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PTSD-related hyperarousal assessed during sleep

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Abstract

Posttraumatic stress disorder is widely understood to include "persistent symptoms of increased arousal." This presumption has rarely been tested under conditions in which effects of anticipatory anxiety could be ruled out. In this study, heart rate and electroencephalogram spectral power were assessed during sleep, a state free of most sources of artifact contaminating indices of tonic arousal. Fifty-six unmedicated nonapneic Vietnam combat-related inpatients with posttraumatic stress disorder (PTSD) and 14 controls spent 3 or more nights in the sleep laboratory during which their electrocardiograms and electroencephalograms were continuously recorded. Heart rate and electroencephalogram spectral power were quantified continuously off-line and averaged by sleep stage over all postadaptational nights. Sleep heart rate exhibited no group differences and no covariation with the severity of subjective hyperarousal reported by PTSD patients. PTSD patients exhibited a trend toward reduced low-frequency electroencephalogram spectral power during nonrapid-eye-movement (NREM) sleep. This reduction was significant during slow-wave sleep in those subjects producing scoreable slow-wave sleep. The relationship of rapid-eye-movement (REM) beta-band power to NREM beta-band power was different in PTSD patients and controls, with the patients exhibiting more beta in REM versus NREM sleep than controls. In patients, NREM sleep sigma-band electroencephalogram spectral power exhibited a positive correlation with subjective hyperarousal. Finally, a novel and surprisingly strong inverse correlation between REM-NREM sleep heart rate difference and REM percent of sleep was observed in PTSD patients only. In summary, peripheral and central measures of tonic arousal during sleep demonstrated contrastive relations to PTSD diagnostic and symptom status. The data suggest that more consideration should be directed to mechanisms of central arousal in PTSD. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Hyperarousal; REM sleep; PTSD

1. Introduction

According to current conceptualizations, a diagnosis of posttraumatic stress disorder (PTSD) requires at least two "persistent symptoms of increased arousal" [1]. This suggests that PTSD should involve measurable activation of one or more physiologic arousal systems. Some data support this concept. Trauma-cue reactivity studies have found elevated baseline heart rate (HR) in PTSD consistent with tonic sympathetic nervous system arousal [2–4]. However, these findings have been based upon recordings only a few minutes in length made immediately prior to the presentation of trauma-related cues, and so may reflect anticipation of exposure to such stimuli [5]. Such findings would then not reflect tonic autonomic arousal in PTSD, but rather experimentally operationalized "baseline" or pretest levels of arousal. Three studies have attempted to exclude anxiety associated with anticipation of explicit trauma cues from estimates of tonic or experimental baseline arousal. Two of these, a laboratory assessment [6] and a 24-h ambulatory monitoring study [7], failed to find evidence of baseline or tonic arousal elevation in PTSD. A third study assessed HR prior to a medical appointment and found evidence consistent with elevated baseline or tonic arousal in PTSD [8]; however, it is not clear that anticipatory anxiety was well-controlled.

Even less is known about measures of central nervous system arousal in PTSD. To our knowledge, only a single unpublished study has examined quantitative electroencephalographic (EEG) measures of tonic waking arousal in PTSD. In that study, Paige et al. [9] found no EEG spectral differences between PTSD patients and controls. Polysomnography provides an excellent opportunity for extended assessments of both autonomic and central nervous system arousal under conditions of reduced physical activity and external stimulation. While prior sleep studies of PTSD patients [10–25] have naturally involved traditional sleep stag-

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ing, none has incorporated quantitative analysis of the EEG. Traditional sleep staging itself relies upon qualitative analysis of spectral features of the EEG, with all sleep stages defined to some degree by reference to the dominant frequencies and amplitudes of the EEG signal. For example, slow-wave sleep is characterized by a predominance of high-amplitude sub-4 Hz activity in the EEG, and REM sleep by a relative predominance of high-frequency EEG activity similar to that of waking [26]. Quantitative spectral analysis of the EEG offers a fine-grained analysis of continuous features of the signal through which small but significant between-subjects and between-groups differences can be distinguished.

The general observation dating back to the first recordings of EEG and by both manual and quantitative analysis of the EEG is that greater cerebral and behavioral arousal is associated with relatively less low-frequency power and relatively more high-frequency power in the EEG [27]. The level of cerebral arousal is principally controlled by diffuse modulatory systems originating in brain stem nuclei. These include the cholinergic parabrachial and pedunculopontine nuclei [28–30], the noradrenergic nucleus locus coeruleus [31–33], the serotonergic raphe nuclei [34,35], the dopaminergic substantia nigra [36] , as well as histominergic tuberomammillary nucleus of the hypothalamus [37] and the cholinergic nucleus basalis/substantia inominata complex [38]. Caveats, which need to be observed within this formulation, will be addressed as necessary below.

2. Materials and methods

2.1. Subjects

Potential subjects with evidence of medical disease and/or chronic pain which could influence sleep were excluded, as were individuals with risk factors for obstructive sleep apnea (frequent snoring, obesity, or partner reports of interrupted breathing during sleep). Subjects were also excluded from analysis if, on any of the laboratory nights, there was evidence of sleep apnea as indicated by an apnea/hypopnea index greater than 10 events per hour or a periodic limb movement arousal index of greater than 10 events per hour. Subjects with heavy use of alcohol (intake greater than 5 oz. per day for any 30 consecutive day period during the preceding 6 months) were excluded. All subjects were studied off medications, and had been abstinent from alcohol for at least 60 days prior to polysomnographic testing. PTSD patients were studied a mean of 38 days after admission to the inpatient unit. For six subjects who were withdrawn from psychotropic medication while on the unit, washout periods exceeded four half-lives.

Combat-related PTSD inpatient subjects were recruited from the Specialized Inpatient PTSD Unit at the Veterans Administration Medical Center, Palo Alto. All were inpatients at the time of polysomnography. A total of 56 individuals met current DSM-IV criteria for current PTSD as the primary diagnosis. They were all male, and ranged in age from 40–48 years (mean age = 45.0, SD = 2.8). As summarized in Table 1, comorbid diagnoses were common: 86% met criteria for recurrent major depressive disorder, 21% for panic disorder, 7% for agoraphobia, without history of panic disorder, 16% for social phobia, 7% for obsessive compulsive disorder, and 7% for simple phobia. Comorbid histories of alcohol abuse and/or dependence (71%) and history of illicit substance abuse/dependence (64%) were also common. On average, PTSD patients met criteria for 2.4 of the principal comorbid diagnoses (MDD, alcohol abuse/dependence, nonalcohol abuse/dependence, panic disorder). These rates of comorbidity are typical of chronic, severe PTSD patients [12–14,39].

Controls were 14 individuals (mean age = 43.8, SD = 6.2) recruited from the VA hospital community. Ten had a history of combat exposure in Vietnam and four were trauma free. Two had a history of alcohol and/or substance dependence but were in remission for periods in excess of 5 years.

2.2. Procedures

All subjects gave informed consent. Both patients and controls underwent the Clinician Administered PTSD scale (CAPS; [40]), the Combat Exposure Score (CES; [41]), and the Beck Depression Inventory (BDI; [42]). In addition, the Structured Clinical Interview for the DSM-III-R (SCID; [43]) was administered to all subjects. The CAPS was designed to provide information directly correspondent to the DSM-III-R diagnostic criteria for PTSD while additionally distinguishing the frequencies and intensities of criterial symptoms, and gathering systematic information on important noncriterial symptoms such as guilt. For the purposes of this study, the CAPS D-criterion subscale score, a measure of subjective hyperarousal, was obtained by summing all frequency and intensity ratings for PTSD D-criterion symptoms. The CES is a validated measure of the severity of an individual's exposure to direct combat and other war zone stressors. The BDI is a measure of dysphoria that has been used in a wide array of study populations. All psychometric data were collected by individuals blind to the polysomnographic data.

Subjects slept 3 or 4 nights in the sleep laboratory located immediately adjacent to the in-patient unit. Schedul-

Table 1
Comorbid diagnoses by group

	PTSD	Controls
MDD—recurrent	86%	29%
MDD—current	68%	7%
Panic disorder	21%	0
Agoraphobia w/o PD	7%	0
Social phobia	16%	0
OCD	7%	0
Simple phobia	7%	0
ETOH	71%	21%
Other substance A/D	64%	14%

ing was arranged to accommodate subjects' typical bed times. In-patient subjects terminated their sleep at will, but not later than 0600 h the standard wake-up time for the in-patient treatment program. Control subjects also terminated their sleep at will. The recording montage included two channels of bipolar electro-oculogram (EOG), four channels of scalp EEG (F3, F4, Cz, and Pz referred to linked mastoids), mentalis and left anterior tibialis electromyograms (EMG), abdominal respiratory effect, ECG, and blood oxygen saturation. ECG was recorded using the "lead 1" derivation and filtered to 1 to 30 Hz prior to digitization. EOG and EEG were filtered to a 0.3 to 30 Hz bandwidth. EMG was filtered to a 30 to 300 Hz bandwidth, then rectified, and integrated over a 20-ms time-constant (yielding an effective upper band limit at 8 Hz). After conditioning, all physiologic data were digitized at 125 Hz and streamed to disk.

Manual sleep stage scoring of paper records was performed by trained sleep technicians following standard criteria [26] applied to 30-s epochs. EEG from the Cz site was used for sleep staging. Indices of sleep architecture extracted included time asleep, time in stages 1, 2, 3, 4, and rapid-eye-movement (REM) sleep, awake, and movement times. Through the use of a chart annotator and custom software, temporal registration of digital and paper data was maintained to an accuracy of ± 1 s throughout the night. This system allowed for comprehensive manual exclusion of artifactual and out-of-bed epochs from the digital record [29]. The per-subject values presented below are, in all cases, means calculated over all postadaptational nights.

A computer-implemented algorithm calculated R-R intervals and HRs for each 30-s epoch of sleep. EEG power was estimated per 30-s epoch via the Welch periodogram method [44]. That is, per 30-s sleep epoch a mean spectrum was calculated from 11 5-s 50% overlapping Hamming-windowed subepochs. The mean spectrum was decomposed into five bands, delta (0.2–3.8 Hz), theta (4–7.8 Hz), alpha (8–11.8 Hz), sigma (12–15.8 Hz), and wide-band beta (16–32 Hz). Power estimates (microvolts-squared/Hertz) were $\log_{10}$ transformed prior to statistical analysis. In the interest of brevity, the analyses presented below are limited to data obtained from the Cz site.

3. Results

Mean CES in the patients was 27 (SD 8), while for the combat-exposed controls it was 24 (SD 10.0). These scores did not differ significantly by t-test. The patient and control groups reported very different levels of dysphoria. Mean BDI score for the patient sample was 24 (SD 11), for controls, 7 [SD 7; $t(66) = 5.2$, $p < 0.00001$; BDI scores were missing for two controls).

Univariate ANOVAs were used to analyze between- and within-subjects effects on sleep architecture. Sleep architecture was generally comparable between PTSD patients and controls (see Table 2), with the exception that REM sleep percent of sleep was slightly but significantly higher in the PTSD patients [26.3 vs. 22.7%; $F(1, 68) = 4.8$, $p < 0.03$]. Within the PTSD sample, current comorbid MDD was not associated with significant effects upon minutes asleep, sleep efficiency, sleep latency, REM latency, REM sleep percent, or slow-wave sleep (SWS) percent [all $Fs(1, 68) \leq 1.0$]. When PTSD subjects were classified according to whether or not they had experienced a depressive episode, sleep architecture differences were generally absent, with the exception that patients denying past depression exhibited significantly more SWS, $F(1, 54) = 7.60$, $p < 0.008$. This is consistent with findings from a smaller sample [25]. In fact, the SWS amounts demonstrated by PTSD patients absent histories of recurrent depression were higher than controls' (17.3 vs. 10.5%, respectively), though not significantly so. (Differences in visually scored SWS percent between PTSD patients and controls remained insignificant when PTSD patients absent histories of depression were excluded.) Histories of alcohol or illicit substance abuse/dependence were not associated with significant effects on sleep architecture within the PTSD subsample [all $Fs(1, 68) \leq 1.0$].

Sleep HR as a function of group and sleep stage (REM versus NREM) is shown in Table 3. Tested via MANOVA, no significant sleep HR differences were detected between PTSD patients and controls, $F(2, 67) = 1.072$, NS; multivariate F-ratio approximated via Pillai Trace, which is exact in the two-group case [45]). The effect of sleep stage on HR, though small (approximately one beat per minute) was significant, $F(1, 68) = 13.4$, $p < 0.0005$. The interaction of group and stage on HR approached significance, $F(1, 68) = 2.17$, $p < 0.15$, with the difference between REM and NREM HR smaller in patients than in controls (0.77 BPM versus 1.8 BPM, respectively).

For the analysis of EEG data, three separate MANOVAs were performed: (a) one considering alpha, sigma, and beta band EEG across the whole night; (b) a second considering delta and theta band EEG for NREM sleep only; and a third (c) considering delta and theta band EEG during SWS sleep

Table 2
Sleep architecture in PTSD patients and controls

	PTSD		Controls	
	Mean	SD	Mean	SD
Time in bed	375	55	380	44
Minutes asleep	348	49	348	45
Sleep efficiency	91.9	4.2	91.0	4.5
Stage 1 min	36	17	46	23
Stage 2 min	189	47	187	36
Slow wave sleep min	31	9.3	35	30
REM sleep min	91	20	80	27
Stage 1 percent	10.4	4.1	13.3	6.8
Stage 2 percent	54.0	9.5	53.6	6.4
Slow-wave sleep percent	9.4	9.3	10.5	9.8
REM sleep percent	26.3*	5.3	22.7	6.4
Wake after sleep onset min	9.4	9.3	10.5	9.8

Standard deviations in parentheses.
*$p < 0.05$.

Table 3
Sleep heart rates in PTSD patients and controls

		NREM		REM	
	n	Mean	SD	Mean	SD
PTSD	56	62.8	8.0	63.6	7.5
Controls	14	62.1	8.6	63.9	8.7

Standard deviations in parentheses.

exclusively for those subjects (47 patients and 13 controls) producing more than 2 min of manually scored SWS per night, on average. These three methods allowed us to operationalize various definitions of delta sleep, and provided an alternative to excluding REM sleep epochs containing rapid-eye movements possibly contributing artifactually to delta and theta band power values.

In analysis (a), PTSD patients exhibited a significantly different multivariate profile of alpha, sigma, and beta EEG power values over NREM and REM sleep than did controls, $F(6, 63) = 2.37, p < 0.04$. Diagnosis did not interact with sleep stage, or with band, but participated in a three-way diagnosis by stage and band by interaction, $F(2, 67) = 6.19, p < 0.003$. Decomposition of this interaction indicated that beta band power varied over NREM versus REM sleep differentially in patients versus controls. That is, as depicted in Fig. 1, PTSD patients exhibited more REM beta power relative to NREM beta power than did controls, although all-night levels of beta were comparable across groups. As expected, the main effect of stage, $F(1, 68) = 11.84, p < 0.001$, and the stage × band interaction, $F(2, 67) = 6.68, p < 0.002$, were highly significant. The main effect of stage reflected generally lower total EEG power in REM sleep. Decomposition of the stage × band interaction indicated that sigma power was relatively high in NREM versus REM sleep. NREM sleep in our subjects consisted primarily of spindle-rich stage 2 sleep.

In analysis (b) considering low-frequency EEG over all NREM sleep, PTSD patients exhibited a trend towards reduced levels of delta and theta EEG power relative to controls, $F(3, 66) = 2.33, p = 0.08$. In analysis (c), focusing exclusively on manually scored SWS in those subjects who exhibited at least 2 min of SWS (47 patients and 13 controls), PTSD patients demonstrated significantly reduced delta and theta band EEG power, $F(3, 53) = 3.82, p < 0.015$. There was no interaction between group and band. Although proportionally fewer patients than controls exhibited at least 2 min of SWS, these rates were not significantly different, $\chi^2(1) = 1.51, p = 0.22$.

Within PTSD patients, the presence or absence of current depression was not associated with effects on sleep EEG power [all $Fs(1, 68) \leq 1.0$]. The same was true for the presence/absence of current depression [all $Fs(1, 68) \leq 1.0$], history of alcohol abuse/dependence [all $Fs(1, 68) \leq 1.0$], and history of substance abuse/dependence [all $Fs(1, 68) \leq 1.0$]. Notwithstanding, the apparently strong effect of recurrent depression on visually scored SWS, no analogous effects were observed on NREM delta power or on SWS delta power (in subjects with more than 2 min of SWS) in PTSD patients. (Over all subjects, the Pearson product-moment correlation of SWS percent and absolute delta band EEG power was $r = 0.56, p < 0.000001$. Within PTSD patients, this correlation was $r = 0.54, p < 0.0002$.)

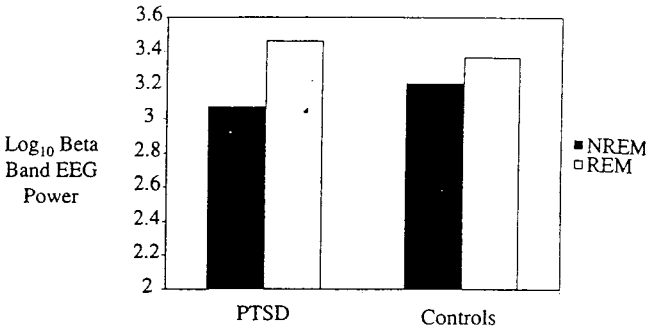

Fig. 1. Graph illustrating the group by sleep stage (NREM versus REM) by beta-band EEG power interaction.

Examination of relationships between psychometric measures of hyperarousal and depression and polysomnographic measures of autonomic and central nervous system arousal indicated that HR in both REM and non-REM sleep was associated with dysphoria as indexed by the BDI ($r = 0.38, p < 0.004$ for REM; $r = 0.37, p < 0.005$ for non-REM). This replicated findings obtained in a smaller sample in our laboratory [25]. After partialing out the linear effect of BDI, correlations between sleep HR and CAPS D-criterion severity were actually negative, although not significantly different from zero ($r = -0.15$, and $r = -0.18$ for REM and NREM, respectively). Sleep EEG power was generally uncorrelated with CAPS D-criterion severity. A salient exception to this pattern was non-REM sigma band power, which was positively correlated with D-criterion severity at a conservative significance level ($r = 0.409, p < 0.002$; Bonferroni-protected $\alpha = 0.0055$).

A final exploratory data analysis examined the interaction of measures of autonomic and central nervous system arousal. This was undertaken by correlating the REM-NREM differences in beta-band EEG power and HR with measures of subjective symptomology and sleep architecture. The impetus for this analysis was the observation of parallel interactions between diagnosis and stage on beta-band power and HR, the former significant, and the latter approaching significance. Insofar as REM and NREM sleep represent distinct regimes of central and peripheral arousal regulation, differences in HR and EEG spectral power drawn exclusively from those states might be expected to carry information. In particular, NREM and REM sleep are characterized by contrastive levels of central noradrenergic [46] and peripheral sympathetic activity [47], both domains of interest in discussions of PTSD arousal dysregulation [48]. A question of interest then is whether state differences in arousal metrics covary systematically with symptomol-

ogy. An attractive feature of this analysis is that REM-NREM difference scores eliminate important sources of nuisance variance associated, for example, with body mass and head size.

Within both PTSD patients and controls, the REM-NREM beta power difference were unrelated to CAPS D-criterion severity, to BDI, or to any of the sleep architecture parameters examined. In PTSD patients, REM-NREM HR differences proved to be unrelated to CAPS D-criterion severity and to BDI; however, REM-NREM HR was strongly and negatively related to REM percentage of sleep (r −0.52, $p < 0.0001$). As depicted in Fig. 2, patients whose REM HRs were lower than their NREM HRs tended to exhibit large amounts of REM sleep, whereas patients with higher REM HRs relative to NREM tended to exhibit small amounts of REM. In PTSD patients, REM-NREM HR difference was also positively correlated with REM latency ($r = 0.42$, $p < 0.001$) such that patients with relatively elevated REM HRs exhibited delayed REM onset and vice versa. In controls, neither of these relationships tested via rank-order correlation approached significance, though statistical power was limited.

4. Discussion

We found no group mean difference in sleep HR distinguishing chronic severe combat-related PTSD inpatient males from an age-matched, mostly combat-exposed control group. Moreover, mean sleep HRs for both groups were well within the normal range for adult men (for comparison, see [47]). The HR data provides strong support for the conclusions reached by others [5,6] that baseline HR is not elevated in chronic combat-related PTSD when the effects of anticipatory anxiety are excluded. Our findings do not rule out baseline HR elevations in acute PTSD or in other populations such as traumatized children. Indeed, Shalev and colleagues [49] have observed that HR measurements taken in the Emergency Room from a sample of accident victims were approximately 12 BPM higher in a subgroup diagnosed with PTSD at 4 months. The possibility that acute PTSD patients exhibit tonic HR elevation while chronic PTSD patients do not suggests that extended follow-up of autonomic function posttrauma may reveal important clues to the course of this disorder. In particular, the assessment of sleep HR in acute PTSD could provide better estimates of baseline HR predicting subsequent PTSD, help determine whether the elevations reported by Shalev were specific to the Emergency Room, and provide information relevant to later sleep disturbance.

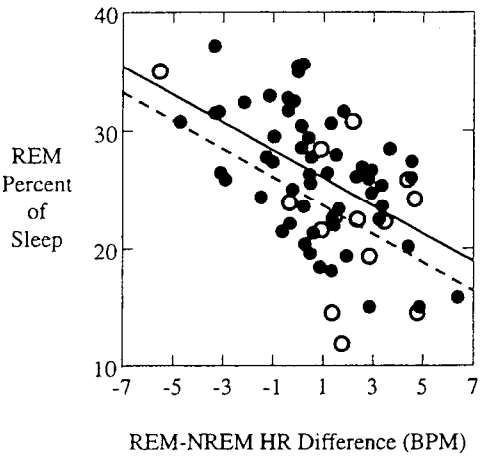

Fig. 2. Scatterplots of REM percent of sleep by REM-NREM HR difference. Squares indicate PTSD patients and circles indicate controls. Solid regression line applies to PTSD patients, dashed line to controls.

In contrast to sleep HR, sleep EEG spectral power demonstrated associations with both PTSD diagnosis and with hyperarousal as indexed by the CAPS D-criterion severity scores. Although there were no differences between PTSD patients and controls in amounts of visually scored SWS, low-frequency EEG power during SWS was significantly reduced in the PTSD patients relative to controls. In addition, PTSD patients tended to exhibit reduced low-frequency EEG power over all NREM sleep ($p < 0.08$). On one hand, these results are consistent with most prior studies finding no significant decrease in visually-scored SWS amounts in chronic PTSD (but see [12] and [50]); however, they suggest that subtle changes in the substrate of delta band sleep EEG may exist. It is worth noting that the comparison of PTSD patients with and without histories of depression produced a converse pattern in that visually scored SWS amounts distinguished these groups whereas delta power did not. Further investigation of this finding may yield new insights into the approximately 70% of the variances of both delta band EEG power and visually scored SWS time that these variables do not share (c.f. [51]).

NREM sigma-band EEG power was positively related to hyperarousal (after partialing out the linear effect of BDI) as indexed by the CAPS. The neurophysiological basis for such a finding is unclear. One possibility is that there exists a direct relationship between thalamocortical arousal, as indexed by the scalp EEG, and PTSD-related hyperarousal as defined by DSM-IV and the CAPS. This straightforward interpretation would be compatible with "dysregulation" of brain stem mechanisms mediating thalamocortical arousal during sleep. Ross et al. [52] have suggested that a dysregulation of brain stem cholinergic mechanisms involved in both ponto-occipito-geniculate (PGO) waves and elicited startle responses may occur in PTSD. The brain stem cholinergic nuclei in implicated by Ross et al. are closely related to those driving basal thalamocortical arousal [28]. Regestein and colleagues [53] have reported positive correlations between waking EEG power and a hyperarousal index in non-PTSD insomniacs.

At least two problems confront such an interpretation. First, no group differences were observed for high-frequency EEG power. Second, sigma-band power in NREM sleep is related primarily to sleep spindles, which are well known to be EEG manifestations of activity in the nucleus

reticularis thalamii [54–56]. It is also known that the nRT applies strong inhibition onto thalamic relay neurons resulting in gating of thalamocortical information flow. From this perspective, the most straightforward interpretation of the observed correlation would be that more severe hyperarousal is associated with stronger gating of thalamocortical information flow during sleep. While this seems broadly inconsistent with anecdotal reports of PTSD patients who often complain of hair-trigger arousability from sleep, it is worth noting that two laboratories have reported elevated arousal thresholds to neutral auditory stimuli during sleep in PTSD patients [10,57,58].

In patients, REM-NREM HR difference was observed to covary strongly with REM sleep measures. This relationship has not been previously reported. If replicable, this observation suggests there exists at some level substantial coupling between mechanisms regulating REM onset/maintenance/offset and HR. This coupling could be direct, with a single mechanism coregulating both phenomena, or indirect, if, for example, relative elevation of HR constituted an endogenous stimulus retarding the onset or accelerating the offset of REM.

In summary, hyperarousal in PTSD is not as straightforward as the DSM-IV would suggest. The data presented here, particularly when combined with those of Shalev, suggest that there is more to be learned about tonic arousal in PTSD. Repeated assessments beginning in the acute phase, involving both the autonomic and central nervous systems, and both waking and sleep, are likely to reveal more clinically relevant aspects of these phenomena.

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