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Cardiac Vagal Tone: Regulator of Inflammation and Clinical Symptoms in Insomnia and Schizophrenia

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy in Psychology

by

Alexandra Claire Reed

2021

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ABSTRACT OF THE DISSERTATION

Cardiac Vagal Tone: Regulator of Inflammation and Clinical Symptoms in Insomnia and Schizophrenia

by

Alexandra Claire Reed

Doctor of Philosophy in Clinical Psychology

University of California, Los Angeles, 2021

Professor Cindy M. Yee-Bradbury, Co-Chair

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Cardiac vagal tone (CVT) reflects the contribution of the parasympathetic nervous system to cardiac regulation and is hypothesized to contribute to the regulation of inflammation and expression of psychopathology. CVT may play an important role in sleep disturbance and insomnia treatment. Through a series of four studies, this dissertation interrogated the associations between CVT, inflammation, and clinical symptoms in sleep disturbed samples and evaluated possible roles for CVT in insomnia intervention. Studies 1 and 2 proposed a specific model: chronic sleep disturbance reduces CVT with downstream effects on inflammation and clinical symptoms. Studies 1 and 2 then evaluated cross-sectional associations between these variables and tested exploratory mediation models in two samples with poor sleep quality: 106 older adults with insomnia and 39 patients with first episode schizophrenia. Overall, results did

not support the mediation models in either sample. However, findings revealed novel associations between CVT and cellular inflammatory processes in older adults and extended a negative association between CVT and systemic inflammation to schizophrenia, consistent with the cholinergic anti-inflammatory pathway. Studies 3 and 4 then evaluated possible roles for CVT in a randomized controlled trial which compared active behavioral treatments (Cognitive Behavioral Therapy for Insomnia and Tai Chi Chih) to sleep education in older adults with insomnia. Study 3 revealed that active behavioral interventions led to improvements in insomnia and clinical symptoms without up-regulating CVT, indicating that CVT is unlikely to be a mechanism supporting insomnia recovery. Study 4 then determined whether individual differences in CVT at pre-treatment moderated the effects of active behavioral interventions on key trial outcomes. Results showed that CVT did not moderate treatment effects. Null findings from Studies 3 and 4 underscore the need for further identification and evaluation of candidate mechanisms and moderators to maximize existing behavioral treatments for insomnia. Taken together, present results add to the mixed literature on CVT. Findings simultaneously challenge the assumption that CVT is a reliable correlate of clinical state and extend prior research on the role of the anti-inflammatory pathway in two unique samples with poor sleep quality.

The dissertation of Alexandra Claire Reed is approved.

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2021

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General Introduction

In the last few decades, there has been a growing interest in cardiac vagal tone (CVT) prompted by findings that suggest CVT is a strong predictor of health. CVT reflects the continuous contribution of the parasympathetic nervous system (PNS) to cardiac regulation through the activity of the vagus nerve (Porges, 1995; 2007). CVT at rest (i.e., tonic CVT) is widely theorized to be an indicator of autonomic flexibility and self-regulatory capacity (Appelhans & Luecken, 2006; Balzarotti, Biassoni, Colombo, & Ciceri, 2017). Generally, high tonic CVT has been linked to optimal physical and psychological functioning; low CVT is associated with physical and psychological morbidity and is a known predictor of mortality (Thayer & Lane, 2007; Tsuji et al., 1994; Wulsin, Horn, Perry, Massaro, & D'Agostino, 2015). As the PNS vagal activity underlying CVT is involved in the regulation of inflammation (Tracey 2002; 2009), inflammation may partially mediate the association between CVT and health. Sleep is another key regulator of health (Irwin, 2014; 2015). Although chronically poor sleep may alter the interplay between the PNS and immune system with implications for physical and psychological health, relatively little is known about whether or how this occurs. The present dissertation is informed by contemporary theory about CVT and PNS-immune interactions and was designed to clarify the pathways associated with these relationships.

Cardiac Vagal Tone

The PNS monitors and responds to changes in the body and environment primarily through tonic and phasic activity of the vagus nerve. The vagus nerve is the longest cranial nerve (Ulloa, 2005). It is composed of approximately 80% afferent (sensory) fibers and 20% efferent (motor) fibers and innervates most essential organs (e.g., heart, lungs, stomach, pancreas, liver)

enabling fast, bidirectional communication between the brain and viscera (Laborde, Mosley, & Mertgen, 2018b).

Heart rate is continuously determined by both sympathetic and parasympathetic innervation of the heart at the sinoatrial node (Berntson et al., 1997). The PNS vagal efferent fibers that innervate the heart originate from somata primarily in the nucleus ambiguus (NA) (McCraty & Shaffer, 2015). Three brainstem regions, the dorsal motor nucleus of the vagus (DMNX), the NA, and nucleus of the solitary tract (NTS) (Berntson et al., 1997), are hypothesized to support the receipt of visceral information from the heart and regulation of vagal efferent signaling. PNS signaling through the myelinated vagal efferent pathways triggers the release of acetylcholine (ACh) by postganglionic terminals at the sinoatrial node; ACh then binds to muscarinic ACh receptors, decreasing spontaneous depolarization and slowing heart rate (Shaffer, McCraty, & Zerr, 2014). In contrast, sympathetic terminals on the sinoatrial node release norepinephrine, initiating a $ß_1$ receptor-mediated second messenger cascade of intracellular events that increase heart rate (Berntson et al., 1997).

At rest, vagal efferent activity tonically inhibits sympathetic influences to the heart, slowing the heart rate (Shaffer et al., 2014). Respiration also has a predictable effect on heart rate and CVT. During inhalation, vagal outflow is inhibited and leads to increases in heart rate. During exhalation, vagal outflow resumes and slows heart rate (McCraty & Shaffer, 2015). The variation in the time interval between successive heart beats, heart rate variability (HRV), fluctuates as a result of these dynamic processes. Research using pharmacological blockade has reported that the vagus nerve is particularly responsible for HRV within the respiratory or high-frequency band (Allen, Chambers, & Towers, 2007). A number of time and frequency domain HRV metrics can be used to estimate CVT including the root mean square of successive

differences (RMSSD), percentage of the absolute differences between consecutive interbeat intervals that are greater than 50 ms (pNN50), high-frequency HRV (HF-HRV), respiratory sinus arrhythmia (RSA), and others. As RSA is sensitive to subtle changes in psychological and behavioral variables, highly correlated with these other measures of CVT, and relatively simple to derive (Berntson, Cacioppo, & Quigley, 1993), the present dissertation operationalized CVT by evaluating RSA as the natural log of the .12-.40 Hz band-limited time-sampled interbeat interval series.

Two foundational theories about CVT, polyvagal theory and the neurovisceral integration model, propose that CVT is an indicator of adaptability and well-being. Polyvagal theory discusses the evolution of the systems involved in cardiac regulation and proposes that tonic and phasic changes in CVT enable appropriate physiological and behavioral states that facilitate prosocial behavior (McCraty & Shaffer, 2015; Porges, 1995; 2007). Specifically, Porges asserts that the vagus functions as a "brake," tonically inhibiting sympathetic control of the heart rate at rest (Porges, 1995; 2007). According to polyvagal theory, high CVT at rest and rapid withdrawal of this "brake" (i.e., suppression of CVT) during stress enables an organism to self-regulate more effectively in response to changes in the environment (McCraty & Shaffer, 2015; Porges, 2007). Specifically, efficient control of the vagal "brake" may facilitate adaptive engagement (i.e., socialization) in safe contexts and rapid disengagement (i.e., increased metabolic output for fight-or-flight responses) in unsafe situations.

Porges also acknowledges that tonic CVT supports survival and health. One of his early studies demonstrated that associations between resting CVT and health status are apparent from birth; in comparison to healthy full-term infants, high-risk preterm infants show reduced CVT at rest (Porges, 1992). From this perspective, depressed CVT at rest and diminished modulation of

CVT during challenge are hypothesized to be indicators of increased susceptibility to the negative effects of stress (Porges, 1992).

Building upon polyvagal theory, the neurovisceral integration model proposes that CVT is an index of the integration of the central and autonomic nervous systems. More specifically, it posits that the prefrontal cortex exerts flexible, inhibitory control on cardiac regulation through the central autonomic network (Gillie & Thayer, 2014; Thayer, Hansen, Saus-Rose, & Johnsen, 2009). Within this framework, CVT is seen as a "meter of system integrity," which can be used to index the body's capacity for regulating attention, executive functioning, emotion, and allostatic systems such as the HPA axis and immune system (Thayer & Lane, 2000; 2009; Thayer & Sternberg, 2006). According to this model, previously reported associations between low CVT, clinical symptoms (e.g., worry, rumination), and indicators of poor physical health (e.g., poor glucose regulation, elevated peripheral inflammation) may be accounted for by dysregulation of this neurovisceral regulatory system (Thayer & Sternberg, 2006).

Cardiac Vagal Tone and Inflammation

The PNS vagal activity underlying CVT is also theorized to play an important role in the regulation of the innate immune system's response to acute infection or injury through the inflammatory reflex (Tracey, 2002; 2009). The inflammatory reflex is comprised of an afferent arc, which senses proinflammatory cytokines in the periphery, and an efferent reflexive arc, which suppresses inflammation (Rosas-Ballina & Tracey, 2009). This efferent arc has been described as the "cholinergic anti-inflammatory pathway" and is characterized by a multi-component sequence. Specifically, vagal efferent signaling activates splenic nerve endings that release noradrenaline, which activates T cells in the spleen. These T cells release ACh, which interacts with the alpha-7 nicotinic ACh receptor (α7nAChR) subunit expressed on cytokine-

producing cells (e.g., monocytes, macrophages), leading to the suppression of nuclear factor kappa B (NF-κB) activation and the inhibition of other innate immune responses (e.g., downregulation of mitogen-activated protein kinases (MAPKs)) (Huston & Tracey, 2011). Cumulatively, these signaling cascades inhibit the production and release of proinflammatory cytokines such as tumor necrosis factor-alpha (TNFα) in innervated tissue and organs including the spleen, liver, gastrointestinal tract, and heart (Huston & Tracey, 2011; Tracey, 2009).

Tracey's model suggests that the anti-inflammatory effects of the vagus are rapid, discrete, and prompted by the presence of acute inflammation (Tracey, 2002; 2009). However, vagus nerve activity can also be relayed to the hypothalamus and dorsal vagal complex, stimulating increased release of ACh from the anterior pituitary, activating systemic, humoral anti-inflammatory effects (Tracey, 2002). From this perspective, PNS activity may exert a tonic inhibitory effect on innate immune responses. While high PNS activity is expected to result in tight regulation of these responses, low PNS activity may lead to prolonged inflammatory responses, gradually contributing to increases in circulating cytokines and the development of chronic low-grade inflammation (Huston & Tracey, 2011; Pavlov & Tracey, 2012; Tracey, 2002). In line with this hypothesis, inverse associations between tonic CVT and markers of systemic inflammation have been documented in healthy adults (Cooper et al., 2014; Hu et al., 2018; Sajadieh et al., 2004; Singh, Hawkley, McDade, Cacioppo, & Masi, 2009; Sloan et al., 2007). Further animal and human evidence in support of this mechanism is reviewed in Study 1.

Current Conceptualizations of CVT: Trait versus State?

The present dissertation's approach to interrogating the role of CVT in the context of chronic sleep disturbance and behavioral interventions for insomnia is informed by an ongoing debate in the literature about the conceptualization of CVT. In general, some researchers posit

that CVT is a trait-like individual difference factor, which predicts behavior and health outcomes (e.g., Berntson et al., 1997), while others argue that CVT is a malleable, state correlate of health and well-being (e.g., Bylsma, Salomon, Taylor-Clift, Morris, & Rottenberg, 2013; Laborde, Mosley, & Mertgen, 2018a). Researchers who claim that CVT is an endophenotype for broad dysregulation of physiological, cognitive, and affective regulatory processes (e.g., Golosheykin et al., 2016; Thayer & Lane, 2009), argue that CVT is heritable, stable, state-invariant, and non-responsive to clinical interventions. In support of this perspective, genetic studies report that CVT is highly heritable; heritability estimates for a variety of vagally-mediated HRV metrics range from 47 to 64% (Golosheykin et al., 2016). Longitudinal studies also demonstrate that within-person estimates of CVT are often stable over periods of weeks or years (Bertsch, Hagemann, Naumann, Schachinger, & Schulz, 2012; Hu, Lamers, Penninx, & de Geus, 2017). Further, CVT appears to be state invariant in some clinical samples. For example, individuals with panic disorder show low CVT, even in the absence of acute panic symptoms (Thayer & Lane, 2009). As further evidence, proponents of the trait conceptualization cite a number of studies which suggest that the diminished CVT seen in samples with psychopathology does not improve when clinical symptoms (e.g., depression) are effectively treated (e.g., Kemp et al., 2010). Brunoni and colleagues (2013) concluded that CVT is likely a trait marker of major depressive disorder as they observed that low CVT in depressed individuals was not enhanced by pharmacological (sertraline) or non-pharmacological (transcranial direct current stimulation) interventions nor did CVT change with reductions in depressive symptoms.

However, other studies highlight the malleability of CVT and its correspondence with changes in clinical symptomatology, challenging the trait conceptualization of CVT. It is well established that normative aging is associated with reductions in tonic CVT over time

(Bonnemeier et al., 2003; Umetani, Singer, McCraty, & Atkinson, 1998). Regular aerobic exercise interventions or use of mind-body practices (e.g., yoga, Tai Chi) can produce within-person increases in tonic CVT (Sandercock, Bromley, & Brodie, 2005; Zou et al., 2018). Sleep may also affect CVT. The evidence for associations between acute and chronic sleep disturbances (e.g., insomnia) and diminished CVT (e.g., Bonnet & Arand, 1998; Palesh et al., 2008; Tobaldini et al., 2013) is reviewed in detail in subsequent studies within this dissertation. Other chronic stressors, including social isolation, have also been shown to modulate CVT. One experimental study in prairie voles demonstrated that chronic isolation led to simultaneous reductions in CVT and increases in depression and anxiety-like behaviors (Grippo et al., 2007). Results of human studies additionally challenge the claim of state invariance. In the context of a cross-sectional study, Blysma and colleagues (2013) reported that CVT is reduced in individuals with current depression and poor sleep, yet is normalized (i.e., increased) in individuals with remitted depression. Even more compelling, a handful of treatment studies demonstrate that increases in CVT can co-occur with improvement in clinical symptoms. For example, pharmacological (Balogh, Fitzpatrick, Hendricks, & Paige, 1993; Hartmann, Schmidt, Sander, & Hegerl, 2019) and non-pharmacological intervention studies (Carney et al., 2000; Karavidas et al., 2007; Liu et al., 2018; Nahshoni et al., 2001) have reported that improvement in CVT co-occurred with a significant reduction or full remission of depressive symptoms. Collectively, these studies suggest that within-person changes in tonic CVT may mirror changes in that individual's health.

Given empirical support for both state and trait conceptualizations of CVT, it is apparent that these conceptualizations are not mutually exclusive. For example, trait-like individual differences in CVT may function as "set points" that limit the malleability of tonic CVT during

health behavior interventions. The present dissertation was designed to interrogate possible trait and state-like properties of CVT in the context of chronic sleep disturbance and recovery.

Sleep, Cardiac Vagal Tone, and Inflammation

It is well established that samples with persistent sleep disruption, such as insomnia, are at increased risk for chronic diseases and psychiatric comorbidity (e.g., depression) relative to healthy sleepers (Irwin et al., 2015; Riemann, 2007). As sleep disruption has reliable effects on inflammatory processes (Irwin, Olmstead, & Carroll, 2016), immune dysfunction is hypothesized to partially mediate the relationship between poor sleep and suboptimal health. Chronic sleep disruption may also affect tonic PNS activity, as indexed by CVT. Acute sleep loss is associated with reduced CVT the next day (Malmberg, Persson, Flisberg, & Ørbaek, 2011; Palesh et al., 2008; Tobaldini et al., 2013) and samples with chronic insomnia tend to show lower CVT at rest than samples without sleep complaints (Bonnet & Arand, 1998; Castro-Diehl et al., 2016). If chronic sleep disruption reduces CVT, this may foster the development of low-grade systemic inflammation and morbidity by diminishing the PNS' ability to suppress inflammation through the cholinergic anti-inflammatory pathway. Further, if CVT is indeed malleable and affected by changes in sleep quality, behavioral interventions that improve sleep, inflammatory markers, and clinical symptoms, may do so in part by enhancing tonic CVT.

At the same time, trait-like individual differences in CVT have been linked to sleep quality and a wide array of inhibitory control processes, which may influence an individual's response to behavioral interventions that target sleep restoration. For example, individuals who showed high CVT during wakefulness before sleep subsequently experienced deeper sleep (i.e., longer delta sleep) and rated their sleep quality as better than individuals with low CVT before sleep (Irwin, Valladares, Motivala, Thayer, & Ehlers, 2006). If, as proposed by the neurovisceral

integration model, stable individual differences in CVT index differences in an individual's capacity to regulate cognition and emotion, CVT may affect one's ability to engage with and benefit from behavioral interventions that restore sleep and improve health.

Project Overview

The present dissertation addressed three gaps in existing research. Although many studies provide insights about the pairwise relationships between specific clinical symptoms (i.e., either depression or anxiety or fatigue) and either CVT or inflammatory biomarkers, only a handful of studies have begun to evaluate PNS-immune contributions to specific disease processes (e.g., depression in coronary heart disease: Frasure-Smith, Lespérance, Irwin, Talajic, & Pollock, 2009; fatigue in cancer patients and chronic fatigue syndrome: Crosswell, Lockwood, Ganz, & Bower, 2014; Park, Jeon, Bang, & Yoon, 2019). Despite the fact that PNS-immune mechanisms may support the constellation of depression, anxiety, and fatigue often observed in samples with insomnia, no studies have assessed these relationships in the context of chronic sleep disturbance or treatment of insomnia. The present dissertation interrogated cross-sectional relationships between these constructs and determined how they changed over time during different behavioral interventions for insomnia. This research aimed to inform our understanding of the mechanisms support insomnia-related impairment and to reveal common pathways to recovery during insomnia treatment.

To continue improving the efficacy of interventions for insomnia, it is also essential to consider patient characteristics and the match between the individual and the treatment approach. A small number of studies have evaluated potential moderators of behavioral interventions for insomnia including patient age (Irwin, Cole, & Nicassio, 2006), physical activity level (Yeung et al., 2018), and circadian preferences (Asarnow et al., 2019) with mixed results. Although CVT

has shown promise as a moderator of behavioral treatments for depression (e.g., Shapiro et al., 2007), no studies have yet determined whether individual differences in CVT moderate the effects of behavioral interventions on insomnia recovery. By evaluating this hypothesis, the present research could lead to enhanced matching of individuals with insomnia to the most appropriate interventions.

This dissertation leveraged current theory and knowledge about CVT to address two overarching aims:

1. **Illuminate the role of CVT in clinical populations with sleep disturbance by interrogating the associations between CVT, inflammation, and clinical symptoms.** Characterize these correlations as a step toward identifying mechanisms supporting the deleterious effects of poor sleep on physical and psychological health.
2. **Evaluate the role(s) of CVT in the context of behavioral interventions for insomnia.** Specifically, determine whether CVT is responsive to and associated with improvement in clinical state during insomnia treatment and whether individual differences in CVT moderate the effects of treatment.

These aims were addressed through a series of four studies in two samples: older adults with insomnia and younger adults with first-episode schizophrenia (SZ).

Study 1 proposed that chronic sleep disturbance may reduce tonic CVT with downstream effects on inflammation and psychiatric morbidity in older adults with insomnia. To address Aim 1, Study 1 characterized the cross-sectional relationships between sleep quality, CVT, inflammation (at cellular and systemic levels of analysis), and insomnia-related clinical symptoms (i.e., depression, anxiety, fatigue, and the negative and positive symptoms of psychosis) in a sample of older adults with untreated insomnia. On an exploratory basis, we

evaluated the hypothesis that the effects of poor sleep quality on clinical symptoms would be serially mediated by CVT and inflammation (Figure 1)**.**

Study 2 built upon Study 1 in addressing Aim 1 by characterizing the same pairwise relationships between sleep quality, CVT, peripheral inflammation, and clinical symptoms in a different population with high rates of chronic sleep disturbance and more severe psychopathology, young adults who were clinically stable and diagnosed with first episode SZ. Study 2 also afforded opportunities to examine relationships with potentially common (e.g., depression) and distinct clinical symptoms (e.g., positive and negative symptoms of psychosis) in SZ and older adults with insomnia. Exploratory analyses were pursued to determine whether the paths between these variables were similar in these distinct samples. This approach aimed **to clarify whether a common mechanism supports the effects of poor sleep on physical and psychological morbidity in SZ and older adults with insomnia**.

Study 3 built upon Studies 1 and 2 and addressed Aim 2 by evaluating the malleability of CVT in the context of behavioral interventions for older adults with insomnia. Specifically, Study 3 **determined whether active behavioral treatments, which promote a remission of insomnia and restore normative sleep, led to within-person increases in CVT from pre-to-post treatment**. Furthermore, Study 3 determined the extent to which any within-person improvements in CVT were associated with improvement in sleep quality, inflammation, and clinical symptoms (i.e., depression, anxiety, fatigue).

Study 4 addressed Aim 2 by determining whether trait-like individual differences in CVT affect how older adults respond to active behavioral interventions for insomnia. Specifically, we **evaluated the hypothesis that individual differences in pre-treatment CVT moderated the effects of established behavioral treatments on improvement in sleep quality, inflammatory**

markers, and clinical symptoms. Knowledge gained from this research could help to distinguish individuals who are likely to benefit from current behavioral treatments from those at greater risk of non-recovery who require a higher level of care.

Study 1: Sleep Quality, Cardiac Vagal Tone, Inflammation, and Clinical Symptoms in Late Life Insomnia

Introduction

Insomnia is characterized by difficulties with sleep initiation, sleep maintenance, and non-restorative sleep, which impair daytime functioning (American Psychiatric Association, 2013). Risk for insomnia increases with age; older adults (>55 years) experience insomnia at nearly double the rate of younger adults (30-50 years) (Irwin, Olmstead, Carrillo et al., 2014; Ohayon, 2002). Relative to older adults without sleep disturbance, those with insomnia are at increased risk for physical and mental health comorbidities (Bonnet & Arand, 2010; Vgontzas et al., 2013). Short sleep duration is also an independent predictor of mortality (Grandner, et al., 2009). Inflammation has been proposed as a key mechanism contributing to insomnia-related health risks (Irwin, Olmstead, Breen et al., 2014; Irwin, Olmstead, & Carroll, 2016). Although acute sleep deprivation is known to elicit increases in circulating cytokines (e.g., Shearer et al., 2001), the mechanisms by which chronic insomnia leads to elevations in systemic inflammation have not been elucidated (Mullington, Simpson, Meier-Ewert, & Haack, 2010). One possibility is that chronic sleep disturbance attenuates PNS activity, which then drives increases in inflammation over time. PNS-mediated efferent vagal activity, which can be assessed by evaluating measures of CVT, is a known regulator of inflammatory responses through the cholinergic anti-inflammatory pathway (Tracey, 2002; 2009). Further, inflammation is known to influence clinical symptoms that are common among individuals with insomnia, including depression, anxiety, and fatigue (e.g., Cho, Kivimäki, Bower, & Irwin, 2012; Gimeno et al., 2008; van den Biggelaar et al., 2007; Wium-Andersen, Ørsted, Nielsen, & Nordestgaard, 2013). The present study proposes a general model to account for the negative effects of sleep

disturbance on health: poor sleep quality reduces tonic PNS activity (CVT), driving increases in inflammation, which then influence clinical symptoms (see Figure 1).

In samples without insomnia, prior studies indicate that CVT is positively associated with sleep quality and negatively associated with circulating cytokines as well as clinical symptoms (e.g., Chalmers, Quintana, Abbott, & Kemp, 2014; Cooper et al., 2014; Gouin, Wenzel, Deschenes, & Dang-Vu, 2013; Meeus et al., 2013; Rottenberg, Clift, Bolden, & Salomon; 2007; Sajadieh et al., 2004; Werner et al., 2015). However, it is unclear if CVT plays an important role in inflammation and clinical symptoms in samples with insomnia. It is particularly important to interrogate the associations among CVT, inflammation, and clinical symptoms in older adults with insomnia because normative aging is associated with decreases in tonic CVT (Bonnemeier et al., 2003) and increases in inflammation (Franceschi & Campisi, 2014), which may heighten these associations and their consequences in this population.

Sleep and Inflammation

Acute sleep loss affects immune function at cellular and molecular levels. Partial sleep deprivation activates immune signaling pathways (Irwin, 2019), whose sustained activation may lead to chronic, systemic inflammation. As monocytes are a key source of proinflammatory cytokines in peripheral blood, prior studies have interrogated stimulated monocyte production of proinflammatory cytokines following ligation of toll-like receptor (TLR)-4 with LPS (Irwin, 2015) in the context of sleep deprivation. In healthy adults, partial sleep restriction increases morning levels of stimulated monocyte intracellular production of IL-6 and TNFα (Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006). Further, sleep loss led to a significant increase in transcription of IL-6 and TNFα messenger RNA in this study.

Elevations in circulating cytokines are also frequently reported in samples with chronic sleep disruption, including insomnia (e.g., Burgos et al., 2006; Irwin, 2015). Specifically, IL-6 and CRP are elevated in samples identified for sleep disturbances by questionnaire (Irwin, Olmstead, & Carroll, 2016). Population studies also indicate that adults with persistent insomnia show both greater CRP and steeper increases in CRP over two decades, compared to individuals without insomnia (Parthasarathy et al., 2015). Yet, the mechanisms supporting sustained increases in systemic inflammation in samples with insomnia are unclear. The present study hypothesizes that tonic PSN activity, as assessed by CVT, partially accounts for the relationship between poor sleep and proinflammatory state in older adults with insomnia.

Cardiac Vagal Tone and Sleep

As previously described in the general introduction, CVT has been conceptualized as a state indicator of health and wellbeing (Bylsma et al., 2013; Kemp & Quintana, 2013). Specifically, CVT is typically reduced in samples with clinically significant symptoms of depression, anxiety, and fatigue, relative to healthy individuals (Meeus et al., 2013; Rottenberg, Chambers, Allen, & Manber, 2007; Thayer, Friedman & Borkovec, 1996) and is negatively associated with the severity of these symptoms (Alvares et al., 2013; Bassett, 2016; Crosswell et al., 2014). Importantly, CVT also appears to fluctuate with sleep quality (Jackowska, Dockray, Endrighi, Hendrickx, & Steptoe, 2012; Malmberg et al., 2011; Tobaldini et al., 2013).

A handful of studies have examined associations between CVT and sleep and demonstrate that reductions in sleep quality and duration prospectively predict decreases in CVT. In healthy college students and young children, CVT is positively correlated with sleep efficiency and quality (Gouin et al., 2013; Michels et al., 2013; Werner et al., 2015). Positive associations between aspects of sleep quality and CVT have also been observed in clinical

populations, including individuals with anxiety (Hovland et al., 2013), depression (Bylsma et al., 2013), alcohol abuse (Irwin, Valladares, et al., 2006), and physical disease (breast cancer: Palesh et al., 2008).

There is also some evidence that disruptions in sleep can alter CVT. For instance, a single night of poor sleep or no sleep predicts reduced CVT on the following day (Malmberg et al., 2011; Palesh et al., 2008; Tobaldini et al., 2013). Sleep patterns may also influence CVT over extended periods of time. In typically developing children, poor sleep quality (i.e., long sleep latency) prospectively predicted low CVT one year later (Michels et al., 2013).

In the context of insomnia, cross-sectional studies often report that patients have lower CVT at rest than healthy sleepers (Bonnet & Arand, 1998; Cellini, De Zambotti, Covassin, Sarlo, & Stegagno, 2014; Spiegelhalder et al., 2011; Yang et al., 2011), though some studies have reported trend level effects (Fang, Huang, Yang, & Tsai, 2008) or failed to replicate these group differences (Jurysta et al., 2009). These mixed findings may be due to differences in selection of insomnia patients and controls and HRV measurement and processing techniques (Dodds, Miller, Kyle, Marshall, & Gordon, 2017). No studies have determined whether poor sleep quality is associated with reduced CVT in older adults with insomnia. It is important to interrogate this relationship because insomnia-related reductions in CVT may have downstream effects on immune regulation and clinical symptoms in older adults.

Cardiac Vagal Tone and the Regulation of Inflammation

Prior research has articulated a mechanism called the cholinergic anti-inflammatory pathway through which PNS vagal activity suppresses acute inflammatory responses (Huston & Tracey, 2011; Tracey, 2002; 2009). Animal models of the cholinergic anti-inflammatory pathway demonstrate that the enhancement of PNS efferent activity through vagal stimulation

produces anti-inflammatory effects (Borovikova et al., 2000; Huston et al., 2007), while inhibition of this efferent activity through vagotomy yields exaggerated inflammatory responses (van Westerloo et al., 2005; van Westerloo et al., 2006). Low PNS activity, as indexed by low CVT, is hypothesized to be a risk factor for gradual increases in systemic inflammation because diminished PNS signaling may fail to resolve acute inflammatory responses and contribute to increases in circulating cytokines (Huston & Tracey, 2011; Tracey, 2002).

Correlational studies in human samples are generally consistent with this hypothesis. CVT and markers of systemic inflammation tend to be inversely associated in adults (Cooper et al., 2014; Sajadieh et al., 2004; Singh et al., 2009), such that individuals with higher CVT have lower levels of circulating inflammatory markers. Similarly, lipopolysaccharide (LPS)-stimulated production of IL-6 and TNFα in whole blood was found to be reduced in healthy middle-aged adults with high CVT relative to those with low CVT (Marsland et al., 2007). However, so far, only two studies have evaluated associations between CVT and levels of resting (i.e., unstimulated) intracellular monocyte production of cytokines or LPS-stimulated monocyte production of cytokines in non-insomnia samples (Irwin, Olmos, Wang et al., 2007; O'Connor et al., 2007). Results from these studies have diverged from the negative associations between CVT and systemic inflammatory markers found in previous studies and do not provide much information about the relationships we might expect to find in older adults with chronic insomnia. Specifically, in the context of study evaluating the chronic and acute effects of cocaine on cellular inflammation, Irwin and colleagues reported positive associations between CVT and unstimulated and stimulated monocyte production of TNFα in a small sample of cocaine dependent men. In comparison to healthy controls, cocaine dependent men showed lower levels of unstimulated and stimulated monocyte production of TNFα, which were further reduced by

acute administration of cocaine. O'Connor et al. (2007) also reported a positive association between CVT and stimulated production of IL-6 in young, healthy sleeping women. It remains unknown how CVT is related to resting levels of intracellular production of cytokines and the magnitude of the cellular, inflammatory response to LPS stimulation in older adults with primary insomnia. It is important to note that there is some uncertainty about what an ideal or healthy stimulated response would be for older adults with chronic insomnia. Though a robust stimulated response could signal over-sensitivity to a bacterial trigger (i.e., a negative health outcome if this response leads to exaggerated, sustained inflammation), it could also signal a capacity for enhanced initial innate immune response to infectious challenge (i.e., a positive health outcome for older adults).

Several experimental studies indicate that vagal stimulation (which increases CVT) can help to reduce peripheral inflammation and clinical symptoms in the context of chronic inflammatory diseases, such as diabetes and rheumatoid arthritis (Johnson & Wilson, 2018; Koopman et al., 2016). Despite the potential importance of the cholinergic anti-inflammatory pathway in older adults with insomnia, this mechanism has not been thoroughly evaluated in this context. This is an important oversight as the combination of insomnia and age-related reductions in PNS activity may contribute to elevations in systemic inflammation and clinical symptoms observed in this population.

Insomnia, Inflammation, and Clinical Symptoms

Individuals with insomnia often experience symptoms of depression, anxiety, and fatigue, which impair daily functioning and reduce quality of life (Kyle, Morgan, & Espie, 2010). As previously mentioned, prior studies in clinical samples without insomnia have reported inverse associations between CVT and the severity of depression, anxiety, and fatigue (Alvares et al.,

2013; Bassett, 2016; Crosswell et al., 2014). The present research proposes that the association between CVT and the expression of these symptoms may be mediated, at least in part, by increases in inflammation.

A large number of preclinical studies indicate that experimental induction of peripheral inflammation, primarily via LPS administration, causes sickness behaviors in animals (Dantzer & Kelley, 2006; Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Hart, 1988). In rodent models, LPS administration induces behavioral changes that resemble depression (e.g., immobility in the tail-suspension test and the forced-swim test) (Frenois et al., 2007), anxiety (e.g., decreases in time spent in open areas in the open field test), (Bassi et al., 2012) and fatigue (e.g., reductions in voluntary wheel-running) (Harden et al., 2011). LPS can also induce parallel increases in anhedonia, state anxiety, and fatigue in healthy humans (Dooley et al., 2018; Eisenberger et al., 2010). There is even preliminary evidence that pre-existing sleep disturbances can amplify inflammation-induced depressed mood, particularly in women (Cho, Eisenberger, Olmstead, Breen, & Irwin, 2016).

Generally, these transient sickness behaviors are conceptualized as adaptive responses to inflammation, which allow the organism to preserve energy and recover from infection or injury. However, continued activation of the peripheral immune system, for instance due to chronic insomnia, is hypothesized to produce enduring, maladaptive clinical symptoms (Bassi et al., 2012; Danzer et al., 2008). Previous studies indicate that elevated systemic inflammation (i.e., high CRP) is a risk factor for the onset of major depressive disorder (Pasco et al., 2010). In a study of elderly adults, elevated CRP preceded accelerated increases in depressive symptoms over 5 years (van den Biggelaar et al., 2007). Similarly, in a large-scale longitudinal study of adults (i.e., Whitehall II), high CRP and IL-6 at initial evaluation predicted new-onset fatigue

over approximately 3 years (Cho et al., 2012). Although CVT may contribute to the expression of clinical symptoms in older adults with insomnia, through effects on inflammatory biology, no studies have evaluated the basic associations between these variables in this context.

Cardiac Vagal Tone, Inflammation, and Psychological Functioning in Older Adulthood

It is particularly important to evaluate the relationships between sleep quality, CVT, inflammation, and clinical symptoms in older adults, because changes associated with normal aging may contribute to more pronounced associations between these variables and greater impairment from chronic insomnia in older adults relative to younger adults. Aging alters sleep architecture and reduces overall sleep quality; sleep onset latency and fragmentation are increased and overall sleep duration is decreased (Mander, Winer, & Walker, 2017). At the same time, aging decreases CVT (Bonnemeier et al., 2003; Umetani et al., 1998) and alters immune system functioning (i.e., immunosenescence) (Aw, Silva, & Palmer, 2007). However, it is unclear if age-related reductions in CVT contribute to immune system dysfunction in normative aging. Older adulthood is characterized by increases in chronic low-grade inflammation, "inflammaging," that are not explained by overt disease or infection (Franceschi & Campisi, 2014; Irwin & Opp, 2017). These increases in systemic inflammation are hypothesized to accelerate biological aging and physical and mental health comorbidities in older adulthood (Franceschi & Campisi, 2014).

Clinical insomnia may exacerbate all of these normative changes associated with aging, potentially increasing the magnitude of associations between sleep quality and CVT, CVT and inflammation, and inflammation and clinical symptoms for a subgroup of older adults. Although it is important to assess these relationships empirically, no prior studies have simultaneously

evaluated relationships between sleep quality, CVT, inflammation, and clinical symptoms or tested crucial paths between these variables in older adults with insomnia.

The Present Study

As a first step toward evaluating the hypothesis that sleep disruption reduces CVT, leading to increases in inflammation and clinical symptoms in insomnia, Study 1 characterized the relationships between sleep quality, CVT, inflammation, and clinical symptoms in a sample of older adults with primary insomnia. Inflammation was assessed at systemic and upstream, cellular levels of analysis through the evaluation of CRP and unstimulated and stimulated monocyte co-production of IL-6 and TNFα.

Based on prior studies, we hypothesized that self-reported sleep quality would be positively associated with CVT and negatively associated with inflammation (i.e., CRP, unstimulated and stimulated monocyte co-production of IL-6 and TNFα) and clinical symptoms (depression, anxiety, and fatigue) (e.g., Gouin et al., 2013; Irwin, 2015; Kyle et al., 2010). Further, CVT would be inversely associated with inflammation and clinical symptoms (e.g., Alvares et al., 2013; Bassett, 2016; Cooper et al., 2014; Crosswell et al., 2014; Marsland et al., 2007). Finally, it was expected that inflammation (across indices) and clinical symptoms would be positively correlated (e.g., DellaGioia, Devine, Pittman, & Hannestad, 2013; Eisenberger et al., 2010; Lasselin et al., 2016). On an exploratory basis, the present study also evaluated the possibility that CVT and inflammatory markers serially mediate the relationship between sleep quality and clinical symptoms. It was expected that inflammation would mediate the associations between CVT and clinical symptoms.

Method

The present study relied on pre-treatment data from a completed RCT that compared Tai Chi Chih (TCC) and Cognitive Behavioral Therapy (CBT-I) to an active control Sleep Education Seminar (SS) for older adults with insomnia (R01 AG026364; PI: Michael Irwin, MD). Primary outcomes of the comparative efficacy trial were published in 2014 (Irwin, Olmstead, Carrillo, et al., 2014). As part of the pre-treatment assessment, participants completed structured clinical interviews (e.g., SCID DSM-IV, clinician-rated Inventory of Depressive Symptomatology). Participants also underwent three nights of polysomnography (PSG) evaluation including one evening to allow for adaptation to the lab setting and to screen for sleep apnea and two consecutive, full overnight recordings at the UCLA General Clinical Research Center (GCRC). At the second and third PSG evaluations, 10-minutes of resting EKG was obtained from awake participants in the 30 minutes before lights out. Lights out occurred between the hours of 9 pm to 12 am and was determined by each participant's average bedtime from two-week sleep diary. Fasting blood draws for the assessment of inflammatory cytokines were scheduled between 8-10 am on the morning after the third evening of PSG. Participants also completed self-report questionnaires for the assessment of sleep quality and clinical symptoms (e.g., anxiety, fatigue) on the second evening of pre-treatment PSG assessments. The clinical interviews, EKG recordings, blood draws, and questionnaires were used to assess the constructs of interest in the present study.

Participants

Participants were community-dwelling older adults between 55-85 years old (n =123) who met criteria for primary insomnia in Diagnostic and Statistical Manual (Fourth Edition, Text Revision) (DSM-IV-TR) (American Psychiatric Association, 2000) and general insomnia according to the International Classification of Sleep Disorders (Second Edition, American

Academy of Sleep Medicine, 2005). Participants were recruited by advertisement from the Los Angeles metro area. Exclusion criteria were consistent with the clinical trial and included: 1. Presence of a comorbid DSM-IV-TR sleep disorder (e.g., sleep apnea) as determined by a single night of PSG; 2. Night-shift work or irregular sleep pattern; 3. Regular ($\geq$ 2 times per week) use of alcohol or hypnotic medications for sleep; individuals using prescription sleep medications < 3 times per week were enrolled after withdrawing from medications; 4. Current diagnosis of major depression, unless treated and in remission; 5. Cognitive impairment as assessed by score < 23 on Mini-Mental State Examination; 6. Abnormal screening of laboratory tests (i.e., complete blood count, liver function tests, thyroid function); 7: Tobacco use; 8. Body Mass Index > 35 kg/m^2; 9. Unavailability during the study period; 10. Debilitating condition, which impeded full participation in the study (e.g., physical disability). Participant characteristics for the full sample are included in Table 1 of the appendix.

Assessment of Cardiac Vagal Tone

Prior to evaluation of resting EKG, participants completed seated measures (i.e., questionnaires) for at least an hour to foster adaptation to the sleep lab environment. During EKG recordings, participants were in the supine position and awake with their eyes closed. They were instructed to minimize movement and breathe normally. EKG was acquired using the EMBLA Sleep System and Somnological Studio software version 5.1 (Somnologica, Flaga hf, Medical Devices, Iceland), with a bandpass of 0.05 to 200 Hz and sampled at 2000 Hz. Offline, recordings were exported from Somnologica software as European data format (.edf) and then converted into text files (.txt) using custom Matlab code. These files were imported into QRSTool (Allen et al., 2007, 16-bit format), which was used to inspect data, classify R waves, and edit the time series for missed beats and artifact. To maximize the quality of the EKG

recordings selected for analysis, trained raters blind to group membership ranked the quality of recordings obtained on the second and third (post-adaptation) evenings of PSG. By consensus, the best quality file was selected for analysis; when files from nights 2 and 3 were of equivalent quality, the file from night 2 was automatically selected. High quality EKG data were available from 79 participants at PSG session 2 and 27 participants at PSG session 3. EKG was excluded if the participant declined PSG (n = 4) or if data was unusable due to technical difficulties (e.g., EKG lead detached) (n = 7), or for atypical sinus rhythm (e.g., cardiac arrhythmia, more than one consecutive ectopic beat) (n = 6). Single ectopic or missed beats were addressed using mid-beat corrections, which divide the inter-beat interval in half. In accordance with the recommendations for short-term EKG by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Camm et al., 1996), each inter-beat-interval (IBI) series was derived from a 5-minute epoch of artifact-free EKG, excluding the first minute of data. RSA was then estimated in the CMetX program as the natural log of the band-limited (.12-.40 Hz) variance of each IBI series (Allen et al., 2007). CMetX estimates of RSA have been shown to correlate > .99 with RSA derived from Porges' MXEdit program (Allen, 2002; Rottenberg, Chambers et al., 2007).

Perceived Sleep Quality

The Pittsburgh Sleep Quality Index (PSQI) is a brief self-report measure of perceived sleep quality, which provides estimates of sleep quality, latency, duration, efficiency, disturbance, medication use, and the severity of daytime impairment related to sleep problems in the last month (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). PSQI total scores range from 0-21, such that higher scores are indicative of worse sleep quality. Total scores > 5 suggest clinically significant sleep problems (Buysse et al., 1989).

Depression

Depressive symptoms in the past week were assessed using the Inventory of Depressive Symptomatology, a 28-item semi-structured interview, with good psychometric properties in adults (IDS-C: Rush et al., 1996). Individual items are scored 0-3; higher total scores from 0-84 reflect greater symptom severity (Rush et al., 2003, Trivedi et al., 2004).

Anxiety

Anxiety in past two weeks was evaluated using the 21-item Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown, & Steer, 1988). The BAI has acceptable psychometric properties for use with older adults (Therrien & Hunsley, 2012). Individual items are rated from 0-3, yielding total scores between 0-63. Higher total scores indicate greater levels of anxiety.

Fatigue

Participants rated symptoms of fatigue in the past week on the 30-item Multidimensional Fatigue Symptom Inventory Short Form (MFSI-SF) (Stein, Jacobsen, Blanchard & Thors, 2004; Smets, Garssen, Bonke, & De Haew, 1995). The MFSI is a valid and reliable measure of fatigue in medically-ill adults (Donovan et al., 2015) that yields a total score and five subscale scores, which reflect several dimensions of fatigue (general, physical, mental, and emotional fatigue) and vigor. Individual items are rated 0-4 and subscale scores range from 0-24. With the exception of the vigor subscale, higher total and subscale scores reflect more severe fatigue. To obtain a total score between -24-96, the vigor subscale was subtracted from the sum of the fatigue subscales.

Assessment of Inflammation

To assess CRP, plasma samples were diluted 1:20 and evaluated via high-sensitivity immunoassay using BN-II system (Dade-Behring, Newark, DE). The lower limit of detection

was .175 mg/L and coefficients of variation were < 4% for both intra- and inter-assay reliability. Samples were assayed in duplicate. As previously reported, unstimulated and stimulated toll-like receptor (TLR)-4 activation of monocytic co-production of proinflammatory cytokines (IL-6 and TNFα) were assessed via flow cytometry (Irwin, Wang, et al., 2006). To evaluate stimulated monocytic co-production of IL-6 and TNFα, blood from heparin-treated tubes was combined with 100 pg/mL LPS (Sigma, St Louis, MO) and 10 μg/mL brefeldin A (Sigma) and incubated at 37°C for 4 hours. Once cells were permeabilized in fluorescence-activated cell sorting permeabilizing buffer (BD Biosciences, San Jose, CA), and fluorescence-conjugated antibodies were added, approximately 12,000 events were counted to determine the net stimulated percentage of cytokine-producing monocytes. Quadrant coordinates were set based on unstimulated cells, which were run in parallel.

As body mass index (BMI) and physical activity levels are known to be associated with inflammatory biomarkers, body weight and height were measured and estimates of weekly physical activity (metabolic equivalents) were derived from self-report on the Yale Physical Activity Survey, a validated measure of physical activity in older adults (Harada, Chiu, King, & Stewart, 2001).

Power Analysis

In order to determine the minimal detectable effect for the planned correlational analyses, a sensitivity power analysis was conducted in G*Power 3.1.9.3 (Faul, Erdfelder, Buchner, & Lang, 2008). Given n =106 participants in the sample with usable data and power of 80% (α = .05), the a priori power analysis revealed that the analyses would be able to detect medium-sized effects (r = .27, d = .56).

Statistical Analysis

After examining the distributions of key variables, zero-order Pearson correlations were used to examine relationships between sleep quality, resting RSA, cellular and systemic indices of inflammation, and clinical symptoms including depression, anxiety, and fatigue. Given that age, BMI, gender, beta blocker use, and physical activity may affect RSA and inflammatory markers (e.g., Kuch et al., 2001; Navarro et al., 2016; Vella et al., 2017), significant associations were followed up by hierarchical linear regressions to assess the impact of these covariates. To address the possibility that observed associations were driven by a subsample of older adults with cardiac complications, analyses were also conducted excluding older adults with known heart disease and cardiac medication use.

Further analyses to evaluate key assumptions of the full path model were also pursued on an exploratory basis. In order to constrain the number of models tested to evaluate relationships with clinical symptoms (depression, anxiety, fatigue), tests of mediation models were limited to those predicting depressive symptoms on the IDS-C. PROCESS for SPSS (Hayes, 2018) was used to evaluate the possibility that RSA and inflammation serially mediate the effects of poor sleep quality on depressive symptoms (Hayes, 2018; model 6). A simple mediation model was also evaluated to determine whether inflammation mediates the association between RSA and depression (Hayes, 2018; model 4). The significance of indirect effects was probed using 95% percentile bootstrap confidence intervals.

Results

Demographic and clinical characteristics of the sample with usable EKG data (n = 106) at pre-intervention are presented in Table 1. On average, participants were in their mid-sixties (M= 65.30, SD=6.83), female, Caucasian, and college educated. About half of all participants endorsed medical comorbidities, the most common of which were cardiac conditions. A total of

21 participants reported a current cardiac condition and 34 participants reported regular use of cardiac medications (e.g., beta blockers). As expected for a sample of older adults with insomnia, participants endorsed poor sleep quality as evidenced by PSQI total scores above the clinical cutoff of 5 (M=10.76, SD=2.86). Participants also reported minimal to mild levels of depression (IDS-C total score: M=9.31 SD= 5.22; Rush et al., 2003, Trivedi et al., 2004) and anxiety (BAI total score: M= 6.79, SD=6.86; Carney et al., 2011). Regarding fatigue, MFSI-SF total scores (M= 10.05, SD=17.56) in this sample were higher than those reported in healthy middle-aged adults (e.g., Ross et al., 2016: M = 3.63, SD =17.95; Shochat & Dagan, 2010: M =7.00, SD =17.40) and comparable to those observed in elderly adults with chronic health conditions (e.g., osteoarthritis, Hawker et al., 2011: M= 10.23 SD=13.68; stroke, Mead et al., 2007: M =10.5 SD =6.46).

To evaluate the hypothesized relationships between sleep quality, resting RSA, cellular and systemic indices of inflammation, and clinical symptoms including depression, anxiety, and fatigue, Pearson correlations were completed (Table 2). First, as expected for a measure of CVT, RSA was negatively associated with heart rate (r =-.20, p =.04) and had a trend-level negative association with participant age (r =-.19, p =.05) (Masi et al., 2007; Shaffer & Ginsberg, 2017). Contrary to expectation, RSA was not correlated with sleep quality and clinical outcomes (i.e., depression, anxiety, fatigue; all ps > .05). As hypothesized, greater RSA at rest was associated with a lower percentage of unstimulated monocytes co-producing IL-6 and TNFα (r =-.23, p =.02). However, greater RSA was also associated with a greater LPS-stimulated inflammatory response (a larger difference between stimulated and unstimulated monocyte co-production of IL-6 and TNFα), r =.25, p =.01. RSA was not related to CRP.

The significant associations between RSA and cellular inflammatory markers were further evaluated using a regression approach to add consideration of key covariates. In step one, all five covariates (age, BMI, gender, beta blocker use, and weekly metabolic equivalency) were added to regressions predicting each index of cellular inflammation. In step two, resting RSA was added. For unstimulated monocyte co-production of IL-6 and TNFα, the full model with all five covariates and RSA accounted for 7% of the variance ($F(6, 93) = 1.18$, $p = .32$). Importantly, the addition of resting RSA in step two led to significant R-square change over and above all covariates such that RSA accounted for 5% of the total variance in unstimulated co-production of IL-6 and TNFα ($\Delta R^2 = .05$, $\beta = -.23$, $p = .03$). For stimulated monocyte production, the full model was significant and accounted for 14% of the variance in stimulated inflammatory response ($F(6, 94) = 2.55$, $p = .03$). Further, the addition of resting RSA in step two predicted a larger R-square change in stimulated intracellular inflammatory response over and above all five covariates ($\Delta R^2 = .06$, $\beta = .25$, $p = .01$).

To evaluate the possibility that a subset of older adults with cardiac conditions were driving these relationships in the present sample, the zero-order Pearson correlations between RSA and cellular inflammation were also repeated after excluding individuals who endorsed heart conditions and/or cardiac medication use at the pre-intervention assessment. In this restricted sample ($n = 63$), the negative correlation between RSA and unstimulated monocyte co-production of IL-6 and TNFα remained significant and was of a similar magnitude ($r = -.30$, $p = .02$). Similarly, the positive correlation between RSA and stimulated monocyte co-production of IL-6 and TNFα retained its size, but no longer reached significance ($r = .19$, $p = .13$) in this subpopulation. Given these results, it seems unlikely that the observed correlations between

resting RSA and indices of cellular inflammation were driven by the subgroup of older adults with comorbid cardiac conditions or medication use.

As mediation can occur in the absence of a total effect (i.e., no effect of RSA on sleep quality or RSA on depressive symptoms) (Hayes, 2018), exploratory mediation analyses were completed. However, analyses did not yield support for serial or single mediation. Briefly, there was no evidence that RSA in combination with any measure of inflammation (i.e., CRP, unstimulated and stimulated monocyte co-production IL-6 and TNFα) serially mediated the effects of poor sleep quality on depressive symptoms. Sample sizes for these serial mediation analyses varied by inflammatory marker (CRP: n = 84; percentage of unstimulated monocytes co-producing IL-6 and TNFα: n =98; percentage of stimulated monocytes co-producing IL-6 and TNFα: n =99). Similarly, none of the assessed inflammatory markers mediated the association between RSA and depression. Again, sample sizes for the simple mediation analyses varied by inflammatory marker (CRP: n = 85; unstimulated monocyte co-production: n = 99; stimulated monocyte co-production: n = 100). For all mediation analyses, all 95% bootstrap confidence intervals for indirect effects contained zero.

Discussion

The present study tested a conceptual, empirically based model of sleep disturbance by characterizing the cross-sectional relationships between sleep quality, CVT, inflammation, and clinical symptoms in a sample of older adults with primary insomnia. Contrary to hypotheses, no significant associations between CVT and sleep quality or CVT and clinical symptoms were observed. However, the present results provide a novel, nuanced characterization of the associations between RSA and inflammation at cellular and systemic levels of analysis in late life insomnia. Specifically, in line with study hypotheses and the literature on the cholinergic

anti-inflammatory pathway, we report that resting RSA was negatively associated with a measure of cellular inflammation at rest (i.e., the percentage of unstimulated monocytes co-producing IL-6 and TNFα). At the same time, greater RSA was also associated with a more robust stimulated inflammatory response at the cellular level (i.e., greater increase in the percentage of monocytes co-producing IL-6 and TNFα from rest to stimulation with LPS). Additionally, RSA was not associated with systemic inflammation as indexed by CRP. Exploratory hypotheses regarding serial mediation, (i.e., RSA and inflammation mediating the relationship between sleep quality and clinical symptoms) and single mediation (i.e., RSA mediating the relationship between sleep quality and inflammation) were not supported. Overall, the present results challenge basic assumptions about the correspondence between CVT, sleep, and psychological wellbeing over the lifespan. Findings also provide novel insights into the links between resting CVT and cellular inflammatory processes in a high health-risk sample of older adults with insomnia.

CVT, Sleep, and Clinical Symptoms

By reporting null associations between both CVT and sleep quality and CVT and clinical symptoms (i.e., depression, anxiety, fatigue) in a large sample of older adults with primary insomnia, the present study contributes to the mixed literature on the correspondence between CVT and wellbeing across the lifespan. Specifically, prior studies have suggested that CVT is positively correlated with sleep quality in generally healthy, young, non-sleep disturbed samples (e.g., Gouin et al., 2013, Werner et al., 2015: college students; Jackowska et al., 2012: healthy women in their 30s; Michels et al., 2013: children). A handful of studies have extended positive associations between CVT and sleep quality to various clinical samples that experience moderate levels of sleep disturbance (e.g., Bylsma et al., 2013: adults in their 30s with depression;

Hovland et al., 2013: adults in their 40s with panic disorder; Irwin, Valladares, et al., 2006; male alcoholics in their 40s; Palesh et al., 2008: women in their 50s with metastatic breast cancer). Although we expected to further extend this association to the context of older adults with insomnia, there was no significant correlation between pre-sleep RSA and sleep quality in the present sample. As prior investigations have focused on younger and middle aged adults almost exclusively, we speculate that the lack of correspondence between CVT and sleep quality in the present sample may be related to the advanced age of the participants (M = 65.30, SD = 6.83). In fact, one recent study that evaluated the association between pre-sleep CVT and difficulties falling asleep (i.e., sleep onset latency) suggested that age affects the strength of the association between CVT and sleep quality. Specifically, Nano et al., (2020) reported that lower pre-sleep CVT was associated with more difficulty falling asleep (i.e., longer sleep onset latency) in younger adults (i.e., ages 20-40), but was not associated with this sleep difficulty in older adults (>50-100) in their sample. As CVT decreases with age (Bonnemeier et al., 2003; Umetani et al., 1998), the coupling of CVT and sleep quality may also diminish over the lifespan, as variance in CVT decreases. Given the restricted age range of the present sample (55-85), age did not moderate the association between sleep quality and RSA in the present study (analyses not reported). However, in light of the strong associations between CVT and sleep quality reported in younger adults it will be important to evaluate this possibility in future studies.

An alternative hypothesis for the lack of correspondence between CVT and sleep quality in this sample may be that chronic insomnia itself, gradually leads to the uncoupling of CVT and sleep quality. If this is the case, it will be important for future studies to determine whether behavioral interventions that improve sleep quality, also restore CVT and the positive association between CVT and sleep quality that has been observed in healthy sleepers.

Lastly, it is also conceivable that some combination of variance in un-assessed insomnia features and the present methodological approach prevented the observation of an association between CVT and sleep quality in this sample. Specifically, worry about falling asleep is a common feature of insomnia (Riemann et al., 2010) and prior research indicates that worry and rumination can decrease CVT (Brosschot, Gerin, & Thayer, 2006). It is possible that variance in worry in the period before bedtime, during the assessment of CVT in the sleep lab, obscured an association between CVT and sleep quality in the present study.

It was also surprising that CVT was not associated with the severity of clinical symptoms including depression, anxiety, and fatigue, in this sample of older adults with insomnia. Previous studies have linked low CVT to greater expression of these symptoms in a wide variety of young and middle-aged clinical populations (Agelink, Boz, Ullrich, & Andrich, 2002; Alvares et al., 2013; Crosswell et al., 2014; Escorihuela et al., 2020). However, the present study is not the first to fail to extend these negative associations between CVT and depression and anxiety severity to older adults. In fact, An et al., (2020) and Brown et al., (2018) reported null associations between CVT and depressive symptoms in adults older than 60. Chen et al. (2012) even reported a positive association between CVT and the anxiety symptoms in adults >65. It is important to note that the older adults with insomnia in the present sample endorsed relatively low levels of clinical symptoms. The majority reported minimal-to-mild symptoms of depression (IDS-C: M=9.31 SD= 5.22) and anxiety (BAI: M= 6.79, SD=6.86) and mild-to-moderate levels of fatigue (M= 10.05, SD=17.56). Although CVT was not associated with any clinical symptoms or sleep quality in the present sample, poorer sleep quality was related to worse clinical symptoms across all of these measures. Additional studies are needed to determine whether null associations between CVT and sleep quality and CVT and clinical symptoms in the present sample reflect

normative aging (i.e., age-related decreases in CVT) or the combination of the effects of aging and untreated insomnia.

CVT and Inflammation

By evaluating the relationships between CVT and inflammation at the systemic level, and CVT and the potential for inflammatory responses at the cellular level of analysis in the context of late life insomnia, the present investigation both challenges and extends the theory of a vagally-mediated anti-inflammatory pathway. First, challenging this theory, we found that resting RSA was unrelated to systemic inflammation as indexed by CRP. This null finding contrasts with previously reported negative associations between CVT and CRP from studies in young and middle-aged adult samples (Cooper et al., 2014; Jarczok et al., 2014; Soares-Miranda et al., 2012; Sloan et al., 2007). However, it is worth noting that the few studies that have been conducted in older adult samples, with and without cardiac complications, have produced more mixed results with some papers replicating negative associations (Frasure-Smith et al., 2009) and others reporting null (Sajadieh et al., 2004) or even positive associations between CVT and CRP (Schäfer et al., 2015; see Williams et al, 2019 for review). Some of the heterogeneity in these findings may be due to the use of different techniques for the assessment of CVT and CRP and the inclusion of elderly participants with a wide variety of co-morbid health conditions. Normative aging may also reduce the strength of the relationship between CVT and CRP. In fact, a recent meta-analysis reported that the association between a measure of CVT (RMSSD) and CRP was moderated by age such that the negative correlation became weaker with increasing participant age (Williams et al., 2019). Although age was not a significant moderator of the relationship between RSA and CRP within this age restricted sample (age 55-85), the present study could not assess how this association differs in young and middle-aged adults with primary

insomnia. Chronic insomnia itself may also disrupt the normative, anti-inflammatory effects of vagal activity, attenuating the negative associations between CVT and systemic markers of inflammation found in healthy sleeping adults.

The present study was also the first to evaluate the associations between CVT and markers of cellular inflammation in a sample of older adults with primary insomnia. Results revealed a nuanced pattern of associations between CVT and unstimulated and LPS-stimulated co-production of cytokines that extend current knowledge about vagal-immune connections and warrant further study. Overall, resting RSA was negatively associated with unstimulated monocyte co-production of IL-6 and TNFα and positively associated with LPS stimulated monocyte co-production of IL-6 and TNFα. The negative association observed between RSA and unstimulated monocyte co-production of cytokines is consistent with the theory of a vagally-mediated anti-inflammatory reflex (i.e., that resting vagal activity tonically inhibits the spontaneous production of pro-inflammatory cytokines) (Tracey et al., 2002). However, it is important to interpret this negative association cautiously as the measure of unstimulated co-production of IL-6 and TNFα, the percent of monocytes positive for intracellular production of both cytokines, was not optimized to detect individual differences (the range was from 0.2-3.2% and the mean was 1.0%). It is not yet known if this variance has biological or clinical significance. However, prior investigations which have relied on the same unstimulated assay have shown that there are group differences between samples with and without inflammatory disease (i.e., patients with rheumatoid arthritis show greater unstimulated co-production of IL-6 and TNFα than age-matched controls (Bjurström, Olmstead, & Irwin, 2017, unpublished data) and demonstrate that unstimulated co-production increases after partial sleep deprivation (Irwin, Wang, et al., 2006).

Only one prior study in a small sample of cocaine-dependent middle-aged men and matched healthy controls, conducted by Irwin et al. (2007), evaluated the association between unstimulated monocyte intracellular cytokine production and CVT. This study reported that CVT was positively associated with unstimulated production of TNFα, but not associated with unstimulated production of IL-6. The present divergent finding of a negative association between CVT and unstimulated co-production of these cytokines may be attributable to the low variance of the unstimulated assay in the current sample or due to important differences between the study samples (e.g., gender, age, drug-dependence, insomnia status). To confidently interpret these different results, additional investigations reporting on the associations between CVT and unstimulated monoctye production of cytokines in identified clinical samples and aged-matched control samples are needed.

The present finding of a positive association between CVT and LPS-stimulated cytokine production does not immediately fit with Tracey's model of a vagally-mediated anti-inflammatory reflex (Tracey et al., 2002). Instead, this association links greater CVT to greater sensitivity to bacterial challenge in older adults with insomnia. With regard to prior investigations of LPS-stimulated response, the aforementioned study of cocaine-dependent and healthy men found that evening CVT was positively associated with evening levels of stimulated monocyte production of TNFα (Irwin, Olmos, Wang et al., 2007). Additionally, one small study in healthy young-middle-aged men and women reported that greater morning CVT was positively associated with morning levels of stimulated intracellular monocyte production of IL-6 in women, but not men (O'Connor et al., 2007). Of note, this study did not evaluate stimulated production of TNFα. Although both of these previous studies were conducted in younger adult samples without insomnia, they reported correlations similar in direction and magnitude between

CVT and LPS-stimulated responses to what we observed in a large sample of older adults with insomnia.

It is worth acknowledging that several factors increase the complexity of directly comparing the present results to those from the few previous studies that have included cellular inflammatory markers. One important consideration is that divergent findings may be partially attributable to normative age-related changes in monocyte populations and functions (Guilliams, Mildner, & Yona, 2018). Specifically, even though the unstimulated and stimulated assays used across these studies control for the total number of monocytes, peripheral blood samples from older adults may contain a larger proportion of senescent cells, particularly non-classical senescent monocytes, than samples from younger adult populations (Ong et al., 2018). These senescent monocytes are primed for greater expression and release of pro-inflammatory cytokines, and greater adherence to endothelial cells, than healthy monocytes (Merino et al., 2011). The former could impact spontaneous, unstimulated cytokine production and acute responses to bacterial stimulation by these cells in peripheral blood samples, while the latter could influence the extent to which these cells are present in peripheral blood vs. tissue. Future studies should more carefully characterize the monocyte populations (e.g., using cell surface markers) to determine how age- and potentially insomnia-related changes in monocyte characteristics might influence inflammatory processes.

In light of the different associations found between CVT and unstimulated and LPS-stimulated responses in the present study, it is also essential to examine assumptions about optimal immune responses. It is generally assumed that having low/near zero or undetectable levels of resting, unstimulated intracellular production of cytokines is beneficial (Walker et al., 2002). However, assumptions regarding whether it is healthy to have a higher or lower

percentage of total monocytes producing cytokines in response to LPS vary between studies. For instance, a report from the present study's parent RCT (Irwin, Olmstead, Breen et al., 2015) suggested that treatment-related reductions in the magnitude of the TLR-4 stimulated response demonstrated less cellular sensitivity to inflammatory signals, which in turn could be beneficial to immune health by reducing chronic systemic levels of inflammation. By this logic, older adults with insomnia showing relatively lower stimulated responses, before any insomnia interventions, may be less prone to inappropriate or exaggerated (and potentially harmful) inflammatory response than older adults with insomnia with more robust stimulated responses. However, since there are no data available from an age-matched population without insomnia, an absolute determination of "better" or "worse" immune health cannot be made.

It has also been suggested that a lack of increase in TLR-4 stimulated responses by older normal sleepers following partial sleep deprivation may actually be a reflection of immune senescence and increased susceptibility to infectious diseases in older adulthood (Carroll et al., 2015). Carroll and colleagues (2015) compared the effects of partial sleep deprivation on TLR-4 stimulated monocyte production of cytokines in healthy sleeping younger (25-39) vs. older adults (60+) and reported no increases in stimulated responses in older adults after partial sleep restriction. The authors suggested that their finding of stable stimulated responses to bacterial/LPS stimulation in older adults following sleep deprivation signaled no additional inflammatory risk related to sleep but could also be an indicator of impaired innate immune function as might be expected in aging adults (Carroll et al., 2015). The implications of these findings from this acute sleep deprivation paradigm are not clear for older adults with chronically disrupted sleep. It is possible that conserved sensitivity to bacterial challenge in older adults with insomnia could support better innate immune resistance to invading pathogens with implications

for risk of infectious diseases and vaccine response. Additional studies in older adults with and without chronic insomnia that incorporate other markers of immune health (e.g., response to vaccination) are needed to clearly define optimal response patterns and determine the clinical implications of the present findings.

Overall, the present results provide preliminary evidence that greater CVT is associated with lower levels of cellular inflammation at rest and a tendency to mount a greater, pro-inflammatory response to bacterial pathogens in older adults with untreated primary insomnia.

Limitations

The present study is limited by a cross-sectional design that precludes causal inferences about the observed relationships between sleep, autonomic function, inflammation, and clinical symptoms in insomnia. Additionally, due to the fact that EKG was collected from participants in the supine position immediately prior to sleep, when PNS activity is at its highest and the contributions of the sympathetic nervous system (SNS) are lowest (Jarczok, Guendel, McGrath, & Balint, 2019; Shaffer et al., 2014), the present study was unable to adequately assess the contributions of the sympathetic nervous system (SNS) or SNS/PNS balance to heart rate variability and outcomes of interest, including inflammation. Future studies should consider evaluating 24-hour EKG or EKG from multiple time points during the day to account for PNS and SNS contributions to sleep, inflammation, and the expression of clinical symptoms in insomnia. Lastly, the present study did not include a comparison group of older adults without primary insomnia. It will also be important for future investigations to determine if the relationships reported in the present study between RSA, sleep quality, inflammatory markers, and clinical symptoms are consistent with those observed in healthy sleeping older adults (i.e., attributable to normative aging) or specific to older adults with chronic sleep disturbances.

Conclusion

The present study provides novel contributions that both challenge and extend prior assumptions about the associations between PNS, immune function, and clinical presentation in late life insomnia. Unexpectedly, CVT was not related to sleep quality, systemic inflammation, or clinical symptoms in this sample. However, greater CVT was associated with lower levels of unstimulated monocyte production of pro-inflammatory cytokines and greater stimulated pro-inflammatory responses to LPS. The major contribution of the present study is this nuanced characterization of the associations between CVT and two upstream measures of cellular inflammation. These initial data provide a rationale for further investigation of CVT and CVT-immune pathways in the context of insomnia treatment and recovery.

Study 2: Sleep Quality, Cardiac Vagal Tone, Inflammation, and Psychological Symptoms in Schizophrenia and Older Adulthood

Introduction

Study 1 proposed that, in the context of late life insomnia, poor sleep quality reduces tonic PNS activity with downstream effects on inflammation that, in turn, impact psychological functioning (see Figure 1). In order to evaluate the general feasibility and utility of this model, Study 2 characterizes the relationships between sleep quality, PNS activity, inflammation, and clinical symptoms in another clinical sample: young adults with a significant psychiatric illness, first-episode (FE) SZ. Although older adults with insomnia and young adults with FE SZ have unique concerns due to divergence in age and clinical symptoms (e.g., positive and negative symptoms of psychosis in SZ), they also have common problems. At the population level, both groups experience high rates of sleep disturbance (Ohayon, 2002; Royuela et al., 2002) and impairing symptoms of depression and fatigue (Hedlund, Gyllensten, & Hanssonet, 2015; Kyle et al., 2010; Reeve, Sheaves, & Freeman, 2019; Waters, Naik, & Rock, 2013). Like samples with insomnia (Bonnet & Arand, 1998; Irwin, Olmstead, Carrillo et al., 2014), patients with SZ show diminished tonic PNS activity, as assessed by measures of CVT, and elevations across several indices of inflammation in comparison to healthy peers (Miller & Goldsmith, 2017; Montaquila, Trachik, & Bedwell, 2015). In light of these common features, the present study sought to determine whether the direction and magnitude of associations between sleep quality, CVT, inflammation, and clinical symptoms in FE SZ are similar to those observed in the sample of older adults with insomnia (Study 1). Further, exploratory evaluation of the crucial paths of the model linking sleep quality to psychological distress, were pursued to determine whether aspects of model fit are similar between patients with SZ and older adults with insomnia. The present study was designed to increase basic knowledge about sleep and PNS functioning in SZ and may

help to clarify whether a common mechanism accounts for variability in depression and fatigue severity in SZ and in older adults with insomnia.

Why Interrogate Sleep Quality in SZ?

High rates of general sleep disruption (52%), insomnia (48%-50%), and hypersomnia (30%) are frequently reported in patients contending with SZ (Laskemoen et al., 2019; Palmese et al., 2011; Reeve et al., 2019; Royuela et al., 2002) and appear to be independent of antipsychotic treatment (Robillard, Rogers, Whitwell, & Lambert, 2012). Poor sleep quality in SZ, as determined by polysomnography (PSG) and self-report, has been linked to poorer clinical outcomes, including more severe depression, fatigue, positive and negative symptoms of psychosis, poorer cognitive functioning, and lower quality of life (Davies, Haddock, Yung, Mulligan, & Kyle, 2017; Hofstetter, Lysaker, & Mayeda, 2005; Palmese et al., 2011; Reeve, Sheaves, & Freeman, 2015; Reeve et al., 2019; Ritsner, Kurs, Ponizovsky, & Hadjez, 2004; Taylor, Goldman, Tandon, & Shipley, 1992). Further, poor sleep is a predictor of psychiatric relapse in previously stabilized SZ patients (Kaskie, Graziano, & Ferrarelli, 2017). Chronic sleep problems in individuals with SZ are also linked to physical health conditions, such as obesity, in SZ samples (e.g., Palmese et al., 2011). Furthermore, sleep-wake disturbances are believed to contribute to early mortality in SZ by increasing physical health comorbidities and suicidal behavior (Kamath, Virdi, & Winokur, 2015; Malik et al., 2014). Despite these associations, the mechanisms by which poor sleep leads to increased physical and clinical symptoms in SZ are unclear.

Poor Sleep Quality, Cardiac Vagal Tone, and Inflammation in SZ

In parallel to Study 1, the present study assumes that CVT is a state correlate of well-being and posits that poor sleep quality may contribute to reduced CVT, elevated inflammatory

markers, and exacerbation of clinical symptoms in SZ. Study 1 reviewed the evidence supporting specific relationships between poor sleep and inflammation, sleep quality and CVT, CVT and inflammation (through the cholinergic anti-inflammatory pathway), and inflammation and insomnia-related clinical symptoms (e.g., depression, fatigue). The expected directions of these associations are illustrated in Figure 1. To understand why similar associations are expected in SZ, a brief review of existing research on CVT and inflammation in SZ is needed.

As previously mentioned, patients with SZ tend to show diminished CVT at rest compared to healthy samples (Bär et al., 2005; Boettger et al., 2006; Clamor, Lincoln, Thayer, & Koenig, 2016; Montaquila et al., 2015). Among patients with SZ, reduced CVT predicts greater total psychotic symptoms and negative symptoms, as assessed by the Positive and Negative Syndrome Scale (PANSS) or Scale for the Assessment of Negative Symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS) (Boettger et al., 2006; Chung et al., 2013; Mathewson, Jetha, Goldberg, & Schmidt, 2012; Okada, Toichi, & Sakihama, 2003). Patients with SZ also endorse high rates of depression and fatigue (Siris, 2000; Waters et al., 2013). Although inverse associations between CVT and the severity of depression and fatigue have been reported in samples with major depression (Agelink et al., 2002; Kemp et al., 2010) and pathological fatigue (e.g., breast cancer survivors) (Crosswell et al., 2014; Fagundes et al., 2011), it remains unclear if CVT accounts for variability in depression and fatigue in SZ.

As reviewed in Study 1, diminished CVT is also theorized to be a risk factor for the gradual development of chronic low-grade inflammation (Tracey et al., 2002). Although sleep-related reductions in CVT may contribute to proinflammatory state and morbidity in SZ, we are not aware of any studies that have evaluated associations between CVT and inflammatory markers in SZ. A number of studies report that patients with SZ show elevated inflammatory

markers, including cytokines such as IL-6, TNFα, interferon gamma (IFNγ), and CRP in peripheral blood in comparison with healthy individuals (Corsi-Zuelli et al., 2017; Goldsmith, Rapaport, & Miller, 2016; Lee et al., 2019; Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011; Miller & Goldsmith, 2017). Acute increases in specific circulating cytokines have also been linked to greater positive and negative symptoms. For instance, increases in IL-6 in peripheral blood coincide with the FE of SZ and periods of acute exacerbation of total psychiatric symptoms (Frommberger et al., 1997; Miller et al., 2011; Pae et al., 2006). In light of these associations, several clinical trials have aimed to improve psychotic symptoms in SZ by reducing systemic inflammation. They determined that adjunctive treatment of SZ with nonsteroidal anti-inflammatory drugs successfully reduced total psychotic symptoms, in a subset of patients (for review see Sommer et al., 2013).

Elevated markers of systemic inflammation are additionally associated with depressive symptoms in SZ; patients with elevated CRP (CRP < 3.0mg/L) tend to report more severe depression than those with normal levels (Faugere et al., 2018), consistent with the broader literature on inflammation and depression (e.g., Haapakoski et al., 2015). Considering that fatigue and depression are highly comorbid (Corfield, Martin, & Nyholt, 2016), and that positive associations between inflammatory mediators and fatigue are frequently reported in other clinical samples (e.g., Bower, 2008), it is conceivable that fatigue and indicators of peripheral inflammation are positively correlated in samples with SZ, though this has yet to be tested.

The Present Study

Study 2 evaluated concurrent sleep quality, CVT, inflammation, and clinical symptoms in a sample with FE SZ as a step toward discovering mechanisms that may account for the observed relationships between poor sleep quality and clinical symptoms in SZ and their relationship to

potentially similar processes in other samples with chronic sleep disturbance (i.e., older adults with insomnia). Overall, it was hypothesized that sleep quality would be positively associated with CVT and negatively associated with inflammation and clinical symptoms including depression, fatigue, and positive and negative symptoms of psychosis (e.g., Gouin et al., 2013; Lee et al., 2019; Reeve et al., 2019). Consistent with the available literature on the cholinergic anti-inflammatory pathway in healthy individuals, it was expected that CVT would be inversely associated with CRP and circulating proinflammatory cytokines (IL-6, IL-8, interferon gamma (IFNγ), and TNFa) (e.g., Cooper et al., 2014; Sajadieh et al., 2004). It was also hypothesized that CVT would be associated with clinical symptoms including depression, fatigue, and psychotic symptoms (e.g., Chung et al., 2013). Finally, a positive correlation was expected between the inflammatory markers and clinical symptoms of SZ (Faugere et al., 2018; Miller et al., 2011).

As we posit that the same mechanism may account for the effects of poor sleep quality on psychological functioning in older adults with insomnia (Study 1) and in patients with FE SZ, the present study also compared crucial components of model fit across the two samples. On an exploratory basis, we evaluated the possibility that CVT and inflammatory markers serially mediate the relationship between sleep quality and clinical symptoms and that inflammation mediates the associations between CVT and clinical symptoms similarly for both groups.

Finally, as it is essential to determine whether sleep quality, CVT, and non-psychotic clinical symptoms are aberrant in FE SZ relative to healthy peers, the present study included a healthy comparison (HC) sample to evaluate group differences between FE SZ and HC on these measures. Based on prior studies, it was hypothesized that patients would endorse worse sleep quality (including complaints consistent with insomnia), greater levels of depression and fatigue,

and show lower CVT at rest than HC (e.g., Frommberger et al., 1997; Laskemoen et al., 2019; Montaquila et al., 2015; Waters et al., 2013).

Method

The present study relied on data collected from individuals with FE SZ and aged-matched healthy individuals as part of a competitive supplement (R01 MH110544: MPIs: Cindy Yee-Bradbury PhD, Gregory A. Miller PhD, Keith Nuechterlein PhD) to an ongoing RCT targeting cognition in SZ (R01 MH110544: PI: Keith Nuechterlein PhD). Once clinically stabilized on antipsychotic medications at the UCLA Aftercare Research Program, FE SZ participants completed comprehensive clinical assessments, venipuncture for the assessment of inflammatory markers, and a psychophysiology study visit at the Laboratory for Clinical and Affective Psychophysiology (LCAP). HC were assessed at a single study visit, which included a comprehensive diagnostic interview (SCID V) and all psychophysiology visit procedures. The psychophysiology study visit included recording of resting EKG and administration of self-report assessments of sleep quality, fatigue, and depression. Study visits occurred between the hours of 10:30 am to 3:30 pm. Resting EKG was recorded for 5 minutes after at least 45 minutes of acclimatization to the lab. During EKG, participants were seated in a sound-attenuated chamber and instructed to breathe normally and minimize movement. Patients' psychotic symptoms were assessed after psychiatric stabilization and every 3 months by the primary clinician; data from the closest symptom assessment in time to the study visit was used for the primary analyses.

Participants

Participants were 39 outpatients diagnosed with FE SZ and 30 HC participants recruited through the UCLA Aftercare Research Program and LCAP, respectively. All participants

provided written informed consent. Inclusion criteria for the FE SZ sample were: 1) diagnosis of schizophrenia, schizoaffective disorder, mainly depressed type, or schizophreniform disorder, as assessed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (SCID V; First, Williams, Karg, & Spitzer, 2015); 2) initial diagnosis made ≤ 2 years ago; and 3) stabilized on antipsychotic medication. Exclusion criteria for patients included: 1) history of alcohol or drug abuse in the past month or dependence in the past 6 months; 2) neurological disorder; 3) traumatic brain injury/major head trauma; and 4) mental retardation. Exclusion criteria for HC included 1) personal history of a DSM-V psychotic disorder, bipolar disorder, obsessive-compulsive disorder, or post-traumatic stress disorder; 2) first-degree family history of any psychotic disorder; 3) personal or family history of psychiatric hospitalization; 4) current major depression; 5) history of alcohol or drug abuse in the past month or dependence in the past 6 months; 6) neurological disorder; 7) traumatic brain injury/major head trauma; and 8) mental retardation.

Assessment of Psychotic Symptoms

Patient's clinical symptoms were assessed via clinician ratings on the SAPS (Andreasen, 1984a), and the SANS (Andreasen, 1984b). The SAPS global positive symptom summary score reflects the sum of hallucinations, delusions, bizarre behavior, and positive formal thought disorder global subscale scores while the SANS global negative symptoms summary score reflects the sum of the affective flattening, alogia, avolition/apathy, and anhedonia/asociality, global subscale scores.

Assessment of Depressive Symptoms

All participants completed the Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996). The BDI-II is a self-report assessment, which is often used to screen for

depression in the context of primary care (Smarr & Keefer, 2011). Each of the 21 items on the BDI is rated 0-3; scores range from 0-63 such that higher scores reflect greater depressive symptoms over the past two weeks. Previous studies indicate that the BDI-II is highly correlated with other valid measures of depression (e.g., CDSS, HAM-D, PANSS-D) in SZ samples and can be used to accurately distinguish individuals with comorbid SZ and clinical depression from patients without depression (Kim et al., 2006).

Fatigue Assessment

Symptoms of fatigue in the past week were self-rated by all participants on the 30-item Multidimensional Fatigue Symptom Inventory Short Form (MFSI-SF; Smets et al., 1995; Stein et al., 2004), as described in Study 1. The MFSI-SF is a reliable and valid measure of fatigue in the context of cancer research (Donovan et al., 2015) and has been used in samples with SZ (e.g., Reeve et al., 2019).

Sleep Quality Assessment

Perceived sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) as described in Study 1. The PSQI has been used in samples with SZ (e.g., Hofstetter et al., 2005; Ritsner et al., 2004) and has strong psychometric properties in psychiatric samples that include patients with SZ (e.g., Doi et al., 2000). All participants completed the PSQI in collaboration with a graduate-student researcher who provided clarification and support when participants had questions or provided incomplete responses.

Assessment of Cardiac Vagal Tone

Resting EKG was collected using two 8 mm electrodes placed symmetrically on the right and left lower ribs. Signals were recorded with a bandpass of 0.05 to 200 Hz and sampled at 2000 Hz. Offline, electroencephalogram (.eeg) files were converted into text (.txt) files using

Brainvision Analyzer 2.0.4 software (Brain Products, 2017). Text files were then imported into QRSTool (Allen et al., 2007). At this stage, all subsequent EKG editing and processing steps to derive RSA were consistent with the methods reported in Study 1.

Assessment of Inflammation

Inflammatory markers were assessed in SZ patients only. Fasting blood draws occurred between 8-11 am. Samples were drawn into EDTA tubes for determination of plasma levels of inflammatory markers. Samples were centrifuged, aliquoted, and stored at −80 °C until batch analysis. CRP levels were evaluated using the Human CRP Quantikine ELISA (R & D Systems, Minneapolis, MN) according to the manufacturer's protocol. The lower limit of detection for this immunoassay was 0.20 mg/L.

Plasma concentrations of IL-6, IL-8, IL-10, IFNγ, and TNFα were evaluated using a custom V-PLEX Human Pro-inflammatory panel by MesoScale Discovery (Rockville, MD). The lower limits of detection were 0.20 pg/mL for IL-6, 0.20 pg/mL for IL-8, 0.10 pg/mL for IL-10, 0.60 pg/mL for IFN-γ, and 0.10 pg/mL for TNF-α. All samples were assayed in duplicate.

Statistical Analysis

To determine whether SZ and HC groups differed on key demographic characteristics, sleep quality, fatigue, depression, and resting RSA, independent samples t-tests and chi-square tests were conducted. As the goal was to assess the same model in SZ and older adults with insomnia, (Study 1 sample), a similar approach was then used to compare SZ and older adult samples.

Based on evaluation of the distributions of continuous variables in SZ, all inflammatory variables were log-transformed prior to correlational analyses. Pearson correlations were then used to examine the associations between resting RSA, inflammatory markers, continuous

measures of sleep quality (i.e., total PSQI score, total sleep duration), fatigue, depression, and negative and positive symptoms of schizophrenia (i.e., SANS and SAPS global scores).

Due to established associations between age, BMI, RSA (Kuch et al., 2001), and inflammation (Navarro et al., 2016), and known effects of gender (Lee et al., 2019) and antipsychotic medications on inflammatory processes (e.g., Meyer et al., 2009), covariate analyses were also completed. Given the small sample size, partial correlations or simple linear regressions were evaluated for each covariate: age, BMI, gender, and chlorpromazine (CPZ) equivalencies (Andreasen et al., 2010; Rothe, Heres, & Leucht, 2018). Correlations were also re-assessed excluding participants reporting regular use of cardiac medications.

On an exploratory basis, we then evaluated key components of the model in FE SZ including the possibility of serial mediation (i.e., that the effects of sleep quality on clinical symptoms are serially mediated by CVT and CRP) and single mediation (i.e., that the effects of CVT on depression and fatigue are mediated by CRP).

In order to compare model fit between FE SZ and older adults, there were two alternative a priori analysis plans based on specific contingencies. If the simple mediation model was supported in either or both samples, a set of multiple group analyses in Mplus version 8 would then be completed. First, a configural model with all paths free to vary between groups would be fit to the data. Then, an invariant model with each corresponding path fixed between the groups will be evaluated. Using the chi square output from both of these models, a chi square difference test would then be used to determine whether the configural or invariant model is a better fit for the data. A non-significant chi square difference test would indicate that the invariant model is preferable to the configural model, suggesting that the hypothesized relationships between sleep quality, CVT, inflammation, and clinical symptoms are similar across both samples. For these

exploratory analyses, the dependent variables (i.e., overlapping clinical symptoms) would be evaluated in the order of importance (i.e., depression and then fatigue). The significance of mediated effects would be probed using 95% bias corrected bootstrap confidence intervals.

If instead the simple mediation model was not supported in either sample, these full model multigroup comparisons would not be completed as, by default, the configural model would be a better fit for the multigroup data than the invariant fixed-paths model. If this was the case, a set of cross-group comparisons would be conducted in MPlus to determine if the path coefficients for specific paths within the serial and simple mediation models (e.g., the relationship between RSA and CRP) differed between the groups. A significant wald test would indicate that the path coefficient differed for FE SZ and older adults.

Results

Characterizing the Samples

Demographic and clinical characteristics of the FE SZ, HC, and older adult samples are presented in Table 3. On average, FE SZ participants were generally in their early 20s (M=22.23, SD=4.17) and had completed approximately two years of college (years of education: M=13.94, SD=2.00). About a third of FE patients were female (30.77%, 12/39). The diagnostic distribution was (*n*=33) schizophrenia, (*n*=5) schizophreniform, and (*n*=1) schizoaffective, depressed type. All FE SZ patients reported use of antipsychotic medications and a total of 3 FE patients endorsed use of cardiac medications (e.g., beta blockers). Psychotic symptoms, as reflected by SAPS and SANS scores, were generally in the mild to moderate range and consistent with levels reported in other FE SZ samples (e.g., Reed et al., 2020). FE SZ patients also endorsed minimal to mild depressive symptoms and mild to moderate levels of fatigue. As expected, average scores

on the PSQI (M=5.55, SD=3.19) were indicative of poor sleep quality in FE SZ; 47.37% of patients (18/38) had scores above the clinical cutoff (> 5).

The mean and standard deviation for resting RSA in this FE SZ sample (M =5.37, SD=1.83) were similar to previous studies that used the same methodology in FE SZ (Reed et al., 2020: M=6.26, SD=1.13) and chronic SZ (Hamilton et al., 2014: M=4.73, SD=1.83). For the subsample of FE SZ patients (n = 31) for whom plasma was available, the mean time between RSA assessment and blood sampling was 21 days (SD= 39.33). Means and SD for inflammatory markers, including CRP, IL-6, IL-8, IL-10, IFN-γ, and TNF-α, are summarized in Table 3. Of note, 38.71% (12/31) of SZ patients had clinically elevated CRP values (> 3 mg/L). Although no patients reported acute illness at the time of blood draw, 19.35% (6/31) participants had CRP values >10 mg/L.

Comparing FE SZ to HC

As expected, chi squared tests and independent samples t-tests showed that SZ and HC were well matched on gender, ethnicity, and smoking status and had similar levels of personal and parental education. An independent samples t-test showed that patients were on average approximately 2 years older than HC, $t(67) = 2.45$, $p = .02$. As hypothesized, SZ patients endorsed more sleep disturbance than HC as indicated by higher average PSQI scores, however this difference did not reach statistical significance, ($t(65) = 1.06$, $p = .29$). Although a greater percentage of SZ patients (47.37%, 18/38) endorsed PSQI scores above the clinical cutoff than HC (37.93%, 11/29), the distribution of participants with elevated scores was not different between the groups. Overall, patients reported spending significantly more time asleep ($t(57.02) = 6.81$, $p < .001$) and more time in bed ($t(65) = 4.09$, $p < .001$) than did HC. Surprisingly, short sleep duration (< 6 hours) was only endorsed by 2.63% of SZ (1/38) and 10% of HC (3/30).

Notably, 28.95% of SZ participants (11/38) endorsed long sleep duration (> 10 hours), while no HC participants endorsed sleep duration above 8.5 hours. SZ participants and HC did not differ with regard to complaints about difficulties falling asleep (i.e., sleep latency, PSQI component 2, $t(65) = -.43$, $p = .63$), sleep efficiency (PSQI component 4, $t(65) = -.29$, $p = .78$), or sleep disturbances (PSQI component 5, $t(66) = 1.37$ $p = .17$). FE SZ patients endorsed greater use of sleep medications (PSQI component 6, $t(47.66) = 3.00$ $p = .004$) and more daytime dysfunction (PSQI component 7, $t(66) = 3.30$ $p = .002$) than HC.

As anticipated, SZ participants reported higher levels of depression ($t(56.75) = 5.45$, $p < .001$) and fatigue ($t(67) = 2.91$, $p = .005$) than HC. There was a trend level effect for SZ to have faster resting heart rates than HC ($t(65.65) = 1.96$, $p = .05$). As hypothesized, patients had lower resting RSA than HC ($t(55.87) = -4.10$, $p < .001$). The group difference in RSA remained significant when adjusting for covariates (age: $F(1, 66) = 12.67$, $p = .001$; BMI: $F(1, 54) = 9.92$, $p = .003$; gender: $F(1, 66) = 13.74$, $p < .001$) and excluding the participants reporting regular use of cardiac medications ($t(53.11) = -3.93$, $p < .001$). Although 11 HC participants and 1 SZ participants were missing BMI data, available data indicated that patients had greater BMIs than HC ($t(55) = 2.10$, $p = .04$).

Comparing FE SZ to Older Adults with Insomnia

The SZ sample was then compared to the older adult sample from Study 1 (Table 3). As expected, FE SZ participants were significantly younger ($t(110.92) = -45.76$, $p < .001$) and less educated than older adults ($t(53.97) = -4.84$, $p < .001$). The gender distribution also differed between groups such that there were more female participants in the older adult sample than the SZ sample (X^2 (1, $n = 145$) = 20.02, $p < .001$). While four SZ patients identified as smokers,

smoking was an exclusionary criterion for older adults in Study 1 (X^2 (1, n = 145) = 11.18, p = .001).

FE SZ patients endorsed lower levels of sleep disturbance on the PSQI (t(141) = -9.32, p <.001) than older adults and similar levels of fatigue on the MFSI-SF (t(142) = 1.24, p =. 22). Depression ratings were similarly in the minimal to mild range on the BDI-II in SZ and on the IDS-C in older adults.

Additionally, FE SZ patients had higher resting heart rates (t(47.55) = 4.85, p <.001) and a tendency toward greater RSA (t(46.52) = 2.05, p =.05) than older adults with insomnia. Differences in RSA between older adults and SZ remained significant with adjustment for BMI (F(1, 141)= 7.14, p=.008) and gender (F(1, 142)= 9.87, p=.002), but were not significant with adjustment for age (F(1, 142)= .20, p=.66). Group differences in RSA persisted when individuals reporting regular use of cardiac medications were excluded from both samples, (t(106) = 3.05, p =.003).

CRP values were elevated in FE SZ patients relative to older adults, (t(36.63) = 2.55, p =.02). Group differences in CRP remained significant with adjustment for BMI (F(1, 112)= 9.77, p=.002), and gender (F(1, 113)= 10.90, p=.001) and when those on cardiac medications were excluded (t(33.33) = 2.46, p =.02), but were not significant when adjusting for participant age (F(1, 113)= 1.48, p=.23).

Test of the Primary Hypotheses

To test the primary study hypotheses, the pairwise associations between continuous measures of sleep quality (i.e., total PSQI score, total sleep time), resting RSA, inflammatory markers, and clinical symptoms were evaluated within the FE SZ sample. Pearson correlations are summarized in Table 4. Briefly, sleep quality as assessed by total PSQI score was not

associated with RSA. However, there were negative correlations between total sleep time and resting RSA ($r(36)= -.48$, $p =.002$) and total time in bed and RSA ($r(36)= -.48$, $p =.002$). These associations remained significant when controlling for age, BMI, gender, or CPZ, and when excluding participants on cardiac medications (total sleep time and RSA: age: $r(35)= -.49$, $p =.002$; BMI: $r(34) =-.54$, p = .001; gender: β = -.49, $p =.002$; CPZ: $r(35) =-.48$, p = .003; exclusion of participants on cardiac medications: $r(33) =-.41$, p = .02; total time in bed and RSA: age: $r(35)= -.50$, $p =.002$; BMI: $r(34)= -.51$, $p=.001$; gender: β = -.49, $p =.002$; CPZ: $r(35) =-.49$, p = .002; exclusion of participants on cardiac medications: $r(33) =-.50$, p = .003).

PSQI scores were not significantly associated with any inflammatory marker. As expected, higher PSQI scores were associated with more severe fatigue ($r(36)= .33$, $p =.04$). The association between PSQI and MFSI remained significant when controlling for BMI, CPZ, or excluding patients on cardiac medications but became a trend when adjusting for age or gender (age: $r(35)= .32$, $p =.05$; BMI: $r(34)= .36$, $p=.03$; gender: β = .33, $p =.05$; CPZ: $r(35)= .37$, $p =.02$; exclusion of participants on cardiac medications: $r(33)= .42$, $p=.01$). A similar positive association between PSQI and BDI-II scores did not reach statistical significance. PSQI was unrelated to total SANS and SAPS scores.

RSA was negatively associated with CRP ($r(29)= -.37$, $p =.04$), but not significantly associated with other inflammatory markers. The negative association between RSA and CRP remained significant when adjusting for age and was in the same direction but no longer significant when controlling for BMI, gender, CPZ, or excluding the participants on cardiac medications (age: $r(28)= -.37$, $p =.04$; BMI: $r(27)= -.34$, $p =.07$; gender: β = -.37, $p =.05$; CPZ: $r(28)= -.36$, $p =.05$; exclusion of participants on cardiac medications: $r(26)= -.28$, $p =.15$.)

Contrary to study hypotheses RSA was not associated with clinical symptoms (depression, fatigue, SANS, and SAPS). Similarly, CRP was not associated with clinical symptoms (depression, fatigue, SANS, and SAPS). However, there were a few significant associations between individual cytokines and clinical symptoms. Specifically, IL-6 and IFN-γ were both positively correlated with SAPS (IL-6: $r(26)= .41$, $p =.03$; IFN-γ: $r(26)= .40$, $p =.03$). The positive association between IL-6 and SAPS remained significant with adjustment for covariates and when participants on cardiac medications were excluded (age: $r(25)= .40$, $p =.04$; BMI: $r(25)= .51$, $p =.006$; gender: $\beta = .41$, $p =.04$; CPZ: $r(25)= .43$, $p =.03$; exclusion of participants on cardiac medications: $r(23)= .45$, $p =.02$.) Similarly, the association between IFN-γ and SAPS remained significant with adjustment for age, BMI, or CPZ, but not gender or the exclusion of the participants on cardiac medications (age: $r(25)= .40$, $p =.04$; BMI: $r(25)= .41$, $p =.04$; gender: $\beta = .39$, $p =.05$; CPZ: $r(25)= .43$, $p =.03$; exclusion of participants on cardiac medications: $r(23)= .40$, $p =.05$.)

There was also a trend-level positive association between IL-10 and BDI scores ($r(29)=.35$, $p =.05$). This association became significant with adjustment for BMI, remained a trend with adjustment for age, gender, or CPZ, and was not significant when the participants on cardiac medications were excluded (age: $r(28)= .33$, $p =.07$; BMI: $r(27)= .38$, $p =.04$; gender: $\beta = .35$, $p =.06$; CPZ: $r(28)= .34$, $p =.07$; exclusion of participants on cardiac medications: $r(26)= .31$, $p =.11$).

Exploratory Mediation Analyses

Exploratory mediation analyses were then completed in the FE SZ sample (see Figure 3). However, analyses did not yield support for serial or single mediation. Briefly, there was no evidence that RSA in combination with CRP serially mediated the effects of poor sleep quality

on depressive symptoms. Similarly, CRP did not mediate the association between RSA and depression. Results were also null when fatigue was assessed as the outcome of interest. For all mediation analyses, all 95% bootstrap confidence intervals for indirect effects contained zero.

Given that we did not find support for serial or single mediation in FE SZ or in the older adult sample (Study 1), the planned full model multigroup comparisons were not completed as, by default, the configural model would be a better fit for the multigroup data than the invariant fixed-paths model. Instead, Wald tests were used to determine if specific paths from the serial or simple mediation models differed between the groups. Results of these analyses are summarized in Table 5. Overall, there was only one path coefficient that had a tendency to differ between the groups across the models (p = .04 or .05); the association between RSA to CRP, which was near zero in older adults, differed from the significant negative coefficient in FE SZ.

Discussion

The present study evaluated sleep quality, CVT, inflammation, and clinical symptoms in a sample with FE SZ as a step toward discovering mechanisms that may account for the previously observed relationships between poor sleep quality and clinical symptoms in SZ and their relationship to potentially similar processes in other samples with chronic sleep disturbance (i.e., older adults with insomnia). The present study also included comparisons between FE SZ and HC and FE SZ and older adults with insomnia to better characterize the extent of sleep complaints, autonomic dysfunction, and pro-inflammatory state in these samples. Overall, cross-sectional tests of the primary hypotheses showed limited support for the full model. Specifically, hypothesized associations between sleep quality and CVT, sleep quality and inflammatory markers, and CVT and clinical symptoms (depression, fatigue and positive and negative symptoms of psychosis) were not supported. However, findings revealed a novel negative

association between sleep duration and CVT in FE SZ. As predicted and extending the literature on the cholinergic anti-inflammatory pathway (Tracey, 2002; 2009) to early psychosis, CVT was negatively associated with CRP. Results also revealed positive associations between both IL-6 and IFN-γ levels and the severity of positive symptoms of psychosis, as assessed by the SAPS, in FE SZ that warrant further investigation. Exploratory mediation hypotheses were not supported in FE SZ or older adults with insomnia. Overall, findings provide new characterization of sleep quality, CVT, and inflammation in FE SZ and enhance knowledge about PNS-immune coordination.

Subjective Sleep Quality in FE SZ

Present findings increase knowledge about subjective sleep quality in FE SZ. Consistent with previous studies that have reported high levels of sleep disturbance in SZ, about half of FE participants (47.37%) endorsed clinically significant sleep problems on the PSQI as indicated by total scores > 5. However, the average PSQI score in the present sample (5.55 ± 3.19) was lower than previously reported scores from SZ patients in the chronic phase of illness (e.g., Hofstetter et al., 2005: 11.6 ± 4.57; Royuela et al., 2002: 6.63 ± 3.79; Waters et al., 2013: 6.62 ± 3.80). Based on prior studies (e.g., Laskemoen et al., 2019), it was hypothesized that short sleep duration would be the dominant sleep complaint among FE SZ participants. However, only one patient reported sleeping less than six hours per night. Instead, long sleep duration was the most common sleep concern in FE SZ; nearly one-third (28.95%) of SZ patients reported sleeping longer than 10 hours per night.

Comparisons with HC and older adults provided helpful contrasts to further contextualize sleep complaints in FE SZ. Overall, it was surprising that the average PSQI score in FE SZ (5.55 ± 3.19) did not differ significantly from HC (4.76 ± 2.82). Nor did FE SZ or HC differ with

regard to difficulties falling asleep (sleep latency), sleep efficiency, or sleep disturbances. However, on average, FE SZ patients reported spending an additional 2.38 hours asleep and 2.48 hours in bed than the young adults in the HC group. As anticipated, FE SZ participants also reported greater use of sleep medications and more daytime dysfunction than HC. Although it was expected that subjective sleep quality would be similar in FE SZ and older adult insomnia samples, PSQI scores in older adults (10.76 ± 2.86) were approximately twice those in FE SZ.

Overall, this characterization of subjective sleep complaints in a FE sample suggests that sleep quality may not be as "damaged" in early psychosis as previously described (Royuela et al., 2002). Specifically, we were expecting to observe greater prevalence of classic insomnia symptoms (e.g., short sleep duration, long sleep latency) in FE SZ and this was the rationale for proposing cross-sample comparisons with older adults with insomnia. Instead, the present findings indicate that long sleep duration and excessive time in bed are major contributors to dissatisfaction with sleep and poor sleep quality in FE SZ.

CVT in FE SZ

As a result of planned comparisons between FE SZ and HC and FE SZ and older adults, the present study confirms and provides further contextualization of previous reports of autonomic dysfunction in SZ. Specifically, results replicated prior studies that have reported diminished CVT in samples with psychotic disorders relative to HC (Bär et al., 2005; Boettger et al., 2006; Clamor, Lincoln, Thayer, & Koenig, 2016; Montaquila et al., 2015) and extended these findings to a FE sample. Covariate analyses confirmed that the group difference in RSA observed in the present study between FE SZ and HC was robust to group differences in age, BMI, gender composition, and not attributable to the subgroup of participants using cardiac medications. There was also a trend-level effect for resting RSA to be higher in FE SZ than in older adults

with insomnia. However, this difference could be attributable to established age-related decreases in RSA (Bonnemeier et al., 2003; Umetani et al., 1998) or unique clinical features associated with early psychosis or chronic insomnia. Although it is unclear why CVT is reduced in FE SZ relative to HC, diminished CVT may contribute mechanistically to or be a predictor of poor health outcomes in SZ (Bär et al., 2005).

Inflammation in FE SZ

With regard to inflammation in FE SZ, the present study also replicated established findings of elevated CRP in SZ (Faugere et al., 2018; Lee et al., 2019; Miller & Goldsmith, 2017). In fact, the rate of elevated CRP (i.e., CRP > 3 mg/L) in the present sample, approximately 39%, was remarkably consistent with previous reports from samples of patients in the chronic phase of SZ (40%, Faugere et al., 2018). Additionally, FE SZ patients had higher average CRP levels than older adults with insomnia. This difference in CRP persisted when controlling for BMI, gender composition, and did not appear to be driven by the subset of patients on cardiac medications. However, as there are many other differences between these samples (e.g., sleep quality, age, antipsychotic use, other clinical symptoms and comorbidities), the drivers of this group difference in CRP are unclear. It was particularly remarkable that nearly 20% of the FE SZ sample had CRP levels greater than 10 mg/L. CRP values between 3-10 mg/L may be attributable to inflammatory conditions, including periodontal disease, infection, lung disease, obesity, and metabolic syndrome (Miller, Culpepper, & Rapaport, 2014), which can occur at high rates in SZ. CRP levels > 10 mg/L often indicate the presence of a chronic inflammatory disease, cancer, or infection (Miller, Culpepper, & Rapaport, 2014). However, CRP levels > 10 mg/L have also been linked to genetic polymorphisms and observed in apparently healthy populations (Kushner, Rzewnicki, & Samols, 2006). Although the cause of elevated CRP in the

present sample of young adults with FE SZ is unclear, the prevalence of this issue is concerning; CRP is an independent risk factor for cardiovascular disease (Windgassen, et al., 2011), the leading cause of death in SZ (Lin et al., 2018).

Tests of the Primary Hypotheses in FE SZ

The main purpose of the present study was to test a specific set of predictions about the relationships among sleep quality, CVT, inflammatory markers, and clinical symptoms in FE SZ, as a step toward evaluating a transdiagnostic model to account for the effects of sleep disturbance on clinical symptoms.

On an exploratory basis, the present study evaluated serial and simple mediation models in FE SZ and compared these results with those from older adults with insomnia (Study 1).

Sleep Quality and Duration: Associations with CVT, Inflammation, and Clinical Symptoms

First, within the FE SZ sample, it was hypothesized that sleep quality would be positively associated with CVT and negatively associated with inflammation and clinical symptoms including depression, fatigue, and positive and negative symptoms of psychosis (e.g., Gouin et al., 2013; Lee et al., 2019; Reeve et al., 2019). Results revealed no associations between overall sleep quality and CVT. However, specific aspects of sleep behavior, sleep duration and total time in bed, were negatively associated with CVT. Sleep quality was also not associated with inflammatory markers (CRP, IL-6, IL-8, IL-10, TNF-α and IFN-γ). As predicted, poorer sleep quality (higher PSQI score) was associated with greater fatigue. A similar positive correlation between PSQI and depression failed to reach statistical significance. Unexpectedly, PSQI scores were not associated with positive or negative symptoms of psychosis.

The negative associations observed in this study between sleep duration and total time in bed and CVT are a novel contribution to the literature. Few previous studies have interrogated the

relationship between sleep duration and CVT. One study in a small sample of apparently healthy hospital employees found no relationship between CVT and sleep duration (Sajjadieh et al., 2020); another, in a large population-based sample of US adults, showed that CVT was lower in individuals who slept between 6 to 6.9 hours per night relative to those who slept 7 or more hours per night (Castro-Diehl et al., 2016). Given that both extremes, short sleep duration and long sleep duration, have been associated with negative health outcomes and early mortality (Cappuccio et al., 2010), one possibility is that the relationship between CVT and sleep duration may be best approximated by an inverted U-shaped curve, such that CVT is maximal in individuals with optimal sleep duration and reduced in populations with extreme (i.e., very short and very long) sleep duration. Given that the FE SZ sample reported long average sleep duration and excessive time in bed, the negative associations observed between CVT and these aspects of sleep appear to be consistent with the proposal that CVT corresponds with health status and health behaviors (Gidron et al., 2018).

The lack of significant associations between PQSI scores or sleep duration and inflammatory markers in the present FE SZ sample was somewhat surprising. One prior study in a large sample with chronic SZ (*n*=144) reported that worse general sleep quality on a 4-item Likert scale was associated with higher levels of CRP and IL-6 (Lee et al., 2018). However, the authors did not find differences in inflammatory profiles among subgroups of patients with varying sleep duration when sleep duration categories were defined as short (<7 hours/night), optimal (7–8 hours/night) and long (>8 hours/night). Though prior large-scale studies and meta-analytic findings provide strong evidence that long sleep duration is generally associated with increased CRP across a variety of adult samples (Grandner et al., 2013; Irwin, Olmstead, & Carroll, 2016; Irwin & Opp, 2017), the present study did not extend this finding to FE SZ.

The finding that worse sleep quality was associated with greater fatigue in SZ was expected and intuitive. Although a similar correlation between PSQI and BDI score emerged in the predicted direction, it did not reach statistical significance. With regard to psychotic symptoms, null results are consistent with two previous studies that did not find associations between insomnia symptoms and positive symptoms (Palmese et al., 2011) and PSQI scores and Positive and Negative Syndrome Scale (Ritsner et al., 2004).

CVT and Inflammation

Based upon the literature on the cholinergic anti-inflammatory pathway in healthy individuals (Tracey, 2002; 2009), it was hypothesized that CVT would be inversely associated with CRP and circulating proinflammatory cytokines. This hypothesis was partially supported. The present study replicated and extended a negative association between CVT and CRP (e.g., Cooper et al., 2014; Sajadieh et al., 2004), to a FE SZ sample. However, no other associations between CVT and individual cytokines emerged. Although causation cannot be inferred from the negative correlation between CVT and CRP in FE SZ, this finding is consistent with prior research and theory about vagal involvement in, and regulation of, inflammatory responses (e.g., Borovikova et al., 2000; Huston et al., 2007; van Westerloo et al., 2005; van Westerloo et al., 2006). We propose that high resting levels of PNS-activity (high CVT) constrain inflammatory responses, while PNS-hypoactivity (low CVT) contributes to sustained inflammatory responses and elevated CRP in FE SZ. Though others have suggested that autonomic dysfunction may contribute mechanistically to proinflammatory state in SZ (Corsi-Zuelli et al., 2017), the present study is the first to document the expected association between CVT and CRP in SZ. This association remained significant when adjusting for age but was not robust to other covariates (i.e., BMI, gender, or exclusion of participants on cardiac medications), possibly due to the small

sample. It may be that the negative association between CVT and CRP is partially due to the joint effects of a third variable on autonomic and inflammatory processes (e.g., adiposity, metabolic syndrome). Additional prospective and intervention studies will be key in determining causality.

Presently, there are few investigations of vagal-immune coordination in clinical samples. Only one prior pilot study that attempted to directly evaluate the effects of vagal stimulation as a treatment intervention for SZ. However, this trial was plagued by poor treatment adherence and inconclusive about the effects of vagal stimulation on proinflammatory cytokines, psychotic symptoms, and cognitive impairment in SZ (Hasan et al., 2015). Given the present finding of an inverse association between CVT and CRP in FE SZ, additional studies are warranted to determine if low efferent vagal activity contributes to the development of systemic inflammation in SZ. Future investigations should also determine if the combination of low CVT and high CRP increases risk for poorer physical and mental health prognoses in SZ.

CVT and Clinical Symptoms

It was also hypothesized that CVT would be negatively associated with clinical symptoms in FE SZ. In contrast to prior studies (Boettger et al., 2006; Chung et al., 2013; Mathewson et al, 2012; Okada et al., 2003), there were no significant associations between CVT and the severity of depression, fatigue, or psychotic symptoms. These null results in FE SZ were consistent with findings from Study 1 in which CVT was also unrelated to severity of depression, anxiety, and fatigue in older adults with insomnia. Taken together, these results challenge the theory that CVT is a reliable correlate of emotion regulation abilities or subjective wellbeing in clinical samples (Balzarotti et al., 2017).

Inflammation and Clinical Symptoms

Lastly, we expected to replicate previously reported positive associations between inflammatory markers and clinical symptoms in SZ (Faugere et al., 2018; Miller et al., 2011). Results revealed positive associations between both IL-6 and IFN-γ levels and the severity of positive symptoms of psychosis (SAPS) in FE SZ. There was also a trend-level positive association between IL-10 and depressive symptoms. There were no other significant associations between other inflammatory markers and clinical symptoms as assessed with the SAPS, SANS, BDI, and MFSI. The finding of an association between IL-6 and positive symptoms of psychosis is consistent with the theory that IL-6 is an acute marker that fluctuates with psychosis (Goldsmith et al., 2016). It may be particularly meaningful that both IL-6 and IFN-γ levels were correlated with SAPS in the present samples of stabilized, medicated FE SZ participants. A prior study reported that initial, pre-treatment elevations in IL-6 and IFN-γ were associated with poor treatment response to antipsychotics in early psychosis (Mondelli et al., 2015). Elevated IL-6 in FE psychosis has also been linked to lower levels of brain-derived neurotrophic factor, a known mediator of neurogenesis and neuroplasticity that may impact recovery trajectories in SZ (Mondelli et al., 2011).

Exploratory Mediation Analyses

The present study also included exploratory mediation analyses to test the full model in FE SZ and older adults with insomnia. It is important to note that the primary correlational analyses in FE SZ revealed a lack of direct effects for the proposed simple mediation model (CVT on depressive symptoms/fatigue) and limited direct effects for the proposed serial mediation model (n.s. association between PSQI and depression and a small positive association between PSQI and fatigue). In light of this and the small sample size (n = 31) for inflammatory measures, it was not surprising that exploratory mediation hypotheses for the serial and simple

mediation models were not supported. As there was no evidence of serial or simple mediation in older adults (Study 1) or the present FE SZ sample, full model multigroup comparisons were not pursued. Comparisons of the mediation model paths between groups revealed no significant differences, except that the negative correlation between RSA and CRP in FE SZ was different from the near zero association between these variables in older adults. Overall, null findings for the proposed model in both groups indicates that further research is needed to understand the transdiagnostic pathways that lead from sleep disturbance to poor physical and mental health outcomes.

Limitations and Future Directions

The present study had several limitations. First, the cross-sectional design precludes causal inferences about the observed relationships between sleep, autonomic function, inflammation, and clinical symptoms in FE SZ. COVID-19 related disruptions to data collection limited the sample size and ability to recruit a larger number of FE SZ patients and a full, aged-matched cohort of HC participants. It is possible that between group comparisons (i.e., t-tests) were affected by unequal sample sizes. With regard to group differences in CVT reported in the present study, it is also important to note that the procedures for the assessment of RSA were consistent for FE SZ and HC (EKG was assessed in the afternoon from seated participants) but differed for older adults with insomnia (EKG was assessed in the evening before bedtime from supine participants). Additionally, the measure of depression differed between study samples (BDI-II in FE SZ and HC and IDS-C in older adults). There are no prior studies which have directly compared correlations between the self-reported BDI-II and clinician rated IDS-C to guide further evaluation of the impact of this methodological difference on the present findings.

Finally, as previously acknowledged, due to small sample sizes the serial and simple mediation analyses in the present study were underpowered, and planned multiple group comparisons to evaluate the full model in FE SZ and older adults were not completed. Future studies would benefit from recruiting larger samples and including age-matched healthy sleeping comparison groups for all clinical samples studied (e.g., FE SZ and older adults with insomnia).

It is concerning that FE SZ patients in this study primarily endorsed long sleep duration and excessive time in bed, given that long sleep duration is a well-established risk factor for mortality (Cappuccio et al., 2010). Long sleep duration may contribute to the mortality gap for populations with serious mental illness (De Mooij et al., 2019). Future studies should determine whether early interventions for psychosis that reduce time in bed and increase daytime activity levels (e.g., treatment programs that include aerobic exercise), have a positive impact on health trajectories for this population. Prior research suggests that a 6-month cognitive training and aerobic exercise intervention can lead to reductions in IL-6 which correlate with improvement in depressive symptoms in FE SZ (Ventura et al. 2021). However, it is unclear if aerobic exercise impacts sleep quality, efficiency, or CVT in FE SZ. In general, further descriptive, longitudinal, and intervention-focused studies are needed to improve knowledge about the prevalence of various sleep concerns (i.e., insomnia, hypersomnolence, obstructive sleep apnea) and their course in early SZ.

Additionally, as the present study was the first to investigate and report a negative association between CVT and CRP in FE SZ consistent with a vagally-mediated anti-inflammatory pathway, future studies are warranted to replicate this finding and assess its potential relevance for clinical practice.

Conclusion

Despite the aforementioned limitations, the present results characterize subjective sleep complaints in FE SZ and extend findings of diminished CVT and elevated CRP to a FE sample. Findings also provide valuable information about the associations between sleep quality, CVT, peripheral markers of inflammation, and clinical symptoms (depression, fatigue, and psychotic symptoms) in FE SZ. Specifically, results extend the previously reported inverse association between CVT and CRP to this novel clinical context, offering preliminary evidence of intact PNS-immune coordination in SZ. Overall, findings provide a rationale for further study of sleep concerns and investigation of PNS-immune pathways in SZ.

Study 3: Changes in Cardiac Vagal Tone during Behavioral Interventions for Late Life Insomnia

Introduction

Insomnia is particularly prevalent among older adults and is a known cause of morbidity and mortality (Dew et al., 2003; Kripke, Garfinkel, Wingard, Klauber, & Marler, 2002; Ohayon, 2002; Parthasarathy et al., 2015). A number of behavioral interventions have demonstrated beneficial effects on insomnia and associated physiological and psychological processes, including inflammation and clinical symptoms of depression, anxiety, and fatigue (Friedrich, Claßen, & Schlarb, 2018; Irwin, Olmstead, Carrillo et al., 2014; Irwin, Olmstead, & Motivala, 2008; Li et al., 2004; Taylor et al., 2014). Of note, these effects have been observed across different types of interventions that target different processes. However, the mechanisms through which these interventions reduce sleep disturbance have not been determined. One plausible candidate is CVT, which has been proposed as a key regulator of inflammation and clinical symptoms (e.g., Pavlov & Tracey, 2012; Thayer & Lane, 2009; Thayer & Sternberg, 2006). Study 3 sought to understand if CVT is malleable in older adults with insomnia in response to two behavioral interventions (CBT-I and TCC) and to determine to what extent any intervention-related changes are associated with improved clinical state (Irwin, Olmstead, Carrillo et al., 2014). This study built upon the cross-sectional approach used in Study 1 by evaluating how behavioral interventions targeting sleep influence CVT and associated symptoms in older adults. The goal of the present study was to inform current knowledge about CVT and determine how behavioral treatments affect CVT and clinical state in this population.

Cardiac Vagal Tone and Behavioral Interventions for Insomnia

Evidence-based behavioral interventions for older adults with insomnia include mind-body interventions such as Tai Chi Chih (i.e., TCC) and CBT-I, the gold standard behavioral treatment for insomnia (Irwin et al., 2008; Irwin et al., 2014; Li et al., 2004). Though these interventions are theorized to impact different targets (i.e., TCC: stress and arousal mechanisms; CBT-I: sleep-related cognition and behavior; Irwin, Olmstead, Carrillo et al., 2014), the present study evaluates the possibility that these distinctive interventions, which restore sleep and improve clinical symptoms, have common effects on CVT.

Preliminary evidence, primarily from the depression-treatment literature, suggests that regular use of mind-body interventions, including Tai Chi and yoga, can simultaneously increase CVT (Zou et al., 2018) and decrease stress in samples without insomnia. For instance, in non-depressed and depressed older adults, 12 and 24-week programs of Tai Chi were associated with increases in CVT (Audette et al., 2006; Liu et al., 2018) and decreases in depressive symptoms (Liu et al., 2018). Similarly, in middle-aged women with fibromyalgia, 12 weeks of Tai Chi produced increases in CVT, along with reductions in pain and fatigue (Wong et al., 2018).

A few studies suggest that CBT-based interventions can produce similar effects in samples without insomnia. For instance, 8 weeks of group CBT resulted in increases in CVT in young women with irritable bowel syndrome (Jang, Hwang, Padhye, & Meininger, 2017). Further, this same study reported that treatment-related increases in CVT were positively correlated with improvement in gastrointestinal symptoms, anxiety, depression, and stress at 16-weeks after CBT completion. Similarly, in adults with depression and poor self-rated sleep quality (i.e., PSQI > 5), 12 sessions of a CBT-based group intervention that integrated core elements of CBT with breathing exercises, led to increased CVT and clinically significant improvement in sleep quality (Chien, Chung, Yeh, & Lee, 2015).

Only one study has specifically examined the impact of CBT-I on CVT (Chung, An, Park, & Kim, 2011). This study, which was conducted with a mixed sample of middle-aged and older adults with insomnia, reported that patients who showed clinically significant reductions in insomnia severity at post-treatment (i.e., treatment responders) experienced significant increases in time domain and trend-level increases in frequency domain measures of CVT, whereas CVT did not change in non-responders (Chung et al., 2011).

Together, these studies provide preliminary support for the hypothesis that behavioral interventions similar to TCC and CBT-I can produce within-person increases in CVT (CBT: Chein et al., 2015; Chung et al., 2011; Jang et al., 2017; Tai Chi: Audette et al., 2006; Liu et al., 2018; Wong et al., 2018; Zou et al., 2018). However, several methodological issues limit conclusions. In particular, these studies have not been well controlled. In fact, out of the aforementioned studies, only Audette and colleagues (2006) employed an active comparison group (brisk walking) to demonstrate that treatment-related increases in CVT in elderly women were specific to their Tai Chi intervention. Comparison samples that receive no treatment interventions at all, as employed by Liu et al. (2018), Wong et al., (2018) and others, are problematic as non-specific treatment factors such as increased social support could potentially contribute to the improvement in CVT and clinical symptoms observed in the active treatment conditions.

Prior studies have also generally focused on one treatment at a time, either Tai Chi or CBT, and have not compared across different interventions. It is essential to compare treatment effects across interventions to determine whether improvement in CVT is restricted to certain types of interventions or is a common signal of improving clinical state regardless of type of intervention. In addition, most previous studies have focused exclusively on the connection

between CVT and mood symptoms; they have not thoroughly assessed relationships with sleep quality or inflammation, despite the fact that sleep complaints and inflammation are important indicators of current health and predictors of health trajectory during older adulthood (Grossman, 2016; Kritchevsky, Cesari, & Pahor, 2005). Most importantly, these previous studies contribute little to knowledge about unique or common mechanisms (e.g., inflammation) supporting the link between intervention-related increases in CVT and improvements in clinical state in insomnia.

The Present Study

Study 3 aimed to address these gaps by means of secondary analysis of data obtained from a completed RCT that compared 4 months of CBT-I and TCC to an education-only control condition, Sleep Seminar (SS), for the treatment of insomnia in older adults (Irwin, Olmstead, Carrillo et al., 2014). Based on the available literature, it was hypothesized that both active behavioral treatments, CBT-I and TCC, would lead to increases in CVT as compared to SS (Audette et al., 2006; Chung et al., 2011; Liu et al., 2018). Given that TCC and CBT-I are hypothesized to lead to improvements in sleep by different mechanisms, differences in treatment-related change in CVT between these interventions were also probed on an exploratory basis. It was further expected that treatment-related improvement in CVT during the intervention period would be associated with increases in sleep quality and reductions in inflammation at systemic and cellular levels of analysis (CRP, unstimulated and TLR-4 stimulated monocyte production of proinflammatory cytokines) and clinical symptoms (depression, anxiety, fatigue) at post treatment and follow-up (3 months and 12 months post-treatment). As a previous insomnia treatment study by Chung and colleagues (2011) reported that CBT-I-related improvements in CVT were only observed within treatment-responders in their sample, the present study also

determined whether change in CVT differed between treatment responders and non-responders across treatment groups as indexed by insomnia remission at post-treatment.

The goal of this study was to learn about the role of CVT in insomnia treatment and recovery. If results indicated that CVT was malleable in older adults with insomnia and the extent of treatment-related improvement in CVT was related to global improvements in clinical state, studies targeting the enhancement of CVT during insomnia treatment would be warranted to determine whether change in CVT contributes mechanistically to sleep restoration. If instead the present research revealed that CVT was unchanged by behavioral treatment or was disassociated from improvements in clinical state, this would suggest that CVT is unlikely to be a mechanism supporting insomnia recovery in older adulthood.

Method

All pre-treatment procedures for the present study, including collection of baseline measures of CVT, inflammation, sleep, and clinical symptoms, were consistent with those described for Study 1. After pre-intervention assessments, participants were randomized to TCC, CBT-I, and SS with a 2:2:1 randomization schedule. Participants then attended 2-hour weekly group classes with 7-10 participants (CBT-I, TCC, SS) for 4 months, with assessments at 2 and/or 3 months (mid-intervention), 4 months (post-intervention), and 7 and 16 months (follow-up). At post intervention, participants completed two consecutive nights of PSG with reassessment of EKG on both evenings and assessment of inflammation on the morning after the second evening of post-treatment PSG. After post-treatment PSG, participants completed follow-up assessments at 7 and 16 months, which included morning assessment of cytokine activity and self-report assessment of sleep and daytime symptoms of insomnia. Figure 2 is the CONSORT diagram from Irwin, Olmstead, Carrillo et al. (2014) that details the flow of participants though

the RCT. The present study relies on EKG data collected at pre and post-intervention, behavioral data collected at pre-intervention, 4, 7, and 16 months, CRP collected at pre-intervention, 4 months, and 16 months, and two measures of cellular inflammation (unstimulated and TLR-4 activation of monocyte co-production of IL-6 and TNFα) assessed at pre-intervention, 4 months, 7 months, and 16 months. Figure 4 is a modified CONSORT diagram which shows the number of participants at each time point in the parent trial against those with RSA data included in the present study.

Participants

Participants and exclusion criteria were fully consistent with Study 1.

Interventions

TCC

TCC is a manualized form of movement meditation based upon the Chinese art of Tai Chi (Stone, 1996). The TCC intervention used in this study emphasized mindful performance of slow-paced, non-strenuous movement, relaxation, and control over the body and its physical functions including arousal-related responsiveness. The first 2 months of TCC focused on increasing mastery of single forms (20 unique exercises) through repetition in class and at home. Months 3-4 targeted consolidation of daily practice routines and integrated natural breathing into group practice. Participants were encouraged to practice TCC between groups and completed diary assessments of the frequency and duration of independent practice.

CBT-I

As previously described (Irwin, Olmstead, Carrillo et al., 2014), traditional CBT-I (Morin et al., 2006) was augmented to teach behavioral strategies for mood and day-time energy enhancement, because individuals with insomnia often report poor day-time functioning

including symptoms of fatigue and mood disturbance. To change sleep-interfering thoughts and behaviors and re-establish restorative sleep, CBT-I included psychoeducation, cognitive restructuring, stimulus control, mood enhancement, and skill consolidation (Irwin, Olmstead, Carrillo et al., 2014). Although sleep restriction is traditionally a core component of CBT-I, it was not emphasized during this intervention as shortened sleep may increase inflammation (Irwin, Wang, et al., 2006).

Sleep Seminar

SS was an active control intervention, which included didactic presentations and interactive discussions on a variety of topics related to sleep hygiene and aging, without directly addressing how participants could apply this information to change their sleep behavior. Participants in SS received similar attention and group support as those randomized to TCC and CBT-I and reported similar expectations of benefit at pre-treatment and treatment acceptability post-treatment (Irwin, Olmstead, Carrillo et al., 2014).

Assessment of Cardiac Vagal Tone

EKG acquisition and processing procedures for data from pre- and post intervention are be consistent with those described in Study 1. To optimize the quality of the EKG data, EKG recordings from pre-intervention PSG nights 2 and 3 (after full night adaptation) and post-intervention nights 1 and 2 were evaluated and ranked by trained raters blind to group membership. By consensus, the best quality files from each time point were selected for analysis. When pre-treatment EKG from nights 2 and 3 were of equivalent quality, the file from night 2 was automatically selected; similarly, when post-treatment EKG data from nights 1 and 2 were of equivalent quality the file from night 1 was selected. Ultimately, high quality EKG data were available from 79 participants at PSG session 2 and 27 participants at PSG session 3 (total pre *n*

= 106), and 57 at post-assessment 1 and 25 post-assessment 2 (total post *n* =82). Eighty participants had high quality data at both pre and post assessments. EKG data was excluded if the participant declined PSG (pre-intervention *n*= 4, post-intervention: *n*=10), dropped out of the intervention before post PSG assessment (*n*=11), or if collected data were unusable due to technical difficulties (e.g., EKG lead detached) (pre-intervention: *n* = 6, post-intervention: *n*=7), or had clear signs of cardiac arrhythmia (e.g., more than one consecutive ectopic beat, pre-intervention: *n* = 7, post-intervention: *n* = 13.)

Insomnia Remission

Insomnia remission was assessed by DSM-IV-TR structured interview with the study psychiatrist (MRI), who was blind to group assignment (Irwin, Olmstead, Carrillo et al., 2014).

Perceived Sleep Quality

As reported in Study 1, sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989).

Depression, Anxiety, and Fatigue

Symptoms of depression, anxiety, and fatigue were assessed using the IDS-C: (Rush et al., 1996), BAI (Beck et al., 1988), and MFSI-SF (Smets et al., 1995; Stein et al., 2004) as described in Study 1.

Inflammation

All assays for CRP and TLR-4 activation of monocyte co-production of IL-6 and TNFα were completed using the same methods described in Study 1.

Power Analysis

The present study relied on data collected as part of an RCT (Irwin, Olmstead, Carrillo et al., 2014) that was powered to detect treatment-related differences in insomnia remission at 4 months and did not include a priori hypotheses about differential effects of active treatments

(CBT-I, TCC) and sleep education (SS) on change in RSA. The limited available literature comparing the effects of behavioral interventions similar to TCC and CBT-I and control interventions on RSA generally suggested that the present study should be powered to find a small to medium effect size (Liu et al., 2018; Zou et al., 2018).

Given the number of treatment groups (2), repeated EKG assessments (2), estimated number of participants in the sample with usable pre-and-post EKG data (n = 83), expected correlation among repeated measures (.5), and $\alpha = .05$, an a priori power analysis to estimate achieved power over a range of small to medium effect sizes (η^2 = .01-.06) was conducted in G*Power 3.1.9.3 (Faul et al., 2008). This protocol suggested that the expected power of this analysis would range from .44-.99 for effect sizes between η^2: .01-.06 (i.e., f: .10-.25; d = .20-.50. Upon further evaluation of the data, the total number of participants with usable pre and post EKG decreased to n=80 and the correlation between repeated measures (RSA at pre and post) was r= .61. Therefore, the power of this analysis ranged from .52-.99 for effect sizes between η^2: .01-.06 (i.e., f: .10-.25; d = .20-.50).

Statistical Analyses

To verify that the treatment groups were not different at pre-intervention on key variables (e.g., RSA, cytokines) one-way ANOVAs and Chi Square tests were performed. Chi Square tests were also used to confirm that intervention effects from the parent study (Irwin, Olmstead, Carrillo et al., 2014) were consistent in this subsample (e.g., that active treatments CBT-I and TCC together yielded higher rates of insomnia remission at post-treatment than SS). To evaluate change in RSA by group from pre-to-post treatment a mixed model approach was employed. The mixed model approach used all available data to generate unbiased estimates under the assumption that data are missing at random (MAR), or missing completely at random (MCAR).

Given that there are no well-established tests of the MAR assumption, the MCAR assumption was tested.

To determine whether active treatment (CBT-I and TCC combined) improved RSA more than education only (SS), a repeated measures mixed model with treatment type as a between subject factor with two levels (active: TCC and CBT-I vs. control: SS), RSA assessment time point as a within subject factor with two levels (pre and post-treatment), and a random intercept was evaluated. To investigate differences between all three treatment groups, this model was then repeated with treatment type as a between subject factor with three levels (TCC, CBT-I, and SS). Pairwise comparisons were then used to determine which group differences (e.g., CBT-I vs. SS) were driving observed effects. This sequence of analyses was then repeated with age, gender, beta-blocker use, BMI, and weekly metabolic equivalents (METs) as covariates (Kuch et al., 2001; Guzzetti, Magatelli, Borroni, & Mezzett, 2001; Huikuri, & Mäkikallio, 2001).

To determine whether the extent of treatment-related change in RSA (i.e., delta RSA) was associated with change in sleep quality, clinical functioning (fatigue, depression, anxiety), and inflammation (CRP, monocytic co-production of IL-6 and TNFα) at post intervention, or predicted change on these outcomes at 7 months, and 16 months, difference scores were created for each of these dependent variables of interest (e.g., delta pre-post depression). After assessment of the distributions of these change scores, regressions predicting change on these key trial outcomes from delta RSA were completed. Next, to test the exploratory hypothesis that treatment group assignment (e.g., TCC vs. CBT-I) would moderate the association between delta RSA and change on key trial outcomes, hierarchical regressions predicting these change scores from delta RSA, treatment group, and the interaction between delta RSA and treatment group were completed. Significant interactions were followed by analyses of simple slopes.

Finally, to evaluate the possibility that treatment-related improvement in RSA would be greater for treatment-responders than non-responders, regardless of treatment intervention type, t-tests were used to compare delta RSA in treatment-responsive and unresponsive participants. Treatment responder status was defined by remission of insomnia diagnosis at post-treatment.

Results

To verify that the three treatment groups did not differ from each other at pre-intervention on key variables (e.g., RSA, cytokines) and demographics (e.g., gender), ANOVAs and Chi Square tests were used. Results of these analyses are reported in Table 6. Overall, treatment groups were similar at pre-intervention. However, the groups did differ on the extent of stimulated monocyte co-production of IL-6 and TNFα at pre-treatment, $F(2, 98) = 9.00$, $p < .001$. Post hoc analyses using the Tukey HSD criterion for significance indicated that the TCC group had greater stimulated monocyte co-production of proinflammatory cytokines at pre-intervention than either the CBT-I or SS groups. Therefore, in subsequent regression analyses examining change in stimulated monocyte production, pre-treatment stimulated monocyte production was entered as an additional covariate.

To confirm that the intervention effects on insomnia observed in the present subsample were comparable to those reported in the parent RCT (Irwin, Olmstead, Carrillo et al., 2014), two Chi Square tests were completed. Results of this analyses verified that active interventions (CBT-I and TCC together) produced higher rates of insomnia remission at post treatment than SS ($\chi^2 = 4.51$, $p = 0.03$). As in the parent trial, the remission rate of CBT-I (52.94%) was significantly greater than that of TCC (29.63%) and SS (15.79%), ($\chi^2 = 8.05$, $p = 0.02$).

Tests of the continuous RSA data at pre and post treatment suggested missing values fit the MCAR assumption ($\chi^2(2) = 2.83$; $p = 0.24$) and that the mixed model approach was

appropriate. In order to evaluate the hypothesis that active insomnia treatment (CBT-I and TCC combined) would improve RSA more than SS, a repeated measures mixed model was completed with a random intercept, treatment type as a between subject factor with two levels (active: TCC and CBT-I vs. control: SS), and RSA assessment time point as a within subject factor with two levels (pre and post-treatment). This analysis revealed no main effect of time ($F(1, 88.96) = .78$, $p = .38$), no main effect of treatment group ($F(1, 103.89 = .55$, $p = .46$; combined main effects model: $F(2, 95.86) = .67$, $p = .51$), and most importantly, no group by time interaction ($F(1, 85.91) = .38$, $p = .54$).

Similarly, there were no main effects of time or group and no group by time interaction when intervention group was assessed as between-subjects factor with three levels (main effect of time: $F(1, 88.68) = .78$, $p = .38$; main effect of group: $F(2, 104.35) = .34$, $p = .71$; combined main effects model: $F(3, 98.55) = .49$, $p = .69$; group x time interaction: $F(2, 86.40) = .28$, $p = .76$). Means and standard deviations for the three group analyses are presented in Table 7 (See Figure 5 for a visualization of change in RSA by group from pre to post intervention.) Results remained similar when these mixed models were repeated with the addition of relevant covariates (age, gender, beta-blocker use, BMI, weekly METs). However, a main effect of participant gender emerged for both main effects models, (treatment as two-level factor: $F(1, 98.27) = 5.73$, $p = .02$; treatment as a three-level factor: $F(1, 97.29) = 5.65$, $p = .02$), such that female gender was associated with higher RSA across all groups over time.

Next, to evaluate whether change in clinical state (e.g., delta sleep quality, delta inflammation, delta depression, delta anxiety, delta fatigue) was associated with delta RSA from pre to post treatment, simple regressions predicting each outcome change score from delta RSA were completed. These analyses showed that delta RSA was not associated with the extent of pre

to post treatment change on any key trial outcome (delta PSQI: p= .46; delta CRP: p= .68; delta unstimulated co-production of IL-6 and TNFα: p= .82, delta stimulated co-production of IL-6 and TNFα: p= .44; delta IDS-C: p= .54; delta BAI: p= .42; delta MFSI: p= .92). Similarly, delta RSA did not predict the total change on these outcomes from pre to 7 and 16-month follow-up assessments (all p values > .14).

On an exploratory basis, we also evaluated the possibility that the associations between delta RSA and change on these key clinical outcomes (e.g., delta sleep quality, delta inflammation, delta anxiety, and delta fatigue) would be moderated by treatment group assignment (i.e., CBT-I vs. TCC vs. SS). A series of hierarchical regressions predicting clinical change scores from delta RSA, treatment group (CBT-I, TCC, and SS), and the interaction between delta RSA and treatment group were completed. Given both the narrow range of delta RSA across all participants (M= -.05, SD =.87) and the lack of significant group differences in delta RSA, unsurprisingly treatment group did not moderate the associations between change in RSA and pre-to-post change on key trial outcomes (all p values >.16). Results were consistent when pre to 7 month and 16-month change scores were evaluated (all p values > .15).

Finally, to evaluate the possibility that treatment-related improvement in RSA would be greater for treatment-responders than non-responders, regardless of treatment intervention assignment, a t-test was used to compare delta RSA between participants still meeting criteria for insomnia (n =51) vs. in remission (n= 29) at post-treatment. This t-test revealed that there was no difference in the treatment-related change in RSA between responders and non-responders, $t(78)$= -.14, p = .89 for the 80 completers with usable RSA data at both time points.

Discussion

The present study evaluated the role of CVT in insomnia treatment and recovery in older adulthood. Specifically, in the context of a previously completed RCT, we assessed whether different active behavioral interventions for insomnia (CBT-I and TCC) increased CVT more than sleep education (SS) and whether treatment-related changes in CVT were associated with the extent of recovery on key trial outcomes including sleep quality, inflammation at multiple levels of analysis, and clinical symptoms. Results indicated that neither CBT-I nor TCC led to significant changes in CVT, even though the rate of insomnia remission was higher for active treatments (CBT-I and TCC together) than SS. In fact, CVT, as indexed by RSA, was remarkably stable across all three groups over the 4-month intervention period ($r(78) = .61$ $p < .001$). As there was little variance in treatment-related change in CVT, change in CVT did not predict insomnia remission at post-treatment or the extent of improvement on key trial outcomes at post-treatment, 7 months (3 month follow-up) and 16 months (1 year follow-up). Overall, this pattern of results indicates that CVT is unlikely to be a common mechanism of behavioral interventions supporting insomnia recovery in older adulthood.

The present study bridges two largely separate literatures that that have begun to probe the mechanisms by which CBT-based treatments or mind-body interventions, such as Tai Chi, improve wellbeing. Specifically, a handful of studies have evaluated the effects of either CBT or Tai Chi on CVT to determine if these interventions up-regulate PNS activity. However, prior studies have typically been limited to one type of active behavioral intervention and have tended to focus on younger clinical samples without primary insomnia.

With regard to CBT-based interventions, three previous studies have reported positive effects of CBT on CVT and clinical symptoms in young adults psychiatric samples without insomnia (Chien et al., 2015; Garakani et al., 2009; Jang et al., 2017). Only one prior study

evaluated the impact of CBT-I, specifically, on CVT and sleep in a small (*n*=26) mixed sample of older and middle-aged adults with insomnia (Chung et al., 2011). In their single arm intervention study of CBT-I, Chung et al., found that treatment responders (i.e., individuals whose sleep quality improved) also showed significant increases in time domain and trend-level increases in frequency domain measures of CVT, whereas CVT did not change in non-responders. As the present study's group CBT-I intervention was longer (4-months) and more comprehensive than Chung et al.'s, it was anticipated that CBT-I would lead to simultaneous improvements in CVT and sleep, relative to SS for the older adults in the present sample. Instead, we found that CBI-I had no effect on CVT, even though CBT-I improved sleep more than SS and TCC (Irwin, Olmstead, Carrillo et al., 2014). There were also no differences in treatment-related change in CVT between treatment responders (i.e., individuals from any intervention group whose insomnia remitted at post-treatment) and non-responders in the present sample.

The present findings likely differ from those of Chung et al. (2011) for several methodological reasons. First, Chung et al. implemented CBT-I as an individualized intervention that included sleep restriction while the present study delivered CBT-I as a group intervention without a sleep restriction component due to concerns about the negative impact of short sleep duration on inflammatory markers (Irwin, Wang, Campomayor, et al., 2006; Irwin, Wang, Ribeiro et al., 2008). Additionally, Chung et al., presumably assessed daytime CVT (no specific time of day nor recording position were noted in their methods), while the present study assessed CVT from supine participants in the sleep lab in the hour before their normal bedtime when CVT was expected to be maximal (Jarczok et al., 2019; Shaffer et al., 2014). It is possible that the treatment-related differences reported by Chung et al. (2011) reflect poor experimental control

for the diurnal variance in CVT. Another difference that may account for the divergent findings is that the mean age of Chung et al.'s sample was about 7 years younger than the present study sample. CVT is known to decrease with age, but it remains unknown whether the malleability of CVT—including its ability to be up-regulated by behavioral interventions such as CBT-I—is also reduced by increasing age (Bonnemeier et al., 2003). Given the present novel result that CBT-I improved clinical state without changing CVT in older adults with insomnia and the prior studies that have reported effects of CBT-based treatments on CVT and clinical state in younger adults (Chien et al., 2015; Garakani et al., 2009; Jang et al., 2017), further research to evaluate the malleability of CVT over the lifespan is warranted. As CBT-I is clearly efficacious for older adults with insomnia, it is also important for future studies to investigate other putative mechanisms (e.g., down-regulation of sympathetic nervous system (SNS) activity) supporting CBT's treatment effects in this population.

Findings from the present study additionally contribute to the growing literature evaluating the health benefits and mechanisms of various forms of Tai Chi. Prior studies have demonstrated that TCC can improve sleep, immune functioning, and clinical symptoms in samples with insomnia (Irwin, Olmstead, Breen et al., 2015; Irwin, Olmstead, Carrillo et al., 2014; Irwin, Olmstead, Carrillo et al., 2017). Although it is frequently proposed that regular practice of Tai Chi enhances physical and mental wellbeing by increasing PNS outflow (Yeung, Chan, Cheung, & Zou, 2018; Zou et al., 2018), the present study was the first to evaluate whether TCC alters CVT in the context of insomnia.

The handful of existing studies in non-insomnia samples have yielded inconsistent results with some trials reporting positive effects of Tai Chi on CVT (Audette et al., 2006; Liu et al., 2018; Wong et al., 2018) and others reporting null effects (Lu & Kuo, 2012; Sato et al., 2010;

Zheng et al., 2018). It is not immediately obvious why these prior findings have been so mixed. A recent meta-analysis of studies evaluating the effects of mind-body interventions (Tai Chi and yoga) on heart rate variability parameters noted that a high proportion of reviewed studies had significant design "flaws," including failure to use blinded assessors and high attrition rates (Zou et al., 2018). It also seems likely that the use of different Tai Chi programs, varied assessment strategies for CVT (i.e., time vs. frequency domain measures, recording position and time of day), and diverse samples with respect to age, gender, and health status, contribute to this pattern of mixed results.

In the present study, the older adults randomized to TCC completed a once weekly 2-hour in-person TCC group for 4 months. Participants were encouraged to practice at home between sessions and reported on their total independent practice time each week. As TCC participants indicated they practiced an average of approximately 2 hours independently each week, it is estimated that they completed about 4 hours of TCC per week for 4 months. Based on the previous studies reporting positive effects of Tai Chi on CVT from interventions of about 3 hours per week (Audette et al., 2006; Liu et al., 2018; Wong et al., 2018), it was expected that a TCC intervention of this intensity and duration would enhance CVT in comparison to SS in the present sample of older adults with insomnia. Instead, the present study found that TCC had null effects on CVT, even though TCC led to greater improvement in sleep quality than SS (see Irwin, Olmstead, Carrillo et al. (2014). These novel findings in an older adult sample with insomnia are similar to those reported by Zheng et al., (2018) in a non-insomnia sample. Zheng and colleagues found that for healthy but stressed young adults, 5 hours of Tai Chi per week produced significant reductions in anxiety in the absence of effects on CVT. Taken together, these studies challenge the theory that the up-regulation of CVT is a primary mechanism

supporting the positive effects of Tai Chi on wellbeing. In contrast to the literature on CBT-based interventions, Tai Chi's effects on CVT do not appear to depend on the age of the sample. However, in light of the limited number of investigations and previously reported concerns about the quality of existing studies, additional studies evaluating the malleability of CVT to mind-body interventions (Tai Chi, yoga, exercise) over the lifespan are needed to clarify the present findings.

Given consistent null effects of the gold standard insomnia intervention (CBT-I) and TCC on CVT, the present study contributes strong evidence that the augmentation of CVT is not required for the remission of insomnia symptoms in older adults. Further, regardless of treatment group assignment, individual differences in intervention-related change in CVT were not associated with insomnia remission or the extent of improvement in sleep quality, inflammatory markers, or clinical symptoms attained at post-treatment and follow-up. These novel findings challenge the notion that CVT fluctuates with changes in clinical state (Bylsma et al., 2013). Instead, given that RSA was stable over four-months and across different intervention groups, the present results are more consistent with the conceptualization of CVT as a trait-like individual difference (Beauchaine, 2015; Thayer & Lane, 2000; 2009). If this is the case, it will be important to determine whether individual differences in CVT at pre-treatment moderate the effects of behavioral treatments for insomnia on key outcomes.

Strengths of the present study include the evaluation of two different active behavioral treatments (CBT-I and TCC) and an active control comparison condition (SS), a large sample (n=80) of older adults who completed interventions and EKG assessments, and vertical assessment of inflammation (i.e., examination of upstream cellular inflammatory processes and systemic inflammation). Confidence in the observed null effects of these behavioral treatments

for insomnia on CVT is bolstered by reliable assessment of RSA in the present study, as evidenced by a high correlation between pre and post treatment assessments and replication of established age and gender effects (Masi et al., 2007; Koenig, & Thayer, 2016; Shaffer & Ginsberg, 2017; Snieder et al., 2007).

The present study also has several limitations. First, as previously noted, CVT was evaluated by assessing RSA prior to participants' typical bedtimes in the sleep lab to capture treatment-related changes in maximal PNS outflow, which could affect sleep quality. However, as CVT was not assessed at other times of day, it is possible that treatment interventions led to undetected changes in daytime or 24-hour CVT. Additionally, the present study exclusively focused on RSA as an estimate of vagally-mediated PNS activity without evaluating SNS activity. This choice was made due to a strong a priori interest in PNS activity and because of specific concerns about the validity of estimating SNS activity with traditional heart rate variability metrics from pre-sleep, resting, supine EKG (e.g., LF HRV; see critique in Shaffer & Ginsberg, 2017). However, as common reductions in SNS activity may support treatment-related improvement in sleep, inflammatory markers, and clinical symptoms, future studies should endeavor to estimate SNS activity from daytime HRV metrics or by using other available techniques (e.g., pre-ejection period). As TCC has been shown to acutely decrease SNS activation as indexed by pre-ejection period in older adults (Motivala, Sollers, Thayer, & Irwin, 2006), investigations of SNS-mechanisms of TCC for insomnia are particularly needed.

Overall, results from the present study challenge the assumption that CVT is a common mechanism contributing to the ameliorative effects of diverse behavioral interventions for late life insomnia. Present null findings should motivate further investigations to improve knowledge about how these treatments exert effects on sleep quality, inflammatory markers, and clinical

symptoms. Identification of these mechanisms is an essential step toward refining and maximizing existing treatments for older adults with insomnia.

Study 4: Cardiac Vagal Tone as a Moderator of Treatment Response to Behavioral Interventions in Older Adults with Insomnia

Introduction

Behavioral interventions including CBT-I and mind-body interventions such as Tai Chi are known to improve sleep quality in older adults with moderate to severe sleep complaints (Irwin et al., 2008; Irwin, Olmstead, Carrillo et al., 2014; Li et al., 2004). These interventions have few contraindications and are reasonably effective treatments for insomnia; TCC and CBT-I are associated with approximately 30% and 54% remission rates in older adults (Irwin, Olmstead, Carrillo et al., 2014; Kyle & Spiegelhalder, 2014). However, this also means that between 46-70% of older adults provided with these interventions will continue to experience clinically significant insomnia and insomnia-related impairment. There is currently no way to predict who these individuals will be. To maximize behavioral interventions for older adults with insomnia, it is essential to identify moderators of treatment response. The present study evaluated CVT, as indexed by RSA at pre-treatment, as a candidate moderator of behavioral interventions for late life insomnia. CVT is worthy of interrogation as a potential moderator as individual differences in CVT are theorized to support differences in cognitive control and emotion regulation (Thayer & Lane, 2000) that may determine whether an individual is able to effectively engage with and benefit from TCC and CBT-I for insomnia. Furthermore, individual differences in CVT predict treatment responses in other clinical contexts (Angelovski, Sattel, Henningsen, & Sack, 2016; Shapiro et al., 2007; Wendt et al., 2018).

Cardiac Vagal Tone as an Individual Difference Factor

As reviewed in the general introduction, CVT is frequently characterized as a trait-like individual difference factor that affects cognitive and psychological functioning (Beauchaine, 2015; Thayer & Lane, 2000; 2009). Although the conceptualization of CVT as a trait is debated (e.g., Bylsma et al., 2013; Kemp & Quintana, 2013), individual differences in CVT are often stable within individuals over periods of weeks and years (Bertsch et al., 2012; Hu et al., 2017) and have prognostic value over time (Jandackova, Britton, Malik, & Steptoe, 2016; Jarczok, Koenig, Mauss, Fischer, & Thayer, 2014; Thayer & Sternberg, 2006).

According to the neurovisceral integration model, individual differences in CVT reflect the activity of a dynamic and integrative neural network (i.e. the central autonomic network), which facilitates effective control over the emotional, cognitive, and behavioral responses supporting goal-directed behavior (Gillie & Thayer, 2014; Thayer & Lane, 2009). The prefrontal cortex exerts inhibitory control over subcortical structures through this network, affecting vagal input to the heart. From this perspective, high tonic CVT (i.e., greater heart rate variability at rest) is the result of top-down prefrontal cortex inhibitory control over subcortical circuitry, which facilitates adaptive responses to environmental changes and challenges (Gillie & Thayer, 2014). In general, high CVT is hypothesized to support cognitive and behavioral flexibility, while low CVT is theoretically linked to poorer attentional control, emotion regulation, and social skills (Beauchaine, Gatzke-Kopp, & Mead, 2007; Porges, 2007; 1995; Thayer & Lane, 2000). A review of the evidence supporting associations between CVT and flexible control of cognition and emotion provides a context for understanding how pre-treatment CVT may moderate the effects of behavioral interventions for insomnia.

Cardiac Vagal Tone and Cognition

Many empirical studies have demonstrated that CVT is associated with automatic and voluntary control of attention and executive functioning in healthy samples (Jennings, Allen, Gianaros, Thayer, & Manuck, 2015). For instance, children with higher levels of CVT, as assessed by RSA at rest, show better performance on a measure of sustained attention than children with lower CVT (Suess, Porges, & Plude, 1994). Similarly, adults with low CVT show more difficulties disengaging from task-irrelevant negative stimuli (i.e., fearful faces) than individuals with high CVT (Park, Vasey, Van Bavel, & Thayer, 2013). Tonic CVT also predicts differences in working memory and executive functioning abilities across non-stressful and stressful contexts (Hansen, Johnsen, & Thayer, 2003; 2009). In particular, high CVT appears to be helpful for navigating complex tasks that require action cascading, such as managing multiple response options and prioritizing when confronted with various task goals (Colzato & Steenbergen, 2017). High CVT may even affect control over memory retrieval by suppressing unhelpful memories or associations (Gillie, Vasey, & Thayer, 2014), which can be adaptive when individuals must inhibit previously learned information to acquire new associations or use new strategies.

Cardiac Vagal Tone and Emotion Regulation

Theoretically, individual differences in CVT also support differences in emotion regulation abilities (Thayer & Lane, 2009). Previous studies have shown that individuals with high tonic CVT, in comparison to those with low CVT, tend to produce more context-appropriate emotional responses as assessed by behavior (e.g., reflexive startle response) and self-reported emotional experience (Appelhans, & Luecken, 2006; Fabes & Eisenberg, 1997; Thayer, & Brosschot, 2005; Williams et al., 2015). There is some evidence that individuals with high CVT also spontaneously regulate more frequently and select more effective or adaptive strategies for

downregulating negative emotions (Balzarotti et al., 2017). And when viewing an unpleasant film or photos selected to provoke disgust in the absence of instruction about how to regulate their emotions, individuals with high CVT reported higher use of cognitive reappraisal and lower use of avoidance than individuals with low CVT (Aldao, Dixon-Gordon, & De Los Reyes, 2016; Volokhov & Demaree, 2010). Greater use of emotion regulation strategies may enable individuals with high CVT to tolerate higher levels of distress, discomfort, or uncertainty, persist longer with difficult tasks (Segerstrom & Nes, 2007), and maintain greater self-confidence after failure (Geisler & Kubiak, 2009) than individuals with low CVT.

Cardiac Vagal Tone as a Moderator of Behavioral Treatments for Insomnia

Given these associations between CVT cognition and emotion regulation, individual differences in pre-treatment CVT may reflect differences in tonic inhibitory control that impact an individual's response to behavioral treatments for insomnia. In the context of CBT-I, older adults with low CVT may experience more difficulties attending to the basic content and acquiring essential cognitive coping skills (e.g., cognitive restructuring, distraction) than high CVT participants. In contrast, individuals with higher pre-treatment CVT may be more likely to acquire these skills and use them outside of group, when they are experiencing challenging emotions related to their insomnia. For instance, high CVT participants may be more likely to restructure upsetting thoughts in real time or use stimulus control techniques (i.e., leave the bed after being unable to fall asleep within 20 minutes) than individuals with low CVT. Given that CVT is associated with persistence and confidence in the wake of failure (Geisler & Kubiak, 2009; Segerstrom & Nes, 2007), older adults with greater CVT at pre-treatment may also be more persistent and consistent in their use of skills, even in the absence of immediate improvements in sleep quality. Conversely, low CVT participants may have trouble inhibiting

old thought patterns and behaviors (i.e., catastrophizing, napping) or engage in more avoidance to cope with negative emotions related to insomnia (Aldao et al., 2016). Prior studies suggest that avoidance predicts decreased benefit from a variety of behavioral therapies for anxiety and depression (Porter & Chambless, 2015; Renaud, Russell, & Myhr, 2013; Wheaton, Gershkovich, Gallagher, Foa, & Simpson, 2018).

For similar reasons, pre-treatment CVT may determine the extent to which an individual benefits from TCC. As TCC is hypothesized to lead to improvement in sleep through increased control over physical functioning and arousal-related responsiveness (Irwin, Olmstead, Carrillo et al., 2014), an individual's ability to pay attention mindfully, "on purpose, in the present moment, non-judgmentally" (Kabat-Zinn, 1982) may be crucial for TCC to be effective in restoring sleep. As individuals with high pre-treatment CVT may be more physiologically equipped at study entry to inhibit irrelevant distractors and sustain attention (Park et al., 2013; Suess et al., 1994), they may benefit more from TCC practice than those with low CVT. If low CVT predicts engagement or learning difficulties in group TCC practice, it may also contribute to reduced willingness or ability to practice TCC independently outside of group (i.e., TCC homework). TCC is likely to be most effective when implemented as a routine, daily practice. Due to potential differences between high CVT and low CVT participants in the spontaneous regulation of emotions, older adults with high pre-treatment CVT may also be more likely to practice TCC despite challenging emotions or clinical symptoms (i.e., fatigue) related to insomnia.

Prior Evidence for Cardiac Vagal Tone as a Predictor of Treatment Response

A handful of studies have examined relationships between pre-treatment CVT and treatment response to behavioral interventions similar to CBT-I and mind-body interventions

(e.g. yoga/ Tai Chi) in samples with depression and anxiety (e.g., Davies, Niles, Pittig, Arch, & Craske, 2015; Shapiro et al., 2007). Wendt and colleagues (2018) reported that individuals who fully recovered after exposure therapy for anxiety had higher pre-treatment CVT than individuals with residual symptoms after treatment. Importantly, individuals with low pre-treatment CVT were more likely to drop out of therapy than those with high pre-treatment CVT. However, the opposite has also been reported: lower pre-treatment CVT predicted greater treatment-related improvement from CBT and Acceptance and Commitment Therapy in adults with mixed anxiety diagnoses (Davies et al., 2015). A single-arm study that employed a mind-body intervention, Iyengar yoga, for depression reported that individuals whose depression remitted had higher pre-treatment CVT than non-remitters (Shapiro et al., 2007). Taken together, these studies suggest that pre-treatment CVT may be an important predictor of treatment response. However, these studies have focused primarily on younger adults and individuals without insomnia.

Only one previous study evaluated CVT as a predictor of CBT-I related improvement in sleep quality in a sample of adults with primary insomnia. In their single-arm trial of CBT-I Gouin and Dang Vu (2015) reported that pre-treatment CVT predicted treatment response to 6-weeks of treatment such that greater CVT was associated with prospective increases in actigraphy-derived sleep efficiency, polysomnography-derived total sleep time, and self-reported sleep quality at post-treatment. Although this study provides preliminary support that pre-treatment CVT may be an important moderator of sleep outcomes in CBT-I, Gouin and Dang Vu did not evaluate the impact of CVT on other indicators of health including inflammation or psychological functioning (i.e., depression). Moreover, this study did not include a control intervention or comparison treatment group to determine whether CVT is a general moderator

across treatment modalities, including mind-body interventions such as TCC, or specifically informative in the context of CBT-I.

The Present Study

The primary goal of Study 4 was to address these important gaps in the literature by means of secondary analysis of data from an already completed study comparing CBT-I and TCC to an active control sleep education seminar (i.e., SS) in older adults with insomnia (Irwin, Olmstead, Carrillo et al., 2014). In the context of this trial, it was hypothesized that participants with higher pre-treatment CVT would benefit more than participants with lower pre-treatment CVT from both active treatments (CBT-I and TCC) compared to SS. As treatment-related changes in sleep quality are often accompanied by improvements on other outcomes, including reductions in inflammation and insomnia-related clinical symptoms (e.g., Barr et al., 2015; Irwin et al., 2017), it was expected that greater pre-treatment CVT, as assessed by RSA, would predict more treatment-related improvement in sleep quality, cellular and systemic markers of inflammation, and psychological functioning (depressive symptoms) from both active interventions. Given that TCC and CBT-I are thought to lead to improvements in sleep by different mechanisms (TCC: arousal mechanisms, CBT-I: sleep-related behavior and cognition; Irwin, Olmstead, Carrillo et al., 2014), the present study also examined the possibility that RSA moderated the effects of one of these active treatments (e.g., TCC but not CBT-I). Finally, as prior research suggests that low pre-treatment CVT may be a risk factor for reduced treatment compliance (i.e., low attendance, drop-out) and unresolved symptoms at post-treatment (Wendt et al., 2018), the relationships between CVT and these outcomes were evaluated. Knowledge gained from this study could help to help to identify who is likely to benefit from behavioral

interventions and may inform the ability to match individuals with insomnia to the most appropriate and efficacious treatment intervention to improve their health.

Method

This study relied on data collected as part of a RCT for older adults with insomnia conducted by Irwin, Olmstead, Carrillo et al. (2014), described in Study 1 and Study 3. Briefly, participants were randomized to a 4-month treatment with CBT-I, TCC, or SS. Out of the 123 participants, this study included data from 106 individuals with pre-intervention RSA data; a total of 95 individuals had both pre-treatment EKG (for determination of RSA) and post treatment sleep quality data available for the for the primary analysis. All EKG acquisition and processing procedures for the evaluation of pre-treatment RSA were consistent with those described in Study 1. To assess sleep quality and depressive symptoms, the present study employed the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and the clinician rated Inventory of Depressive Symptoms IDS-C: (Rush et al., 1996). These measures were assessed at pre-intervention, 4, 7, and 16 months. Regarding the assessment of inflammation, all assays were completed using the same methods described in Study 1. CRP was assessed at pre-intervention, 4 months, and 16 months and TLR-4 activation of monocyte co-production of IL-6 and TNFα assessed at pre-intervention, 4 months, 7 months, and 16 months.

Power Analysis

The parent study (Irwin, Olmstead, Carrillo et al., 2014) was designed to be adequately powered to detect significant treatment-related remission of insomnia diagnosis, but did not include hypotheses about moderators of treatment. In their study of CBT-I, Gouin and Dang Vu (2015) reported that pre-treatment CVT was correlated with treatment-related improvement in sleep quality on the PSQI with a large effect size (r = .52). However, no studies have evaluated

how pre-treatment CVT and different insomnia interventions interact to predict improvement in sleep quality. Although it is likely the effect size for an interaction would be smaller than the effect reported by Gouin and Dang Vu (2015), it is unclear how small of an effect the present study should have been powered to find (Miller & Yee, 2015). In order to determine the minimal detectable effect for the moderation analysis, a sensitivity power analysis was conducted in G*Power 3.1.9.3 (Faul et al., 2008). Given the number of predictors (3) and interaction terms (2) in the regression, the estimated number of participants in the sample with usable data on all measures (n = 95) and power of 80% (α = .05), the a priori power analysis revealed that the analyses would be able to detect small to medium effects (f^2 = .084).

Statistical Analyses

Moderation hypotheses were tested using PROCESS for SPSS (Hayes, 2018; model 1) via multiple linear regression with effects for intervention type (active intervention: TCC and CBT-I vs. control: SS), a single continuous moderator (i.e., pre-treatment RSA), and the interaction between intervention type and pre-treatment RSA on pre-to-post treatment change scores on the primary outcome (i.e., sleep quality on the PSQI). Similar moderation models were evaluated for secondary outcomes including pre-to-post treatment change in depression (IDS-C), and inflammation (CRP, monocytic co-production of IL-6 and TNFα). Pre-to-follow-up (7 month and 16 month) changes in sleep quality, depression, and monocytic co-production of IL-6 and TNFα, and pre-to-16 month changes in CRP were also examined. On an exploratory basis, these analyses were repeated with intervention type as a 3-level factor (TCC vs. CBT-I vs. SS). These moderation analyses were completed with and without age, gender, BMI, beta-blocker use, and weekly metabolic equivalents as covariates in the model. Significant interactions were followed by analyses of simple slopes. Missing data was addressed by listwise deletion.

To evaluate the hypothesis that low pre-treatment RSA would predict lingering insomnia at post-treatment, regardless of intervention group, a logistic regression predicting responder status (responder vs. non-responder) from pre-treatment RSA with and without relevant covariates (gender, age, BMI, beta-blocker use, and weekly metabolic equivalents) was completed. Treatment responder status was defined by remission of insomnia diagnosis at post-treatment. To evaluate the possibility that pre-treatment RSA would predict individual differences in treatment engagement, pre-treatment RSA and relevant covariates were regressed on a measure of treatment participation (i.e., session attendance). Finally, to explore the relationship between pre-treatment RSA and treatment dropout, a t-test was used to determine whether RSA differed between treatment completers and non-completers.

Results

To evaluate the hypothesis that pre-treatment RSA would moderate the effects of active vs. control treatment on the primary outcome of sleep quality, a regression predicting pre-to-post change on the PSQI from pre-treatment RSA, treatment group, and their interaction was completed. This analysis revealed that pre-treatment RSA was not a significant moderator of intervention-related change in sleep quality (n = 95, β= -.75, t(91) = -1.41, p =.16). The full model explained 6% of the variance in delta sleep quality, with the simple effects accounting for 4% of the variance. The interaction effect size was small (f^2 = .02). Similarly, pre-treatment RSA did not moderate intervention-related changes from pre-to-post treatment on secondary outcomes including depression (IDS-C: n = 96, full model R^2 =.05, β=.76, t(92) = 1.43, p =.16) and inflammation (CRP: n = 78, full model R^2 =.07, β=-.20 , t(74) =-.34 , p =.74; unstimulated monocyte co-production of IL-6 and TNFα: n = 79, full model R^2 =.02, β=.41, t(75) = .73, p

=.47; stimulated monocyte co-production of IL-6 and TNFα: n = 80, full model R^2 =.02, β= -.10, t(76) = -.18 , p =.86).

To determine whether moderation effects of pre-treatment RSA emerged during the follow-up period after the interventions ended, similar regressions were completed for key trial outcomes using pre-to-3 month follow up (7 month) and pre-to-12 month (16 month) change scores. Pre-treatment RSA did not moderate the effects of treatment on change in sleep quality (n = 93, full model R^2 = .06, β=-.77, t(89) = -1.44, p =.16), depression (n = 92, full model R^2 =.03, β=.67, t(88) = 1.24, p =.22), or inflammation (unstimulated monocyte production: n = 84, total R^2 =.04, β=-.28 , t(80) =-.51, p =.61; stimulated monocyte production: n = 83, full model R^2 =.06, β=-.58, t(79) =-1.03 , p =.31) at 3-month follow up (7 months). Consistent null results were also found at the one year follow up (sleep quality: n = 93, full model R^2 =.03, β=-.54, t(89) =-1.01, p =.32; depression: n = 93, full model R^2 =.005, β=.31, t(89) = .56, p =.58; CRP: n = 74, full model R^2 =.004, β=-.14, t(70) =-.22, p =.83; unstimulated monocyte production: n = 80, full model R^2 =.04, β=.10 , t(76) =.17 , p =.87; stimulated monocyte production: n = 81, full model R^2 =.009, β=-.20, t(77) =-.36, p =.72). The inclusion of covariates (gender, beta blocker use, age, BMI, weekly METs) did not alter null findings for moderation by pre-treatment RSA at any time point. Additionally, in exploratory analyses, when treatment type was evaluated as a three-level predictor (TCC vs. CBT-I vs. SS), null results remained.

Next, in order to evaluate the hypothesis that low pre-treatment RSA would predict unresolved insomnia at post-treatment, a logistic regression was performed to ascertain the effects of pre-treatment RSA on the likelihood of still meeting criteria for a diagnosis of insomnia at post treatment. Diagnostic status at post-treatment was available for 97 out of 98 treatment completers (remitters: n = 37, non-remitters: n =60). The logistic regression model was

not significant, $\chi^2(1) = .14$, $p = .71$. Adding relevant covariates (gender, beta-blocker use, age, BMI, and weekly metabolic equivalents) to this model did not alter the results. Further, results remained similar when all non-completers ($n = 8$) were coded as non-remitters (total $n = 105$, $\chi^2(1) = .02$, $p = .89$).

To determine whether pre-treatment RSA was associated with important variability in treatment participation, RSA was regressed on a measure of treatment group attendance. Complete treatment attendance data were available for $n = 101$ participants who enrolled in treatment interventions and also had pre-treatment RSA data. Across all treatment groups, there was a tendency for lower RSA to predict higher attendance ($n = 101$, $\beta = -.19$, $F(1, 99) = 3.72$, $p = .06$). However, this tendency did not account for attendance behavior over and above relevant covariates (age, BMI, gender, beta blocker use, weekly METs) (Table 8).

Finally, on an exploratory basis we also evaluated whether pre-treatment RSA was different between treatment completers ($n = 98$) and non-completers (i.e., individuals who dropped out of treatment during the 4-month treatment intervention, $n = 8$). Result revealed that the treatment dropout group (M= 5.54, SD= .72) had higher pre-treatment RSA than the treatment completers group (M= 4.69, SD= .99), $t(104) = 2.42$, $p = .02$.

Discussion

The present study evaluated pre-treatment CVT as a candidate moderator of the effects of behavioral interventions for late life insomnia, using data from a three-arm RCT evaluating CBT-I, TCC, and SS. Contrary to hypotheses, pre-treatment CVT did not moderate intervention effects on key trial outcomes including sleep quality, inflammation at cellular and systemic levels of analysis, or clinical symptoms. Nor was pre-treatment CVT a strong predictor of remission of insomnia diagnosis at post-treatment. Contrary to study hypotheses, the present

study did find a trend-level relationship between lower pre-treatment CVT and greater treatment engagement throughout the intervention period as indexed by treatment group attendance. Similarly, individuals who dropped out of treatment had greater pre-treatment RSA than treatment completers. Overall, the present investigation provides compelling evidence that pre-treatment CVT is not a crucial moderator of these behavioral treatments for older adults with insomnia and shows that further research is needed to identify other individual differences that impact the efficacy of these interventions for this high health-risk population.

The present findings add complexity to a developing literature that evaluates the utility of CVT as a predictor or moderator of behavioral treatments. Prior studies conducted in non-insomnia clinical samples have generally examined either CBT-based or mind-body interventions, focused on middle-aged or young adults, and have not assessed treatment-related changes in inflammation. Existing studies have typically reported positive relationships between pre-treatment CVT and clinical outcomes. In three different investigations, participants with high pre-treatment CVT had better outcomes than those with low CVT including lower drop out rates and more complete remission of anxiety symptoms in response to exposure therapy for panic disorder (Wendt et al., 2018), greater remission of depressive symptoms after Iyengar yoga for depression (Shapiro et al., 2007), and greater improvement in PTSD symptoms after CBT-based interventions for comorbid PTSD and substance abuse disorders (Soder et al., 2019). However, one investigation found an effect in the opposite direction. In their trial of CBT and Acceptance and Commitment Therapy for mixed anxiety disorders, Davies et al. (2015) found that participants with high pre-treatment CVT experienced worse outcomes (i.e., less improvement in anxiety symptoms) than those with low pre-treatment CVT.

Only one prior study evaluated whether pre-treatment CVT had prognostic value in the context of insomnia treatment. In their single-armed trial of CBT-I for adults with primary insomnia, Gouin and Dang Vu (2015) found that pre-treatment CVT was a strong predictor of CBT-I related improvement in sleep quality as assessed by actigraphy-derived sleep efficiency, polysomnography-derived total sleep time, and self-report on the PSQI (Gouin & Dang Vu, 2015). Building on this study, the present investigation was the first to interrogate pre-treatment CVT as a moderator of multiple behavioral interventions for insomnia in older adulthood. As Gouin and Dang Vu implemented a short (6 week) group CBT-I protocol, we expected to extend the relationships they found between pre-treatment CVT and change in sleep quality to the present sample of older adults randomized to a longer (4-month) CBT-I intervention. The present study also probed whether CVT was a general or specific moderator of active behavioral treatments for insomnia by first comparing two active interventions (TCC and CBT-I) to a sleep education control group (SS) and then evaluating differences between the active treatments on an exploratory basis. Like Gouin and Dang Vu, change in sleep quality was the primary outcome of interest in the present study. However, we also evaluated change on systemic and cellular markers of inflammation and clinical symptoms associated with insomnia (i.e., depression). The present study's primary result, that pre-treatment CVT did not moderate the effects of active behavioral interventions vs. SS on any of these outcomes, was a surprising departure from previous findings. Contrary to study hypotheses, CVT did not predict remission status at post treatment. Additionally, findings regarding relationships between pre-treatment RSA and treatment compliance (attendance and dropout) were in the opposite direction of the exploratory hypotheses. There was a trend-level negative association pre-treatment RSA and treatment engagement as indexed by group attendance and, in contrast to the findings of Wendt et al.

(2018), the small number of participants who dropped out of treatment interventions actually had higher pre-treatment CVT than treatment completers.

It is unclear why individual differences in pre-treatment CVT did not moderate the effects of active behavioral interventions for insomnia on treatment outcomes or relate to treatment engagement in expected ways in this sample. The advanced age of the present participants (M = 65.30, SD = 6.83) and their chronic insomnia are two important considerations. Although it is well established that CVT decreases with increasing age (Bonnemeier et al., 2003; Umetani et al., 1998), the implications of age-related reductions in CVT for cognitive, emotional, and behavioral flexibility in older adulthood are unclear. The neurovisceral integration model postulates that CVT is a relatively stable index of the efficiency of central–peripheral neural feedback mechanisms that support self-regulation and behavioral flexibility (Thayer & Lane, 2000). The present study assumed that the links between CVT and these adaptive response tendencies, which could impact treatment engagement and success, would be robust to age-related changes in CVT. However, several studies have failed to extend positive associations between CVT and cognition (Dalise et al., 2020; de Oliveira Matos et al., 2020), emotion regulation (Batselé et al., 2019), and effective daily behaviors (e.g., health behaviors, Kluttig et al., 2010) to older adult samples. One possibility is that aging attenuates relationships between CVT and self-regulatory capacity. Chronic insomnia, which has been linked to accelerated biological aging (Carroll et al., 2017; Carroll et al., 2016) and cognitive decline in elderly adults (Cricco, Simonsick, & Foley, 2001; Yaffe, Falvey, & Hoang, 2014), further complicates the picture for this sample. Additional studies testing the basic assumptions of the neurovisceral integration model in elderly adults with and without insomnia would help to clarify and contextualize the present findings.

It is important to note that the statistical properties of the measure of CVT in this study, RSA, do not account for the present null results. RSA was normally distributed and, as expected for an elderly sample with chronic insomnia, mean RSA was significantly lower in the present participants (M= 4.73, SE=.10) than in young adults without insomnia (*n*=96, M =6.7, SE=.10; Allen et al., 2007). Further, standard errors around the group means were identical. Crucially, null effects for CVT as a moderator also cannot be attributed to a general lack of treatment effects in this trial. In particular, with regards to the primary outcome of sleep quality, CBT-I and TCC together led to greater improvement in sleep quality from pre-to-post treatment than SS in both the parent RCT and the present subsample.

The present investigation of CVT must also be considered in the context of the limited literature on moderators of behavioral treatments for insomnia, in which elderly adults with insomnia are particularly underrepresented (Irwin, Cole, & Nicassio, 2006). A few studies have assessed individual differences in clinical and demographic factors as candidate moderators, but have had limited success identifying reliable moderators of in-person and web-based behavioral treatments for insomnia. Null results have been reported for variables such as gender, age, education, treatment credibility, insomnia duration, physical activity levels, psychological comorbidities, circadian preference, and pre-treatment PSG-derived sleep duration (Ström et al., 2004; Yeung et al., 2018; Vincent, Walsh, & Lewycky, 2013; Manber et al., 2014; Asarnow et al., 2019; Rochefort et al., 2019). Mixed results have been found for insomnia severity, such that studies have linked lower-levels of pre-treatment insomnia to both greater odds of remission (Savard, Savard, & Ivers, 2018) and treatment dropout (Hebert, Vincent, Lewycky, & Walsh 2010; Ström et al., 2004). Out of the aforementioned studies on treatment moderators, only one, Yeung et al., (2018), was conducted in a sample of older adults with insomnia. Taken together,

these previous studies and the present null results suggest further investigations are needed to identify reliable moderators of behavioral interventions for late life insomnia.

The present study has several notable strengths. Moderation analyses were conducted in a large sample of older adults who completed pre-treatment EKG, 4-months of treatment interventions, post-treatment and follow-up assessments; participants were randomly assigned to treatment groups; additionally, the parent RCT design afforded evaluation of CVT as a general moderator of active treatments (i.e., CBT-I and TCC vs. SS) and as a specific moderator of different interventions with unique putative mechanisms (i.e., CBT-I: sleep related-thoughts and behaviors vs. TCC: arousal mechanisms, Irwin, Olmstead, Carrillo et al., 2014). This study was also the first to evaluate pre-treatment CVT as a potential moderator of treatment-related changes in inflammation, which may be crucial for reducing morbidly and mortality in elderly, sleep-disturbed adults.

An important limitation of the present study was the exclusive focus on CVT. The present investigation did not measure other individual differences in pre-treatment autonomic function that could moderate the effects of behavioral interventions for insomnia. Due to a specific interest in CVT and primary outcome of treatment-related change in sleep quality, CVT was assessed at bedtime when PNS activity would be near maximal. However, this approach does not allow for assessment of reliable estimates of SNS activity (Shaffer et al., 2014). As aging decreases PNS but also increases SNS outflow (Irwin, 1993), future studies should consider assessing EKG at multiple times of day or employing 24-hour EKG to more fully assess autonomic profiles that capture PNS, SNS activity and the coordination of PNS and SNS activity over a full day at pre-treatment. It is possible that older adults with the combination of low CVT and high SNS activity benefit less from active behavioral treatments for insomnia than their

same-aged peers with high CVT and low SNS activity at pre-treatment. In addition to assessing profiles of autonomic activity, to further test the neurovisceral integration model in older adults, future studies may also benefit from including assessment of individual differences in cognitive control, emotion regulation abilities, and behavioral flexibility at pre-treatment.

Overall, results from the present study indicated that individual differences in pre-treatment CVT did not moderate the efficacy of active behavioral interventions, CBT-I and TCC, for late life insomnia. In the present study's parent trial, active treatments together yielded a 42% remission rate, still leaving approximately 58% of participants with clinically significant insomnia after treatment (Irwin, Olmstead, Carrillo et al., 2014; Kyle & Spiegelhalder, 2014). Given this large percentage of individuals who fail to respond to the best available treatments and limited knowledge about the patient-characteristics that enable treatment success, including the present null findings for CVT, the identification of reliable moderators should be a top priority for future insomnia research.

General Discussion

Through a series of four studies, the present dissertation leveraged existing theory about CVT and PNS-immune interactions to accomplish two aims: To illuminate the role of CVT in clinical populations with sleep disturbance, studies 1 and 2 interrogated and described the associations between CVT, inflammation, and clinical symptoms in two unique samples with poor sleep quality. Studies 3 and 4 evaluated potential roles for CVT in the context of behavioral interventions for older adults with insomnia.

Aim 1: Summary of Studies 1 and 2

Based on prior literature on CVT and the anti-inflammatory reflex, Studies 1 and 2 proposed a specific model to account for the negative effects of chronic sleep disturbance on physical and psychological wellbeing. Specifically, we posited that chronic sleep disturbance drives reductions in CVT with downstream effects on inflammation and psychiatric symptoms. It was expected that the cross-sectional analyses undertaken in older adults with insomnia and FE SZ would reveal pairwise associations that were consistent with this model. On an exploratory basis, the two studies also evaluated a) serial mediation of the effects of sleep quality on clinical symptoms by CVT and inflammation, and b) single mediation of the effects of CVT on clinical symptoms by inflammation and compared findings from both clinical samples.

Contrary to expectations, Study 1 revealed that CVT was not related to sleep quality, systemic inflammation, or clinical symptoms (e.g., depression, anxiety, or fatigue) in older adults

with insomnia. Nor was either exploratory mediation model supported. Instead, the primary finding was novel characterization of the associations between CVT and two upstream measures of cellular inflammation. In older adults with current insomnia, greater CVT was associated with lower levels of unstimulated monocyte coproduction of proinflammatory cytokines and greater stimulated proinflammatory responses to LPS. These initial results suggest PNS-immune coordination at an intracellular level and require further replication and investigation to articulate clear clinical implications for older adults with and without insomnia.

Similarly, Study 2 found that CVT in FE SZ was not related to sleep quality as reflected on the PSQI, levels of individual proinflammatory cytokines, or clinical symptoms (e.g., depression, fatigue, positive and negative symptoms of psychosis). However, sleep duration and total time in bed were negatively associated with CVT. As predicted, and in line with prior research on a vagally-mediated anti-inflammatory pathway (Tracey et al., 2002; 2009), we extended a previously reported negative association between CVT and CRP in healthy individuals to patients with FE SZ (e.g., Cooper et al., 2014; Sajadieh et al., 2004). This inverse association between CVT and systemic inflammation provides preliminary evidence of intact PNS-immune coordination in FE SZ. As hypothesized, results also revealed positive associations between specific circulating cytokines, IL-6 and IFNγ, and the severity of positive symptoms of psychosis.

Neither exploratory mediation model was supported in FE SZ. Given null mediation results in both older adults and FE SZ and major differences in the drivers of poor sleep quality in these clinical samples (i.e., insomnia vs. long sleep duration), comparisons of model paths between groups were of limited consequence.

Aim 1: Implications of Studies 1 and 2

Across both studies, the lack of associations between CVT and clinical symptoms is inconsistent with influential theories about CVT and argues against an essential role for CVT in the symptoms of insomnia and SZ. Specifically, polyvagal theory, the neurovisceral integration model, and other recent adaptations (e.g., vagal tank theory: Laborde, Mosley, & Mertgen, 2018b) commonly propose a link between CVT and a broad capacity for self-regulation (e.g., context appropriate physiological responses, attentional regulation, social behavior, emotion regulation, and executive functioning). CVT is theorized to reflect prefrontal inhibitory control, and disinhibition (i.e., low tonic CVT) has been associated with increased risk for psychopathology (e.g., Beauchaine, 2015; Thayer & Brosschot, 2005). Though there is relatively little research directly examining the contributions of CVT to clinical symptoms of insomnia, prior findings have linked low CVT to a variety of psychiatric disorders in which cardinal symptoms and sleep disturbance co-occur, such as major depressive disorder (Agelink et al., 2002) and generalized anxiety disorder (Thayer, Friedman, & Borkovec, 1996). However, the lack of correspondence between CVT and levels of depression, anxiety, fatigue, or positive and negative symptoms of psychosis across Studies 1 and 2 challenges the proposition that CVT is a reliable index of emotion dysregulation in insomnia and FE SZ.

Findings also provide mixed evidence for a vagally-mediated anti-inflammatory pathway in sleep disturbed samples. Although the negative association between CVT and CRP in FE SZ is consistent with Tracey's model of the cholinergic anti-inflammatory pathway (2002; 2009), results obtained in older adults were not. It is unclear why the relationship between CVT and systemic inflammation differed between the two samples. One possibility is that age moderates the negative association between CVT and CRP (Williams et al., 2019), such that the integrity of this mechanism for PNS inhibition of inflammation diminishes with increasing age. Age-related

decreases in CVT may have also restricted the variance in RSA in the older adult sample, limiting our ability to detect both within and between subject correlations. As there were many other important differences between the older adult insomnia and FE SZ samples in this dissertation (e.g., sleep quality, primary sleep complaints, gender distribution, antipsychotic use), other explanations cannot be ruled out. The novel associations observed between CVT and cellular inflammation in older adults with insomnia further suggests that PNS-immune coordination may occur at the level of the monocyte. These findings are not accounted for by Tracey's existing model and require further critical evaluation, including replication and extension to non-insomnia samples to determine their biological and clinical implications.

Aim 2: Summary of Studies 3 and 4

In service of the second aim, the present investigation evaluated potential roles for CVT in the context of behavioral interventions for older adults with insomnia. As prior studies have conceptualized CVT as either a state correlate of health and wellbeing that is malleable (Bylsma et al., 2013; Laborde, Mosley, & Mertgen, 2018a) or a stable trait marker with the power to predict divergence in health trajectories over time (Berntson et al., 1997), both state and trait-based roles for CVT within behavioral treatments for insomnia were evaluated in Studies 3 and 4.

Consistent with a state model of CVT, Study 3 evaluated whether CVT would increase as a result of behavioral treatments that improve sleep quality, inflammation, and clinical symptoms and whether intervention-related changes in CVT would be associated with the extent of improvement on these outcomes. It was expected that both TCC and CBT-I would enhance CVT more than SS, as a handful of prior studies reported positive effects of Tai Chi practice on CVT (Audette et al., 2006; Liu et al., 2018; Wong et al., 2018), and a single study found augmented

CVT in CBT-I treatment responders (Chung et al., 2011). Contrary to expectations, the results of Study 3 indicated that CVT did not change significantly in response to 4 months of CBT-I, TCC, or SS in older adults. Instead, CVT showed remarkable trait-like stability from pre-to-post treatment. Additionally, intervention-related change in CVT did not predict the extent of improvement on key trial outcomes, such as sleep quality, inflammation, or clinical symptoms. Instead, behavioral treatments led to recovery from insomnia without significantly altering CVT.

Based on a trait conceptualization of CVT, and consistent with findings from Study 3 that CVT was state invariant over 4 months of treatment, Study 4 evaluated whether pre-treatment CVT moderated the effects of active treatment (CBT-I and TCC) vs. sleep education on key trial outcomes (i.e., change in sleep quality, cellular and systemic markers of inflammation, and depressive symptoms). As a previous study in younger adults with insomnia reported that pre-treatment CVT predicted the extent of sleep recovery in response to CBT-I (Gouin & Dang Vu, 2015), it was hypothesized that participants with greater CVT at pre-treatment would benefit more from active behavioral treatments than those with lower CVT at pre-treatment. Instead, results from Study 4 revealed that pre-treatment CVT was not a moderator of response to these behavioral interventions in late life insomnia. In fact, beyond failing to predict change on key trial outcomes, pre-treatment CVT was found to be counterintuitively associated with treatment engagement and drop out.

Aim 1: Implications of Studies 3 and 4

Overall, results obtained in Studies 3 and 4 challenge the idea that CVT plays a central role in insomnia recovery. Novel findings from Study 3 extend treatment research by indicating that change in CVT is unlikely to be a mechanism supporting improvement in insomnia, inflammation, and clinical state in late life insomnia. This contribution is particularly informative

to the literature on mind-body interventions (e.g., Tai Chi, yoga), as it is often assumed that beneficial effects are at least partially attributable to the upregulation of PNS activity (e.g., Liu et al., 2018; Zou et al., 2018). Results of Study 3 echo those of Studies 1 and 2 and provide similar challenges to contemporary theories about CVT by demonstrating very little correspondence between CVT and symptoms. Results also raise an important set of new questions that require further interrogation. For example, does the malleability of CVT change over the lifespan? And is the stability of CVT observed in the present study attributable to normative aging processes or a combination of aging and a chronic illness, such as insomnia? Additionally, given that the results of Study 3 provide strong evidence that the upregulation of CVT is not a common mechanism of these behavioral interventions in older adults, it is essential to identify and investigate other candidate mechanisms to understand how CBT-I and TCC exert their effects on sleep quality, inflammation, and clinical symptoms in this population.

Results of Study 4 further challenge current conceptualizations of CVT by providing limited support for its utility as an individual, trait-like predictor of treatment response to behavioral interventions for insomnia. As some of the results of Study 4 were in the opposite direction of predictions based upon the neurovisceral integration model, they reveal a need for careful empirical evaluation of the model's assumptions and generalizability to clinical samples across the lifespan. CVT is often heralded to be a stable, trait-like indicator of self-regulatory capacity, with broad implications for physiological, emotional, and cognitive regulation, from infancy to older adulthood (Thayer & Lane, 2009). However, present findings linking lower CVT to greater treatment engagement in older adults with insomnia are inconsistent with such assumptions. One possibility is that effect sizes for the associations between CVT and self-regulatory capacity may be overestimated due to publication bias (e.g., Zahn et al., 2016) and

limited evaluation in older and chronically ill samples. Additional lifespan research is needed to determine whether normative aging processes or the presence of chronic insomnia attenuate relationships between CVT and self-regulatory capacity that were established earlier in life. Null findings for CVT emphasize the need for further identification and evaluation of candidate moderators to improve current knowledge about the patient characteristics that determine treatment responses to behavioral interventions for insomnia.

Limitations and Future Directions

The present investigations had some important limitations. First, all four studies exclusively focused on CVT, without evaluating other aspects of autonomic function (e.g., SNS activity) that could more broadly inform knowledge about the interplay between chronic sleep disturbance, variability in autonomic function, the regulation of inflammation, and the expression of clinical symptoms. Although there were strong a priori reasons for the exclusive focus on CVT, future studies should consider assessing profiles of autonomic activity using measures from multiple times of day or 24-hour EKG to capture the stability and malleability of the coordination of PNS and SNS activity in clinical samples with sleep disturbance. Another limitation of the current research is that the interpretation of the reported associations between CVT and cellular inflammatory processes in Study 1 (i.e., the negative correlation between CVT and unstimulated monocyte production of pro-inflammatory cytokines and the positive association between CVT and stimulated monocyte production of pro-inflammatory cytokines in older adults) is constrained by a lack of prior studies evaluating these inflammatory measures in healthy sleeping older adults. Additionally, COVID-19 related disruptions to data collection impacted recruitment of the intended larger sample of FE SZ patients and aged-matched HCs for Study 2. Finally, EKG acquisition methods (e.g., recording setting, time of day, and position)

differed between older adults with insomnia, FE SZ, and HC, potentially impacting between group comparisons for RSA in Study 2.

Conclusions

Despite the noted limitations, present results contribute novel descriptions of the associations between CVT and clinical state in two unique clinical samples with sleep disturbance and demonstrate that CVT is neither a key mechanism nor moderator of behavioral interventions for insomnia in older adults. As CVT appears to be less integral to sleep disturbance and insomnia recovery than expected, results draw attention to a need for empirical assessment and critical evaluation of theories about CVT in complex samples contending with a chronic illness across the lifespan. Further studies are particularly needed to evaluate the clinical implications of the correlations reported between CVT and cellular inflammation in older adults and CRP in FE SZ. Null findings for CVT as a mechanism and moderator of treatment effects are a reminder that we do not know, and must conduct additional research to determine, how the best behavioral interventions work and for whom they will be most effective. Identification and evaluation of mechanisms and moderators should be a top research priority to refine and maximize existing treatments for insomnia.

Tables

Table 1. Baseline characteristics of participants in the sample with valid electrocardiogram data (Study 1).

Variable	Participants *n* = 106
Age	65.30 (6.83)
Female, *n* (%)	76 (71.70)
Ethnicity, Hispanic, *n* (%)	8 (7.55)
Race, Non-White, *n* (%)[a]	14 (13.59)
Marital Status, Married, *n* (%)	47 (44.34)
Education (years)	15.64 (1.48)
Body Mass Index (kg/m^2)	25.63 (3.53)
Medical Comorbidity, *n* (%)	49 (46.23)
Cardiac Condition or Medication use, *n* (%)	39 (36.79)
Beta blocker use, *n* (%)	8 (7.55)
Heart Rate	63.56 (8.74)
RSA	4.73 (1.00)
PSQI, total score	10.76 (2.86)
IDS-C, total score	9.31 (5.22)
BAI, total score	6.79 (6.86)
MFSI, total score	10.05 (17.56)
CRP (mg/L)	1.85 (1.93)
% Unstimulated monocytes co-producing IL-6 and TNFα	1.02 (.54)
% Stimulated monocytes co-producing IL-6 and TNFα	49.53 (18.47)

Note: All values are mean (SD) unless noted with percent. [a]Total *n*=103 with self-reported race (Non-white). RSA, Respiratory Sinus Arrhythmia; PSQI, Pittsburgh Sleep Quality Index; IDS-C, Inventory of Depressive Symptoms-Clinician Rating Scale; BAI, Beck Anxiety Inventory; MFSI, Multidimensional Fatigue Severity Index Short Form; CRP, C-reactive Protein.

Table 2. Correlations between RSA, inflammation, sleep, and clinical symptoms in older adult participants at pre-intervention (Study 1).

Variable	RSA	Heart Rate	CRP (mg/L)	% Unstim. IL-6/TNFα	% Stim. IL-6/TNFα	PSQI, total score	IDS-C, total score	BAI, total score	MFSI, total score	Age (years)	BMI (kg/m^2)	Weekly METs
RSA	1											
Heart Rate	-.20*	1										
CRP (mg/L)	.03	-.02	1									
% Unstim. IL-6/TNFα	-.23*	.08	.06	1								
% Stim. IL-6/TNFα	.25*	-.20*	-.02	.11	1							
PSQI, total score	-.06	-.03	-.05	.08	.15	1						
IDS-C total score	-.08	.21*	-.17	.07	.01	.25**	1					
BAI, total score	-.03	.13	-.08	.07	-.03	.20*	.29**	1				
MFSI, total score	.00	.23*	-.06	.00	-.05	.37**	.51**	.53**	1			
Age (years)	-.19$^+$	-.27**	.13	-.02	.17	-.02	-.13	-.27**	-.18$^+$	1		
BMI (kg/m^2)	-.08	.21*	.26*	.06	-.09	.08	.08	.07	.09	-.08	1	
Weekly METs	.16	.04	-.20*	-.11	.10	-.01	-.01	.01	-.11	-.28**	-.08	1

Note: ^+p = .05-.07, $*p < .05$, $**p < .01$, $***p < .001$. RSA, Respiratory Sinus Arrhythmia; CRP, C-reactive Protein; % Unstim. IL-6/TNFα, the percentage of unstimulated monocytes co-producing IL-6 and TNFα; % Stim. IL-6/TNFα, the percentage of stimulated monocytes co-producing IL-6 and TNFα; PSQI, Pittsburgh Sleep Quality Index; IDS-C, Inventory of Depressive Symptoms-Clinician Rating Scale; BAI, Beck Anxiety Inventory; MFSI, Multidimensional Fatigue Severity Index Short Form; BMI, body mass index; Weekly METs, metabolic equivalents.

Table 3. *Demographic and clinical characteristics of participants* (Study 2)

	Schizophrenia Patients (n = 39)		Healthy Comparison Subjects (n = 30)		Older Adults with Insomnia (n = 106)	
Characteristic	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age (years)*/***	22.23	4.17	20.17	2.25	65.30	6.83
Education (years)***	13.94	2.00	13.70	1.30	15.64	1.48
Highest Parental Education (years)[1]	14.89	3.26	14.52	3.05	-	-
Antipsychotic Dosage (mg/day, CPZ equiv.[2])	332.86	194.60	-	-	-	-
SAPS Total Score[3]	7.69	4.59	-	-	-	-
SANS Total Score[4]	11.59	4.83	-	-	-	-
PSQI Total Score[5]***	5.55	3.19	4.76	2.82	10.76	2.86
Total Sleep Time (hours)***	9.30	1.87	6.92	0.93	-	-
Total Time in Bed (hours)***	10.94	2.88	8.46	1.76	-	-
BDI-II Total Score[6]***	11.28	8.23	3.19	3.78	-	-
IDS-C Total Score[7]	-	-	-	-	9.31	5.22
MFSI Total Score[8]**	14.31	20.43	1.30	15.47	10.05	17.56
BMI[9]*	27.62	6.77	24.00	4.53	25.63	3.53
Mean Resting Heart Rate/+/***	76.05	15.19	70.08	10.03	63.56	8.74
Resting RSA (ln ms^2)[10]***/*	5.37	1.83	6.72	0.83	4.73	1.00
CRP (mg/L)[11]*	5.90	9.59	-	-	1.85	1.93
IL-6 (pg/mL)[12]	0.60	0.53	-	-	-	-
IL-8 (pg/mL)[13]	1.44	0.53	-	-	-	-
IL-10 (pg/mL)[14]	0.30	0.24	-	-	-	-
TNFα (pg/mL)[15]	0.79	0.18	-	-	-	-
IFNγ (pg/mL)[16]	4.86	3.95	-	-	-	-
	N		*N*		*N*	
Gender (Female/Male)***	12/27		13/17		76/30	
Race/Ethnicity						
African American	5		1		-	
Asian American	8		9		-	
Caucasian	11		7		-	
Latino/Latina	12		8		-	
Mixed Race	3		5		-	
Smoking Status (Smoker/Nonsmoker)***	4/35		2/28		0/106	
Diagnosis (Schizophrenia/Schizoaffective/ Schizophreniform)[17]	33/1/5		-		-	

Note: $^+p = .05$, $^*p < .05$, $^{**}p < .01$, $^{***}p < .001$.

* indicates significant difference between SZ and HC.

* indicates significant difference between SZ and older adults.

[1]Highest parental education (SZ *n* =37, HC *n* = 30).
[2]CPZ equiv. = chlorpromazine equivalents (SZ *n* =39).
[3]SAPS = Scale for the Assessment of Positive Symptoms (SZ *n* =35).
[4] SANS = Scale for the Assessment of Negative Symptoms (SZ *n* =39).
[5]PSQI = Pittsburgh Sleep Quality Index (SZ *n* =38, HC *n* = 29, older adults *n* =105).
[6]BDI = Beck Depression Inventory II (SZ *n* =39, HC *n* = 28).
[7]IDS-C= Inventory of Depressive Symptoms (older adults, *n* = 105).
[8]MFSI = Multidimensional Fatigue Symptom Inventory Short Form (SZ *n* =39, HC *n* =30, older adults *n* = 105).
[9]BMI = Body Mass Index(SZ *n* =38, HC *n* = 19, older adults *n* =106).
[10]RSA = Respiratory Sinus Arrhythmia.
[11]CRP = C-reactive Protein (SZ *n* =31, older adults *n* =85), mg/L = milligrams per liter
[12]IL-6 = Interleukin-6 (SZ *n* =31), pg/mL = picograms per milliliter
[13]IL-8 = Interleukin-8 (SZ *n* =31)
[14]IL-10 = Interleukin-10 (SZ *n* =31)
[15]TNFα = Tumor necrosis factor alpha (SZ *n* =31)
[16]IFNγ = Interferon gamma (SZ *n* =31)
[17]Diagnoses (SZ *n*=36)

Table 4. Associations between sleep quality, RSA, inflammatory markers, clinical symptoms, and relevant covariates in patients with first-episode schizophrenia (Study 2).

	PSQI	Total Sleep Time	Total Time in Bed	Mean Heart Rate	RSA	Log CRP	Log IL-6	Log IL-8	Log IL-10	Log TNF α	Log IFNγ	BDI Total Score	MFSI Total Score	SANS	SAPS	Age	BMI	CPZ
PSQI	1	-.21	$.30^{+}$	.02	.08	-.03	.06	.04	.08	.07	.27	.25	.33*	.05	.02	-.08	$.29^{+}$	.02
Total Sleep Time	-	1	.73***	.37*	-.48**	.23	.10	.23	$.36^{+}$	.14	-.04	.01	.08	.14	.07	-.26	-.21	.01
Total Time in Bed	-	-	1	.41*	-.48**	-.07	-.12	.43*	.24	.15	-.14	.18	.22	.10	-.08	$-.29^{+}$	-.11	-.06
Mean Heart Rate	-	-	-	1	-.56***	.29	$.31^{+}$	.25	.12	.22	.17	-.08	.08	.18	.12	-.09	.04	.09
RSA	-	-	-	-	1	-.37*	-.17	-.06	-.01	-.10	.09	-.15	-.10	-.09	.01	.03	-.17	-.11
Log CRP	-	-	-	-	-	1	.82***	-.10	.27	.21	.39*	.07	-.13	.18	.30	-.14	.65***	.11
Log IL-6	-	-	-	-	-	-	1	-.19	$.33^{+}$	.09	.48**	.00	-.19	.16	.41*	-.09	.60***	.19
Log IL-8	-	-	-	-	-	-	-	1	.09	.37*	-.09	-.02	.00	.29	-.13	-.24	.00	-.01
Log IL-10	-	-	-	-	-	-	-	-	1	.20	.39*	$.35^{+}$	.27	.16	.28	-.22	-.08	-.12
Log TNFα	-	-	-	-	-	-	-	-	-	1	.13	.06	.19	.27	.27	-.48**	.17	-.15
Log IFNγ	-	-	-	-	-	-	-	-	-	-	1	-.18	-.10	.14	.40*	.00	.13	.20
BDI Total Score	-	-	-	-	-	-	-	-	-	-	-	1	.75***	-.04	.07	-.15	.23	-.45**
MFSI Total Score	-	-	-	-	-	-	-	-	-	-	-	-	1	.02	.02	-.10	-.05	-.44**
SANS	-	-	-	-	-	-	-	-	-	-	-	-	-	1	.55**	-.21	.04	.09
SAPS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-.05	-.01	-.08
Age	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-.10	.18
BMI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-.02
CPZ	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1

Note: $^{+}$ <.09; $p < .05$, $^{**}p < .01$, $^{***}p < .001$.

Table 5. Summary of path comparisons for the serial and simple mediation models between the schizophrenia and older adult samples (Study 2).

Model	Outcome	Path	Older adults β	SZ β	Wald test	Wald test *p*-value
Serial mediation	Depression	$a_{1,\ PSQI\text{-}RSA}$	-.06	.08	.45	.50
		$a_{2,\ PSQI\text{-}CRP}$	-.07	-.01	.02	.90
		$d_{21,\ RSA\text{-}CRP}$	.04	-.34*	3.90^{+}	.05
		$b_{1,\ RSA\text{-}Depression}$	-.06	-.17	.24	.63
		$b_{2,\ CRP\text{-}Depression}$	-.08	-.02	.13	.72
		c', PSQI-Depression, direct effect	.24**	$.26^{t}$	.27	.60
		c, PSQI-Depression, total effect	.25**	.25	-	-
		m, PSQI-Depression, indirect effect	.01	-.01	-	-
Serial mediation	Fatigue	$a_{1,\ PSQI\text{-}RSA}$	-.06	.08	.45	.50
		$a_{2,\ PSQI\text{-}CRP}$	-.08	-.04	.00	.97
		$d_{21,\ RSA\text{-}CRP}$	.04	-.35*	4.01^{+}	.05
		$b_{1,\ RSA\text{-}Fatigue}$	.03	-.19	1.13	.29
		$b_{2,\ CRP\text{-}Fatigue}$	.02	-.22	1.08	.30
		c', PSQI-Fatigue, direct effect	.37***	.33*	.04	.85
		c, PSQI-Fatigue, total effect	.37***	.33*	-	-
		m, PSQI-Fatigue, indirect effect	.00	.00	-	-
Simple mediation	Depression	a, RSA-CRP	03	-.34*	3.86^{+}	.05
		b, CRP-Depression	-.10	-.01	.19	.66
		c', RSA-Depression, direct effect	-.08	-.15	.09	.76
		c, RSA-Depression, total effect	-.08	-.15	-	-
		m, RSA-Depression, indirect effect	.00	.00	-	-
Simple mediation	Fatigue	a, RSA-CRP	.03	-.35*	4.10*	.04
		b, CRP-Fatigue	.00	-.26	1.03	.31
		c', RSA-Fatigue, direct effect	.00	-.18	.61	.43
		c, RSA-Fatigue, total effect	.00	-.10	-	-
		m, RSA-Fatigue, indirect effect	.00	.09	-	-

Note: $^{+}$<.09; *p < .05, **p < .01, ***p < .001. Wald tests compare the relative strength of the path between groups (all df = 1). All results are standardized coefficients. CRP data were log transformed for both samples for these analyses.

Table 6. Characteristics of participants by treatment group at pre-intervention (Study 3).

	TCC *n* = 38	CBT-I *n* = 45	SS *n* = 23
Age (years)	66.39 (7.32)	64.20 (5.98)	65.65 (7.51)
Gender, Female, *n* (%)	26 (68.42)	34 (75.56)	16 (69.57)
Ethnicity, Hispanic, *n* (%)	2 (5.26)	3 (6.67)	3 (13.04)
Race, Non-White, *n* (%)[a]	5 (13.51)	5 (11.36)	4 (18.18)
Marital Status, Married, *n* (%)	17 (44.74)	22 (48.89)	8 (34.78)
Education (years)	15.76 (1.48)	15.78 (1.44)	15.17 (1.48)
Body Mass Index (kg/m^2)	26.03 (3.64)	25.36 (3.33)	25.48 (3.80)
Medical comorbidity, *n* (%)[b]	19 (50.00)	18 (40.00)	12 (52.17)
Depression history, *n* (%)	9 (23.68)	12 (26.67)	8 (34.78)
Other psychiatric history, *n* (%)	5 (13.16)	8 (17.78)	2 (8.70)
Cardiac condition, *n* (%)	10 (26.32)	7 (15.56)	4 (17.39)
Cardiac medication use, *n* (%)	13 (34.21)	13 (28.89)	8 (34.78)
Heart Rate	62.94 (9.71)	64.10 (7.86)	63.51 (8.99)
RSA	4.76 (.92)	4.80 (1.05)	4.57 (1.03)
PSQI total score[c]	11.01 (2.96)	10.32 (2.72)	11.24 (2.98)
IDS-C, total score[c]	9.51 (4.77)	8.68 (4.71)	10.23 (6.73)
BAI, total score	7.26 (6.19)	7.02 (7.93)	5.57 (5.66)
MFSI, total score[d]	9.87 (16.56)	10.11 (18.68)	10.22 (17.74)
CRP[e]	1.83 (1.95)	1.85 (1.97)	1.87 (1.92)
% Unstimulated monocytes co-producing IL-6 and TNFα[f]	.99 (.41)	1.02 (.61)	1.10 (.55)
% Stimulated monocytes co-producing IL-6 and TNFα[g]***	59.23 (19.94)	44.59 (15.43)	43.24 (15.27)

Note: All values are mean (SD) unless noted with percent. Between-group differences were tested with a chi-square test for categorical variables and one-way analysis of variance for continuous variables. *$p < .05$, **$p < .01$, ***$p < .001$.

[a]Total *n*=103 (Non-white)

[b]Total *n*=102 (Medical Comorbidity)

[c]TCC *n*=37, CBT-I *n*=45, SS *n*=23. (PSQI and IDS-C)

[d]TCC *n*=38, CBT-I *n*=44, SS *n*=23. (MFSI)

[e]TCC *n*=28, CBT-I *n*=36, SS *n*=21. (CRP)

[f]TCC *n*=35, CBT-I *n*=44, SS *n*=21. (Unstimulated Monocytes)
[g]TCC *n*=36, CBT-I *n*=44, SS *n*=21. (Stimulated Monocytes)
TCC, Tai Chi Chih; CBT-I, cognitive behavioral therapy for insomnia; SS, Sleep Seminar; RSA, Respiratory Sinus Arrhythmia;
PSQI, Pittsburgh Sleep Quality Index; IDS-C, Inventory of Depressive Symptoms-Clinician Rating Scale; BAI, Beck Anxiety Inventory; MFSI, Multidimensional Fatigue Severity Index Short Form; CRP, C-reactive Protein

Table 7. Means and standard deviations of RSA by treatment group at pre and post intervention (Study 3).

Group	Pre-Treatment RSA	Post-Treatment RSA
Active Treatments (TCC + CBT-I)[a]	4.78 (.99)	4.61 (.92)
TCC[b]	4.76 (.92)	4.48 (.80)
CBT-I[c]	4.80 (1.05)	4.71 (1.01)
SS[d]	4.57 (1.03)	4.59 (1.12)

Note: All values are mean (SD). RSA, Respiratory Sinus Arrhythmia; TCC, Tai Chi Chih; CBT-I, cognitive behavioral therapy for insomnia; SS, Sleep Seminar. All $p > .05$. Total n at pre *n*=106, post *n*=82.
[a]For Active Treatments: pre *n*=83, post *n*=63.
[b]For TCC: pre *n*=38, post *n*=29.
[c]For CBT-I: pre *n*=45, post *n*=34.
[d]For SS: pre *n*=23, post *n*=19.

Table 8. Hierarchical regressions predicting the percent of group treatment sessions attended from relevant covariates and pre-treatment RSA (Study 4).

Predictors	Percent of treatment sessions attended	
	ΔR^2	β
Step 1:		
Age	.02	.14
BMI		-.03
Gender		.05
Beta blocker use		-.04
Weekly METs		-.03
Step 2:		
Pre-treatment RSA	.03	-.17
Step 1: Total R^2	.03	
Step 2: Total R^2	.05	

Note: Total $n = 101$. All $p > .05$. BMI: body mass index; METs: metabolic equivalents; RSA: Respiratory Sinus Arrhythmia.

Figures

Figure 1. General model of the proposed directional relationships between sleep quality, CVT, inflammation, and clinical symptoms.

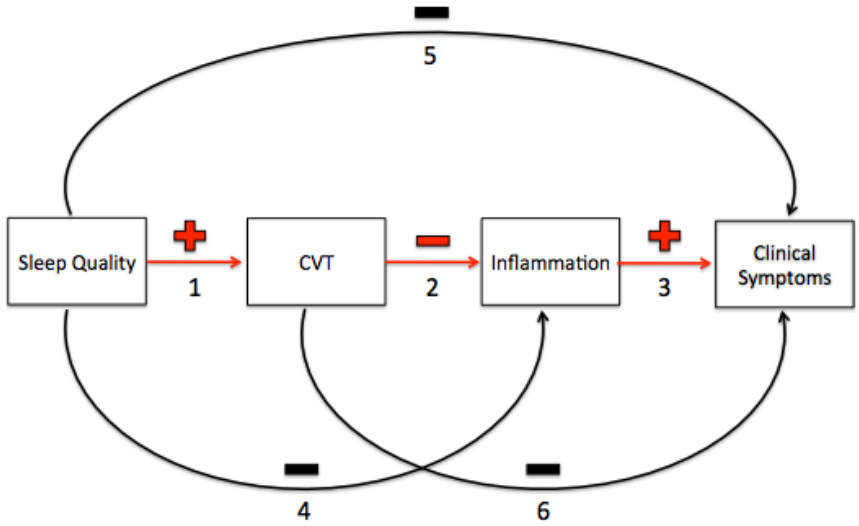


Figure 2. Screening, randomization, and completion of post-intervention, 7-month, and 16-month evaluations (from Irwin et al., (2014)).

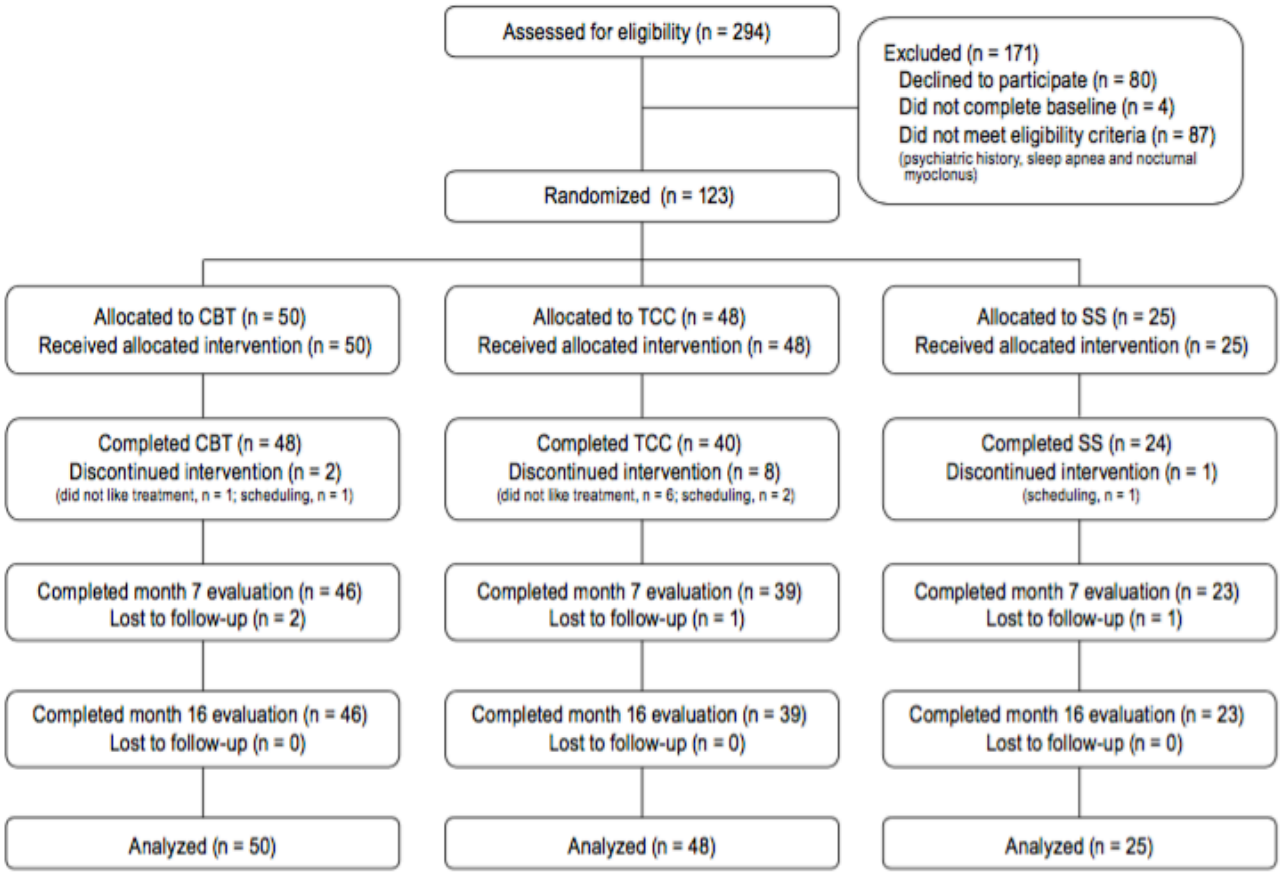


Figure 3. Statistical models of the serial and single mediation models (Study 2).

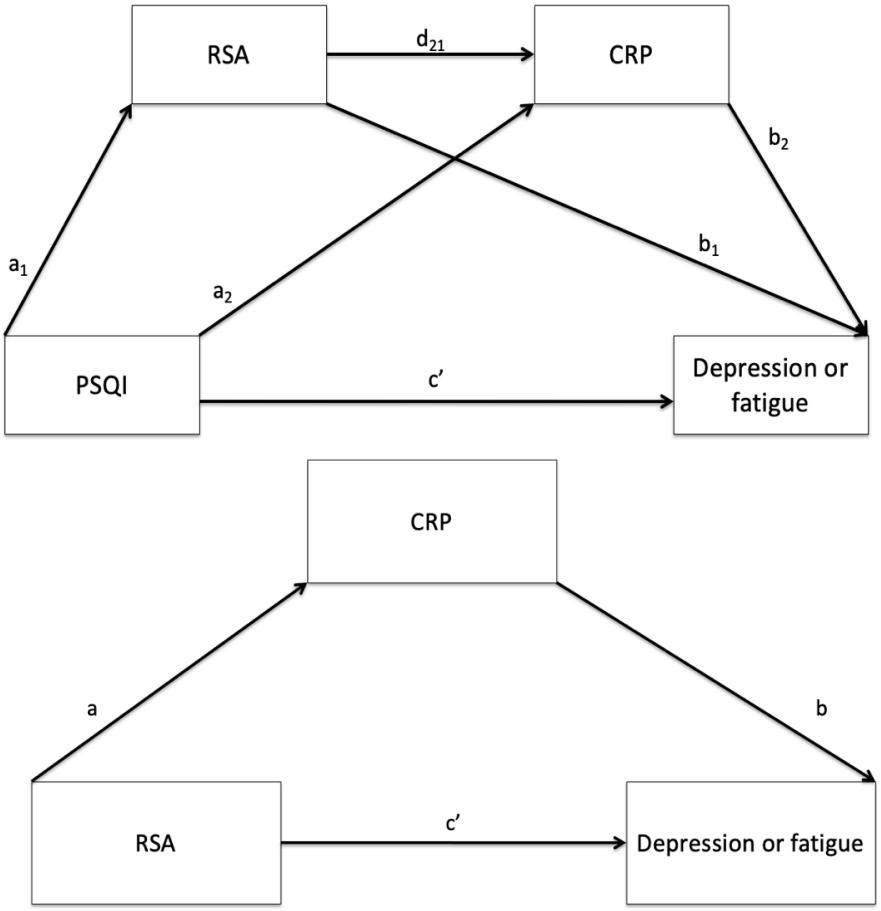
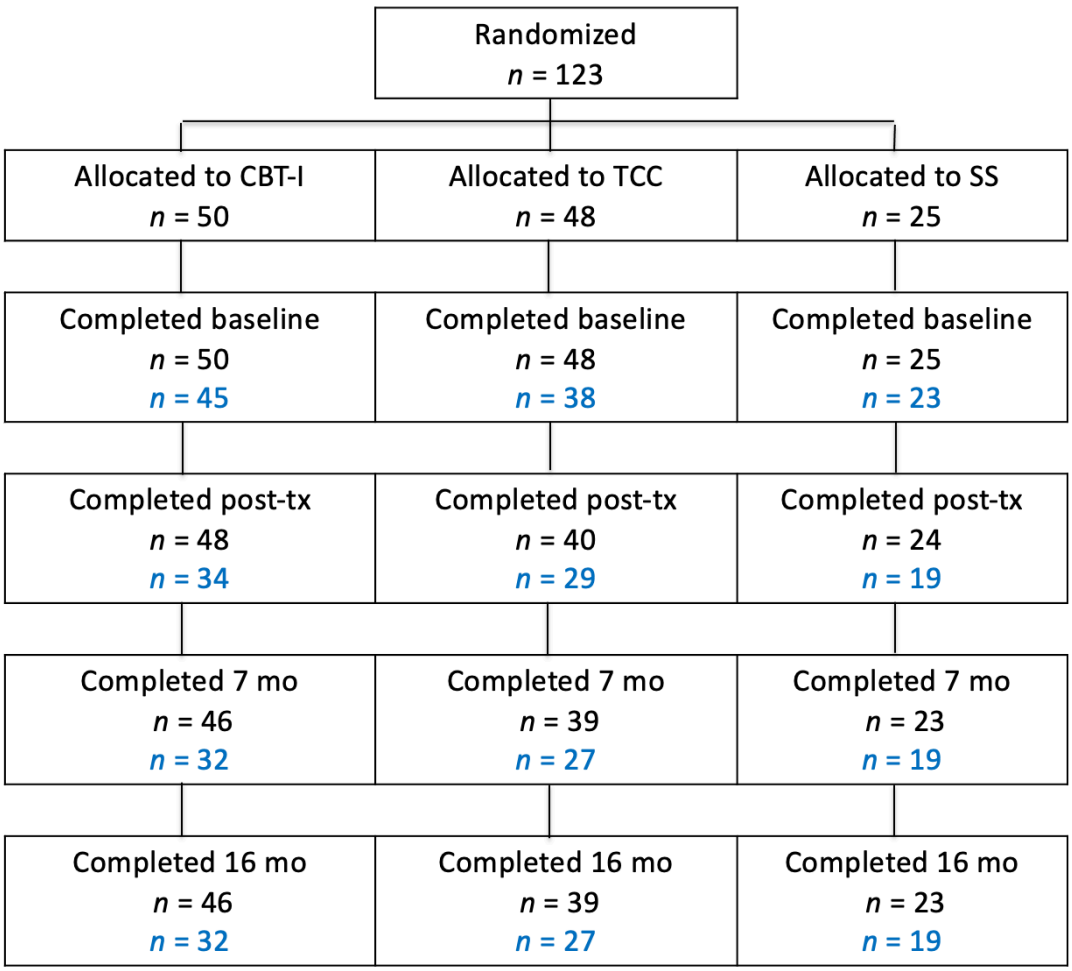
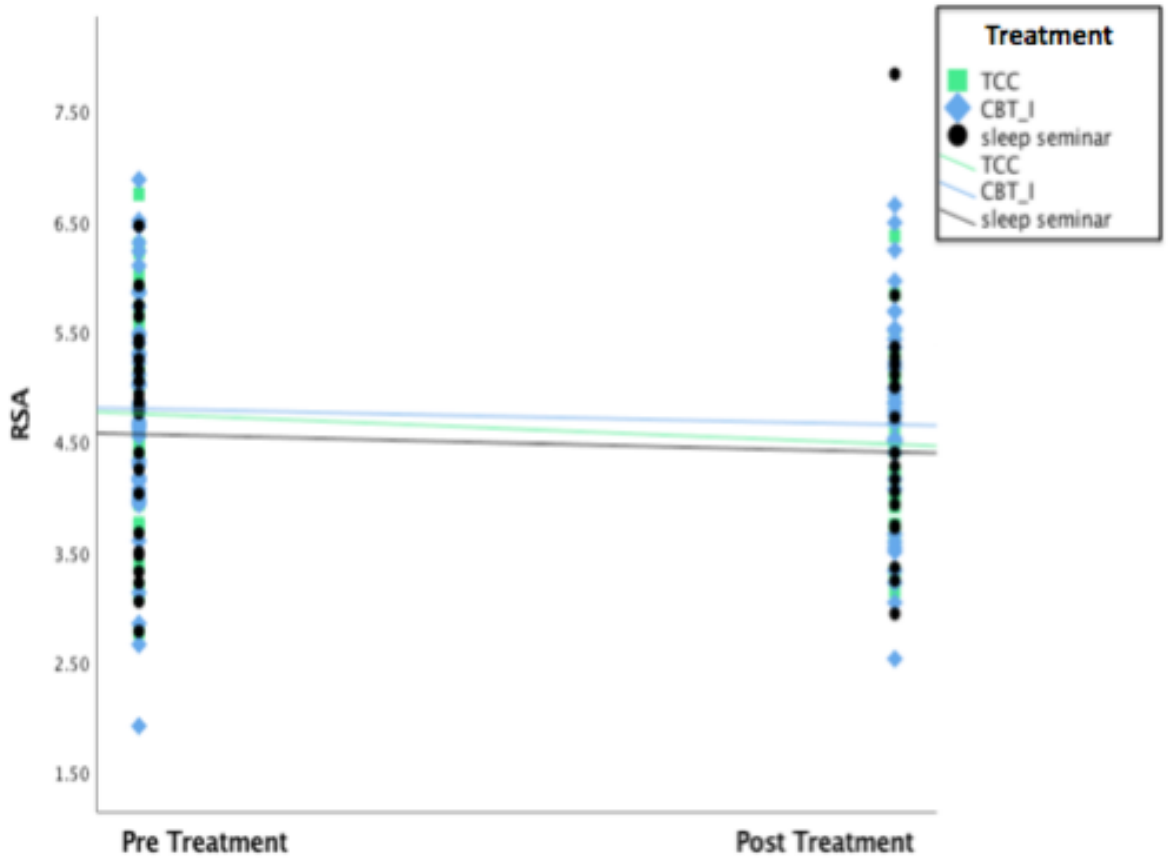


Figure 4. Modified CONSORT diagram showing randomization and completion of post-intervention, 7-month, and 16-month evaluations for the parent trial and Study 3.



Note: *N*s from the parent trial are listed in black. *N*s below, in blue, represent the number of participants with complete RSA data included in Study 3.

Figure 5. Pre to post change in RSA by treatment group (Study 3).



Note: Total *n*= 80.

Appendix

Table 1A. Baseline characteristics of older adult participants, by treatment group (Study 1).

Variable†	CBT-I (N = 50)	TCC (N = 48)	SS (N = 25)
Age (55 to 85 years)	64.4 (6.1)	66.3 (7.4)	66.4 (7.7)
Female, n (%)	39 (78.0)	31 (64.6)	18 (72.0)
Ethnicity, Hispanic, n (%)	3 (6.0)	3 (6.4)	3 (12.5)
Race, Non-white, n (%)	6 (12.2)	7 (14.9)	4 (16.7)
Marital status, Married, n (%)	25 (50.0)	21 (43.8)	8 (32.0)
Working, n (%)	21 (42.0)	20 (41.7)	10 (40.0)
Education (years)	15.8 (1.4)	15.7 (1.5)	15.3 (1.5)
Body mass index (kg/m2)	25.4 (3.3)	26.4 (4.0)	26.3 (4.5)
Medical comorbidity, n (%)*	19 (39.6)	22 (48.9)	14 (56.0)
Depression history, n (%)	12 (24.0)	12 (25.0)	8 (32.0)
PSQI total score	10.4 (2.9)	10.7 (3.1)	11.1 (2.9)
MFSI total score	9.8 (18.4)	8.5 (17.1)	10.4 (17.0)
IDS-C total score	8.7 (4.8)	9.1 (4.5)	10.8 (6.8)
CRP (mg/L)	1.9 (1.9)	2.0 (2.1)	2.1 (2.2)
Proportion with high CRP (> 3.0 mg/L) (%)	20.0	20.8	21.7

Adapted from Irwin et al., (2014). All values are mean (SD) unless noted with percent. †All P values were $p > 0.19$. *Among those who reported medical comorbidity, 95% reported cardiovascular disease.

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