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Physiological responses to acute psychosocial stress in women with menopausal insomnia☆

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ABSTRACT

Introduction: Insomnia disorder is a common sleep disorder and frequently emerges in the context of menopause, being associated with menopause-specific factors such as hot flashes and other psychosocial variables. Increased vulnerability to stress may also contribute to the development of insomnia in midlife women. Here, we aimed to investigate whether there are differences in physiological reactivity to acute psychosocial stress in women with menopausal insomnia compared with controls.

Methods: We investigated cortisol and heart rate [HR] responses to an acute experimental psychosocial stress (Trier Social Stress Test, TSST) approximately 1 h after waking in the morning in midlife women with ($n = 22$) and without ($n = 16$) DSM-IV insomnia disorder (Age: 50.05 ± 3.10 years), developed in the context of menopause.

Results: Despite similar perceived stress levels, women with insomnia showed blunted HR increases (~29% HR acceleration) to the TSST compared to controls (~44% HR acceleration) ($p = 0.026$). No group differences in HR were detected at baseline or during post-task recovery. Cortisol stress responses were inconclusive, with most of the women (60%) failing to exhibit significant cortisol increases in response to the TSST. A greater magnitude of the cortisol awakening response (CAR) predicted the likelihood of being a non-responder ($p = 0.036$), showing the confounding effect of CAR on cortisol stress responses.

Discussion: Women with menopausal insomnia show blunted cardiac responses to stress, suggesting alterations in the autonomic reactivity to acute stress. Whether these alterations are pre-existing or are a consequence of insomnia, needs to be determined.

1. Introduction

Sleep disturbances are prevalent in women approaching menopause, with about 40–56% of menopausal women exhibiting insomnia symptoms (Baker et al., 2018; Joffe et al., 2010) and 26% of them meeting the criteria for a clinical insomnia diagnosis (Ohayon, 2006). Even though some women may report sleep difficulties before menopause, 31.8% of midlife women indicate that the onset of insomnia symptoms was related to their menopausal transition (Ohayon, 2006).

Insomnia disorder in the general population is associated with a generalized up-regulation (chronic hyperarousal) across multiple domains such as increased heart rate or brain activation (Riemann et al., 2015), which is strongly implicated in the pathophysiology of the disorder. Some features of menopausal insomnia reflect those characterizing insomnia in the general population. For example, perimenopausal women with insomnia report higher levels of neuroticism (Sassoon et al., 2014), lower mood (Terauchi et al., 2010), and exhibit signs of autonomic (de Zambotti et al., 2017) and central nervous system arousal at least during REM sleep (Baker et al., 2015), compared to menopausal women without insomnia. Further, a comparison of characteristics of menopausal and non-menopausal women with insomnia showed similar subjective sleep measures and depression, anxiety, and fatigue levels for

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both groups (Xu et al., 2011). Distinctive menopause-specific characteristics, including changes in reproductive hormone levels (i.e. reductions in estradiol levels and an increases in follicle stimulating hormones in women approaching menopause) (de Zambotti et al., 2015) and hot flashes (characterized by a sensation of heat, sweating, anxiety lasting between 1 and 5 min) (Baker et al., 2015; Ohayon, 2006), also uniquely contribute to insomnia in menopause. Importantly, menopausal insomnia is associated with significant objective sleep alterations, including increased wakefulness after sleep onset and shorter total sleep time (Baker et al., 2015), which could negatively impact their health-related quality of life.

Stress and the susceptibility to stress are well-recognized factors implicated in the pathophysiology of insomnia (Basta et al., 2007). The onset of insomnia is associated with a greater incidence of stressful life events (Healey et al., 1981) and insomnia sufferers perceive similar stressful events as more stressful compared to those without insomnia (Morin et al., 2003). Similar links between higher perceived stress levels and sleep disturbances were reported specifically in menopause as well (Cuadros et al., 2012). Also, chronic stressful life events predict subsequent poorer subjective sleep quality and more wake after sleep onset (assessed with objective measures of in-home polysomnography) in midlife women, linking chronic stress exposure to development of sleep disturbances (Hall et al., 2015).

In the context of stress and sleep disruptions, it has been hypothesized that a trait-like vulnerability to insomnia disorder exists, which is triggered by an altered stress reactivity caused by genetics and personality factors (Harvey et al., 2014). Limited research has investigated physiological responses to acute stress in relation to insomnia and findings are mixed, depending on response examined (heart rate or cortisol) and whether the group examined was comprised of people with insomnia or at risk for insomnia. For example, Stepanski et al. (1994) found significantly higher heart rate (HR) in middle-aged men with chronic insomnia compared to healthy controls during a stressful reaction-time-task.

The Trier Social Stress test (TSST) is a well-established controlled laboratory method to induce and study psychosocial stress reactivity (Allen et al., 2014; Kirschbaum et al., 1993a). It is designed to expose participants to situations that include a social evaluation of their actions. The anticipation and perception of negative judgments from a panel of judges sets the TSST apart from other stress protocols by creating a unique experience of social-evaluative threat (Dickerson and Kemeny, 2004). Saliva cortisol levels as well as HR rise as a reaction to acute stress with up to 4-fold elevations above baseline in healthy participants (Kirschbaum et al., 1993b).

Chen et al. (2017) found increased cortisol responses, cortisol reactivity and perceived stress during the TSST in young men and women with insomnia disorder compared with good sleeper controls with a low vulnerability to insomnia. However, they reported no differences in HR reactivity to acute stress. Drake et al. (2017) examined stress responses as a function of vulnerability to insomnia disorder in healthy middle-aged men and women with and without familial risk for insomnia, and found a blunted cortisol response to the TSST in participants with high risk for insomnia, but no differences in HR responses. Those at high risk for insomnia also showed increased reactivity to personal life stressors (e.g., increased sleep disturbances and cognitive intrusions).

In prior work, we found that stress anticipation (before bedtime, participants were told that they were to complete a stress task the following morning) was associated with higher pre-sleep cortisol levels, faster pre-sleep HR and lower vagal activity (that persisted into the sleep period) in women with and without menopausal insomnia. However, women with insomnia lacked a within-night recovery in vagal activity across the stress night, suggesting a prolonged effect of stress anticipation, in contrast to overnight recovery seen in controls (de Zambotti et al., 2016). Other work has shown that midlife women meeting criteria for psychophysiological insomnia (i.e. women having a confirmed objective sleep efficiency lower than 85%) and women with subjective insomnia exhibited higher levels of psychological distress, especially somatization, compared to healthy sleepers. Women with psychophysiological insomnia showed the highest early morning urinary cortisol levels in all groups (Shaver et al., 2002), suggesting a link between higher emotional arousal and chronic stress neuroendocrine activation in midlife insomnia. Finally, Bertisch et al. (2019) examined cardiovascular responsivity to acute stress (Stroop task, Montreal Imaging Stress Task, cold pressor test) in *peri-* and postmenopausal women with hot-flash associated insomnia compared to those without insomnia and found that neither HR nor blood pressure responses differed between groups or correlated with insomnia symptom severity. The authors conclude that hot flash-associated insomnia is not associated with cardiovascular responsiveness to acute stress. Taken together, while abnormalities in the stress response systems may be an underlying biological mechanism for the development of insomnia (Drake et al., 2017), the literature about stress reactivity in insomnia disorder, whether in the general population or specifically in peri/postmenopausal women, is sparse and inconclusive.

To further study stress reactivity in insomnia disorder, specifically developed in the context of the menopausal transition, we aimed here to investigate psychophysiological reactivity to acute psychosocial stress (TSST) in women with menopausal insomnia compared to healthy sleepers. In line with comparable studies that indicated a higher physiological reactivity to acute stress in insomnia (Chen et al., 2017; Stepanski et al., 1994), we hypothesized that women with insomnia would show exaggerated cardiac and cortisol responses as compared to healthy sleepers.

2. Material and methods

2.1. Participants and screening

Details about the sample characteristics and the screening procedures are fully described in Sassoon et al. (2014). All participants were recruited in the San Francisco Bay Area and gave written informed consent. SRI International's Institutional Review Board reviewed and approved the study.

Twenty-two women with and 16 women without current DSM-IV

Table 1
Characteristics of the sample of women in the menopausal transition with and without DSM IV insomnia disorder developed in the context of menopause. Data are reported as numbers or mean ± standard deviation (SD), separately for women with menopausal insomnia and controls.

	Menopausal Insomnia Mean ± SD	Controls Mean ± SD	
Sample (N)	22	16	
Caucasian (N)	16	13	
Age, years	50.95 ± 2.82	48.81 ± 3.12	*
BMI, kg × m^{-2}	24.49 ± 3.53	24.21 ± 4.30	
Menopausal status			
- Early (N) / late (N)	11 / 11	13 / 3	*
Reprodutive hormones			
- Progesterone (ng.ml^{-1}),	4.64 ± 6.45	4.21 ± 5.66	
- Estradiol (pg.ml^{-1})	62.44 ± 63.48	56.88 ± 34.36	
Greene Climacteric Scale, total scores	11.0 ± 6.53	5.81 ± 4.19	*
Greene Climacteric Scale, vasomotor subscale	2.45 ± 1.44	1.06 ± 0.99	**
BDI, total scores	7.09 ± 4.01	2.19 ± 2.37	**
Life experiences			
- Positive, mean number	3.89 ± 3.79	4.21 ± 5.15	
- Negative, mean number	−6.11 ± 4.48	−2.29 ± 3.85	*
- Sum, mean number	−2.21 ± 4.88	1.93 ± 5.38	*

* Significant ($p < 0.05$).
** Highly significant ($p < 0.01$) group differences. BMI = Body Mass Index; BDI = Beck Depression Inventory.

insomnia (First et al., 1998) constituted the final sample (see Table 1). All women were in the early or late menopausal transition according to the Stages of Reproductive Aging Workshop (STRAW) criteria (Harlow et al., 2012), had an intact uterus, at least one ovary, and a body mass index (BMI) of $\leq$32 kg.m^{-2}. The women were free from severe medical conditions (e.g., hypertension or diabetes), and none of them currently used sleep medication and/or antidepressants. None of the women was currently using hormone replacement therapy.

All women underwent a structured clinical interview (SCID, First et al., 1998) including detailed sleep assessment for DSM-IV insomnia (Morin and Espie, 2003). None of the women had a history of DSM-IV insomnia disorder. Those women with current DSM-IV insomnia developed insomnia in the context of menopause. None of the women met criteria for current other Axis-I disorders except for nicotine dependence (2 in the control group and 5 in the insomnia group). None of the women had a sleep disorder other than insomnia disorder as confirmed with a clinical polysomnographic (PSG) assessment. The Beck Depression Inventory (BDI) was used to measure depressive symptoms in all women (Beck et al., 1996). All women also completed the Greene Climacteric Scale (GSC) (Greene, 1998), a 21-item validated questionnaire that measures the presence and severity of menopausal symptoms on a 4-point scale, yielding scores for three main symptom domains: psychological, somatic, and vasomotor and a single item about loss of interest in sex (libido). Here, we report total scores (calculated by summing all symptom scores (range from 0 to 63) (Barentsen et al., 2001), and scores on the vasomotor subscale (2 items, about hot flashes and sweating at night, total summed score ranging from 0 to 6). We also used this subscale to categorize women in each group as those who were bothered at least 'quite a bit' by vasomotor symptoms (scores of 3 or above on the vasomotor subscale) versus bothered 'a little' or 'not at all' (scores of 0–2 on the vasomotor subscale). Additionally, all women completed the life experiences survey to assess positive and negative life changes and experiences in the previous year (Sarason et al., 1978). The survey assesses the impact of 50 potential positive and negative changes or experiences in life (e.g., "marriage", " death of spouse", or "being fired from job"), which all women had to rate from −3 (extremely negative) to +3 (extremely positive) if they occurred in the last year. We report the effects of positive and negative changes in life, and an overall score to summarize the overall impact of both negative and positive experiences.

2.2. Trier Social Stress Test

The laboratory stress protocol consisted of 1) the pre-sleep stress anticipation procedure in the evening before the PSG recording night (de Zambotti et al., 2016) and 2) the morning stress task, based on the TSST protocol (Allen et al., 2014; Kirschbaum et al., 1993a). The morning stress task protocol is presented in Fig. 1. Effects of the stress anticipation on PSG macro- and microstructure and on sleep ANS function in women with menopausal insomnia were extensively analyzed and published in a previous publication (de Zambotti et al., 2016).

Briefly, in the evening before the stress task participants were told that they would need to prepare and give a recorded speech in the morning on a topic that would only be revealed to them the following morning, followed by a math task in front of a panel of judges, who would assess and judge their performance and ask questions. Participants were shown the speech assessment room, set up with chairs for the assessors, a video camera and microphone.

Upon awakening, participants showered and had a light caffeine-free breakfast. Approximately 1 h after waking, participants were prepared for the TSST. Electrocardiographic (ECG) and skin conductance sensors were attached, and they had to sit quietly for at least 15 min to obtain baseline resting measures of HR. They then followed the TSST procedure as described in (Allen et al., 2014; Kirschbaum et al., 1993a). Participants were instructed to take over the role of a job applicant who has to give a speech to a committee, convincing them that she is the perfect applicant for a vacant position ('dream job'). They were given 5 min to prepare the speech. After preparation, the participant gave her speech in front of the committee. If she finished her speech in less than 5 min, the committee leader instructed her that she still had time left, and if necessary, prompted her with prepared questions. At the end of 5 min, the participant was asked to complete a mental arithmetic task (serially subtraction) for 5 min. On every failure, a committee member interfered, and the participant had to start again. The committee consisted of two-three persons (mixed gender), who were instructed to act in a cold and reserved manner. When the TSST had been completed, participants were required to sit quietly for another 25 min during the recovery assessment. Following the final saliva sample, sensors were removed, and participants were debriefed and allowed to leave.

2.3. Self-report acute stress anticipation and post stress ratings

During the 5-min preparation period before the TSST, participants completed the Primary Secondary Appraisal Scale (PASA), a validated questionnaire on cognitive appraisal of the anticipated stressful situation, which includes 16 statements such as 'I do not feel threatened by the situation' and 'This task challenges me', with six response categories ranging from 'totally disagree' to 'totally agree' (Gaab et al., 2005). Derived measures of the subscales threat, challenge, self-competence and control expectancy were calculated and used in analyses. Also, participants completed a visual analogic scale (VAS) after the TSST to rate how stressful they rated the speech and arithmetic tasks on a scale from 0 (not at all stressful) to 100 (very stressful).

2.4. Physiological measures during the TSST

2.4.1. Heart rate

ECG signals from Ag/AgCl Meditrace surface spot electrodes in a modified Lead II Einthoven configuration were acquired using the ambulatory Compumedics Somté device (Compumedics, Abbotsford,

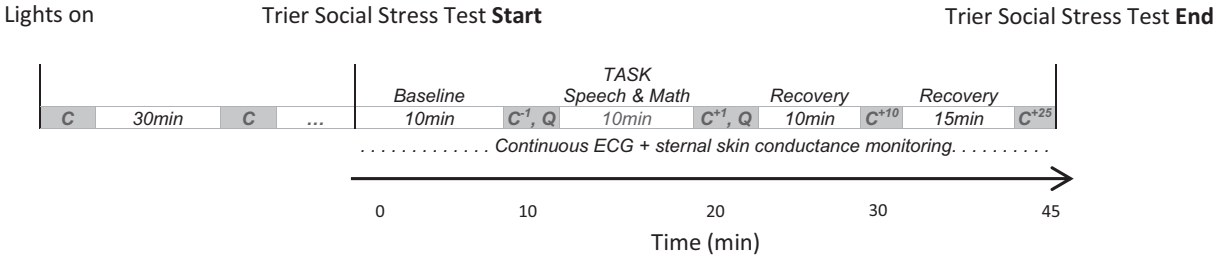

Fig. 1. Procedure of the morning stress task protocol.

Victoria, Australia). Data were continuously collected at 200 Hz. HR was assessed via dedicated software developed at the University of Melbourne and according to procedures previously described (Trinder et al., 2001). Briefly, R waves were automatically detected by the software, visually checked and manually adjusted by trained technicians when necessary, and HR calculated by computing the inter-beat-intervals. HR was averaged across resting baseline (10 min), speech task (5 min), arithmetic task (5 min), and recovery (25 min) periods.

2.4.2. Saliva cortisol

Saliva samples were collected immediately on awakening and 30 min later. The cortisol awakening response (CAR) was defined as the difference between the two values (Elder et al., 2014). There was insufficient sample for analysis for one insomnia women. CAR data are therefore available for 16 controls and 21 insomnia women. For the TSST, saliva samples were collected 1 min before (−1 min) and 1 min right after (+1 min) the TSST, and then 10 (+ 10) min and 25 (+25) min later. All saliva samples were collected with the Salivette system (Salimetrics, Carlsbad CA, USA) to assess salivary free cortisol levels.

Samples were frozen at −70 °C for subsequent analysis of cortisol by a commercial laboratory (ZRT laboratory, Beaverton, OR, USA) using a standard immunoassay kit (inter- and intra-assay coefficients of variation, 7.1% and 5.4%, respectively; sensitivity 0.1 ng/mL). Values are reported in $nmol.l^{-1}$. In order to maintain comparability of the current study with others, cortisol responders to the TSST were defined as those who showed an increase of >1.5 $nmol.l^{-1}$ in cortisol at +10 min relative to −1 min, a definition used by others (Engert et al., 2014; Miller et al., 2013; Schmalbach et al., 2020; Skoluda et al., 2015; Stephens et al., 2016). Cortisol levels in all TSST samples for one control participant were greater than 3 SD away from the mean and were therefore excluded from analysis. TSST cortisol data are therefore available for 15 controls and 22 insomnia women.

2.4.3. Hot flashes

The presence of hot flashes was assessed by measuring skin conductance using two silver/silver chloride electrodes filled with 0.05 M potassium chloride Velvachol/glycol gel (Dormire and Carpenter, 2002) placed on either side of the sternum, connected to an ambulatory 3991/1-SCL Biolog based hot flash monitor (UFI, Morro Bay, CA) using a 0.5 V constant voltage circuit (Lykken and Venables, 1971) at a sampling rate of 16 Hz. Two independent scorers determined the presence of hot flashes based on an increase in skin conductance levels of ≥2 micromhos within 30 s (Freedman, 1989). The number of hot flashes was calculated for the resting baseline, during the stress task, and recovery periods. Physiological hot flash data is missing from two controls and two insomnia women due to technical failure.

2.4.4. Reproductive hormone levels

Women were assessed regardless of menstrual cycle phase. A blood sample was collected the night before the TSST, centrifuged and serum samples were frozen at −70 °C until analysis for progesterone and estradiol using standard immunoassay kits. The intraassay and interassay coefficients of variations were 4.0% and 5.7%, respectively, with a sensitivity of 0.2 $ng.ml^{-1}$ for progesterone ($ng.ml^{-1}$; Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA), and 6.7% and 7.6%, respectively, with a sensitivity of 3 $pg.mol^{-1}$ for estradiol ($pg.mol^{-1}$; Beckman Coulter Inc., Fullerton, CA, USA). Given evidence of menstrual cycle and endogenous and exogenous reproductive hormone effects on heart rate, which is increased in the luteal phase when progesterone is increased (de Zambotti et al., 2017; Godbole et al., 2016), and potentially also on heart rate and cortisol stress responses (Childs et al., 2010; Kirschbaum et al., 1999), progesterone was used as a covariate in the analysis.

2.5. Statistical analyses

Unpaired *t*-tests were conducted to examine any differences between groups (insomnia vs control) for age, BMI, GCS total scores and the vasomotor subscale scores, BDI scores, the impact of stressful life events, progesterone and estradiol levels. A Chi-Square test was used to analyze differences between women with insomnia and controls in menopausal status (early vs late menopausal transition) and in the extent to which women were bothered by vasomotor symptoms (bothered vs not bothered on the vasomotor subscale of the GCS).

Self-reported measures of anticipated stress (PASA scores) and post-task stress levels (VAS) were compared between groups using unpaired *t*-tests. HR across the TSST was analyzed using repeated measurement ANCOVAs with *group* (insomnia and control) as a between factor and *time* (baseline, speech task, arithmetic task, and recovery) as a within factor. Progesterone was included as a covariate. Subsequently, differences between groups in HR reactivity to the task (= change in HR between first 5 min of the TSST task (speech) and pre-speech baseline) was analyzed with unpaired t-tests. A power analysis employing the program G*Power suggested that a total N of 36 is required to find a significant repeated measures between-factors effect at 90% power with an alpha error probability of 0.05 using an ANOVA with 2 groups and 4 measurement time points, indicating that our total sample size of $N = 38$ women is an adequate sample size for the employed statistical analyses.

To investigate the cortisol awakening response and potential group differences in the response, a 2-way repeated measurement ANOVA was conducted with *time* (cortisol at wake-up, cortisol 30 min after wake-up) as a within subject factor and *group* as a between factor, and progesterone as a covariate. Cortisol levels during the TSST were analyzed using a repeated measurement ANCOVA with *group* as a between factor and *time* (−1 min, +1 min, +10 min, +25 min, relative to the TSST) as within factor, with progesterone as a covariate. We also examined group differences in categorization of women as a cortisol 'responder' or 'non-responder', using a chi-square test. To analyze the predictive value of CAR on having a cortisol stress response, a binary logistic regression was performed with *cortisol response status* ('responder' vs 'non-responder') as dependent variable and *CAR* as the predictor, in the combined group of women. Nagelkerke R Square values are reported for the logistic regression. The Geisser–Greenhouse (G–G) correction was applied when variables with more than 2 levels were involved and only results remaining significant are reported. Effects sizes are reported using the partial eta squared (ηp^2) for repeated measurement ANCOVAS and Cohen's d (d) for unpaired *t*-tests. An effect size of 0.2 = low, 0.5 = moderate, 0.8 = high was assumed for Cohen's d, and an effect size of 0.01 = low, 0.06 = moderate, 0.14 = high was assumed for partial eta squared.

3. Results

3.1. Menopausal symptoms, depression symptoms, and stressful life events

Characteristics of the sample are presented in Table 1. The insomnia group was significantly older than controls ($t = -2.21$, $p = 0.034$), but did not differ on BMI ($t = -0.22$, $p = 0.825$). Women with insomnia had higher scores than controls on the GCS, reflecting more severe menopausal symptoms ($t = -2.97$, $p = 0.005$), including higher scores on the vasomotor subscale $t = -3.52$, $p = 0.001$), and higher scores on the BDI, reflecting more depressive symptoms ($t = -4.32$, p = 0.001). Further, more women with menopausal insomnia (10) compared with controls (2) reported being bothered at least 'quite a bit' by vasomotor symptoms ($\chi^2 = 4.66$, $p = 0.033$). While both groups were comprised entirely of women in the menopausal transition according to STRAW criteria (Harlow et al., 2012), the control group had fewer late menopausal transition women than the insomnia group. Women with insomnia reported more impact of negative life events in the previous year ($t = 2.56$, $p = 0.015$) and consequently more total negative impact of life events (*t*

= 2.30, $p = 0.028$) compared with controls. There was no group difference in the impact of positive life events in the past 12 months.

3.2. Cognitive appraisal of the (anticipated) stressful situation

Both groups rated the anticipated stressful situation equally stressful. There were no significant group differences in the PASA subscales of threat (Controls: $M = 3.05 \pm 1.17$; Insomnia: $M = 3.88 \pm 1.14$), challenge (Controls: $M = 4.06 \pm 0.76$; Insomnia: $M = 4.08 \pm 0.81$), self-concept (Controls: $M = 4.31 \pm 1.08$; Insomnia: $M = 4.10 \pm 0.92$), or control expectancy (Controls: $M = 4.23 \pm 0.92$; Insomnia: $M = 3.81 \pm 0.89$) (all $p > 0.05$).

Furthermore, the post speech VAS ratings indicated that all participants perceived the speech (Controls: $M = 58.88 \pm 26.66$; Insomnia: $M = 58.59 \pm 25.72$) as well as the arithmetic task (Controls: $M = 68.44 \pm 25.88$; Insomnia: $M = 72.95 \pm 22.79$) as stressful with no significant group differences in the ratings (all $p > 0.05$).

3.3. Cardiac reactivity to stress

Repeated measurement ANCOVA showed a significant main effect of time ($F(1, 35) = 80.05$, $p = 0.001$, $\eta p2 = 0.696$) and time*group interaction ($F(1,35) = 4.82$, $p = 0.018$, $\eta p^2 = 0.121$) for HR, indicating similar HR at baseline and during recovery after the TSST in insomnia women and controls, but blunted increases in HR in response to the stress task (speech) in women with insomnia (see Fig. 2). A subsequent unpaired *t*-test on HR reactivity showed that women with insomnia exhibited significantly less HR reactivity to the speech task ($t = 2.27$, $p = 0.029$, $d = 0.746$) compared with controls. Progesterone was a significant main factor in the repeated measures ANCOVA model ($F(1,35) = 4.69$, $p = 0.037$, $\eta p^2 = 0.118$) and there was a significant time*-progesterone interaction effect ($F(1,35) = 4.82$, $p = 0.018$, $\eta p^2 = 0.121$), with HR being higher in those women with higher progesterone levels, particularly during the speech and arithmetic tasks.

3.4. Cortisol awakening response

All women showed a robust CAR with higher cortisol levels (148.48% increase) 30 min after waking relative to right after waking ($F = 28.39$, $p = 0.001$, $\eta p^2 = 0.455$). Repeated measurement ANCOVA showed no significant time, group or time*group interaction, indicating that both groups showed a similar cortisol awakening response. Progesterone was not a significant factor in the model.

3.5. Cortisol reactivity to stress

An examination of cortisol changes across the TSST showed no group differences in cortisol stress responses. Progesterone was a significant factor in the model ($F(1,34) = 5.24$, $p = 0.028$, $\eta p^2 = 0.134$), with higher progesterone levels being associated with higher cortisol levels right before and after the TSST.

The majority of women in both groups were classified as non-responders to the psychosocial stress based on a cutoff of an increase >1.5 nmol.l^{-1} (Engert et al., 2014; Miller et al., 2013; Schmalbach et al., 2020; Skoluda et al., 2015; Stephens et al., 2016) in cortisol responses to the TSST (10 controls, 13 insomnia sufferers, group comparison Chi square, $p > 0.05$).

A binary logistic regression indicated that the CAR was a significant predictor of the likelihood of being a cortisol responder / non-responder in the combined group of women ($R^2 = 0.186$, $B = 0.134$, S.E. 0.064, Exp (B) = 1.14, $p = 0.036$). CAR, as well as cortisol responses to the TSST in the combined group of responders vs. non-responders, are presented in Fig. 3.

3.6. Hot flashes

Nine women in the insomnia group and four controls had at least one physiological hot flash either right before (during speech preparation) or during the stress task, which did not differ according to group (Chi-square, $p > 0.05$). None of the women had a hot flash during the recovery period.

4. Discussion

In the current study, we investigated cortisol and HR reactivity to acute psychosocial stress in midlife women with and without insomnia disorder developed in the context of menopause. While both groups reported similar levels of perceived stress before and during the task, we found a blunted HR increase in response to stress in women with insomnia, suggesting an altered cardiac reactivity to stress in menopausal insomnia. We did not find any group differences in cortisol stress responses, however, there was a high number of cortisol non-responders in both groups of women, which limits our ability to make conclusions from those data. Our results, while inconclusive for cortisol, have

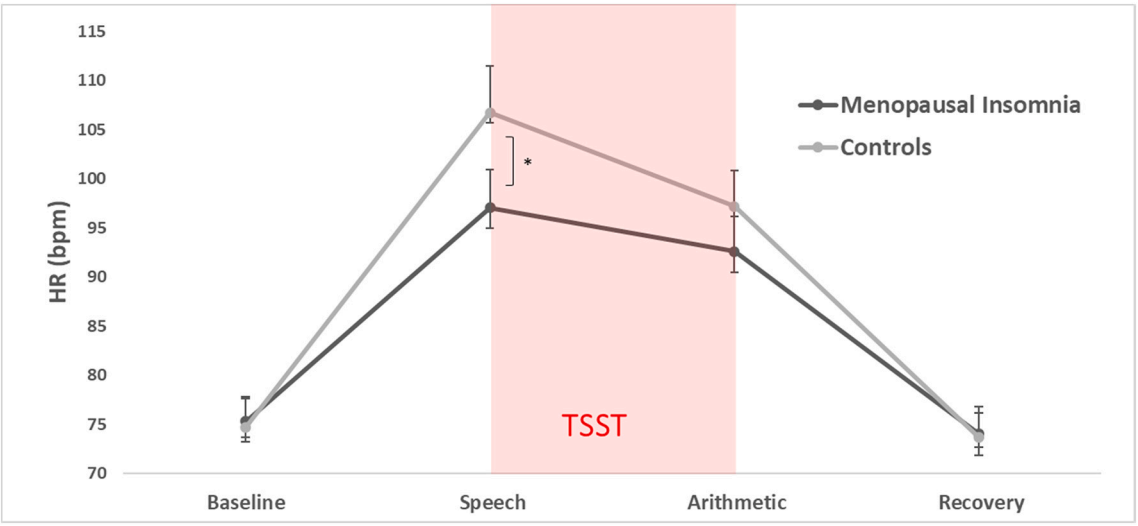

Fig. 2. Heart rate (HR) (mean +/− SE) during baseline (10 min), speech (5 min) and arithmetic (5 min) portions of the Trier Social Stress Test (TSST), as well as during recovery (25 min) in women with DSM-iV insomnia developed in the context of the menopausal transition and healthy controls. Women with insomnia showed similiar HR levels at baseline and recovery, but exhibited a blunted increase in HR in response to the TSST relative to controls.

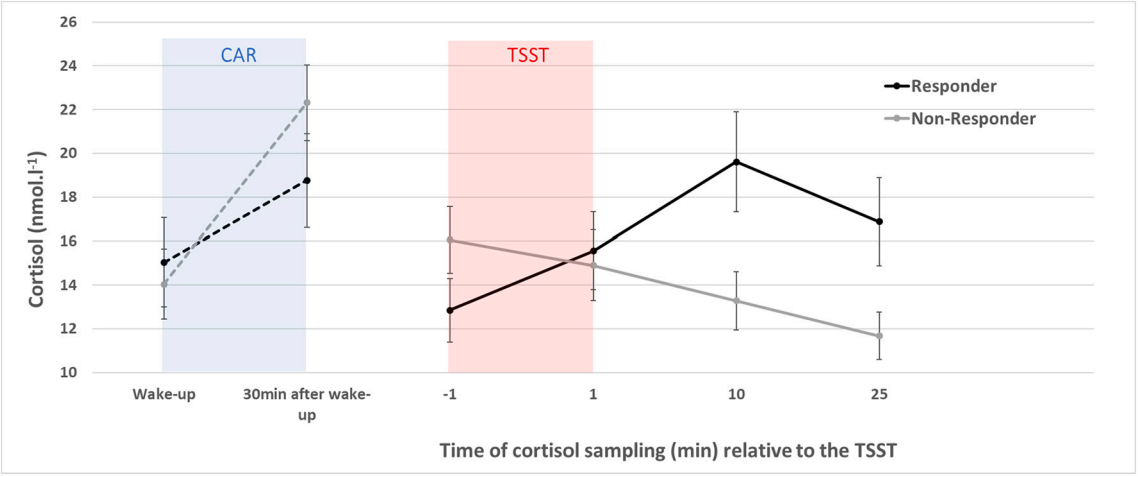

Fig. 3. Illustration of average cortisol (mean +/− SE) awakening responses (CAR) and cortisol responses to the Trier social stress test (TSST) in cortisol-responders ($n = 14$) vs. non-responders ($n = 23$) to the TSST, for the combined group of menopausal insomnia and control women. Women with a larger CAR were more likely to be cortisol non-responders to the TSST (see text for details).

important methodological lessons: first, we found that those participants with a higher cortisol awakening response were more likely to be non-responders, showing the potential confounding effect of the CAR on cortisol stress responses when the TSST is conducted early in the morning. Second, we show that progesterone was a significant factor in the analysis, associated with higher absolute HR and cortisol levels during the TSST and also with the extent of HR increase during the TSST, supporting the need to consider reproductive hormone levels or an indicator of menstrual cycle phase when studying stress responses in women, as advocated elsewhere (Allen et al., 2014).

Both women with menopausal insomnia and healthy sleepers reported high perceived stress levels either before or during the TSST, with our sample perceiving the impending situation to be as stressful as other samples have found it to be (Gaab et al., 2005). While women with menopausal insomnia did not report differing subjective stress levels compared to controls, they did show an altered cardiac reaction towards acute stress. During the stress-recovery period, however, HR levels were not different between groups, indicating that it is the initial response to stress that differs. To our knowledge, only one other study has investigated acute stress reactivity specifically in midlife women with insomnia. In contrast to our findings, Bertisch et al. (2019) found that hot-flash associated insomnia disorder in peri-menopausal women was not associated with an altered cardiovascular responsiveness during acute stress compared to women without insomnia. Different results between the two studies may be due to the nature of induced experimental stress, since Bertisch et al. (2019) employed three different (social-evaluative, cognitive, and nociceptive stress) paradigms in their study (stroop task, montreal imaging stress task, cold pressure test), while we investigated psychosocial stress during the TSST. The TSST is a unique stress test that creates an experience of social-evaluative threat through the presence of an audience of judges (Dickerson and Kemeny, 2004). Furthermore, the two studies differed in study samples – we studied women all in the menopausal transition whereas the sample in the Bertisch et al. (2019) study were mainly post-menopausal, and all participants in their insomnia group reported awakenings attributed to hot flashes. Even though almost half the participants in the insomnia group in our study reported being bothered quite a bit by hot flashes, we did not include participants based on this criterion. Of note, since we recorded the presence of hot flashes throughout the TSST, we were able to show that some women (4 controls and 9 women with insomnia) had a hot flash during the task but none had hot flashes during recovery, likely reflecting the stressful effect of the TSST, since hot flashes can be triggered by acute psychosocial stress (Kronenberg, 1990).

While insomnia that develops in the menopausal transition may have different triggers from insomnia in the general population (e.g. hot flashes, changes in the hormonal milieu), characteristics of hyperarousal, poorer mood, greater perceived stress, are shared, as described in the introduction. It is pertinent, therefore, to contextualize our results more broadly with also studies including individuals with sleep disturbances or familial insomnia risk. Chen et al. (2017) found greater cortisol reactivity but no differences in heart rate responses in insomnia sufferers during the TSST, suggesting a higher physiological reactivity of cortisol to stressful situations in these individuals. Notably, they only included 10 insomnia participants of mixed sex between the ages of 19 and 40 years. Stepanski et al. (1994) found increased HR during a stressful performance task in 24 adult men (21–50 y) with chronic insomnia compared to healthy sleepers. In contrast, stress reactions in our study were characterized by blunted cardiac stress responses in insomnia. Bassett et al. (2015) analyzed the association between sex, sleep quality and quantity and the reactivity to acute social stress (TSST) in healthy college-aged males and females. They found that women who reported alterations in sleep quality (i.e. daytime dysfunctions) showed a blunted cortisol response to the TSST, while men with poor sleep quality exhibited exaggerated cortisol responses. This finding implies sex differences in physiological stress responses in individuals with sleep disruptions, and might therefore help to explain the outcomes of the current study indicating a blunted physiological stress response in women, as well as differences between the current study and other studies investigating only male participants e.g. Stepanski et al. (1994). Similarly, Wright et al. (2007) found that middle-aged healthy women with poor sleep quality during the night before the stress task (stroop test) showed blunted cortisol responses to acute stress. Contrary to the current study, they did not examine HR responses to acute stress. Finally, Drake et al. (2017) also reported a blunted cortisol response to the Trier Social Stress Test,but again no differences in heart rate in participants with high familial risk for insomnia disorder (men and women). Our finding of a blunted response therefore differs from some studies and our initial hypothesis, and further work is needed to better understand physiological stress responses in the context of not only menopausal insomnia, but also insomnia in other populations. Notably, most studies however reported physiological deviations in the acute stress response in individuals with sleep disturbances compared to controls. Both exaggerated physiological stress responses and blunted physiological stress responses – as reported in the current study – indicate a loss of flexibility in autonomic responses, i.e. impairments of ANS function, and deviations in both directions from the normal response have potential negative health outcomes (Allen, 2013; Lovallo, 2011). Notably, a blunted cardiac reactivity to an acute stressor has been found

in major depressive disorder (Phillips, 2011; Salomon et al., 2009). While none of the women in our study met criteria for clinical depression, the insomnia group had higher scores on the BDI, reflecting more depressive symptoms, compared with controls. Insomnia and depressed mood are tightly entwined, and the potential contributions to blunted HR reactivity to stress of insomnia, sub-clinical depression symptoms, as well as other features of menopausal insomnia (e.g. hot flashes, stressful life events) remain to be determined in future studies. It is also unclear how the time of day during which the stress manipulation was performed affects the results, as existing studies have conducted the task at different times of day, for example in the morning (Bertisch et al., 2019; Stepanski et al., 1994), afternoon (Bassett et al., 2015; Drake et al., 2017) or evening (Chen et al., 2017).

Our findings also show a higher impact of negative life events in the last year in the insomnia group as compared with the control group. Stressful life events are associated with chronic insomnia as well as the onset of insomnia disorder (Healey et al., 1981). Literature further indicates links between stress and insomnia symptoms during the menopausal transition (Cuadros et al., 2012). It is possible that the exposure to chronic subjective stress may influence cardiac responses to acute stress in midlife insomnia women, however, we did not track the development of insomnia disorder in our sample and more research is needed to address how chronic stress and the susceptibility to stress are associated in menopausal insomnia.

The TSST has been particularly studied with respect to cortisol responses to acute experimental stress (Allen et al., 2017) (see above). Our results do not indicate significant differences in cortisol stress responses in menopausal insomnia, however, findings are confounded by the fact that the majority of participants (13 insomnia and 10 controls) did not respond to the TSST, which is a limitation of the study. Further data exploration provided two relevant observations: First, data indicate that TSST responders - independent of group - displayed the expected cortisol increase to the induced experimental stress, confirming the functionality of the protocol. Second, our results indicate that participants with a higher cortisol awakening response were more likely to be non-responders, suggesting that the cortisol stress response to the TSST was confounded by the cortisol awakening response. Cortisol has a daily rhythm, increasing rapidly after waking (Elder et al., 2014) before slowly decreasing across the day. There is substantial individual variability in the extent of the cortisol awakening response (Kudielka et al., 2006), which can impact baseline cortisol levels when the TSST is conducted in the morning, as shown in our study. Indeed, conducting the TSST in the afternoon is considered more reliable for inducing a strong cortisol stress response (Goodman et al., 2017). We modified the TSST to enable examination of the effects of anticipation of stress on sleep (de Zambotti et al., 2016), and therefore needed to conduct the TSST in the morning. However, a longer delay between wake-up time and the TSST might have provided better results and we suggest that the stress task should be conducted further from the time of waking if examining cortisol responses in the morning. We note that this confounding effect does not affect our results about HR stress responses. Finally, it is also possible that our results may be affected by the modification we made to the TSST, with introduction of the stress anticipation protocol the evening before, and therefore a long delay between a component of the stress anticipation and the actual task, although subjective stress responses during speech preparation in the morning were similar to those reported for other studies that used the traditional protocol (Gaab et al., 2005).

4.1. Conclusion and future directions

Our results show alterations in cardiac responses to acute stress, characterized by a blunted cardiac response, in women with menopausal insomnia. Stress and particularly alterations in the stress response are implicated in the pathophysiology of insomnia disorder. Long-lasting chronic stress may trigger insomnia; however, sleep disturbances can also increase stress levels. Clinical characteristics including subthreshold clinical depression and vasomotor symptoms such as hot flashes are integrated components of menopausal insomnia disorder, and future studies in larger samples of women are needed to fully understand the factors that are driving the observed alterations in physiological stress responses in menopausal insomnia. Given the small and discrepant literature about acute stress responses in individuals with insomnia, and particularly in women with menopausal insomnia, further work is needed, considering factors like menopausal stage and symptoms (hot flashes), history of chronic stress, and comorbid symptoms (like depression), in order to establish whether menopausal insomnia is characterized by altered stress reactivity either as a pre-existing factor or as a consequence of insomnia, which could potentially be an important factor in the etiology of the disorder.

Declaration of competing interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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