SUPPLEMENTARY INFORMATION

Methods

Protocol

Auditory stimulation

Stimuli were scheduled to begin at time points corresponding to either the onset or halfway point of a 30-sec sleep epoch. All sounds used within the study were digitally normalized such that the "burst" of each sound had equivalent A-weighted root mean square (RMS) amplitude. The audio presentation system was calibrated prior to each nocturnal recording. The experimental iPhone application for administering auditory stimulation is illustrated in Figure S1.

Disruptive condition details. Presentation loudness increased with each stimulus in a sequence, with each sequence continuing until either the sequence was completed (maximum of 9 stimuli) or the RPSGT detected evidence of a sleep disruption (see “Polysomnography processing” section below for disruption criteria). Figure S2A portrays the schematic decision tree used live by the RPSGT in the Disruptive condition.

Enhancing condition details. The RPSGT set a maximum dBA presentation loudness for stimuli (maximum of 12 per sequence in the Enhancing condition). Maximum presentation settings were adjusted throughout the night and were based on the most recent dBA level that induced a disruption, in an attempt to reduce the number of sleep disruptions related to sound presentation on the Enhancing night (eg, maximums were generally 5 dBA lower than those observed to consistently cause disruption in previous presentation). Figure S2B portrays the schematic decision tree used live by the RPSGT on the Enhancing night.

Analyses

Processing

Power Spectral Density (Delta and Slow-Oscillatory)

Data selection and artifact rejection. Any stimulus that was ended by the RPSGT prior to completion or that was associated with a cortical arousal within 15 sec of stimulus onset was excluded from power spectral density (PSD) change analysis.[1] Delta and slow-oscillatory (SO) PSD related to each stimulus presentation was baseline corrected by subtracting the $\log_{10}$ delta PSD within the pre-stimulus baseline (-5,000 to -5 ms) from the $\log_{10}$ delta PSD within the corresponding post-stimulus period (5 to 10,000 ms). Log_{10} delta PSD within both windows (baseline, stimulation) for each participant in each condition (Enhancing, Disruptive) was extracted with parameters identical to those for sleep epoch PSD. Whole-night PSD artifact rejection was accomplished by removing any epoch that contained amplitudes exceeding ± 500 μV, a linear trend with slope ≥ 60 μV, $r^2 \geq .5$ over the epoch, a probability of > 5 standard deviations (*SD*) from the mean of recorded epochs, or a kurtosis of > 5 *SD* from the mean of recorded epochs (using pop_eegthresh, pop_rejtrend, pop_jointprob, and pop_rejkurt, respectively). Momentary (stimulation-proximal) PSD artifact rejection was similar to whole-night PSD, excepting that the slope threshold was adjusted to correspond to the shorter epoch length.

Welch method. The Welch method computes power across several overlapped segments via a Hamming-windowed fast Fourier transformation (FFT), averaging across the segments to reduce variance. Specifically, for each epoch, PSD was calculated over a series of windows 2 sec (400 samples) in length with 50% (1 sec, corresponding to 200 samples) overlap, with the power in each window extracted via an FFT 400 samples in length.

Stimulus association. Each auditory stimulus was associated with the sleep stage that occurred immediately prior to stimulus onset. For a stimulation scheduled to begin at the onset of a 30-sec sleep epoch, this corresponds to the sleep stage of the previous sleep epoch. For a stimulation scheduled to begin at the halfway point of a 30-sec sleep epoch, this corresponds to the sleep stage of the current epoch.

Temporal alignment of data. Polysomnography data were temporally aligned with auditory stimulation in two steps. Timestamps from the iPhone presenting stimulation provided a coarse

measure of sound onset. Further alignment was accomplished by adjusting the offset and drift of coarse timestamps to correspond with the audio waveform that was recorded and displayed with the PSG data.

References

1. Vallat R, Lajnef T, Eichenlaub JB, et al. Increased evoked potentials to arousing auditory stimuli during sleep: implication for the understanding of dream recall. *Front Hum Neurosci.* 2017;11:132.

Supplementary Figures and Captions

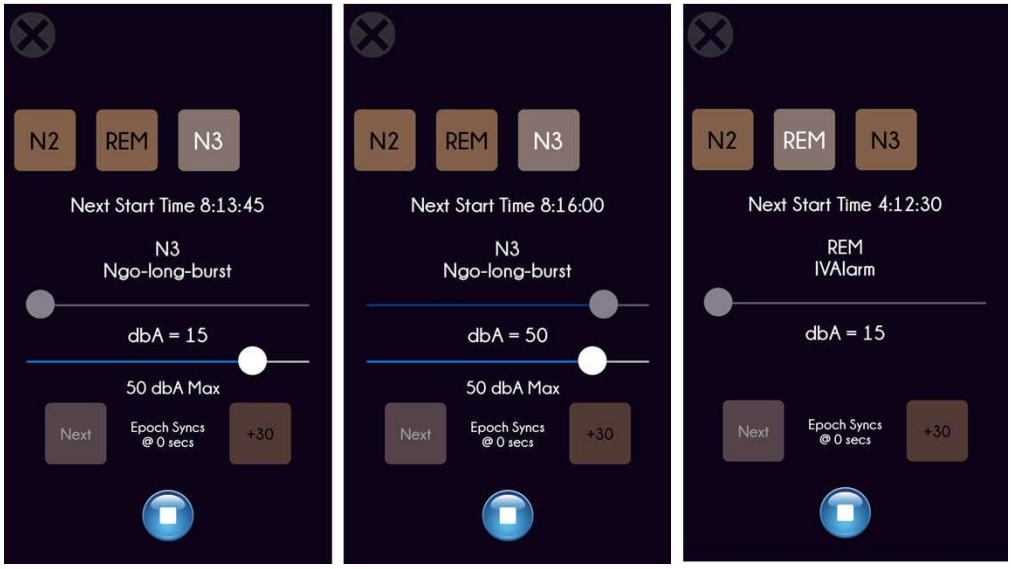
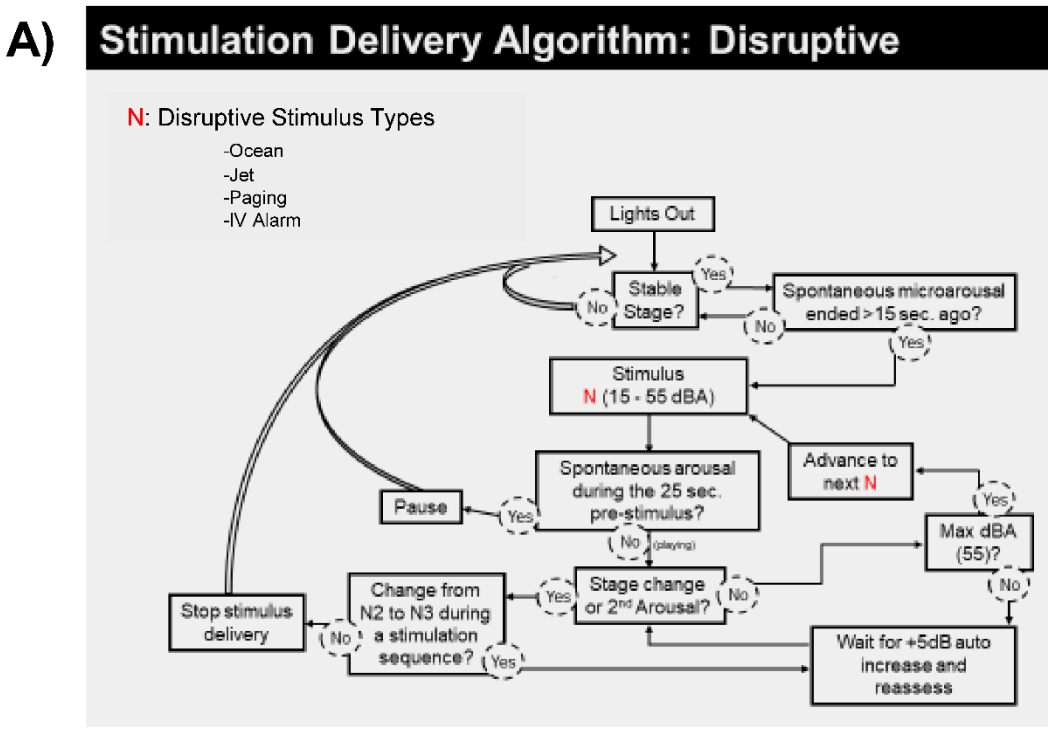
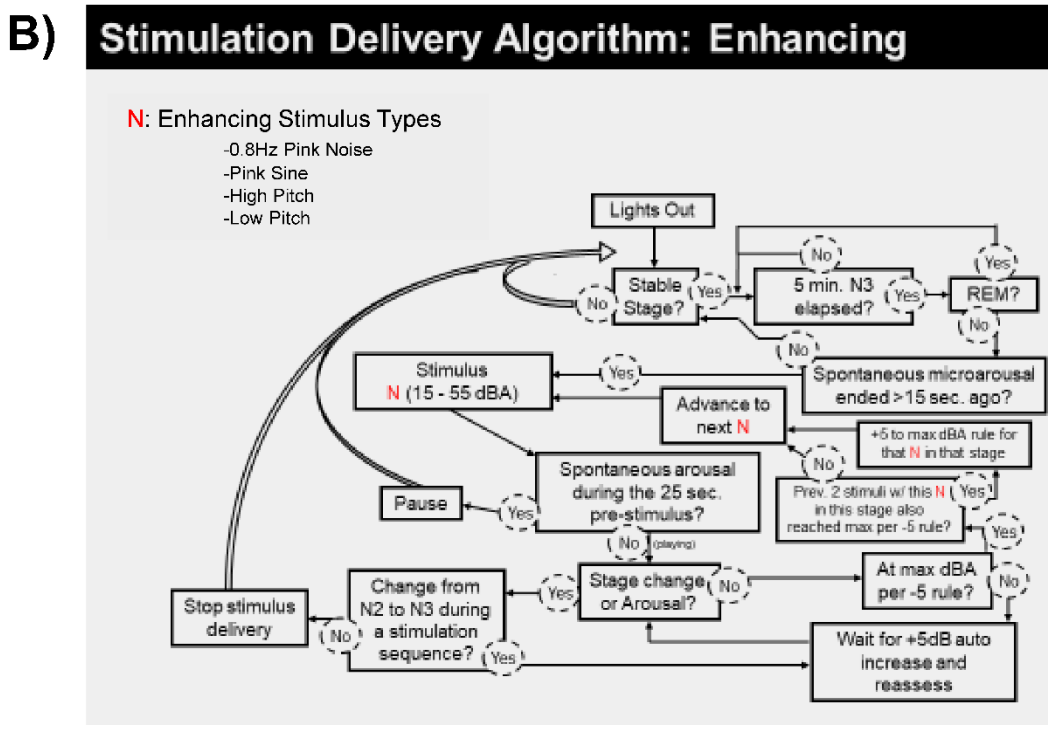


Figure S1. Experimental iPhone application for administering auditory stimuli. Abbreviations: N2 (non-rapid eye movement sleep, Stage 2), N3 (non-rapid eye movement sleep, Stage 3), REM (rapid eye movement sleep), dBA (A-weighted decibels).





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63 **Figure S2. A**: Decision flow for sound presentation on the Disruptive condition night. Sounds were
64 delivered during stages N2, N3, and REM. “Stable” stage was defined as at least 2 sequential epochs of a
65 given stage. Initial sound pressure level (SPL) for each sound presentation sequence (consisting of one

sound type) was 15 dBA. SPL was increased by 5 dBA every stimulus presentation until either sleep disruption criteria or maximum dBA (55) were reached. 10-sec sounds were automatically separated by 20 sec start-to-start, and by 5 sec end-to-start. Sequences of stimulus sub-types were randomized in their automated presentation order. **B**: Decision flow for sound presentation on the Enhancing condition night. Sounds were delivered during stages N2 and N3. “Stable” stage was defined as at least 2 sequential epochs of a given stage. Initial sound pressure level (SPL) for each sound presentation sequence was 15 dBA. Maximum dBA was determined according to the previous SPL of stimulus delivery (for that particular stimulus type and sleep stage) at which a sleep disruption was evoked, less 5 dBA, up to 55 dBA. SPL was increased by 5 dBA every stimulus presentation until either sleep disruption criteria or a maximum dBA setting determined by the technologist was reached. 10-sec sounds were automatically separated by 20 sec, start-to-start, and by 5 sec, end-to-start. In the absence of sleep disruption, a sound presentation sequence continued for up to 5 mins. Stimulation sequences consisted of two sound types; all stimuli except one, administered as the 10th stimulus in each sequence, were the same designated stimulus sub-type. The 10th stimulus was one of two variants of a 0.8 Hz noise stimulus (randomized). Sequences of stimulus sub-types were randomized in their automated presentation order. Abbreviations: N2 (non-rapid eye movement sleep, Stage 2), N3 (non-rapid eye movement sleep, Stage 3), REM (rapid eye movement sleep), dBA (A-weighted decibels).

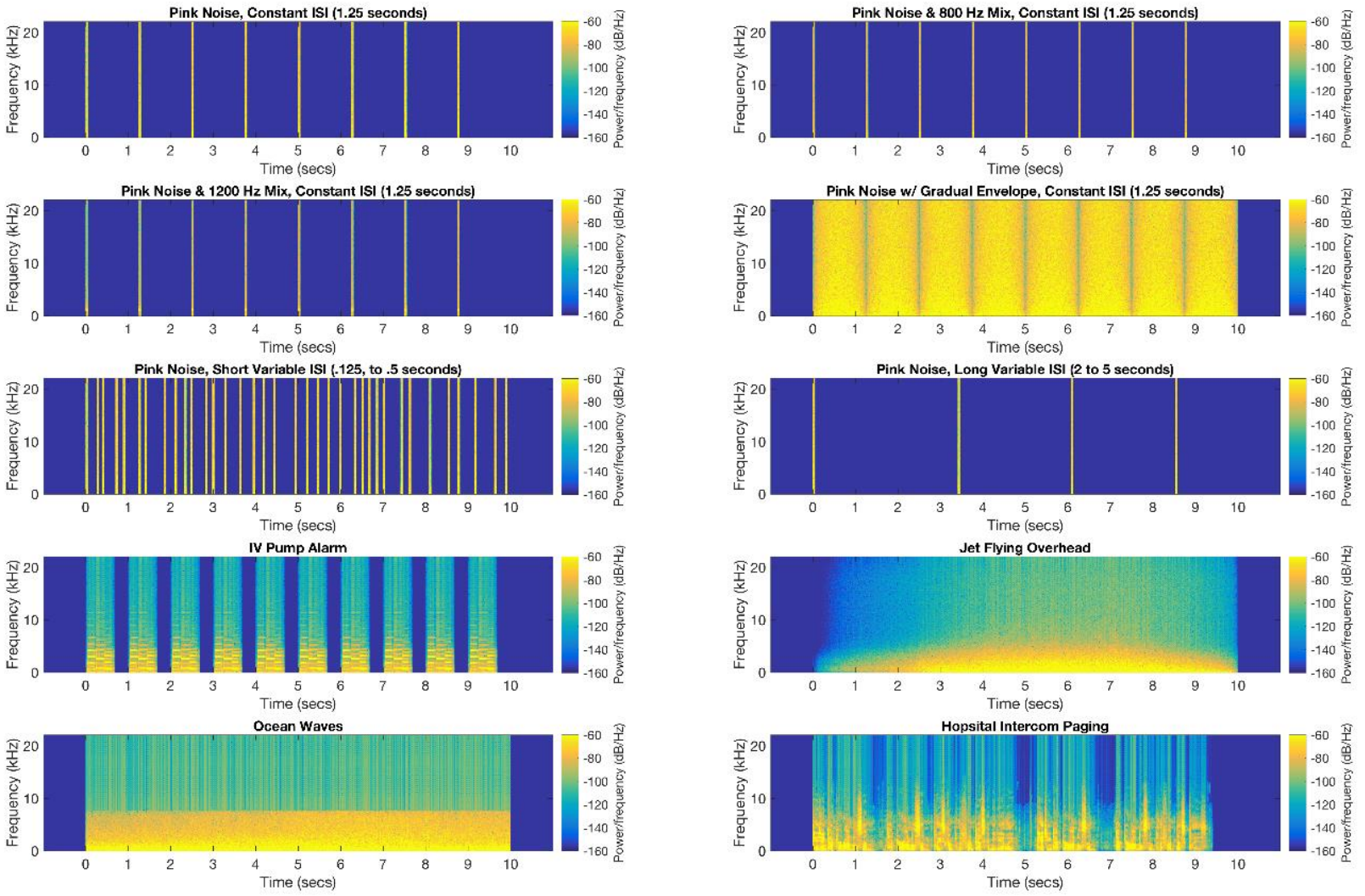
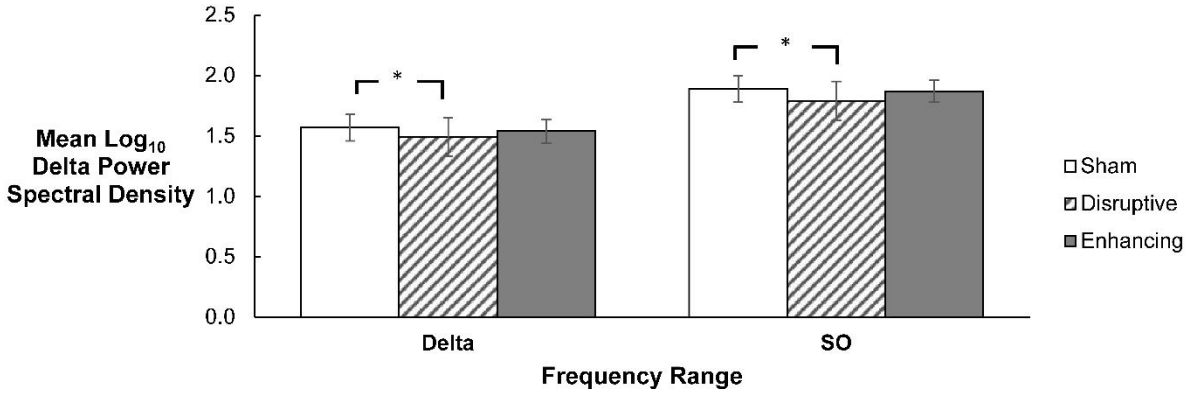


Figure S3. Characteristics of each auditory stimulus used in the Enhancing (pink noise) and Disruptive conditions. Abbreviations: kHz (kilohertz), Hz (hertz), dB (decibels), ISI (inter-stimulus interval), IV (intravenous).



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87 **Figure S4.** Mean whole-night $\log_{10}$ delta (0.5-4 Hz) and slow oscillation (SO; 0.5-1 Hz) power spectral
88 density (PSD) within each study condition (Sham, Disruptive, and Enhancing) during sleep. Neither
89 whole-night delta nor SO PSD differed between Enhancing and Sham conditions, but both delta and SO
90 PSDs were significantly lower in the Disruptive condition versus Sham. Error bars represent standard
91 deviation. *$p < .05$.

Table S1 Sleep Characteristics Measured by Actigraphy for Screening, Pre-Inpatient, and Inpatient Periods

	Screening		Pre-Inpatient		Inpatient	
	M	***SD***	***M***	***SD***	***M***	***SD***
Major nighttime sleep interval						
Sleep duration (mins)	496.70	44.37	514.20	59.76	531.30	1.10
Sleep midpoint (midnight-centered)	2.85	0.63	2.56	0.78	3.39	0.22
Wake after sleep onset (mins)	33.08	1.22	3.26	1.14	26.00	12.23
Daytime naps						
Number of napper(s)	1		2		---	
Nap duration/day for napper(s) (mins)	29.57	---	56.04	1.83	---	---

Estimated sleep based on motion-sensitive actigraphy monitoring of participants during screening, 3-day pre-inpatient study preparation with an 8-hr instructed sleep schedule, and the 4-night inpatient study. Sleep durations did not differ.

Table S2 Sound Administration by Stimulus Type, Sleep Stage, and Study Condition

	Disruptive				Enhancing			
	N1	**N2**	**N3**	**REM**	**N1**	**N2**	**N3**	**REM**
Stimulus type								
Pink noise 0.8 Hz	---	---	---	---	X	X	X	---
Pink sine	---	---	---	---	X	X	X	---
Pink low-pitch	---	---	---	---	X	X	X	---
Pink high-pitch	---	---	---	---	X	X	X	---
Physician paging	X	X	X	X	---	---	---	---
IV pump alarm	X	X	X	X	---	---	---	---
Ocean	X	X	X	X	---	---	---	---
Jet	X	X	X	X	---	---	---	---

Schematic representation of the study conditions and sleep stages during which the auditory stimulus delivery algorithm scheduled each stimulus type to be played by the registered polysomnographic technologist (RPSGT). Sleep staging and sound delivery decisions were performed live, but final staging of data was performed after data collection by the RPSGT, blinded to auditory stimulation.

Table S3 General Linear Model Summaries and Omnibus Outcomes for Momentary Change in Delta and Slow Oscillatory Power Spectral Density, Net of Decibel Level

Power Spectral Range	Change in Power Spectral Density[a]	df[b]	F	*p*
Delta (0.5-4 Hz)	0.11 (0.46)	1, 7	17.57	**< .001**
Slow oscillation (0.5-1 Hz)	0.15 (0.57)	1, 7	15.26	**< .001**

[a]M (*SD*)

[b]Numerator, denominator

Omnibus linear mixed model summary of change in momentary delta (0.5-4 Hz) and slow oscillatory (SO, 0.5-1 Hz) power spectral density from the 5-sec window preceding auditory stimulation (baseline) to the 10-sec window during auditory stimulation. The effect of stimulus type (8 sounds) was fixed; subject and decibel level effects were random. *p*-values in **bold** are interpreted as significant ($p < .05$).

Table S4 General Linear Model Summaries and Omnibus Outcomes for Inpatient (PSG) Sleep Characteristics for Study Condition Nights

	SHAM		ENHANCING		DISRUPTIVE				
Order (1st):	**Disruptive[a]**	**Enhancing[a]**	**Disruptive[a]**	**Enhancing[a]**	**Disruptive[a]**	**Enhancing[a]**	**df[b]**	**F**	***p***
SLEEP METRIC									
TST (mins)	480.2 (33.7)	488.3 (33.7)	463.1 (34.5)	478.0 (35.2)	478.6 (18.7)	461.8 (21.1)			
Condition							2, 16	0.78	.475
Efficiency (%)[c]	87.9 (6.5)	89.9 (6.5)	85.5 (6.3)	87.3 (7.0)	89.1 (2.3)	84.7 (4.0)			
Condition							2, 16	0.63	.545
N3 (% of TST)	15.8 (4.7)	10.8 (3.8)	12.5 (5.3)	13.9 (0.7)	6.3 (6.4)	5.9 (1.5)			
Condition							2, 16	40.23	**< .001**
Interaction							2, 16	6.56	**.008**
N3 (mins)	75.5 (21.7)	51.8 (15.0)	57.7 (23.7)	66.2 (4.1)	30.5 (31.3)	27.3 (6.8)			
Condition							2, 16	39.71	**< .001**
Interaction							2, 16	6.85	**.007**
N2 (% of TST)	49.9 (5.4)	55.6 (5.9)	50.9 (5.0)	50.2 (3.6)	54.4 (7.7)	58.4 (8.5)			
Condition							2, 16	4.29	**.032**
N2 (mins)	240.2 (36.2)	272.8 (46.6)	235.4 (28.1)	240.3 (29.7)	259.6 (32.9)	268.5 (27.7)			
Condition							2, 16	3.67	**.049**
REM (% of TST)	25.1 (3.2)	22.4 (0.8)	24.9 (2.6)	23.3 (5.1)	23.9 (6.9)	19.5 (2.3)			
Condition							2, 16	0.75	.490
REM (mins)	120.8 (18.9)	109.3 (8.9)	115.6 (14.6)	111.8 (27.3)	114.9 (35.9)	90.5 (14.9)			
Condition							2, 24	0.56	.576
N1 (% of TST)	9.2 (3.5)	11.3 (4.4)	11.7 (1.4)	12.6 (7.9)	15.4 (5.9)	16.2 (6.3)			
Condition							2, 16	6.22	**.010**
N1 (mins)	43.7 (15.8)	54.3 (20.0)	54.4 (10.0)	59.7 (36.1)	73.6 (28.4)	75.5 (33.2)			
Condition							2, 16	7.55	**.005**
Overall arousal index[d]	13.6 (4.0)	15.2 (2.5)	14.1 (4.3)	13.4 (2.7)	19.9 (4.0)	19.7 (3.8)			
Condition							2, 24	10.91	**< .001**
N2 arousal index[d]	13.7 (6.6)	17.1 (1.6)	12.8 (3.4)	15.2 (4.6)	23.7 (5.2)	22.0 (5.9)			
Condition							2, 24	10.18	**.001**
N3 arousal index[d]	4.8 (3.0)	12.5 (9.8)	6.9 (2.5)	10.8 (8.7)	18.2 (3.9)	22.3 (6.4)			
Order							1, 23	6.35	**.019**
Condition							2, 23	13.90	**< .001**
REM arousal index[d]	22.5 (15.0)	20.6 (13.0)	25.5 (16.7)	17.7 (7.2)	24.8 (13.9)	26.7 (5.7)			
Condition							2, 16	1.11	.355
All-night delta power[e]	65.7 (18.8)	57.7 (13.9)	60.8 (17.8)	57.6 (5.9)	51.8 (24.6)	50.5 (11.0)			
Condition							2, 16	7.60	**.005**

[a]Presentation order of study conditions (randomized to night 2 or night 4). Disruptive condition 1st *n* = 5, except for N3 arousal index, where one outlier was excluded; Enhancing condition 1st *n* = 3. Mean (*SD*).

[b]Numerator, denominator

[c]Percentage of time spent asleep relative to sleep opportunity time (scheduled as 9 hrs in the laboratory).

[d]Number of spontaneous and stimulation-associated arousals (either microarousals or awakenings) out of sleep, per hour of total sleep or per hour of that sleep stage.

[e]Log-transformed values were used in analyses; untransformed values are reported here.

Omnibus outcomes of general linear model analyses evaluating differences in polysomnography-evaluated sleep metrics across study conditions. Analyses interpreted as statistically significant are indicated with *p*-values in **bold** ($p < .05$). N1, non-rapid eye movement sleep stage 1; N2, non-rapid eye movement sleep stage 2; N3, non-rapid eye movement sleep stage 3; PSG, polysomnography; REM, rapid eye movement sleep; TST, total sleep time.

Table S5 Descriptive Statistics of Psychomotor Vigilance Task (PVT) Outcomes by Condition

	Disruptive vs. Sham		Enhancing vs. Sham	
	Sham	**Disruptive**	**Sham**	**Enhancing**
	EMM (SEM)	*EMM (SEM)*	*EMM (SEM)*	*EMM (SEM)*
Median RT (ms)[a]	270.00 (1.21)	271.00 (1.25)	270.00 (1.06)	267.00 (1.10)
Lapse[b] count	0.39 (.30)	0.82 (.25)	0.39 (.30)	0.65 (0.22)
False start count[c]	0.66 (.29)	0.51 (.39)	0.62 (.29)	0.46 (0.36)

EMM, estimated marginal mean; RT, reaction time; SEM, standard error of the mean.

[a]Includes RT ≥ 500 ms (lapses) but not RT < 100 ms (false starts).

[b]Reaction time ≥ 500 ms.

[c]Reaction time < 100 ms.

Marginal median reaction time (RT, in ms) per 10-min test to respond to a visual stimulus, the number of responses ≥ 500 ms in RT (lapse count), and the number of responses < 100 ms in RT (false start count), during the 10-min psychomotor vigilance task (PVT) administered the day after an Enhancing or Disruptive night relative to the day after Sham.

Table S6 Model Summaries and Omnibus Outcomes[a] for Subjective Sleep Assessments[b] after the Sham, Enhancing, or Disruptive Night (Condition).

	SHAM[c]		ENHANCING[c]		DISRUPTIVE[c]				
Condition order (1st):	**Disruptive[d]**	**Enhancing[d]**	**Disruptive[d]**	**Enhancing[d]**	**Disruptive[d]**	**Enhancing[d]**	**df[e]**	***F***	***p***
Subjective assessments									
Number of awakenings	2.8 (0.7)	3.0 (1.0)	2.4 (0.7)	3.0 (0.6)	12.4 (2.5)	8.3 (2.7)	2, 24	18.41	**<.001**
Total sleep time[f]	486.0 (34.4)	500 (15.3)	477.0 (38.1)	476.7 (8.8)	390.0 (30.0)	450 (30.0)	2, 16	7.87	**.004**
Sleep quality	5.0 (0.4)	4.3 (0.3)	4.2 (0.6)	5.0 (0.6)	2.0 (0.4)	2.7 (0.3)	2, 24	17.33	**<.001**
Residual sleepiness	0.6 (0.4)	1.0 (0.0)	1.2 (0.7)	0.7 (0.3)	2.0 (0.5)	1.7 (0.3)	2, 24	2.99	.069†
Sleep's restorative value[g]	4.6 (0.2)	3.7 (0.7)	4.2 (0.8)	4.3 (0.7)	1.8 (0.6)	2.3 (0.3)	2, 24	11.17	**<.001**

[a]As reported through post-wake survey following a given condition.
[b]General linear model.
[c]Mean (standard error of the mean); Disruptive 1st, *n* = 5 (except for total sleep time, *n* = 4); Enhancing, 1st, *n* = 3.
[d]Presentation order of study conditions (randomized to night 2 or night 4). The possibility of sleep rebound exists for cases where the Disruptive condition was presented two nights prior to Enhancing.
[e]Numerator, denominator.
[f]Not including time elapsed during nocturnal awakenings; participants were asked to report in hours and minutes, and data were converted to minutes.
[g]How "refreshed" participants felt.

Omnibus outcomes of general linear model analyses evaluating differences in subjectively-assessed sleep features across study conditions. Analyses interpreted as statistically significant are indicated with *p*-values in **bold**. †$p < .100$ (marginally significant).