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Menstrual cycle-related variation in autonomic nervous system functioning in women in the early menopausal transition with and without insomnia disorder

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ABSTRACT

Insomnia is considered a hyperarousal disorder, in which several psychophysiological domains including the autonomic nervous system (ANS) are over-activated, potentially contributing to increased risk for cardiovascular (CV) disease. Here, we aimed to determine whether insomnia that develops in the context of the transition to menopause (menopausal transition insomnia, MTI) is similarly characterized by autonomic arousal. We also took into account modulation of the ANS by the hormonal changes of the menstrual cycle, a factor that has not previously been considered in studies on insomnia. Twenty one women with insomnia (49.0 ± 3 y) and 25 controls (48.8 ± 2.6 y), also in the menopausal transition, had overnight laboratory-based polysomnographic recordings, including electrocardiograph, during the follicular and/or luteal (progesterone ≥ 3 ng ml^{-1}) phases of the menstrual cycle, with 21 women having recordings in both phases. Nocturnal time and frequency-domain heart rate variability (HRV) measures were calculated. Heart rate (HR) was significantly elevated (by ~4 bpm) in MTI compared to controls in both follicular and luteal phases, across hours of the night, including during undisturbed periods of NREM and REM sleep ($p < 0.05$). A higher HR tended to be associated with lower frequency- and time-domain vagal HRV indices in MTI compared with controls. In both groups, HR was significantly higher and total and high frequency HRV measures were lower in the luteal phase compared to the follicular phase ($p < 0.05$). In addition, REM compared to NREM sleep was characterized by increased HR coupled with decreased vagal modulation and increased sympathovagal balance ($p < 0.01$). Insomnia in the menopausal transition is characterized by nocturnal autonomic hyperarousal during both follicular and luteal phases of the menstrual cycle, which could be a factor in the etiology of MTI as well as a potential CV risk factor.

1. Introduction

Insomnia is the most common sleep disorder and a public health concern; it is defined by difficulty initiating or maintaining sleep, with associated distress and impairment in daytime functioning (Levenson et al., 2015). One-third of the general population reports insomnia symptoms with 6–10% meeting the diagnostic criteria for an insomnia diagnosis (Ohayon, 2002). Importantly, female sex is a strong risk factor, with a female/male risk ratio of 1.41/1 (Zhang and Wing, 2006). The prevalence of insomnia increases with age and varies as a function of a woman's reproductive state, being particularly evident during the menopausal transition, with 26% of women in the menopausal transition developing the disorder (Ohayon, 2006). Insomnia that develops in association with the menopausal transition (MTI) is unique because it is time-linked with the menopausal transition and associated hormonal changes (increase in follicle-stimulating hormone (FSH) and decrease in estradiol reflecting aging of the reproductive system). It is consequently linked with menopause-specific symptoms, such as hot flashes, which can act as triggers for insomnia (Ohayon, 2006). Indeed, hot flashes are associated with awakenings from sleep (Baker et al., 2015; Bianchi et al., 2016; Joffe et al., 2013) and account for a significant proportion of total objective awake time during the

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night (de Zambotti et al., 2014b). Also, greater perceived interference from hot flashes is a predictor of MTI (Sassoon et al., 2014).

Insomnia is considered a hyperarousal disorder in which several psychophysiological domains are over-activated (Levenson et al., 2015). Growing attention is being paid to hyperactivation of the autonomic nervous system (ANS) given that insomnia disorder is an independent risk factor for developing CV disease (Fernandez-Mendoza et al., 2012; Sofi et al., 2014). A number of studies of insomnia disorder in mixed populations of men and/or women of varying ages have reported altered ANS measures in insomnia, including elevated cardiac sympathetic activity (de Zambotti et al., 2014a, 2013b, 2011), elevated HR (Bonnet and Arand, 1998; de Zambotti et al., 2011; Farina et al., 2014), and/or high sympathovagal balance and depressed heart rate variability (HRV) (Bonnet and Arand, 1998; Farina et al., 2014; Spiegelhalder et al., 2011), although alterations are not always evident or even consistent across studies (reviewed in (Riemann et al., 2015)). None of the previous studies focused on MTI, although we recently reported that women with MTI have elevated beta EEG activity in REM sleep reflecting heightened EEG arousal compared to controls (Baker et al., 2015). We also previously demonstrated (de Zambotti et al., 2016a,b) that women with MTI have blunted vagal recovery during the night following an experimental pre-sleep stressor, suggesting altered ANS function, at least in response to stress.

Previous studies of ANS function in insomnia have not considered the potential impact of the menstrual cycle and associated reproductive hormone changes on the ANS, yet the effect is substantial. Estradiol is cardio-protective, associated with higher vagal activity and lower SNS activity (Saleh and Connell, 2007), while progesterone is associated with higher SNS activity (Genazzani et al., 2000). Most studies based on short-duration ECG recordings found that there is a reduction in cardiac vagal activity and a shift to sympathetic dominance in the luteal phase compared with the follicular phase (see von Holzen et al., 2016; for review). We had similar findings based on recordings made during sleep in young healthy women in the mid-luteal phase relative to the follicular phase (de Zambotti et al., 2013c) and also showed that women with severe premenstrual syndrome had altered sleep-related HRV measures in response to the luteal phase compared with controls (Baker et al., 2008; de Zambotti et al., 2013c). HRV measures also change with age and in association with menopausal hormone changes: there is a reduction in vagal activity and a shift to sympathetic dominance that emerges one year after menopause, when estradiol levels are low (von Holzen et al., 2016). Women in different menstrual cycle phases or different stages of the reproductive lifecycle, therefore, may have altered ANS function due to the hormone environment over and above any effects of insomnia.

Here, we aimed to investigate vagal activity and sympathovagal balance based on HRV measures during sleep in still-cycling women with insomnia disorder, in the early menopausal transition compared with controls. We also evaluated the potential modulatory effect of menstrual cycle-related hormone fluctuations on the ANS in the two groups of women.

2. Method

2.1. Participants

Forty-six women in the menopausal transition (MT) according to Stages of Reproductive Aging Workshop criteria (Soules et al., 2001) (i.e. menstrual cycle lengths that differed by >7 days from normal (early MT) or an amenorrhea interval of >60 days (late MT) but not >12 months), were recruited in the San Francisco Bay Area and constituted the final sample. According to these criteria, 17 women with insomnia and 22 controls were in the early menopausal transition while the remaining women were in the late menopausal transition (4 MTI and 3 controls). They were participants in a larger study of sleep quality in 72 women with and without insomnia in the MT, which involved between one and four recording nights scheduled at different phases of the menstrual cycle for cycling women or across a month for women with infrequent or skipped cycles. Data about sleep macro- and micro-structure have been published elsewhere (Baker et al., 2015), including at different menstrual cycle phases in a subsample of 20 women (de Zambotti et al., 2015). The main polysomnographic variables for the current subset of women, separately by group (insomnia and control women) and menstrual cycle phase (follicular and luteal), are shown in Supplementary Table 1. The current analysis focuses on measures of heart rate and heart rate variability and includes only women having recordings in the follicular and/or luteal phases of the menstrual cycle.

All women gave written informed consent and received compensation for participation. The study was reviewed and approved by SRI International's Institutional Review Board. Details on sample and screening procedures are fully described in Sassoon et al. (2014).

Briefly, all participants had a structured clinical interview for DSM-IV-TR Axis I Disorders (First et al., 1998) including a customized module evaluating sleep history and DSM-IV criteria for insomnia (Morin and Espie, 2003). Twenty-one women met criteria for an insomnia diagnosis with an onset of insomnia that was coincident with the menopausal transition (menopausal transition insomnia, MTI). 6 MTI participants (28.6%) reported difficulty falling asleep (reporting sleep latency > 30 min), 13 (61.9%) reported experiencing nocturnal awakenings, 8 (38.1%) reported early morning awakening, and 10 (47.6%) reported non-restorative sleep, on at least three nights per week, for at least a month. These symptoms were associated with clinically significant distress or impairment. Twenty-five women did not report clinically-significant sleep difficulties and were categorized as menopausal transition controls.

Exclusion criteria for both groups of women were having a body mass index (BMI) $\geq$33 kg m^{-2}, taking hormone therapy or hormonal contraception during the previous 3 months, hysterectomy and/or bilateral oophorectomy, amenorrhea for $\geq$12 months, current severe medical conditions (e.g. hypertension), current Axis I disorders (e.g. major depressive disorder, generalized anxiety disorder) other than insomnia in the MTI group, lifetime history of DSM-IV insomnia, apnea-hypopnea index >5 and/or periodic leg movement index >10 (based on a laboratory clinical PSG assessment), and current use of medication (e.g. hypnotics, antidepressants) and/or supplements (e.g. melatonin, black cohosh, soy products) that could affect sleep quality or menopausal symptoms.

2.2. Procedure

Participants had a laboratory adaptation/screening night to adapt to the laboratory and to confirm absence of clinical sleep disorders other than insomnia. Following adaptation, all participants had one or two PSG assessments in the sleep laboratory at SRI International in the follicular (2–10 days after onset of menstruation) and/or luteal phases (plasma progesterone levels $\geq$3 ng ml^{-1}) of the menstrual cycle. Twenty one women (11MTI and 10 controls) had recordings in both the follicular and luteal phases, 17 other women (8 MTI and 9 controls) had a single recording in the follicular phase, and 8 other women (2 MTI and 6 controls) had a single recording in the luteal phase. Participants slept in sound-attenuated and temperature-controlled bedrooms; they self-selected lights-out and lights-on times. Participants were instructed not to drink beverages containing alcohol or caffeine after 3 p.m. of each record-