank tests were performed (for normal or non-normal distributions, respectively) to determine whether differences between baseline and post-treatment values were significant. Assuming a medium effect size of 0.5 in a within-subjects design for 80% power, sample size of 34 was needed. However, analyses were performed on our sample size of 26 due to limitations of data collection

following the onset of the COVID-19 pandemic. Limitations of a small sample size are discussed.

Results

The demographic and clinical characteristics of the sample are summarized in Table 1. Insomnia severity decreased following CBT-I as measured by the ISI score from baseline to post-treatment ($t = 9.21$, $p < 0.001$) with a large effect size (Table 2). Following treatment with CBT-I, self-reported depressive symptoms (PHQ-9) significantly decreased ($t = 6.34$, $p < 0.01$) with a large effect size, and anxiety (STICSA) decreased with a medium effect size ($t = 3.46$, $p < 0.01$).

Lower ISI scores at post-treatment (i.e., greater improvement in insomnia symptoms) were significantly correlated with higher peripheral oxidative stress, as reflected by lipid peroxidation (TBARS) ($Rho = -0.53$, $p < 0.01$). TBARS measured at post-treatment was significantly positively correlated with post-treatment total sleep time measured with actigraphy ($Rho = 0.48$, $p < 0.05$). Change in sleep onset latency (post-treatment - baseline) measured with actigraphy was significantly negatively correlated with TBARS levels at post-treatment ($Rho = -0.54$, $p < 0.01$). At baseline, the levels of TBARS were not significantly correlated with measures of sleep from self-reported sleep diaries or baseline actigraphy-measured sleep (Table 3). TBARS did not significantly change from baseline to post-treatment ($t = 0.10$, $p > 0.05$). Baseline TBARS were not significantly related to subjective change in insomnia symptoms, as measured by change in ISI scores from baseline to post-treatment ($Rho = -0.001$, $p > 0.05$).

Discussion

To our knowledge, this is the first study to explore the relationship between CBT-I treatment response and a biomarker of oxidative stress (TBARS). With regard to the primary

objective of investigating the relationship between TBARS and insomnia, we found there were associations between the level of TBARS at post-treatment with specific objective and subjective sleep outcome measures following CBT-I. Higher TBARS levels following CBT-I were associated with lower self-report insomnia symptoms (ISI scores) and greater improvements in self-reported sleep efficiency based on sleep diary calculations. Improvement in actigraphy-measured sleep variables, including longer total sleep time (TST) and greater improvement in sleep onset latency (SOL), were also associated with higher TBARS levels following CBT-I. Taken together, these results suggest a significant relationship between levels of lipid peroxidation and objective sleep outcomes following CBT-I.

Regarding the secondary aim, our findings showed that mean level of lipid peroxidation did not significantly change from baseline to post-treatment. Similar to our results, Redeker et al. (2018) reported that mean levels of biomarkers of stress response did not significantly change across treatment with CBT-I. However, there were significant negative correlations between urinary cortisol ratios and sleep disturbance, suggesting a possible relationship between hypothalamic-pituitary-adrenal axis activity and symptom improvement following CBT-I (Redeker et al., 2018). It is possible that the mean level of lipid peroxidation was not likely to change in such a short time period (8-10 weeks), since it is a somewhat stable marker.

Lastly, our results showed a correlation between severity of insomnia and TBARS levels at post-treatment, but baseline TBARS was not significantly related to amount of change in insomnia symptoms. This improved sleep following CBT-I may re-align these measures with oxidative stress, rather than related to prediction of treatment response. The significant correlation between post-treatment lipid peroxidation and self-reported insomnia severity

indicated that CBT-I changed the relationship between biomarkers and sleep characteristics/clinical factors, rather than changing levels of TBARS across treatment per se.

Oxidative stress has been identified as a potential biomarker for insomnia. A small cross-sectional study showed that participants with insomnia exhibited increased systemic oxidative stress (Liang et al., 2013). TBARS levels have been shown to be elevated in postmenopausal women with insomnia symptoms (Hachul de Campos et al., 2006). It has also been shown that uric acid, which is a major antioxidant, has been shown to be negatively correlated with a self-report measure of sleep disturbance in those with insomnia, such that lower antioxidant levels were associated with greater severity of sleep disturbance (Zhao et al., 2017).

The results of our study demonstrated that several objective sleep measures measured with actigraphy were significantly related to TBARS, whereas the same sleep characteristics measured by sleep diary or self-report were not related. Self-report insomnia symptoms (ISI) was the main treatment outcome of CBT-I; however, objective and self-report sleep measures are also important metrics to determine what sleep characteristics change across time. Interestingly, the sleep diary measures showed significant improvements across treatment with large effect sizes whereas most of the objective sleep measures determined by actigraphy did not shift significantly (Table 2). Self-report and objective measures of sleep have been identified as potentially reflecting very different domains/processes (Danzig et al., 2020). This is exemplified in the current study in that the sleep diary showed a significant increase in TST, while actigraphy simultaneously showed a significant decrease in TST (Table 2). Disparities in sleep variables measured with sleep diary versus actigraphy have been shown in previous studies (Maich et al., 2018). Although self-report and objective sleep characteristics are assumed to capture the same concepts, it seems more likely that they represent different variables (Cudney et al., 2022). In

fact, a recent study has identified that objective TST shows little reliability in predicting effectiveness of CBT-I measured with actigraphy or polysomnography (Galbiati et al., 2021). This may explain why the objective measures in this study (i.e., actigraphy and TBARS) did not change across treatment.

Limitations and Future Directions

The exploratory nature of this study was designed to evaluate the TBARS measure across treatment with CBT-I. The sample size may not have been adequately powered for determining change in biomarkers across treatment, although significant correlations with sleep measures post-treatment were observed. A larger sample size may be needed to determine change in oxidative stress markers across time, and possibly, with a longer follow up to detect change. TBARS has been identified as a stable marker of lipid peroxidation, so we may observe an effect following a longer follow-up period. Future studies are warranted to examine markers of oxidative stress over a more extended timeframe than the 8-10 weeks utilized in this study, to assess whether mean levels significantly change from baseline. In addition, given the sample was predominantly Caucasian, future studies are warranted in more ethnically diverse population to determine whether these findings are independently replicated.

Future studies should implement a control group for those with current insomnia. There is not a known range of "normal" TBARS levels so a control group would allow for direct comparison of sleep measures and biomarkers with a similar, but control population, and determine further impact of CBT-I on this biomarker.

Conclusions

This study was the first to investigate the levels of lipid peroxidation, as a marker of oxidative stress, in response to a psychological/behavioural intervention for insomnia. Taken

together, the findings of this study suggest a potential relationship between improvement of sleep measures (both self-report and objective TST and change in SOL) and oxidative stress following CBT-I treatment. Oxidative stress is a possible link between the poor sleep and overall health, such as increased risk of cardiovascular disease (Tobaldini et al., 2017), increased fatigue and poorer health-related quality of life (Fortier-Brochu et al., 2010), and diminished cognitive performance (Yaffe et al., 2014). These results contribute to understanding the underlying biological mechanisms of insomnia and how CBT-I may impact oxidative stress, a biological pathway previously implicated as a link between poor sleep and overall health (Gulec et al., 2012). Further work is needed to determine the impact of CBT-I on biological systems implicated within insomnia disorder, such as oxidative stress, and how this is related to differential treatment response to CBT-I.

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Table 1: Demographic and Clinical Characteristics

Sample (N=26)	Mean (SD)	Frequency
Age	52.54 (13.33)	
Sex		Male: n = 8 Female: n = 18
Ethnicity Caucasian Mixed race		 n = 23 (88.5%) n = 3 (11.5%)
Insomnia duration (years)	15.12 (11.28)	
Comorbid sleep diagnoses, currently managed Sleep Apnea Restless Leg Syndrome Periodic Limb Movement Disorder		 n = 10 n = 4 n = 2
Comorbid psychiatric diagnoses Major Depressive Disorder Social Anxiety Disorder Generalized Anxiety Disorder Panic Disorder Post-Traumatic Stress Disorder Agoraphobia		 n = 8 n = 3 n = 3 n = 1 n = 1 n = 2
Comorbid medical diagnoses, currently managed Arthritis Asthma Diabetes type II Fibromyalgia Hypertension Irritable bowel syndrome		 n = 4 n = 4 n = 1 n = 2 n = 4 n = 2
Medication Use (average number of medications) Antidepressants Benzodiazepine hypnotics Non-benzodiazepine hypnotics	0.96 (0.92)	 n= 12 n= 4 n= 6

Table 2: Clinical scales and objective sleep measures at baseline and post-treatment

Measures (N=26)	**Baseline** Mean (SD)	**Post Treatment** Mean (SD)	**Test statistic**	**Effect Size** (Cohen's D)
TBARS (μmol/ml)	0.36 (0.02)	0.36 (0.02)	t(25) =0.10	
ISI	18.08 (4.30)	7.73 (5.10)	t(25) =9.21**	D= 1.81
PHQ-9	9.00 (5.36)	4.38 (3.89)	t(25) =6.34**	D = 1.24
STICSA	38.92 (10.35)	34.54 (8.31)	t(25) = 3.46*	D = 0.68
Consensus Sleep Diary				
TST (minutes)	335.20 (77.22)	358.75 (70.59)	t(25) = -2.27*	D = 0.45
SE (%)	67.46 (14.13)	82.82 (12.56)	t(25) = -6.99**	D = 1.37
SOL (minutes)	56.27 (45.41)	21.75 (25.03)	V = 351**	D = 1.01
WASO (minutes)	70.71 (50.30)	32.22 (26.06)	t(25) = 5.79**	D= 1.13
Actigraphy measures				
TST (minutes)	448.62 (74.46)	429.85 (82.13)	t(22) = 2.73*	D = 0.57
SE (%)	84.16 (5.27)	84.16 (7.37)	t(22) = -0.25	
SOL (minutes)	15.72 (10.42)	12.83 (13.69)	t(22) = 1.01	
WASO (minutes)	49.37 (18.46)	45.33 (19.28)	t(22) = 1.56	

*$p < 0.05$

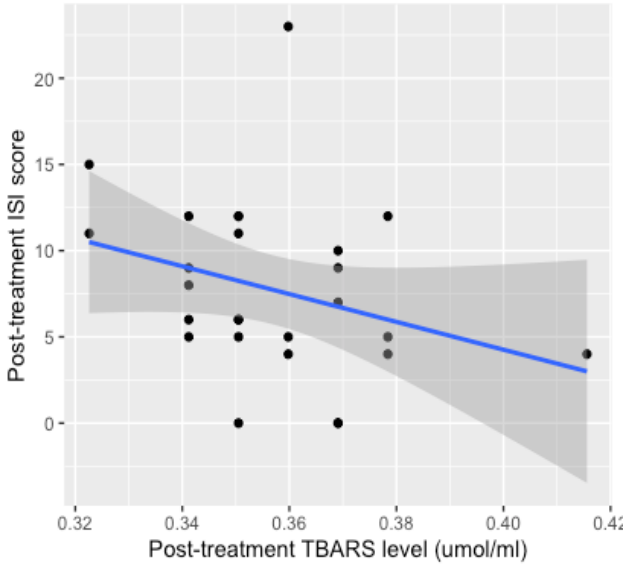
**$p < 0.01$

Table 3: Spearman Rank-Order Correlations with TBARS at Baseline and Post-treatment

Measure	**Baseline TBARS**	***p*-value**	**Post-treatment TBARS**	***p*-value**
Insomnia (ISI)	-0.002	0.99	**-0.53**	**0.009**
Depression (PHQ)	0.11	0.60	-0.07	0.75
Anxiety (STICSA)	0.04	0.84	0.08	0.71
Age	-0.13	0.54	-0.38	0.07
Consensus Sleep Diary				
TST	-0.39	0.06	0.30	0.16
TIB	-0.07	0.71	0.24	0.28
SE	-0.27	0.19	0.23	0.29
SOL	0.32	0.13	0.20	0.36
WASO	0.05	0.81	-0.21	0.33
Actigraphy (Mean scores)				
TST	0.23	0.28	**0.48**	**0.02**
SE	0.02	0.91	0.13	0.54
SOL	0.28	0.16	0.05	0.82
WASO	-0.07	0.73	0.08	0.70
Actigraphy (Change scores)				
TST	0.04	0.85	-0.08	0.71
SE	0.27	0.21	-0.20	0.36
SOL	**-0.43**	**0.04**	**-0.54**	**0.008**
WASO	-0.09	0.69	-0.20	0.35

SUPPLEMENTAL FILE

Figure 1. Scatter plots of the association between post-treatment TBARS levels and self-report sleep measures



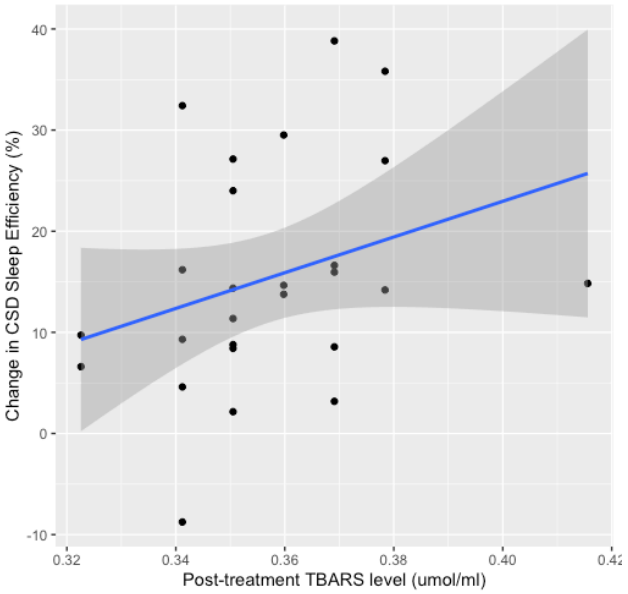
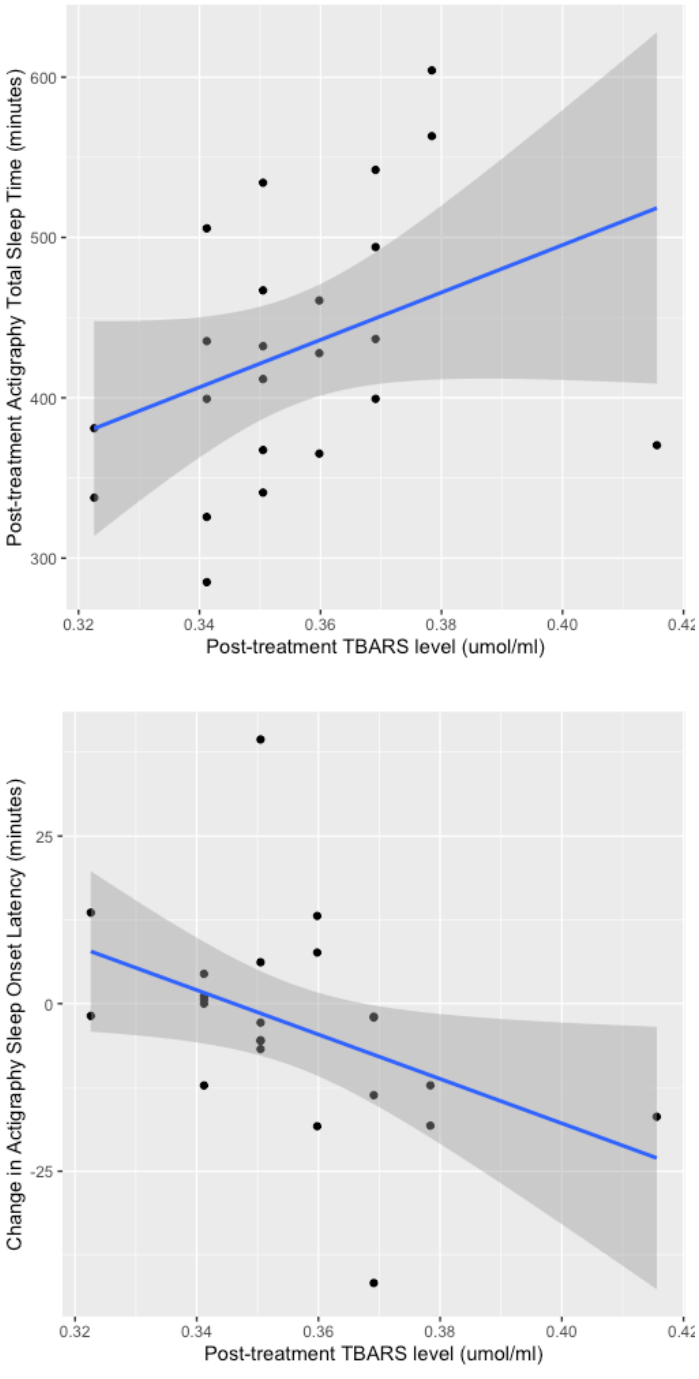


Figure 2. Scatter plots of the association between post-treatment TBARS levels and actigraphy sleep measures



CHAPTER 5: GENERAL DISCUSSION

This thesis examined markers of treatment response across cognitive behavioural therapy for insomnia (CBT-I). Insomnia disorder is a highly prevalent health concern, with nearly 10% of the adult population meeting DSM-5 diagnostic criteria (Morin & Jarrin, 2022). Given the high prevalence, there is an increased need for effective treatment for insomnia with an emphasis on identifying factors that influence treatment outcomes, particularly for more accessible forms of treatment like group formats or online delivery (Chaput et al., 2022). CBT-I is a well-established psychological treatment for insomnia disorder with strong evidence for efficacy in decreasing symptoms (Edinger et al., 2021). Many studies to date have focused on evaluating demographic characteristics (e.g., age, education level) that may influence response to treatment with CBT-I (Wei et al., 2024). However, the correlates of change across CBT-I remain poorly understood. Thus, the aim of this thesis was to expand our knowledge of the multimodal factors that change across a group CBT-I program. We have focused on understudied aspects which have been associated with insomnia disorder and have yet to be studied across group CBT-I treatment in a well-characterized sample. We have employed multimodal measurements with both objective and subjective measures across each study.

Summary of Findings

The aims of this thesis were to examine multimodal correlates of change across group CBT-I. Specifically, we investigated: (1) the relation between cognitive and psychosocial function across CBT-I; (2) subjective-objective sleep discrepancy across CBT-I and the relation to clinical variables such as depression, anxiety, fatigue and beliefs about sleep; and (3) the association between a biological marker of lipid peroxidation and treatment response to CBT-I.

The central hypothesis tested was that multimodal assessment of factors associated with insomnia disorder significantly influenced the degree of symptom improvement across CBT-I.

Study 1

Study one (Chapter 2) examined cognition and psychosocial functioning across a 6-session group CBT-I treatment, measured both objectively with a broad test battery of cognitive domains, as well as using self-reported measures. The objective cognitive assessment revealed significant pair-wise improvements in sustained attention following CBT-I, but there were no changes in the domains of memory or executive functioning after controlling for practice effects. We saw significant improvements in self-reported cognitive and psychosocial functioning from baseline to post-treatment, which included domains such as attention, memory, planning/organization, autonomy, occupational functioning, financial issues, interpersonal relationships, and leisure time.

CBT-I was effective at improving self-reported difficulties with cognition and psychosocial functioning following treatment, relative to the degree of improvement in severity of insomnia across treatment and age. Our results suggest that cognitive and psychosocial functioning improved when insomnia symptoms improved across treatment controlling for age. The baseline objective cognitive domains and premorbid functioning were all within the average range, suggesting that our sample was a high functioning group from a cognitive perspective. Therefore, the self-reported cognitive deficits observed at baseline did not align with their objective cognitive test performance since participants reported having cognitive difficulties despite their cognitive abilities objectively being within normal limits. This is in line with the CBT-I treatment literature showing only small to moderate effects on some objective cognitive

deficits in people with insomnia disorder, despite the subjective experiences of broad daytime functioning impairment (Fortier-Brochu & Morin, 2014).

In summary, these findings suggest that CBT-I is associated with broader benefits to cognitive and psychosocial functioning in a well-characterized sample with insomnia disorder. Improvements were observed in subjective experiences of cognition more so than objectively measured domains of cognition. This study contributes to the understanding of how objective and self-report cognitive functioning tell different stories following CBT-I. Future research is needed to further investigate this effect on a larger sample compared to a control group.

Study 2

The second study (Chapter 3) examined the session-by-session changes in the discrepancy between subjective and objective measures of sleep variables across a 6-session group CBT-I treatment. We first demonstrated the discrepancy that exists between subjective (self-reported sleep diary) measures of sleep and objective (wrist worn actigraphy) measures across all sleep variables (i.e., SE, SOL, TST, WASO) early on in CBT-I. However, the discrepancy between the subjective-objective sleep measurements decreased as treatment progressed. These findings are in line with previous studies examining session-by-session change across CBT-I (Janků et al., 2020), along with studies of older adults engaging in CBT-I (Ahn et al., 2022; Dzierzewski et al., 2019; Kay et al., 2013; Lovato et al., 2021; Lund et al., 2013). Since this change in discrepancy was ‘corrected’ early on in treatment and maintained throughout the course of treatment, it is possible that psychoeducation and early implementation of behavioural components, such as stimulus control and time in bed restriction, are helpful in aligning the data captured between objective and subjective sleep.

The secondary aim of this study was to explore the association between changes in the subjective-objective sleep discrepancy with clinical measures, including depression, anxiety, fatigue, and dysfunctional beliefs about sleep across CBT-I. The decrease in depression symptoms, dysfunctional beliefs about sleep, fatigue symptoms and insomnia symptom severity overall were significantly correlated with changes in WASO, SE, TST and SOL discrepancy scores. These results suggest that the degree of clinical symptom improvement occurs alongside the improvement in sleep discrepancy. These clinical symptoms may bias the subjective sleep diary reports at baseline and improvement in these clinical symptoms may help with reducing the discrepancy by post-treatment. Further, higher severity of insomnia symptoms at baseline was associated with a greater subjective-objective sleep discrepancy at baseline. Improvement of clinical symptoms was related to decreased sleep discrepancies across treatment.

Overall, higher severity of insomnia symptoms was associated with a greater subjective-objective sleep discrepancy and improvement of clinical symptoms was related to decrease in sleep discrepancies across treatment. These findings suggest the subjective-objective sleep discrepancy is quickly improved during CBT-I and is associated with clinical factors that typically improve with treatment as well, which make it an important clinical correlate. Future research should investigate the clinical utility of using objective measures of sleep, in addition to subjective measures to illustrate the subjective-objective sleep discrepancy to individuals during treatment.

Study 3

Lastly, the third study (Chapter 4) examined a biomarker of oxidative stress across treatment with CBT-I. Oxidative stress was investigated as previous studies identified it as a potential link between the poor sleep and overall health (Tobaldini et al., 2017). The main aim of

the study was to investigate the relationship between oxidative stress and the severity of insomnia symptoms and measures of sleep, derived from both objective and subjective sleep measures. To our knowledge, this is the first study to explore the relationship between CBT-I treatment response and a biomarker of oxidative stress (i.e. lipid peroxidation as measured by TBARS). We found there were associations between the level of lipid peroxidation at post-treatment with objective and subjective sleep outcome measures following CBT-I. Following CBT-I, higher lipid peroxidation levels were associated with lower self-reported insomnia symptoms and greater improvements in subjective sleep efficiency based on the sleep diary. Improvement in objective (actigraphy-measured) sleep variables, including longer TST and greater improvement in SOL, were also associated with higher lipid peroxidation levels following CBT-I. Taken together, these results suggest a significant relationship between levels of lipid peroxidation and objective and subjective sleep outcomes measured with self-report and actigraphy following CBT-I.

We also assessed mean levels of change in lipid peroxidation across treatment and did not observe a significant change in our sample following CBT-I. However, we did find significant associations between self-reported severity of insomnia and lipid peroxidation levels at post-treatment. This result indicated that CBT-I changed the relationship between biomarkers and sleep characteristics/clinical factors, rather than changing levels of lipid peroxidation across treatment per se. We did not see significant associations between baseline lipid peroxidation levels and the degree of change in insomnia symptoms following treatment with CBT-I. This suggests improved sleep following CBT-I may re-align these measures with oxidative stress, rather than being related to prediction of treatment response.

The results of this study demonstrated that several actigraphy-derived objective sleep measures were significantly related to lipid peroxidation at post-treatment, whereas the same subjective sleep characteristics measured by sleep diary or self-report were not related. Self-report insomnia symptoms were the main treatment outcome of CBT-I; however, objective and subjective sleep measures are also important metrics to determine what sleep characteristics change across time. Interestingly, the subjective sleep diary measures showed significant improvements across treatment with large effect sizes whereas most of the objective sleep measures determined by actigraphy did not shift significantly. The findings of this study suggest a potential relationship between improvement of several sleep measures (both self-report and objective) and a marker of oxidative stress following CBT-I treatment.

Significance

Overall, the aim of these studies was to contribute to the knowledge surrounding markers of change across treatment for insomnia. We examined clinical, cognitive, and biological domains that were distinct yet interrelated in that they have been implicated as important factors which contribute to the experience of insomnia disorder, and may be influenced by proper treatment, such as a well-established CBT-I protocol. Thus, this thesis has expanded the understanding of multimodal factors which change alongside insomnia symptoms following group CBT-I treatment.

The findings from this line of research are significant for several reasons. First, the research provides us with more insight into understanding the baseline clinical, cognitive, and biological profiles of a well-characterized sample of treatment-seeking individuals with chronic insomnia disorder. It appears that prior to treatment, individuals with insomnia are reporting significant difficulties with cognitive and psychosocial functioning despite their cognitive

performance being within a normal range, on average. These findings can be used to aid in the assessment of functioning and sleep disturbance in insomnia disorder. For instance, it may be important to understand examples of where cognition and functioning are impacted in the day-to-day experiences of those with insomnia. This research also contributes to the narrative that objective and subjective functioning tell different stories in those with insomnia disorder. In line with previous research, we also observed a significant discrepancy between subjective sleep and objectively measured sleep at baseline. Taken together, these findings may be helpful for assessment of factors which influence symptomatology of insomnia disorder and guide future research on understanding multifaceted profiles of chronic insomnia disorder.

Second, this research identified several broader benefits to treatment with CBT-I beyond insomnia symptom improvement. Following CBT-I, there was improvement in sustained attention but not in other domains of cognition after controlling for practice effects. The improvement in self-reported cognitive and psychosocial functioning and objectively measured sustained attention suggest that CBT-I acts on improving daytime dysfunction in a relatively short timeframe. We also identified how a marker of oxidative stress (specifically lipid peroxidation) was related to both subjective and objective measures of sleep following CBT-I. This study found significant correlations between the lipid peroxidation marker and treatment response between baseline and post-treatment. These results identify a novel biomarker that should be further investigated to disentangle how both insomnia disorder and CBT-I may impact biological pathways of oxidative stress. This study sets the groundwork to further elucidate the mechanisms for which CBT-I may modulate oxidative stress levels.

Strengths of the current body of research within this thesis include the longitudinal collection of validated measures for examination of both self-reported and objective measures

across each study. Based on our findings, the methods by which we measure factors (i.e., subjective or objective measures) often result in quite different findings and conclusions. For example, the method of measuring treatment response to CBT-I, with self-report questionnaires, or sleep variables subjectively measured with the sleep diary or objectively with actigraphy, have different results. This speaks to the unique experience of those with insomnia disorder, wherein the objective and subjective experiences differ significantly. This discrepancy is associated with increased symptom distress and is an important target for treatment.

A key strength of our research is the well-defined "real world" sample of participants diagnosed with insomnia disorder and comorbid conditions, enhancing the clinical relevance of our studies. As our sample was drawn from tertiary healthcare settings (e.g., mood disorders outpatient clinic and outpatient sleep medicine clinics), we included a sample with multiple sleep disorders and psychiatric disorders representative of those suffering moderate-to-severe insomnia disorder (Raglan et al., 2019). Prior to inclusion, participants underwent thorough diagnostic interviews based on DSM-5 criteria and a range of assessment tools to diagnose comorbid sleep disorders and psychiatric conditions (as comorbid psychiatric disorders are the norm, not the exception; Reesen et al., 2024). This is a methodological strength of our research, as the use of standardized diagnostic criteria and validated research instruments has been highlighted as critical for advancing research in the field of insomnia disorder (Riemann et al., 2022). This psychodiagnostic screening process was essential for ensuring insomnia disorder was properly identified and other necessary treatments (e.g., CPAP and pharmacotherapy) were being adhered to and clinically managed throughout the studies. The balance between the meticulous screening process and being relatively inclusive with including those with comorbid conditions greatly enhanced the rigor and practical applicability of our research.

Our results demonstrate that group CBT-I therapy was effective at reducing symptoms of moderate-to-severe insomnia, even in participants with an average illness duration 14 years, and in some cases, as long as 45 years. Meta-analyses have shown that group CBT-I is effective at improving sleep outcomes and that these changes are maintained beyond the period of treatment (Goa et al., 2022; Koffel et al., 2015). Moreover, group therapy offers unique benefits, such as the opportunity for participants to support and learn from each other. I observed this firsthand during my research, where it became evident that some lessons were more effectively learned through interacting with fellow group members who were willing to engage in significant behavioral changes, rather than merely through clinician instruction. It was truly inspiring to see the significant changes individuals made in the matter of weeks, especially when aiming to alleviate symptoms that had persisted for decades prior. In summary, our studies support existing research that underscore the effectiveness of group CBT-I. This aligns with the call to provide a stepped-care model for increasing access to psychological treatments for insomnia and optimizing resource allocation beyond individual therapy (Riemann et al., 2022).

Limitations and Future Directions

Limitations for each empirical study can be found in each of the respective chapters. However, there are several overarching limitations that are important to address. This research included a relatively small sample size and runs the risk of experiment-wise error. The study was intended to have a larger sample size and longer follow-up period (3-months following the completion of CBT-I), with the intention of analyzing differences between responders and non-responders. However, the COVID-19 pandemic unfortunately impacted the recruitment and continuity of the study. In spite of this, there was adequate power to perform each of the individual analyses, although there is an important consideration that there is an increased chance

of experiment-wise error due to the analyses conducted on the same samples. Future studies should recruit larger sample sizes with plan to have a longer follow-up period to further improve the reproducibility of our findings.

Another limitation of our studies is the within-sample design. The lack of a control group did not allow us to compare results to those with insomnia disorder who did not receive this treatment (e.g., a wait-list control group) or to those without insomnia disorder. Since CBT-I is an established evidence-based treatment and this research was conducted in connection to existing clinical services, we were unable to create a separate wait-list control group. Instead, we attempted to control for this by implementing statistical models which allowed for within-group analysis longitudinally and controlled for practice effects where relevant. In study 1 (chapter 2), we employed the reliable change index for practice effects for each of the measures which produced significant repeated measures results (Iverson, 2011). We attempted to use more stringent statistical testing to account for the increased risk of type II statistical errors. Now that we have identified potential markers of change across CBT-I, including cognitive and psychosocial functioning, sleep discrepancy, and a lipid peroxidation marker, future research is needed to extend these correlational results by including a control group. Further, to establish these markers of change as being unique to insomnia disorder and amenable to change with CBT-I, a large-scale randomized controlled trial is needed as a crucial next step.

Additionally, a longer follow-up period after the completion of the CBT-I program would clarify whether the changes we observed at post-treatment are maintained. We initially had a 3-month follow-up visit as part of the study design but were unable to gather enough data due to attrition and the subsequent COVID-19 pandemic. The COVID-19 pandemic limited our ability to conduct study visits in the necessary time frame and ended our recruitment early.

A further limitation was that the project included a rather homogenous participant sample. Most participants in our sample were white, female, with higher education. This limits the generalizability of our current findings to patient profiles similar to our own sample. Participants were recruited from a tertiary care setting (Sleep Medicine Program and Mood Disorders Program, St. Joseph's Healthcare Hamilton), and the patient population in this setting is not necessarily representative of the cultural and ethnic diversity of Southern Ontario. This speaks to whether there may be barriers to accessing healthcare or accessing mental healthcare particularly. We were more inclusive of those from diverse age groups (e.g., participants ages ranged from 22 to 70) and those who had comorbid psychiatric and sleep disorders (e.g., obstructive sleep apnea [OSA]), to improve generalizability; however, it is critical for research efforts to be inclusive of a more representative population. This is often not done in sleep research due to the difficulty of disentangling the influence of various disorders on results. For example, in attempting to include a 'real world' sample, inclusion of those with OSA may have influenced the results of Study 1 due to the impact on cognition. A recent systematic review identified that CBT-I was the most frequently culturally adapted treatment for sleep disorders (Alcántara et al., 2021). This review found that adapted CBT-I for underserved adult populations (e.g., veterans, women, racial/ethnic minorities, low socioeconomic status, disability status) showed consistent improvement in symptoms compared to controls. Cultural adaptations of CBT-I could include surface-level changes (i.e., language adaptation, mode of delivery), or deep-level cultural adaptations (e.g., content and intervention components, such as including sociocultural values within the treatment protocol). As our studies included a group-based intervention, individual cultural adaptations were not provided and could have been a limiting factor leading to decreased diversity within our sample. Future studies should expand inclusivity

and ensure that underserved adult populations gain access to evidence-based treatment for insomnia disorder, such as culturally adapted CBT-I.

Identifying mediating and moderating factors of response to CBT-I has been identified as a significant research target for improving treatment outcomes (Schwartz & Carney, 2012). Moderating factors are baseline variables which suggest whom or under what conditions a treatment produces its effects, while mediating factors are events during treatment that suggests how or why a treatment produces works. The body of research presented in this thesis identified several correlates of insomnia disorder and observed whether they changed across CBT-I treatment. However, we did not differentiate participants who were more or less likely to respond to CBT-I treatment based on these correlates at this stage. The clinical, cognitive, and biological factors identified across this research may be further studied to understand the moderating effects they have on CBT-I outcomes. Future research could also study how certain components of CBT-I influence each of these factors. For example, our research in Study 2 indicated that the subjective-objective sleep discrepancy decreased early on in treatment, and it would be helpful for future studies to evaluate the critical components of treatment that are necessary and associated with this change. Additionally, we did not include self-efficacy or locus of control measures in our study, which are identified as important mechanisms of change (Altena et al., 2023) and may mediate the relationships identified in Study 1.

The limitations of actigraphy as a measure of sleep is important to consider when interpreting the results of Study 2 and Study 3. As actigraph watches measure movement and light as a proxy for estimating sleep, there are inherent concerns about the ability of this technology to differentiate sleep in those with insomnia disorder compared to controls (Rösler et al., 2023). Actigraphy has been shown to overestimate total sleep time compared to PSG and

have less accuracy with increased age (Danzig et al., 2020), suggesting there could be validity concerns of using actigraphy. We did not observe significant changes in the actigraphy sleep measures despite large effect sizes for self-reported sleep. This provides further support that actigraphy is measuring a different construct and is not the gold standard for assessment of sleep in insomnia disorder. Importantly, recent review suggests that much of the research on the subjective-objective sleep discrepancy is related to misestimation of sleep by objective measures, or an inability of the technology to capture sleep/wake activity (Stephan & Siclari, 2023)

The research presented in this thesis identified factors which influence or are related to treatment outcomes to CBT-I, which assumes there is a link between psychological and behavioural change from the treatment occurring between baseline and post-treatment. A future direction of this research is to understand the relationship between adherence to specific treatment strategies and the specified outcome measures. Adherence has been defined as a set of interacting behaviours that are influenced by individual, social, and environmental factors (Matthews et al., 2013). The participants included in our research were required to attend a minimum of four of the six group CBT-I sessions, and completion of the CSD-M sleep diary was necessary clinicians to guide clinical recommendations for time-in-bed restriction. However, adhering to the behavioural treatment strategies and "homework" completion was not directly measured. Methods for measuring adherence to psychological treatments include self-reported ratings, spouse/clinician ratings, or indirect measures of adherence (Agnew et al., 2021). The relationship between adherence and outcomes was recently reported as being small-to-moderate based on a recent systematic review of adherence to CBT-I (Agnew et al., 2021), such that greater adherence may lead to greater improvement in symptoms. Adherence to prescribed time in bed was the most reported indirect measure of adherence; however, it was also identified that

there is not a consensus on optimal adherence to each individual component of CBT-I, which makes it difficult to compare across studies (Agnew et al., 2021). Future studies should identify how clinical, cognitive, and biological factors may influence ability to adhere to different components of CBT-I with both direct and indirect measures, and how this in turn affects treatment outcome.

General Conclusions

This thesis examined various facets of change across a group CBT-I treatment program in a well-characterized sample. This body of research was focused on understanding the cognitive, clinical, and biological factors that may be impacted during insomnia disorder and subsequently changed across CBT-I. Moreover, this thesis makes a significant contribution to the growing efforts to address both subjectively and objectively measured factors related to insomnia disorder. This line of research provides insight into multiple factors that may influence an individual's treatment response to CBT-I, and thus lead to improvements in tailoring treatments to optimize outcomes for treatment of insomnia disorder.

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