Temporal relations between peripheral and central arousals in good and poor sleepers

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Good sleepers and patients with insomnia symptoms (poor sleepers) were tracked with two measures of arousal; conventional polysomnography (PSG) for electroencephalogram (EEG) assessed cortical arousals, and a peripheral arterial tonometry device was used for the detection of peripheral nervous system (PNS) arousals associated with vasoconstrictions. The relationship between central (cortical) and peripheral (autonomic) arousals was examined by evaluating their close temporal dynamics. Cortical arousals almost invariably were preceded and followed by peripheral activations, while large peripheral autonomic arousals were followed by cortical arousals only half of the time. The temporal contiguity of these two types of arousals was altered in poor sleepers, and poor sleepers displayed a higher number of cortical and peripheral arousals compared with good sleepers. Given the difference in the number of peripheral autonomic arousals between good and poor sleepers, an evaluation of such arousals could become a means of physiologically distinguishing poor sleepers.

arousal | insomnia | sympathetic | autonomic | cortical

Major trends in neurophysiological work in recent decades have been focused on specific sensory systems, directed motor acts, and specific cognitive capacities, especially learning and memory. Less studied has been the most elementary function of the mammalian central nervous system (CNS), generalized CNS arousal (1–3). This innate property of the nervous system underlies our ability to both sense and respond to internal and external stimuli.

Generalized arousal mechanisms have been hypothesized to arise from medullopontine gigantocellular regions of the brain stem, the nerve cells of which serve to permit or prevent arousal information originating in the body from reaching and activating central arousal circuits and vice versa. The relationship between CNS and peripheral arousal mechanisms is important in basic biology for understanding the initiation of a wide variety of behaviors and is also critical for our understanding of disease states of lowered or heightened arousal. States of lowered arousal levels range from comatose and semivegetative states to milder conditions of excessive daytime sleepiness, depression, and apathy (4). At the other extreme of the spectrum and just as debilitating are states of heightened arousal, which include attention deficit hyperactivity disorders, posttraumatic stress disorders, anxiety, and insomnia (5).

Arousals occur throughout the night and occasionally, result in full-fledge awakenings. These arousals can be measured at the cortical level, observed in the electroencephalogram (EEG), and in peripheral tissues, observed in measures of sympathetic tone. The relationship between central and peripheral arousals has been of interest, as it could provide new details about states of decreased vigilance or hypervigilance (6–12).

Examining the correlation between these two arousal systems and the exact timing of these events was undertaken to elucidate the relationship between signals originating in the periphery (e.g., poor oxygen saturation, a painful stimulus on the skin, etc.) and subsequent awakenings of the cerebral cortex to overcome/respond to these signals. Also studied was the converse, the relationship between cortical arousals and subsequent changes in autonomic tone in the periphery (6–12). Sleep studies provide a well-established precise and comprehensive way of examining the relationship between central and peripheral aspects of arousal mechanisms.

The current study was aimed at characterizing the timing and frequency of central and peripheral arousal events. To do so, central arousals were evaluated using conventional polysomnography (PSG) criteria, and peripheral autonomic arousals were identified using an opticopneumatic sensor (Watch-PAT) to detect vasoconstrictive events, an indirect measure of changes in sympathetic tone. Changes in peripheral autonomic tone were recorded on a moment-by-moment basis, and the intensity of these vasoconstrictive events was further classified using a proprietary software (zzzPAT) as a

Significance

Arousals represent a fundamental property of the nervous system that enables organisms to perceive and properly respond to internal and external challenges. Arousal mechanisms are evident during wakefulness hours to mitigate external stressors and also, during sleep periods. Among the questions that have remained elusive are when and how central and peripheral arousals are coordinated or integrated. This study evaluated the temporal correlation between central and peripheral arousals. Poor sleepers exhibit a heightened arousal phenotype, and the communication between central and peripheral arousal mechanisms is inherently different from that of good sleepers. The etiology of insomnia remains poorly understood, but screening for peripheral arousal events may be a valuable tool in the assessment and diagnosis of poor sleeping.

peripheral activation index (PAI) of 15, 18, 30, 40, or 50 (representing 15, 18, 30, 40, or 50% vasoconstriction, respectively). In addition to evaluating the timing, frequency, and intensity of PAI events in good sleepers, we also examined it in subjects with symptoms of insomnia (poor sleepers; insomnia severity index [ISI] $\geq$ 8), with the goal of enhancing our understanding of these events by evaluating a variant phenotype. Patients with insomnia symptoms have been consistently reported to exhibit a hyperarousal phenotype (12–39).

We simultaneously recorded central arousals and peripheral autonomic arousals from good and poor sleepers and examined the timing and frequency of these two arousal events. For example, do they always occur together, does one always precede the other, and what proportion of the time does one occur without the other? We also assessed the temporal dynamics among these arousals by defining the timing between the events when one preceded or followed the other. Our study revealed that timings between peripheral and central events were different in poor sleepers compared with good sleepers, suggesting differences in the dynamics in this component of CNS arousal systems.

Results

Demographics of the Study Population. The study population consisted of good ($n = 8$; ISI ≤ 7) and poor sleepers ($n = 9$; ISI ≥ 8) who were simultaneously evaluated using conventional PSG and a peripheral arterial tonometry device (Tables 1 and 2). The average age for the participants was 39.9 y, and the population was composed of 6 males and 11 females (Tables 1 and 2).

The good sleeper group had an average ISI of 3.1 on the study night and consisted of an equal number of males and females ($n = 4$), with an average age of 38.0 y (Table 2). The poor sleeper group had an average ISI of 16.0 on the study night and was composed of two males and seven females, with an average age of 41.7 y (Table 2).

Body mass index (BMI) for the study population was 23.0 and was not different for the two study groups (good sleepers: 23.1 $\pm$ 1.5; poor sleepers: 22.9 $\pm$ 1.0) (Table 2).

Table 1. Demographic data of study population

Age, y	Gender	Sleep group	BMI	ISI study night	ISI 2 wk
41	Female	Good sleeper	20	0	20
53	Male	Good sleeper	29	1	1
19	Female	Good sleeper	20	2	3
65	Male	Good sleeper	23.2	2	2
26	Female	Good sleeper	23	3	0
45	Male	Good sleeper	29	4	0
20	Female	Good sleeper	16.7	6	9
35	Male	Good sleeper	24	7	7
26	Female	Poor sleeper	19.9	10	4
50	Female	Poor sleeper	26.6	10	13
41	Female	Poor sleeper	22.5	12	11
25	Female	Poor sleeper	21	12	13
68	Male	Poor sleeper	24.4	14	16
48	Female	Poor sleeper	22	16	16
33	Female	Poor sleeper	19	21	22
58	Male	Poor sleeper	28.3	24	20
26	Female	Poor sleeper	22.7	25	20

Good sleepers were subjects with an ISI ≤ 7; poor sleepers were subjects with an ISI ≥ 8. ISI study night indicates the ISI evaluated the night of recording, and ISI 2 wk indicates the ISI evaluated the last 2 wk. BMI, kg/m^2.

Distribution of Peripheral Autonomic Arousals and Cortical Arousals throughout the Night. The number of all PAI events across all subjects steadily increased after sleep onset until 1:00 AM when, on average, there were ~77 PAI 15, 70 PAI 18, 56 PAI 30, 47 PAI 40, and 18 PAI 50 episodes per hour. The number of PAI events decreased slightly in the next 2 h and then, had their highest levels of the night at 4:00 AM, with 80, 77, 61, 38, and 17 events of PAI 15, 18, 30, 40, and 50, respectively, per hour (Fig. 1A). PAI events of different intensities all followed similar temporal dynamics throughout the night and gradually decreased toward morning. In all subjects, cortical arousals gradually increased early in the night, reaching a plateau between midnight and 2:00 AM; then, they steadily decreased for the remainder of the night (Fig. 1B).

Comparisons of good and poor sleepers revealed that poor sleepers had more PAI events at three separate times during the night: at 1:00 AM (PAI 40 and 50; $P < 0.05$), at 5:00 AM (PAI 15, 18, 30, and 40; $P < 0.01$), and at 6:00 AM (PAI 18, 30, 40, and 50; $P < 0.05$) (Fig. 2 A–E). For instance, compared with good sleepers, subjects with insomnia symptoms had more than double the number of PAI 40 events at 5:00 AM (good sleepers: 16.8 $\pm$ 3.8 events per hour vs. poor sleepers: 39.0 $\pm$ 4.8 events per hour; $P < 0.01$) (Fig. 2D). Poor sleepers, likewise, exhibited a significantly higher number of cortical arousals, especially at midnight ($P < 0.10$) and 2:00 AM ($P < 0.05$), with the maximal difference between the groups observed at 3:00 AM when poor sleepers had five times more cortical arousals compared with good sleepers (5.4 $\pm$ 2.4 vs. 27.1 $\pm$ 6.2 arousals per hour; $P < 0.001$) (Fig. 2F).

Evaluating the night as a whole revealed similar findings, with poor sleepers exhibiting significantly more PAI 15 to 40 events compared with good sleepers (Fig. 3A). On average, poor sleepers had between 60 and 92% higher numbers of PAI events during the night: good sleepers vs. poor sleepers: PAI 15: 353 vs. 568 ($P < 0.001$); PAI 18: 319 vs. 536 ($P < 0.001$); PAI 30: 241 vs. 439 ($P < 0.001$); PAI 40: 148 vs. 285 ($P < 0.001$); PAI 50: 74 vs. 130 (not significant [n.s.]; $P = 0.071$) (Fig. 3A). The PAI values were consistently elevated in poor sleepers compared with good sleepers for PAI 15 to 40 ($P < 0.001$).

PSG-defined cortical arousals for the entire night were likewise significantly elevated in poor sleepers compared with good sleepers (49 vs. 131 per night; $P < 0.05$) (Fig. 3A).

Distribution of Peripheral Autonomic Arousals and Cortical Arousals across Vigilance States. For the purposes of evaluating the changes in central and peripheral arousals across vigilance states, we assessed the concordance between Watch-PAT–defined sleep staging and PSG-scored stages. Our study revealed that on an epoch-by-epoch basis, PSG and Watch-PAT scored the same sleep stage 61.5 $\pm$ 3.4% of the night (*SI Appendix*, Fig. S1). The most common disagreements occurred with PSG wakefulness being mis-scored as Watch-PAT light sleep (LS; 9.5 $\pm$ 1.4%) and PSG stages 1 and 2 (LS) being mis-scored as deep sleep (DS) by Watch-PAT (7.5 $\pm$ 1.2%). PSG-defined stage 3 (DS) and rapid-eye movement sleep (REMS) were rarely mis-scored by Watch-PAT.

We also expanded this scoring approach to a previously untested population—patients with insomnia symptoms. Much to our surprise, the scoring accuracy was significantly higher in poor sleepers compared with good sleepers; in fact, among poor sleepers the correlation coefficient was ~0.69 compared with ~0.57 in good sleepers (*SI Appendix*, Fig. S2A). Concordance was similar among the genders (females: 0.64 $\pm$ 0.04 vs. males: 0.62 $\pm$ 0.04) (*SI Appendix*, Fig. S2B), and with increasing age,

Table 2.   Demographic data of the study population

	All subjects (n = 17)	Good sleepers (n = 8)	Poor sleepers (n = 9)
Age, y	39.9 ± 3.7	38.0 ± 5.7	41.7 ± 5.2
BMI	23.0 ± 0.9	23.1 ± 1.5	22.9 ± 1.0
Gender (male/female)	6/11	4/4	2/7
ISI study night	9.9 ± 1.9	3.1 ± 0.9	16.0 ± 2.0
ISI 2 wk	10.4 ± 1.9	5.3 ± 2.4	15.0 ± 1.8

Values represent the mean for each group ± SEM. Good sleepers were subjects with an ISI ≤ 7; poor sleepers were subjects with an ISI ≥ 8. ISI study night indicates the ISI evaluated the night of recording, and ISI 2 wk indicates the ISI evaluated the last 2 wk. BMI, kg/m2.

concordance increased slightly (18- to 30-y-old patients had a concordance of 0.62 ± 0.04, 30- to 45-y-old patients had a concordance of 0.61 ± 0.05, and 46- to 60-y-old patients had a concordance of 0.66 ± 0.03) (*SI Appendix*, Fig. S2C). Overall, on an hour-by-hour basis, there were no significant differences between the two sleep-staging methods.

The vigilance state with the highest levels of PAI events was LS followed by REMS and DS, and wakefulness had the least. When comparing poor sleepers with good sleepers, a significantly higher number of PAI events (PAI 15 to 40) occurred in poor sleepers during wakefulness, LS, and REMS compared with good sleepers (Fig. 3B). In wakefulness, PAI events were an average of 40 to 50% higher in poor sleepers; in LS, they were between 41 and 77% higher in poor sleepers, and in REMS, PAI events were 51 to 69% higher in poor sleepers compared with good sleepers (Fig. 3B).

While the focus of this study was on the occurrence of PAI events and their association with cortical arousals, it was a dramatic finding that the vast majority of PAI events, whether of small or large intensity, seemed to have no influence on the EEG and EEG arousals. The vast majority of autonomic nervous system activations causing vascular constrictions did not pass to the cortex as far as one can tell and did not cause any visible change in the EEG.

Co-occurrence of Peripheral Autonomic Arousals and Central Arousals in Good and Poor Sleepers. To examine the temporal correlations between cortical arousals and peripheral autonomic activations, two types of analysis were done. First, the number of cortical arousals that had a high-intensity peripheral arousal (PAI 40 or 50) within a 2-min period was determined. When a cortical arousal was scored, a high-intensity peripheral activation preceded this cortical arousal 96.7% of the time, and it was followed by a PAI 40 or PAI 50 97.1% of the times. Meaning, only very rarely did a cortical arousal occur

unaccompanied by a peripheral activation both before or after the cortical (3.2 and 2.9%, respectively) (Fig. 4). Evaluation of subjects by ISI did not reveal any significant difference between good sleepers and poor sleepers in terms of this temporal coupling of arousal events. Given the high prevalence of PAI events throughout the night, an analysis was done to determine the likelihood of a PAI event occurring at random times when no cortical arousals are observed. The temporal association of PAI 40 and 50 events to randomly selected times during the night when no cortical arousals occurred was between 50 and 60%, illustrating that throughout the night, there are many random peripheral sympathetic activations. However, when a cortical arousal occurred, the likelihood of having a high-amplitude PAI event was statistically significantly higher (Fig. 4).

The likelihood of a high-intensity PAI event (40 or 50) occurring within a 2-min window of a cortical arousal was likewise examined. Across all the subjects, the likelihood that a PAI 40/50 event was temporally correlated with a cortical event was 46.4 ± 3.9% compared with 53.6 ± 3.9% when a PAI 40/50 does not have an accompanying cortical arousal. Examining good sleepers and poor sleepers independently did not reveal any differences between the groups (good sleepers "yes before or after" temporally correlated: 47.3 ± 6.6% vs. poor sleepers: 45.7 ± 3.7%, n.s.; good sleepers "no before or after" not temporally correlated: 52.7 ± 6.6% vs. poor sleepers: 54.3 ± 3.7%, n.s.). These findings revealed that, as mentioned earlier, a large proportion of peripheral sympathetic arousals did not have a cortical arousal in close temporal proximity.

Temporal Dynamics between Peripheral Autonomic Arousals and Central Arousals in Good and Poor Sleepers. To further characterize the temporal coupling of cortical and peripheral autonomic activations, the total number of PAI 40 and 50 events associated with a cortical arousal and the exact timing between these events were assessed. The total numbers of PAI
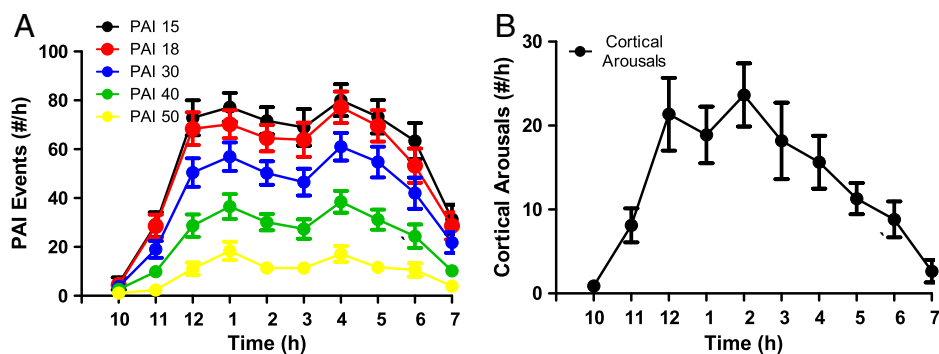

Fig. 1. Distribution of PAI events in all subjects throughout the night. (A) Total numbers of each PAI event by intensity were summed per circadian hour starting at 10:00 PM and ending at 7:00 AM. Black symbols indicate PAI 15 events. Red symbols indicate PAI 18 events. Blue symbols indicate PAI 30 events. Green symbols indicate PAI 40 events. Yellow symbols indicate PAI 50 events. (B) Distribution of cortical arousal events in all subjects throughout the night.
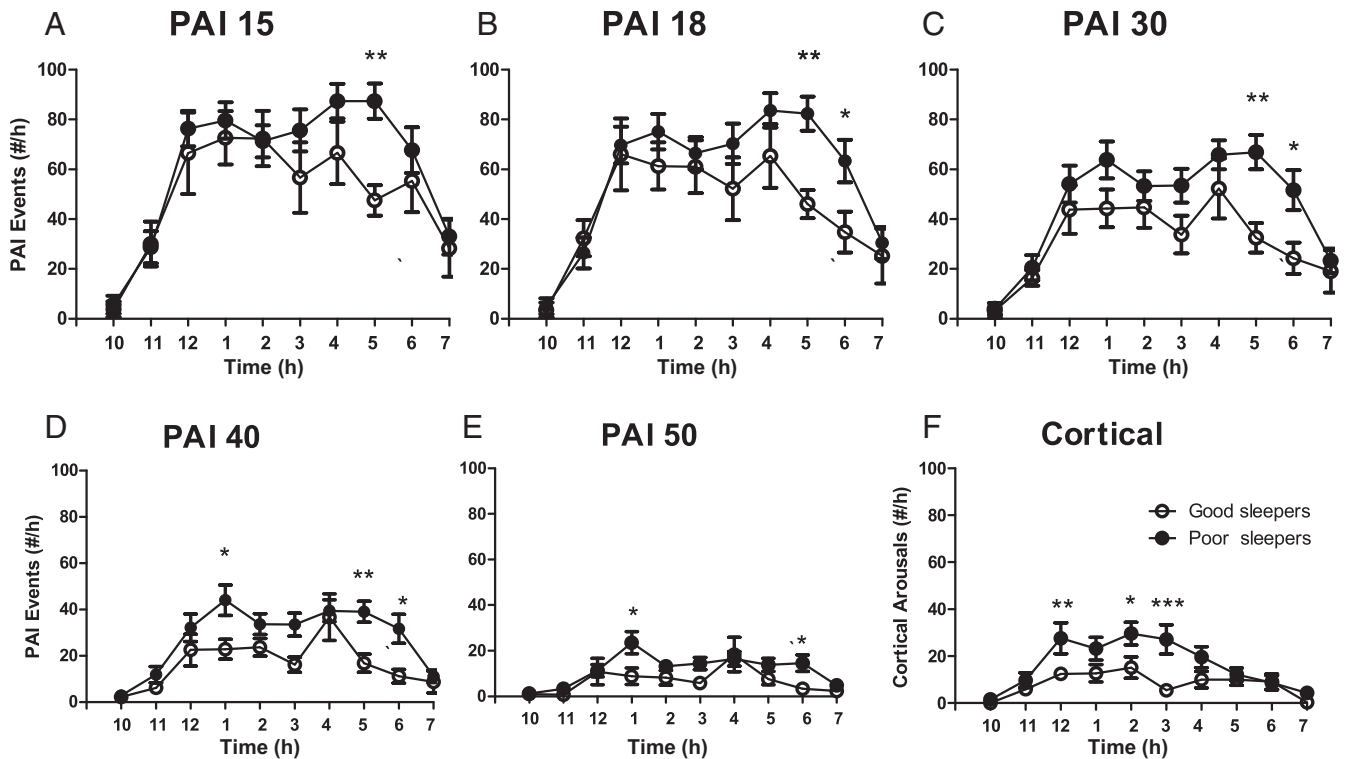
Fig. 2. Comparative amount of PAI events among good sleepers and poor sleepers throughout the night. Total numbers of each PAI were summed per hour for good sleepers and poor sleepers. (*A*) PAI 15. (*B*) PAI 18. (*C*) PAI 30. (*D*) PAI 40. (*E*) PAI 50. (*F*) Cortical arousals. ○, Good sleepers; ●, poor sleepers. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

40 and 50 events were evaluated in defined time intervals that spanned the 2 min before and after each cortical arousal. In the 2-min period before a cortical arousal, there was an average of 7.5 ± 2.9 PAI 40 or 50 events in good sleepers and 14.9 ± 3.6 PAI 40 or 50 events in poor sleepers ($P < 0.001$). Of those events, 3.5 ± 1.2 occurred between 2 and 1 min before the cortical arousal in good sleepers compared with 7.0 ± 1.8 in poor sleepers ($P < 0.05$) and 3.9 ± 1.8 occurred in the 1-min period immediately before the cortical arousal compared with 7.8 ± 2.0 in poor sleepers ($P < 0.05$) (Fig. 5*A*). In the 2-min interval following a cortical arousal, there were an average of 8.2 ± 3.1 PAI 40 or 50 events in good sleepers compared with 13.8 ± 3.4 in poor sleepers ($P < 0.001$). In the 1-min interval following the cortical arousal, good sleepers had an average of 4.7 ± 1.9 PAI 40 or 50 events compared with 6.8 ± 1.8 in poor sleepers (n.s.), and the next minute (the interval between 1 and 2 min following the cortical arousal), there were 3.5 ± 1.3 PAI 40 or 50 events in good sleepers compared with 6.9 ± 1.8 events in poor sleepers ($P < 0.05$) (Fig. 5*A*). In summary, the number of PAI events in the 2-min period before and after a cortical arousal was significantly higher in poor sleepers compared with good sleepers.

The timing between cortical and peripheral autonomic arousals was similarly evaluated. In the 2-min period before a cortical arousal, the average time between a PAI 40 or 50 event and a cortical arousal was 40.8 ± 4.3 s for good sleepers and 59.6 ± 4.5 s in poor sleepers ($P < 0.001$). These differences held true for the period 2 to 1 min before the cortical arousal (60.4 ± 2.4 s in good sleepers vs. 90.9 ± 3.0 s in poor sleepers; $P < 0.001$) and in the 1-min period immediately preceding the cortical arousal (19.3 ± 2.4 s in good sleepers vs. 32.7 ± 2.5 s in poor sleepers; $P < 0.001$). In the 2-min period following a cortical arousal, the time coupling to PAI 40 or 50 events followed a similar trend (41.9 ± 4.6 s in good sleepers vs. 61.1 ± 4.2 s in

poor sleepers; $P < 0.001$). In the 1-min interval following the cortical arousal, a PAI 40 or 50 event occurred on average at 22.4 ± 2.6 s in good sleepers vs. 30.4 ± 2.9 s in poor sleepers ($P < 0.001$), and in the period 1 to 2 min after the cortical arousal, a PAI 40 or 50 event occurred at 63.5 ± 3.2 s in good sleepers vs. 88.5 ± 2.9 s in poor sleepers ($P < 0.001$) (Fig. 5*B*). These data show that in addition to poor sleepers having a higher number of PAI events in close temporal proximity to cortical arousals compared with good sleepers, the timing between these two types of arousals is also different between good sleepers and poor sleepers (the elapsed time between a cortical and peripheral arousal is larger in poor sleepers compared with good sleepers).

The distribution of PAI 40 or 50 events in the minute before a cortical arousal was further evaluated in 10-s epochs, and the temporal dynamics revealed a difference between good sleepers and poor sleepers. In addition to the higher number of PAI 40 or 50 events observed previously in poor sleepers (average number of PAI 40 or 50 events in the period 50 to 40 s before the cortical arousal: good sleepers 1.2 ± 0.5 vs. poor sleepers 3.2 ± 1.0 [$P < 0.001$]; average number of PAI 40 or 50 events in the period 40 to 30 s before the cortical arousal: good sleepers 0.9 ± 0.5 vs. 3.0 ± 0.8 poor sleepers [$P < 0.001$]; average number of PAI 40 or 50 events in the period 30 to 20 s before the cortical arousal: good sleepers 1.0 ± 0.6 vs. 2.5 ± 0.7 poor sleepers [$P < 0.001$]), the timing of these events before the cortical arousal was also altered (Fig. 6). In good sleepers, the average number of PAI 40 or 50 events steadily increased in the four 10-s epochs up to the cortical arousal, while in poor sleepers, the average number of PAI 40 or 50 events peaked in the interval 40 to 50 s before the cortical event and decreased steadily thereafter (Fig. 6). The number of PAI 40 or 50 events remained slightly elevated after the cortical arousal in poor sleepers compared with good sleepers (Fig. 6).
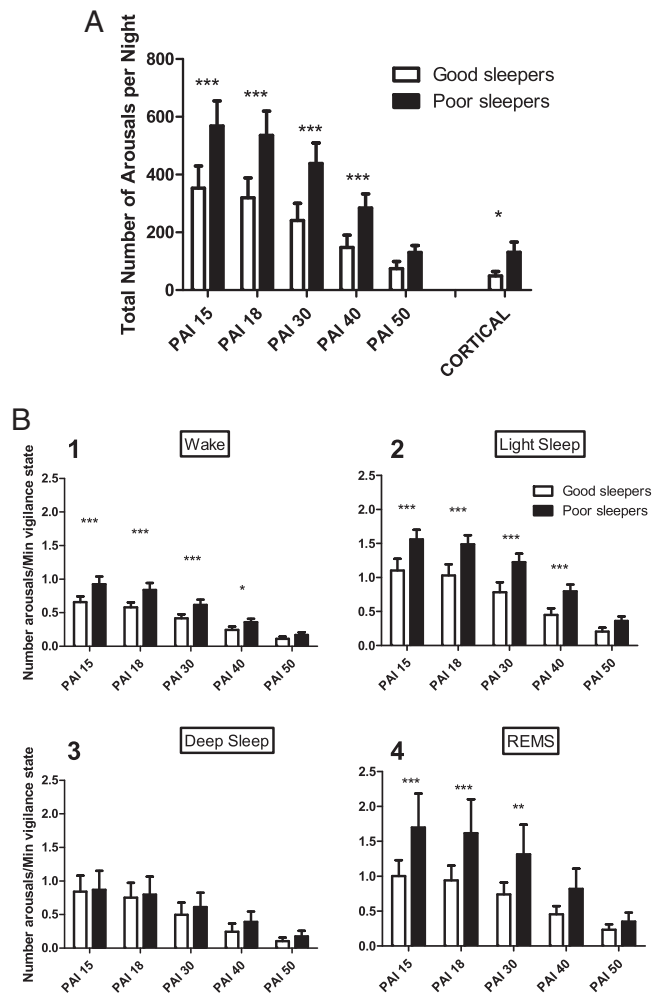
Fig. 3. Comparative nightly amounts of PAI and cortical arousals in good and poor sleepers. White bars indicate good sleepers, and black bars indicate poor sleepers. (*A*) Cumulative number of PAI events per night. (*B*) Number of PAI events per PSG-defined sleep state. (*B, 1*) Wake. (*B, 2*) LS: NREMS stages 1 and 2. (*B, 3*) DS: NREMS stage 3. (*B, 4*) REMS. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Poor Sleeping as a Hyperarousal State. As evidenced above, comparing good and poor sleepers revealed many differences in both autonomic arousals as well as cortical arousals throughout the night (Figs. 1 and 2). Not only were the numbers of arousals both cortical and autonomic elevated in poor sleepers compared with good sleepers, but the temporal distribution during the night was different.

Given that the number of peripheral autonomic arousals was significantly different between good and poor sleepers, screening for such events may be a good tool for assessment and aid in the diagnosis of insomnia.

Poor sleepers also had an altered relationship between cortical and peripheral autonomic arousals (Figs. 4 and 5). This was evident both in the percentage of events that were in close temporal proximity and also, in the elapsed time between one event and the other (Figs. 4–6).

Discussion

The purpose of this study was to explore the activity of the peripheral autonomic nervous system during sleep and its relation to CNS arousals. Across the night, considering all of the subjects together, the number of peripheral sympathetic activations (PAI events) reached a peak at 1:00 AM and after a brief trough, was

elevated to the highest levels of the night at 4:00 AM. This distribution was observed in all intensities of PAI events, albeit with a smaller number the higher the intensity of the PAI. When data from good sleepers and poor sleepers were separated, however, the curves were quite different. Poor sleepers showed a significantly higher number of peripheral arousals sustained through 6:00 AM, while peripheral arousals in good sleepers started decreasing at 4:00 AM. Cortical arousals in all subjects were at their highest between 12:00 and 2:00 AM and then, gradually decreased. The distribution of cortical arousals was also different in good sleepers and poor sleepers; poor sleepers had a significantly higher number of cortical arousals at 12:00, 2:00, and 3:00 AM compared with good sleepers. Taken together, these findings demonstrate that at both the peripheral and central levels, good sleepers and poor sleepers have fundamental differences in activation both in the number and in the distribution of these events. This study provides a detailed analysis of the timing of sympathetic and cortical arousals across the night in good sleepers and in poor sleepers and compares this timing in the two groups.

Taking the night as a whole, poor sleepers, again, had statistically significantly more PAI events compared with good sleepers, and the same was observed for cortical arousals. When examining the distribution of these arousals across vigilance state during the night, it was observed that the highest levels of PAI events occurred during LS and REMS in both good sleepers and poor sleepers. Poor sleepers had significantly more arousals of all intensities compared with good sleepers during wakefulness, LS, and REMS. DS, as a state of decreased arousability, seemed to dampen the occurrence of peripheral and cortical arousals in both good sleepers and poor sleepers compared with both LS and REMS.

The characterization of insomnia as a hyperarousal state has been widely recognized (12–39). Numerous studies have demonstrated that insomniacs exhibit elevated sympathetic activity, including elevated body temperature (40–42), increased heart rate (40, 42–47), increased heart rate variability (43, 45, 46, 48), increased skin resistance (40), elevated cortisol (41, 49–56) and norepinephrine levels (41, 42, 57), increased body (12, 42) and brain metabolism (12, 58, 59), and increased risk for
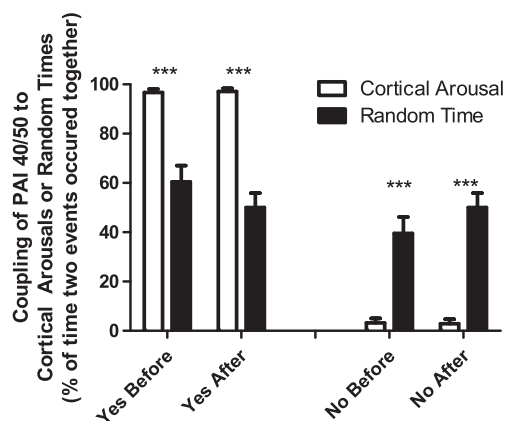

Fig. 4. Percentage of cortical arousals that had a PAI 40 or 50 event in close temporal proximity (±2 min). The first pair of bars indicates the percentage of events (cortical arousals or random times) that had a PAI 40/50 event in the 2-min period preceding it (Yes Before). The second pair of bars indicates the percentage of events (cortical arousals or random times) that had a PAI 40/50 event in the 2-min period following the event (Yes After). The third pair of bars indicates the percentage of events (cortical arousals or random times) that did not had a PAI 40/50 event in the 2-min period preceding it (No Before). The fourth pair of bars indicates the percentage of events (cortical arousals or random times) that did not had a PAI 40/50 event in the 2-min period following the event (No After). ***$P < 0.001$.
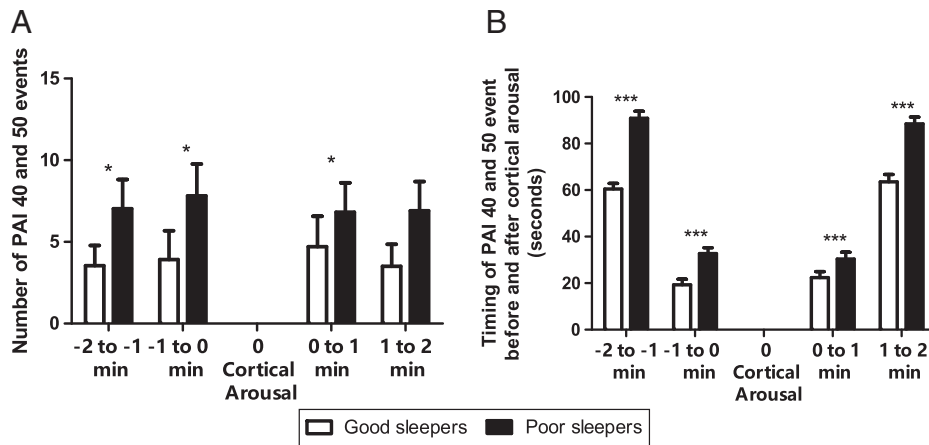
Fig. 5. Dysregulation in poor sleepers in the number (*A*) and timing (*B*) of PAI events relative to a PSG-defined cortical arousal. (*A*) Total number of PAI 40 or 50 events in close temporal proximity to a PSG-defined cortical arousal. (*B*) Average time in seconds between PAI 40 or 50 and a PSG-defined cortical arousal. White bars indicate good sleepers, and black bars indicate poor sleepers. The first pair of bars is the total number of PAI 40 or 50 in the 2- to 1-min period preceding a PSG-defined cortical arousal. The second pair of bars is the total number of PAI 40 or 50 in the 1-min period preceding a PSG-defined cortical arousal. The third pair of bars is the total number of PAI 40 or 50 in the 1-min period following a PSG-defined cortical arousal. The fourth pair of bars is the total number of PAI 40 or 50 in the 1- to 2-min period following a PSG-defined cortical arousal. *$P < 0.05$; ***$P < 0.001$.

hypertension (60, 61). This study details yet another measure of poor sleep as a hyperarousal state and again, demonstrates dramatic core physiological differences between good sleepers and poor sleepers.

The temporal relationship between peripheral and central arousals has stirred considerable interest in the last few decades (8, 11, 32, 62–69), but there is still no standard for what time period may suggest a relationship between central and peripheral arousals, and further exploration and definition are necessary (70, 71). Furthermore, how these relationships change in individuals with altered states of arousal remains to be evaluated.

Throughout the night, almost all cortical arousals occurred in close temporal proximity to peripheral autonomic events; ~97% of cortical arousals were preceded by a high-intensity PAI event, and ~92% of cortical arousals were followed by a high-intensity PAI event. In spontaneous activations during nonrapid-eye movement sleep (NREMS), Togo et al. (11) found that peripheral arousals usually preceded the onset of EEG changes. Bonnet and Arand (12) found that heart rate increases ~10 beats before a cortical arousal and suggested that such peripheral activations could play a role in the initiation of central arousals. Togo et al. (11) reported that following a cortical arousal, heart rate remained elevated for 12 beats. From the literature, we note that EEG arousals can occur before, simultaneous with, or after a periodic

leg movement, and previous authors have considered the leg movement and central arousal to be related using time frames from 0.5 to 10 s (67, 72–74).

While different from spontaneous arousals, sympathetic activations in response to an auditory stimulus have been previously studied and were shown to be followed a fraction of a second later by an EEG arousal (8, 62). Simultaneous plethysmographic studies showed vasoconstriction not occurring until 3 to 4 s after the auditory stimulus and EEG activations (8). In general, in these studies, EEG changes occurred before peripheral arterial signs of arousal. Likewise, Pitson and Stradling (63) reported that an auditory external stimulus could cause falls in pulse transit time, indicating an increase in blood pressure and therefore, indicating an arousal even when EEG changes were not discernible, thus suggesting that an external stimulus can arouse the brain stem cardiovascular centers without that arousal progressing to and arousing the cortex in ways that are visible in the EEG (63). They suggested that peripheral vascular changes indicating an arousal response could supplement the EEG or even replace the EEG in assessing the presence of an arousal to a stimulus (63).

In the present study, only about half of the high-intensity peripheral autonomic arousals were temporally associated with cortical arousals; only 46 to 53% of the time do high-intensity PAI events have an accompanying cortical arousal. This is consistent with previous assessments that half of electrocardiogram arousals (bouts of tachycardia–bradycardia) were associated with an EEG arousal and that half were not (11). In other words, whenever a cortical event occurs, there was almost always a peripheral arousal accompanying it, but peripheral arousals only activate central arousal mechanisms approximately half of the time. This dichotomy suggests that ascending and descending arousal mechanisms have different temporal dynamics (75) and offers areas of exploration into their medical importance and neurobiological underpinnings; for example, are vestibular inputs to lower brain stem reticular neurons differentially sorted among ascending and descending pathways?

While we focused on the occurrence of PAI events and their association with cortical arousals, it is important to note that a large proportion of PAI events, whether of small or large intensity, seemed to have no influence on the EEG and classically-defined cortical arousals. However, recent studies have suggested that transformations of the EEG, such as fast Fourier, can reveal
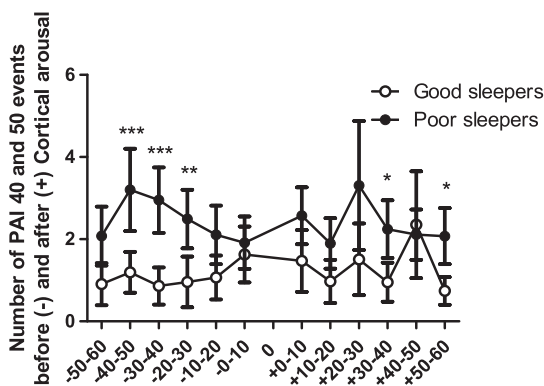

Fig. 6. Temporal relationship between PAI 40 and 50 events and PSG-defined cortical arousals. The numbers of PAI 40 and 50 events in the 10-s epochs in the 1 min preceding and following a PSG-defined cortical arousal are shown. ○, Good sleepers; ●, poor sleepers. *$P < 0.05$; ***$P < 0.001$.

cortical activations not visible on standard EEGs that are potentially linked to sympathetic activity from the periphery (e.g., beta activity) (6, 10, 76).

The average delay between peripheral sympathetic activation and cortical arousal was ∼19 s, and when a peripheral arousal followed a cortical activation, it occurred on average 22 s later in good sleepers. These findings are consistent with previous reports that 8 to 10 heartbeats elapsed between a cardiovascular event and a cortical arousal (32). With regard to the degree of sympathetic stimulation that occurs around a cortical event, on average there were four high-intensity PAI events in the 1-min interval preceding a cortical event and five sympathetic events in the 1 min following the cortical event. This study evaluates the intensity of peripheral activity associated with activations of the cortex to elucidate the exact timing that spans between the two events.

Also, this study found that the timing between peripheral and central arousals is longer in poor sleepers compared with good sleepers. The delay is 33 s in poor sleepers compared with 7 s in good sleepers for sympathetic arousals preceding a cortical arousal and 30 s in poor sleepers compared with 7 s in good sleepers for sympathetic arousals following cortical arousals. The numbers of high-intensity PAI events preceding and following a cortical event are also higher in poor sleepers. In other words, it took longer for peripheral signals to be manifested at the cortical level, and a larger number of higher-intensity sympathetic stimulations preceded a cortical arousal in poor sleepers compared with good sleepers. So, poor sleepers are not only hyperaroused centrally and peripherally compared with good sleepers; they are also centrally more refractory to peripheral activations. We postulate that arousal-related neurons, already active, may not have further capacity to initiate high levels of electrical activity.

When examining the curves of the distribution of peripheral activations surrounding a cortical arousal in good sleepers, the peripheral activations crescendo the closer they are to the cortical arousal as if a buildup was leading to, or even causing, the cortical arousal. Once the cortical arousal had occurred, sympathetic activity quickly returned to normal levels. This is dramatically different in poor sleepers who exhibited their highest peripheral activations ∼40 s before a cortical arousal, with levels then gradually decreasing toward the cortical arousal. Likewise, following the cortical arousal, peripheral activations remained elevated compared with good sleepers. It appears that temporal regulation of arousal mechanisms is more sluggish and imprecise in poor sleepers compared with good sleepers. These data are consistent with the theoretical notion that poor sleepers require a higher number of peripheral activations and that the peripheral activations take longer to elicit a cortical response. Whether and how that dysregulation of timing might lead to poor sleep remain to be discovered.

This study revealed that poor sleepers exhibit a dysregulation between central and peripheral mechanisms of arousal. Specifically, the numbers of high-intensity PAI events before and after a cortical arousal were nearly doubled in poor sleepers compared with good sleepers. In addition, the timing between central and peripheral arousals was likewise different in poor sleepers, who consistently had longer delays between a peripheral and central arousal and vice versa. The temporal dynamics of central and peripheral activations are different in poor sleepers compared with good sleepers not only in the timing but also, in the number of peripheral intrusions in a manner that suggests sluggish and imprecise regulation of arousals in poor sleepers.

Methods

Subjects. All subjects were screened at the Rockefeller University Hospital, and the nature of the study and the procedures were explained. Institutional review board (IRB)–approved written consents were obtained from all subjects prior to commencing the study. Demographic data, including gender, age, and BMI, were collected for all subjects (Table 1). Each subject completed a self-reported medical history and underwent a symptom-targeted physical examination, which included weight, height, temperature, blood pressure, and pulse. None of the subjects had a history of illicit drug use; diabetes; or neurological, cardiovascular, or psychological disease. Other exclusions included restless leg syndrome, known periodic limb movements during sleep, heavy smoking and/or alcohol use, and any sleep disorder besides insomnia, including loud snoring, sleep apnea, irregular breathing, and apneic pauses. In addition, subjects with sleep disordered breathing (or excessive restlessness in sleep) on their PSG night were eliminated. Subjects were administered the Epworth Sleepiness Scale and ISI to assess quality of sleep over the 2 wk prior to the study. Based on this information, subjects were grouped into categories: good sleepers (ISI ≤ 7) or poor sleepers (ISI ≥ 8); males or females; and aged 18 to 30 y, aged 31 to 45 y, or aged 46 to 68 y. The study protocol was approved by the Rockefeller University IRB.

Study Design. Subjects spent the night in the Rockefeller University Hospital, where full PSG was performed along with simultaneous collection of peripheral arterial tone (PAT), pulse, and actigraphy data using the Watch-PAT 200. All setup and monitoring procedures were performed by a registered polysomnographic technician.

PSG data were gathered using Grass amplifiers and Grass Twin software (Natus Medical Inc.; https://www.natus.com). All electrophysiological parameters were recorded using silver chloride disk electrodes filled with conductive gel. The recording montage selected was that recommended by the American Academy of Sleep Medicine (AASM) in *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications* (72). The recommended EEG derivations that were used were (frontal) F4-(mastoid) M1, (central) C4-M1, and (occipital) O2-M1. Backup recordings of F3-M2, C3-M2, and O1-M2 were also done to protect against loss of data from electrode malfunction. For the electrooculogram, the recommended electrode derivations were again used: (eye for the electrogram) E1-M2 and E2-M2. To record the chin electromyogram, the recommended montage used was Chin 1 or 2 to ChinZ. Bilateral anterior tibialis leads were used to document leg movements. Oronasal thermal airflow sensors were used to monitor airflow through the nose and mouth. Respiratory inductance plethysmography was used to measure chest and abdominal excursion. Cardiac monitoring was achieved with a single modified electrocardiogram channel. Oxyhemoglobin saturation was measured by means of a finger pulse oximeter. Sleep staging was performed by a registered polysomnographic technologist and classified into stages 1, 2, 3, REMS, and awake.

PAT, pulse, and actigraphy were collected using the Itamar Watch-PAT 200 device. The PAT signal was generated by a plethysmographic-based finger-mounted probe. The PAT signal is a measurement of the pulsatile volume changes in the fingertip arteries that reflect the relative state of arterial vasomotor activity and thus, indirectly the level of sympathetic activation. The PAT signal was recorded continuously and stored on an embedded micro-SD card together with data from a built-in pulse-oximetry sensor (mounted on an adjacent finger) and an actigraph (embedded in the Watch-PAT 200). Following the study, the recordings were downloaded and analyzed in an off-line procedure using the proprietary zzzPAT software. Watch-PAT scoring relies on a proprietary algorithm that uses PAT and heart rate to stage sleep and uses actigraphy to distinguish wake from sleep. Watch-PAT classified sleep as LS, DS, or REMS.

In addition to scoring sleep stages, Watch-PAT also calculates a PAI, reflective of peripheral sympathetic tone and activity. This index is calculated on a second by second basis and normalized to a baseline level per subject. When peripheral autonomic activations occur, they are categorized based on the maximal intensity reached, with cutoffs at PAI 15, 18, 30, 40, and 50. PAI of 15 reflects very mild peripheral autonomic activation (corresponding to a 15% vasoconstriction event), and PAI 50 is the maximal peripheral autonomic activation category (corresponding to a 50% vasoconstriction event). Based on the timing of arousal-related neuronal responses in recordings from laboratory animal brains and in the human

cerebral cortex, a time window of 2 min was used to indicate a physiologically relevant link between peripheral and central arousals (77–80).

As a single night study, the present work might be subject to limitations compared with two-night studies, limitations such as "first night effects" and their reverse. The data do not reveal obvious evidence of the same, but the potential limitation must be noted.

Our sample size did not allow us to determine differences in poor sleepers or good sleepers in terms of peripheral activations and cortical arousals based on age or gender.

Statistical Analysis. PAI levels per subject were summed by hour starting at 10:00 PM and ending at 7:00 AM based on the predefined categories of PAI 15, 18, 30, 40, and 50. PAI values were averaged among good sleepers (ISI $\leq$ 7) and poor sleepers (ISI $\geq$ 8) and compared using paired Student's t tests. In addition, PSG-defined cortical arousals (based on a consensus among an independently accredited PSG technologist and two board certified polysomnographers) were also compared between good sleepers and poor sleepers using Student's t tests. These comparisons were performed on an hour-by-hour basis as well as across the entire night (by summing the numbers of PAIs or cortical arousal per subject over the night).

Distribution of PAIs in PSG-defined sleep stages was also examined (i.e., the number of PAIs [15 to 50] in LS [stages 1 and 2], DS [stage 3], REMS, and wakefulness). Statistical comparisons were made between stage-specific PAIs in good and poor sleepers as well as between the number of PAI events in each vigilance state in each group (good sleepers and poor sleepers).

Recordings of PSG and Watch-PAT parameters were performed simultaneously. In addition to documenting the exact start and end times of each study, synchronizations throughout the night were verified by the timing of behaviors and of major cortical and peripheral arousals.

To evaluate the coupling between cortical arousals and peripheral autonomic events, the percentage of cortical arousals that had a high-intensity autonomic activation (PAI 40 or 50) event in close temporal proximity (within 2 min before or after cortical arousal) was calculated (cortical arousals with a PAI 40 or 50 event divided by the total number of cortical arousals multiplied by 100). Likewise, the percentage of cortical events without a PAI 40 or 50 was calculated as described above. A similar analysis was conducted for randomly timed events throughout the night where none of the 17 subjects displayed a cortical arousal. There were a total of eight separate 4-min time windows (equivalent to event $\pm$ 2 min) during the night when none of the subjects had a cortical arousal. The numbers of PAI 40 or 50 events occurring within 2 min before or after this time point were counted, divided by the total number of random events, and multiplied by 100. The percentage of random events without a PAI 40 or 50 was calculated as described above. Statistical comparisons were made between the percentage of cortical arousal accompanied by a PAI 40 or 50 and cortical arousals that did not have a PAI 40 or 50 using a paired Student's t test. Similar testing was done for the random time points where no cortical arousals were observed to compare those events that had a PAI 40 or 50 with those that did not also using a paired Student's t test. In addition, comparisons were made between the percentage of cortical arousals associated with a PAI 40 or 50 and the percentage of random times that had a PAI 40 or 50 associated with them using a Student's t test. Likewise, to evaluate the coupling of peripheral sympathetic events to cortical arousals, the number of high-intensity PAI events (PAI 40/50) that had a cortical arousal within a 2-min period (before or after) of a cortical arousal was calculated. Total numbers of PAI 40/50 events were summed

for the night per subject, and the percentage of those who had a cortical event (yes before or after) vs. did not have a cortical event (no before or after) was calculated. Statistical comparisons between good and poor sleepers were performed using a Student's t test. The likelihood of a PAI 40/50 event having a cortical arousal (yes before or after) vs. no cortical arousal (no before or after) was also evaluated using a Student's t test.

The total numbers of PAI 40 or 50 events within 2 min (before and after) of a cortical arousal were summed into time bins (from 2 min before the cortical arousal to the cortical arousal, from 2 min before the cortical arousal to 1 min before the cortical arousal, from 1 min before the cortical arousal to the cortical arousal, from the cortical arousal to 1 min after the cortical arousal, from 1 min after the cortical arousal to 2 min after the cortical arousal, and from the cortical arousal to 2 min after the cortical arousal) for good sleepers (ISI $\leq$ 7) and poor sleepers (ISI $\geq$ 8). Statistical comparisons were made between good sleepers and poor sleepers for each of these intervals using a Student's t test. Using these same time bins, the average time to cortical arousal was calculated in seconds between the time of the cortical arousal and the PAI 40 or 50 events (before the cortical arousal: -2 to 0, -2 to -1, and -1 to 0 min or after the cortical arousal: 0 to 1, 1 to 2, and 0 to 2 min). These calculations were performed for good and poor sleepers, and comparisons between these groups were done using a Student's t test.

In addition, the average number of PAI 40 or 50 events was counted in 10-s bins in the minute preceding and following a cortical arousal. Comparisons were made between good and poor sleepers using Student's t tests.

For the purposes of comparing sleep staging by the two methods, Watch-PAT–scored LS was considered PSG stages 1 and 2, and DS was considered PSG-defined stage 3. Sleep data from the two devices were imported into Excel files in minute epochs for the entire night. Minute-by-minute comparisons were evaluated, as were hourly averages and sleep amounts for the entire night.

For the concordance index (percentage concordance), exact vigilance state matches were totaled for the entire recording and divided by the total number of minutes for the recording. The concordance index was evaluated for the entire group as well as by age, gender, and ISI. When the vigilance states were not a match, the discordance was categorized by its type: for instance, LS in PSG for DS in Watch-PAT, etc. In addition to exact concordance by vigilance state, comparisons were also made to see if both scoring methods classified sleep as REMS or NREMS (PSG stage 1, 2, or 3 and Watch-PAT LS or DS); for instance, when Watch-PAT scored LS but PSG scored stage 3, both scoring methods still scored it as NREMS.

Statistical comparisons of the data were made by ANOVA followed by paired two-tailed Student's t tests. All results are presented as mean $\pm$ SEM.

Study Approval. All subjects were screened at the Rockefeller University Hospital, and the nature of the study and the procedures were explained. The study protocol was approved by the Rockefeller University IRB. IRB-approved written consents were obtained from all subjects prior to commencing the study.

Data Availability. All study data are included in the article and/or *SI Appendix*.

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