Autonomic regulation during sleep in PTSD

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ABSTRACT

The following article reviews the existing data on autonomic nervous system status in posttraumatic stress disorder. This review is embedded in a framework that considers the comparative ethology of sleep under threat. In sum, the current literature, though still quite limited, supports a role for impaired parasympathetic drive but not for increased sympathetic drive in the periphery during sleep in PTSD. Understanding this domain better can be expected to provide insights into the elevated prevalence of cardiovascular disease in posttraumatic stress disorder (PTSD) and may help to identify as-yet unrecognized medical comorbidities. Measurement issues and future opportunities are considered.

1. Introduction

Sleep is a restorative process that plays a crucial role in preparing us to meet the challenges of the coming day. It is also a period of vulnerability in which we humans, for most of our evolutionary history, lay on the ground, unprotected and relatively unresponsive, neither inacces- sible in trees or on cliff faces like primates, nor hidden in burrows like rodents. Balancing restoration and security during sleep is a challenge we share with other similarly-sized, ground-dwelling prey animals (Hart and Sussman, 2005). The following review covers what we know about autonomic nervous system (ANS) status measured during sleep in posttraumatic stress disorder (PTSD), a diagnosis characterized by a history of exposure to extreme threat, by sleep disturbances, and by elevated risk for cardiovascular disease (CVD). As only a small number of studies have directly addressed the question of ANS status during sleep in PTSD, the following discussion will extend to measurement issues which may inform future work.

Not surprisingly, prey animals modify their sleep behaviors in response to threat of predation. The beginnings of a taxonomy of adaptations to sleeping under threat exhibited by birds and mammals can be found in the works of Lima, Amlaner, Lesku, and Rattenborg (Lesku et al., 2008a,b; Lesku et al., 2006; Lima et al., 2005; Rattenborg et al., 2000, 2001; Rattenborg et al., 2007; Rattenborg et al., 2012; Roth et al., 2006). Some of these adaptations are fascinating, such as unihemi- spheric sleep (Rattenborg et al., 1999, 2000), and others unsurprising. For example, doves exposed to a ferret will, during a subsequent sleep bout, awake more frequently to “peek” at their surroundings (Lendrem, 1984). Pigeons forced to sleep near the ground will exhibit reduced REM sleep, a state associated with elevated arousal thresholds in most ani- mals (Tisdale et al., 2018). Wild-type rats exposed to predator scent will delay slow wave sleep (SWS) and attenuate its intensity (Lesku et al., 2008a), in line with findings that SWS is also associated with elevated arousal thresholds (Neckelmann and Ursin, 1993).

PTSD can be understood as a constellation of adaptations to environmental threat that persist despite resolution of the threat. In PTSD, across polysomnographic (PSG) studies, the most consistently reported modification of sleep is a general lightning combined with a reduction of SWS (de Boer et al., 2020; Kobayashi et al., 2007; Wang et al., 2020). This pattern is consistent with the increased frequency of awakenings observed in many species when sleeping under threat. Rates of self-reported sleep maintenance difficulties in PTSD have been observed to exceed 90% (Neylan et al., 1998), a near-universality suggestive of a genetically-programmed response. In the general population, the propensity to sleep deeply or lightly exhibits substantial genetic determi- nation (reviewed in Van Someren, 2021). In laboratory species, accruing evidence implicates activation of the pontine nucleus locus coeruleus (LC) in the reduction of arousal thresholds during sleep and in sponta- neous sleep-to-wake transitions (reviewed in Oserio-Förero et al., 2022). As the source of diffuse noradrenergic modulation in most of the forebrain, the LC plays a central role in alertness, vigilance, and interoceptive alarms (Aston-Jones, 2005; Aston-Jones et al., 1986, 1991; Aston-Jones and Cohen, 2005; Berridge and Foote, 1991; Berridge and Waterhouse, 2003; Foote et al., 1983, 1991; Page et al., 1993; Pieribone and Aston-Jones, 1988; Poe et al., 2020; Usher et al., 1999; Valentino et al., 1983). Sometimes called a sympathetic ganglion in the brain, the LC-noradrenergic axis has long been a source of interest to PTSD

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researchers (Bremner et al., 1996a, 1996b; Morgan et al., 1995; Southwick et al., 1993, 1999), if one without commensurate support from clinical trials of noradrenergic agents (Krystal et al., 2017, 2018; Neylan et al., 2006; Raskind et al., 2018) (but see Raskind et al., 2006; Raskind et al., 2007; Raskind et al., 2003). Relevant here is that Van Someren (2021) has recently advanced a model of primary insomnia in which excess central noradrenergic drive plays a central role.

A noteworthy feature of the adaptations catalogued by Lima and colleagues is that they “preserve some or most of the functions of sleep” (Lima et al., 2005, pp. 9) and so can be sustained for long periods. The sleep disturbances associated with PTSD, like primary insomnia, and those of work-related circadian misalignment are, on acute and sometimes, unfortunately life-long. McEwen has identified chronic sleep disturbance as a source of “allostatic load” (McEwen, 2006; McEwen and Karatsoreos, 2015), a constellation of biological adaptations to persistent stress that can be sustained for long periods but eventually lead to chronic diseases. PTSD (Beristianos et al., 2016; Boscaino, 2008; Brudney et al., 2015; Edmondson et al., 2013; Gilsanz et al., 2017; Koenen et al., 2017; Nicter et al., 2019; O’Donnell et al., 2021; Sommer et al., 2021; Summer et al., 2016; Wolf and Schnurr, 2016), primary insomnia (He et al., 2017; Hu et al., 2021; Sofi et al., 2014) and circadian misalignment (Lin et al., 2015; Su et al., 2021; Wei et al., 2021) are all associated with elevated rates of CVD. After the review of studies, we will reconsider whether observed features of ANS function during sleep in PTSD support a framework in which some portion of sleep’s restorative function are sacrificed in favor of arousability.

2. Studies of ANS status in PTSD

Roughly paralleling waking and sleep, the ANS is comprised of two branches, the sympathetic nervous system (SNS), which adjusts metabolic support for motivated behavior, and the parasympathetic nervous system (PNS), which orchestrates a range of short- and long-term downregulatory and restorative functions. Comprehensive texts detail the central and peripheral neuroanatomies of the sympathetic and parasympathetic branches in rat (Paxinos, 2015) and human (Mai and Paxinos, 2012). Clinical assessment of ANS function during waking utilizes a number of challenges including the Valsalva maneuver, paced breathing, rapid postural change, and cold pressor (reviewed in Zygmont and Stanczyk, 2010). In PTSD, studies have also assessed autonomic responses to trauma reminders (Bauer et al., 2013), and begun to link the outcomes of such assessments to CVD risk (e.g. Clausen et al., 2016). Such ANS challenges are clearly incompatible with sleep. The literature provides us with two broad avenues for measuring ANS function during the sleep period. One approach focuses on blood pressure (BP) and the other on HR variability. Both methods have been employed in large samples outside of the PTSD literature and hold promise for efforts to link sleep behavior and CVD in this diagnosis.

3. Non-dipping of blood pressure during sleep

During stable uninterrupted NREM sleep, sympathetic nervous system (SNS) drive is substantially reduced (Guazzi et al., 1968; Somers et al., 1993; Trinder et al., 2012; Zemaitietε, 1984). The SNS plays a prominent role in BP control through regulating cardiac contractility and exclusively innervating the smooth muscles determining peripheral vascular resistance (Joyner et al., 2008; Joyner and Limberg, 2014; Raven and Chaplaε, 2014). The development of ambulatory BP monitoring (ABPM) has enabled the acquisition of BP during the sleep period. ABPM is an extension of clinic-based BP testing that uses a wearable device programmed to perform scheduled cuff inflations on the arm and automated processing of heart sounds. BP values are stored for later download and analysis. In most people, the reduction or “dip” in mean BP during the night exceeds 10%, with “non-dipping” defined as a failure of BP to decrease by 10% below mean waking levels. There is no consensus as to whether this criterion should be applied preferentially to systolic, diastolic, or mean arterial BP (the average BP over the cardiac cycle). Non-dipping of BP during sleep has been shown to be associated with blunted reduction in urinary epinephrine and noradrenaline, and with increased reactivity of BP to exogenous isoproteinol, an α1-adrenergic agonist (Darr et al., 2016; Sherwood et al., 2002). Kastrup et al. (1993) authored the first report that non-dipping of nocturnal BP was associated with congestive heart failure. Since that time, BP non-dipping during sleep has proven so strong a predictor of incident CVD that some have suggested it should replace both clinic and day-time ambulatory BP measurements in treatment decision-making (Cho, 2019; Kwon et al., 2020; Palatini et al., 2013, 2019, 2022). One advantage of BP dipping as a measure is that it incorporates a within-subject control. Studies of waking BP in PTSD lacking such a control have been inconclusive (Fu, 2022). While SNS drive is reduced during NREM sleep, REM sleep is punctuated by bursts of sympathetic outflow detectable in skeletal muscles and associated with transient increases in both HR and BP (Somers et al., 1993). It would therefore be optimal to distinguish NREM and REM when recording BP dipping during sleep, but measurement issues discussed below make this infeasible. It can be seen that, by virtue of its reliance on the SNS, this route of approach to ANS regulation is aligned with PTSD researchers’ pre-existing focus on central noradrenergic (NA) mechanisms. It is not surprising, then, that studies of ANS function during sleep in PTSD began here.

Studies of BP dipping in PTSD are summarized in Table 1. The first study bearing on BP dipping during in sleep in PTSD was performed by Buckley et al. (2004) in an all-male sample of Vietnam war veterans with a mean age 50 years, 19 of whom were diagnosed with PTSD versus, and 17 of whom were not. Participants were screened for beta-blockers, tricyclic antidepressants, psychosis, and current treatment for alcohol or substance dependence. Sleep measurement was via activity logs. The 10% dipping criterion was not specifically evaluated; however, Buckley et al. observed no diagnosis by time of measurement interaction. Though the formal assessment of BP dipping, per se, was not the goal of their study, the result must be considered negative. Mellman et al. (2009) studied BP dipping explicitly in a sample of 30 African-Americans, mean age 20, 60% female, all of whom had been exposed to civilian trauma. Their focus on African-Americans was responsive to the well-established excess of CVD mortality in this sub-population (Post et al., 2022) largely associated with social factors (Shah et al., 2022). African-Americans are also at elevated risk for trauma (Roberts et al., 2011) and PTSD (Alegria et al., 2013). Fifteen participants met full or partial criteria for current or lifetime PTSD and 15 were free of lifetime PTSD. Mean arterial pressure was obtained every 30 min contrasting wake and sleep periods as reported via sleep diary. Non-dipping was found to be more frequent in the PTSD group than in controls. Ulmer et al. (2013) compared sleep period BP to wake period BP in 61 civilian women diagnosed either with current PTSD or with no history of PTSD, current or lifetime. Sixty-three participants were excluded after measurement because fewer than three night-time or fewer than ten day-time non-artifactual BP readings had been obtained. The frequency of non-dipping did not vary significantly by PTSD diagnosis. Finally, Cave and Hough (2019) performed a retrospective chart review of 470 ambulatory BP monitoring studies and failed to find an association between a chart diagnosis of PTSD and systolic BP measured across wake and sleep. It was unclear from their report how sleeping status or the sleep period was established.

Only one of four published studies reviewed above found evidence of excess BP non-dipping during sleep in PTSD. The sole positive result was observed in a sample of African-Americans who may not generalize to the broader population of persons with PTSD. Reliance on cuff inflation limits the number of measurements that can be made without disturbing sleep (Domsdale et al., 1993; Gaffney et al., 2021; Staats et al., 2020; Tan et al., 2020), perhaps reducing the reliability of the dipping measure and impairing statistical power. On the other hand, applying strict data quality criteria can lead to large numbers of exclusions perhaps biasing a sample away from more severe cases. Though these issues may be difficult to resolve, it would be premature to rule out further research
analyses. Shaffer and Ginsberg (2017) have reviewed the more expirations concurrently derived from a respiratory signal; howev
spectrum of heart rate variability (HRV), which includes additional
approximately 0.15
imperfect method involves a frequency transformation of the
mated by quantifying inter-beat-inter (IBI) variation over inspirations
relationship between non-dipping and adverse CVD outcomes.
4. Reduced high-frequency heart rate variability during sleep
The second major approach to measuring ANS function in sleep is to estimate PNS drive by quantifying variation in HR or heart period (HP) over the respiratory cycle. The sinoatrial node of the heart receives co-active inputs from both the SNS and PNS, the latter via the vagus nerve. When vagal input is blocked by the anticholinergic agent, atropine, resting HR is approximately 100 beats per minute (Pyetan et al., 2003), indicating that HR/HP is under tonic parasympathetic control. During inspiration, vagal input is gated so that HR/HP variation over the respiratory cycle alternates between its set point and zero, generating the “respiratory sinus arrhythmia” (RSA). Detailed expositions of the full spectrum of heart rate variability (HRV), which includes additional lower-frequency components, have been published (Bernston et al., 1992, 1993, 1994, 1997; Cacioppo et al., 1994). Ideally, RSA is estimated by quantifying inter-beat-inter (IBI) variation over inspirations and expirations concurrently derived from a respiratory signal; however, this requires recording and analyzing a second signal and cross-signal analyses. Shaffer and Ginsberg (2017) have reviewed the more easily-implemented time- and frequency-domain methods that have been developed to quantify HRV and RSA based on ECG alone. A popular if imperfect method involves a frequency transformation of the (resampled) HP time series, and summation of the coefficients over that section of the HRV spectrum corresponding to respiration, approximately 0.15–0.40 Hz (or 9–24 breaths/min; Bernston et al., 2007; Grossman, 1992; Grossman and Taylor, 2007). Because “heart rate variability” is the most common terminology used to refer to this family of phenomena in both the scientific and lay literatures even when RSA is the actual target, this review will default to HF-HRV with the goal of balancing precision and readability.2
It is now well-established that the brain regions involved in the regulation of HF-HRV include the anterior cingulate cortex (ACC: Chang et al., 2013; Crichtley et al., 2000; Gianaros et al., 2005; Jennings et al., 2016; reviews in Mulcally et al., 2019; and Thayer et al., 2012), a brain region also implicated in PTSD. An influential model of neural circuit dysfunction in PTSD posits inadequate inhibitory regulation of the amygdala by the ACC (Admon et al., 2013; Bremner et al., 2005, 2008; Fitzgerald et al., 2018; Herringa et al., 2013; Shin and Liberzon, 2010). Consistent with this framework is evidence of structural compromise of ACC in PTSD (Hinojosa et al., 2019; Karl et al., 2006; Rauch et al., 2003; Rinne-Albers et al., 2017; Rogers et al., 2009; Thomaes et al., 2010; Woodward et al., 2006, 2013; Yamase et al., 2003). Like BP non-dipping, reduced amplitude of HF-HRV is associated with elevated rates of CVD (reviewed in Thayer and Lane, 2007). A recent meta-analysis concluded that PNS drive to the heart during waking is compromised in PTSD (Campbell et al., 2019). These authors analyzed 67 published and unpublished studies that enrolled 6689 participants in comparisons of PTSD and control samples and observed the following effect sizes across different indices of waking parasympathetic drive, HR-HRV: −0.26, RMDD: −0.39, pNN50: −0.66, and SDNN: −0.40. The current review will include three studies included in Campbell et al. but not identified as involving measurement during sleep.
Sleep is an excellent time to obtain RSA and HF-HRV estimates as these are dependent on stable respiration not characteristic of movement or speech. This literature is summarized in Table 2. Woodward et al. (2009) performed an in-home study of 59 community-residing middle-aged, mostly female sample screened using laboratory PSG for obstructive sleep apnea (OSA) and periodic limb movement disorder (PLMD). Users of hypnotics or beta-blocking medications were also excluded. Participants were tested in their homes for an average of 12 nights using mattress actigraphy, a methodology employing accelerometers embedded in a mattress topper to detect the thoracic pulse (AKA kinetocardiogram or esimocardiogram; Woodward et al., 2007), as well as respiration, snoring, and body movement. After controlling for age and residual sleep apnea (i.e. variation in the range below 10 events/hour), HF-HRV during the sleep period was found to be lower and HR higher in participants diagnosed with PTSD or PTSD with comorbid panic disorder compared those with panic disorder alone or no mental illness. Kobayashi et al. (2014) obtained one night of ambulatory Holter-monitored ECG and actigraphy from a sample of 38 African-Americans, mean age 23, approximately two-thirds female, all of whom had been exposed to civilian trauma. They contrasted 20 participants who met full or partial criteria for either current or lifetime PTSD with 18 “resilient” participants who had been exposed to “high-impact trauma” but never met criteria for PTSD. Exclusions were imposed for sleep apnea assessed via laboratory PSG, obesity, medications which could affect BP, excessive caffeine or alcohol use, and phase-shifted sleep. Based on spectral analysis of ECG, the participants with PTSD were found to exhibit significantly lower amplitude of HF-HRV than resilient participants during an actigraphically-defined sleep period. Bertram et al. (2014) obtained 24-h ambulatory ECG recordings from a mixed sample of US military veterans and non-veterans, all male. Forty-five met criteria for current PTSD and 33 were free of lifetime PTSD. Participants were screened for psychosis, recent substance abuse, beta-blocking medication, and more than mild traumatic brain injury. Neither HF-HRV nor HR exhibited a significant group by

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2 Among the many methods of quantifying cardiac inter-beat interval variation, only some are preferentially sensitive to variation in the respiratory band, RMSSD, the root mean square of successive differences between inter-beat intervals, pNN50, the percentage of neighboring normal intervals differing by more than 50 ms, and spectral power in the respiratory band (Shaffer and Ginsberg, 2017).

3 An important caveat is that most 24-h Holter-based studies in the cardioligic literature have employed a measure of HRV, the standard deviation of “normal” inter-beat intervals (often labeled SDNN), that does not exclusively quantify vagal drive (Shaffer and Ginsberg, 2017).

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| Authors | Study Type | N | Subgroups | Subgroup N’s | Age (mean) | % Female | Race/Ethnicity | Trauma type | Sleep Measure | Results |
|---------|------------|---|-----------|-------------|-----------|---------|--------------|-------------|--------------|---------|
| Buckley et al. (2004) | observational | 36 | PTSD Control | 19/17 | 50 | 0% | 25% non-white | combat | diary | PTSD–Controls |
| Mellman et al. (2009) | observational | 30 | PTSD + Resilient | 15/15 | 20 | 60% | African-American | various | diary + actigraphy | PTSD > Controls |
| Ulmer et al. (2013) | observational | 124 | PTSD-only | 32/40/52 | 38 | 100% | 49% Caucasian, 34% African-American | various | diary | PTSD–Controls |
| Cave and Hough (2019) | chart review | 470 | PTSD Control | 73/397 | 67 | UR | UR | UR | UR | PTSD–Controls |

Table 1
Summary of studies of blood pressure dipping during the sleep period in PTSD.
time of measurement interaction. Rissling et al. (2016) collected 24-h Holter monitor recordings from a large (n = 209) mixed civilian-veteran sample of young adults, 18–39, approximately 50% female. Screening exclusions for psychiatric and medical conditions were substantial but did not include objective screening for sleep apnea. Participants with PTSD were over-sampled. Using concurrent actigraphy, time periods were labeled as active, rest, or sleep. Complex demodulation, a method robust to respiratory rate variability (Gilfriche et al., 2018), was used to calculate HRV power in the respiratory band. That power decreased as PTSD severity increased but only when measured during periods labeled “sleep” and not in periods labeled “rest” or “active”.

The following two studies are distinguished from those above by employing PSG which allowed them to report on associations with rapid eye movement (REM) versus non rapid eye movement (NREM) sleep. Kobayashi et al. (2016) compared 38 participants with PTSD to 33 resilient participants free of lifetime PTSD despite exposure to high-impact civilian trauma. All participants were African-Americans. Approximately two-thirds were female. Exclusions were imposed for sleep apnea assessed on a screening night in the laboratory, current substance abuse, positive urine Toxicology, and current psychiatric disorder other than PTSD, Phobia, GAD, or Depression. The investigators employed a spectral analysis method robust to artificial inter-beat intervals (Clifford and Tarassenko, 2005). No main effects of group on HF-HRV or HR were observed, a surprising result given their earlier positive findings obtained in a similar sample and similar methods (Kobayashi et al., 2014). They did observe novel associations with sleep stage, however, as REM-NREM differences in HR-HRV were elevated in PTSD, a finding pertinent to the question of whether REM sleep SNS drive is elevated in this disorder. Ulmer et al. (2018) also employed laboratory PSG enabling analysis of effects of sleep stage. Their study of a largely male sample (87%) was collated from four different parent studies of recent US military veterans and active-duty personnel and contrasted those with (n = 29) and without PTSD (n = 32). Common across all four studies were exclusions for sleep apnea based on a screening PSG, beta-blockers, psychosis, current substance abuse, and positive toxicity screen. ECG was sampled at 1000 Hz and analyzed using commercially-available software (Mindware) applied to manually-extracted, 2-min epochs of NREM and REM sleep free of artifact and intercurrent wake. Up to four NREM-REM cycles were sampled in this manner, though the total numbers of epochs of NREM and REM sleep were not reported. HF-HRV power in REM and NREM sleep were modeled separately. Ulmer et al. found lower HF-HRV in the PTSD sample but only during NREM sleep. This pattern did not interact significantly with sleep cycle.

Four of the six between-group comparisons just reviewed found evidence of reduced HF-HRV amplitude during sleep in PTSD. Before moving on, we will turn to two within-group correlational studies from the Mellman group which assessed ANS status during sleep in relation to subjective estimates of environmental threat. Mellman et al. (2018) studied a sample of 136 urban-dwelling African-American adults, mean age 23, 54% female. All had been exposed to civilian interpersonal violence. The sample was heterogeneous as to PTSD diagnosis (16% current PTSD, 15% partial PTSD, 21% remitted PTSD, 17% trauma-exposed only, 32% non-trauma-exposed). In this sample, trend-level covariance was observed between a ratio measure of BP dipping and a self-report measure of environmental risk, the “Neighborhood Disorder” subscale of the City Stress Index (Evatt and Suchdaly, 2002). Employing a subset of the same sample (n = 85) held to a stricter apnea screening criterion (apnea-hypopnea index <5 events/hour), Mellman et al. (2018) observed normalized HF-HRV to significantly covary - inversely - with the same measure of subjective environmental threat. These last two studies align with the between-groups studies reviewed above in highlighting PNS over SNS adaptations. They also directly support the proposition that human sleep, like that of other animals, adapts to threat, but they point to effects on PNS rather than SNS regulation.

### Table 2

Summary of studies of high-frequency heart rate variability during the sleep period in PTSD.

| Authors            | Study Type | N    | Subgroups     | Subgroup N’s | Age (mean) | % Female | Race/ Ethnicity | Trauma type                | DV                        | ACT vs PSG | Results               |
|--------------------|------------|------|---------------|--------------|------------|----------|----------------|---------------------------|--------------------------|------------|-----------------------|
| Woodward et al. (2009) | observational | 59   | PTSD          | 13/13/ 22/11 | 42         | 67%      | UR             | various civilian traumas including natural disaster physical assault sexual assault | HF-HRV                   | ACT        | PTSD < Controls        |
|                    |            |      | Panc + PTSD   |              |            |          |                |                           |                          |            | PTSD + Panic < Controls |
|                    |            |      | Control       |              |            |          |                |                           |                          |            | Panic = Controls       |
| Kobayashi et al. (2014) | observational | 38   | PTSD          | 20/18        | 23         | 39%      | African-American | HF-HRV ‘normalized’       | ACT         | PTSD < Controls        |
|                    |            |      | Resilient     |              |            |          |                |                           |                          |            | PTSD = Resilient       |
| Bertram et al. (2014)  | observational | 110  | PTSD          | 56/54        | 53         | 0%       | 16% Caucasian 44% African-American 27% Other | combat physical assault sexual assault | HF-HRV       | ACT                    |
|                    |            |      | Control       |              |            |          | 45% Caucasian 1% Other |                           |                          | Act         | PTSD = Controls        |
| Rissling et al. (2016) | observational | 209  | continuous    | N/A          | 29         | 50%      | UR             | HF-HRV estimated via complex demodulation | ACT         | high PTSD < low PTSD   |
|                    |            |      | index of PTSD |              |            |          |                |                           |                          |            |                       |
| Kobayashi et al. (2016) | observational | 71   | PTSD          | 38/33        | 21         | 59%      | African-American | HF-HRV estimated via Lomb periodogram | ACT        |                       |
|                    |            |      | Resilient     |              |            |          |                |                           |                          |            |                       |
| Ulmer et al. (2018)   | observational | 62   | PTSD          | 29/33        | 32         | 13%      | 89% Caucasian 11% Other | HF-HRV                  | PSG        | PTSD (NREM sleep only) |
|                    |            |      | Control       |              |            |          |                |                           |                          |            |                       |
5. Summary of studies exploring ANS status during sleep in PTSD

The failure to find strong evidence of SNS adaptation in the studies reviewed above is surprising in light of the role central noradrenergic “overdrive” has been thought to play PTSD (Charney and Bremer, 1999; Morgan et al., 1995; Naegeli et al., 2018; Southwick et al., 1993; van der Kolk and Fisher, 1993), in primary insomnia (Van Someren, 2021), and in arousal and vigilance (Aston-Jones et al., 1991, 2001). What adaptive advantage might be conferred by reduced peripheral PNS drive to one sleeping under threat? There is no ready answer to this question. No studies have considered associations between PNS drive during sleep and arousal thresholds or the state of temporary cognitive and motor impairment immediately following awakening known as sleep inertia. Is nevertheless intriguing that Miller et al. (2018), in a sample of military veterans with PTSD, found HF-HRV to be lower on nights followed by a morning report of a nightmare. This question might be addressed further in translational studies which could employ direct measurement of vagal efference. It is also possible that reduced HF-HRV is simply a correlate of one or more adaptations promoting arousability. Whatever its source, it is clear that downregulation of vagal influence during sleep in PTSD could have accumulating negative impacts on a wide range of organ systems which could then interact with other sources of risk to promote a diversity of late-life disease conditions (Bonaz et al., 2018; Brudey et al., 2015; Koraishi et al., 2021; Thayer et al., 2021; Thayer and Sternberg, 2006; Thurston et al., 2020).

6. Guidance for future studies: opportunities and caveats

A literature comprising just twelve studies cannot support firm conclusions regarding ANS status during sleep in PTSD, and more work will need to be done in this area to understand its relevance to long-term medical comorbidities associated with PTSD. The current literature does provide guidance for future studies. All considered age which strongly impacts both HF-HRV (De Meersman and Stein, 2007) and BP non-dipping (Ben-Dov et al., 2007; Cuspidi et al., 2018). All considered BMI. The Mellman-Kobayashi studies have promoted the consideration of race as a moderator of ANS status during sleep in PTSD (Mokwatsi et al., 2019). As noted above, African-Americans are at elevated risk for trauma, PTSD, and CVD. Fonkoue et al. (2020) have argued that sex differences in ANS function in PTSD deserve additional research.

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For the calculation of HF-HRV, robust, multi-platform software packages and toolboxes with long lineages are now available at no or low cost (https://rhrv.r-forge.r-project.org/; https://physionet.org/content/pcst/1.0.0/; https://www.kubios.com/hrv-premium/). Their use could promote comparability of absolute values across studies. We may note a caveat and an opportunity pertaining to the utility of LF-HRV, alone, or as a component of “normalized” HF-HRV. While supported in 1996 as an index of sympathetic input to the heart (“Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology,” 1996), recent studies have challenged this proposition (Martelli et al., 2014; Moak et al., 2009; Reyes del Paso et al., 2013). Insofar as HF-HRV, only, is of interest, it may be useful to consider IBI epoch length. Five minutes epochs are necessary only for the estimation of the ultra-low component of HRV, and 2 min, only, for the estimation of the now-depreciated LF-HRV. A 1-min epoch will typically include ten or more cycles of respiration, and so may be sufficient for the valid estimation of HF-HRV. Using such a short epoch to calculate the HRV spectrum treads close to the lower limit; but sleep contains hundreds of 1-min epochs which are more likely to be artifact-free and much easier to co-register with sleep staging.

In light of the relative accuracy of HR estimates from inexpensive PPG-based devices, it is noteworthy that HR, like BP, dips during the night. Using the criterion of a 10% drop relative to waking HR, Ben-Dov et al. (2007) observed HR non-dipping to be associated with a 34% increase in all-cause mortality in an at-risk sample referred for ambulatory BP monitoring. Cuspidi et al. (2018) observed a 13% increase in adverse CVD outcomes over a 12-year follow-up in subjects with the smallest dips in HR. Baka and Simko (2021) have provided a narrative review of HR dipping/non-dipping as an index of CVD status and its relevance to other disease states. Low-cost, low-burden HR and HF-HRV recording devices should facilitate the large-sample, prospective studies that will test putative links between PNS drive during sleep and late-onset chronic disease in PTSD. Such studies could estimate HR dipping and HF-HRV simultaneously as the information provided by these metrics are likely non-redundant.

7. Concluding remarks

Though the list of studies examining ANS status during sleep in PTSD is currently short, the field appears poised for a new generation of...
studies employing devices enabling the collection of ANS-relevant indices in larger samples and over longer periods. Such studies may provide further insights into the etiologies of both the known and as-yet-unknown long-term health risks of PTSD. It is also possible that they will be of use in the sleep clinic. A growing literature supports the ability of cognitive-behavioral treatment for insomnia (CBT-I), originally developed to address primary insomnia (Morin, 2004), to effectuate treat insomnia in PTSD (Kanady et al., 2018; Kuhn et al., 2022; Laurel Franklin et al., 2018; Margolies et al., 2013; Pigeon et al., 2022; Ranney et al., 2022; Talbot et al., 2014). The primary outcomes of these interventions are improvements in subjective sleep quality and increases in diary-reported sleep efficiency through sleep consolidation. Objective validation of increased sleep efficiency is rare, and actigraphy may be insensitive to the subtle sleep adaptations associated with PTSD (Lewis et al., 2020). Palesh et al. (2019) have shown that a brief behavioral sleep intervention can increase post-sleep HRV in cancer patients. Elevating HF-HRV during sleep, re-establishing the “cardiovascular holiday” (Trinder et al., 2009), may be an appropriate target for behavioral sleep interventions in PTSD. If feasible at all, this might result from the same sleep restriction interventions that consolidate sleep; or, it may respond to more formal titration and scheduling of physical activities and meals (Gupta et al., 2022), and other ANS-relevant, pre-sleep behaviors than is typically incorporated into the sleep hygiene components of CBT-I.

Disclaimer

The opinions expressed in this publication are those of the author. They do not purport to reflect the opinions or views of the Department of Veterans Affairs.

CRediT authorship contribution statement

Steven H. Woodward: Am the sole author of this review.

Declaration of competing interest

The author holds patent 10856800 for a “Portable polysomnography apparatus and system” awarded 12/8/2020 and assigned to the Department of Veterans Affairs which is unlicensed.

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