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Bupropion response on sleep quality in patients with depression: implications for increased cardiovascular disease risk

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Abstract

Depression could be an independent risk factor for cardiovascular disease. We assessed bupropion response in depressed patients by polysomnography (PSG) and cardiopulmonary coupling (CPC) variables. Nineteen subjects participated in a two-session, two consecutive night PSG protocol. Participants received either placebo or bupropion-SR 150 mg, orally, in a randomized, double-blind cross-over fashion on night two. Outcome variables were: sleep stages, REM latency, stable, unstable sleep and very low frequency coupling (VLFC). CPC analysis uses heart rate variability and the electrocardiogram's R-wave amplitude fluctuations associated with respiration to generate frequency maps. Bupropion increased REM latency ($p=0.043$) but did not impact PSG sleep continuity, architecture and CPC variables. A trend ($p=0.092$) was observed towards increasing VLFC duration. Bupropion increased the number of stable-unstable sleep transitions ($p=0.036$).

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Authors/Contributions:

Preetam J. Schramm, PhD, RPSGT¹ / PSG review, CPC analysis, statistical analysis, first and final draft.

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Moderate to strong correlations between PSG and CPC variables were found on placebo and bupropion nights. Limitations include a small sample size, limited power to detect CPC changes and lack of normal controls for comparison. Increased stable-unstable sleep transitions and VLFC duration may indicate vulnerability to cardiovascular disease due to their association with low heart rate variability that has been associated with increased mortality raising the question whether the beneficial effects of the antidepressant medication outweighs the impact on cardiopulmonary dynamics.

Keywords

depression; cardiopulmonary coupling; bupropion; sleep quality

INTRODUCTION

Some literature identifies depression as an independent risk factor for cardiovascular disease (Mallik et al. 2005; Rugulies 2002). Higher levels of depressive symptoms at the time of coronary bypass surgery were shown to be a strong predictor for lack of functional surgical benefit after six months (Mallik et al. 2005). In contrast, low preoperative measures of depression and sleep problems predicted better recovery six months after cardiac surgery (Jenkins et al. 1994). The mechanisms responsible for the relationship between depression and cardiovascular health are unknown; however a unifying hypothesis may be stress-related.

Stress often refers to a physiological, neurochemical or emotional factor related to physical or mental pressure and may be related to a disease state. An earlier study investigating bupropion response in 17 patients with depression found reduced heart rate variability (HRV) at rest compared to controls (Straneva-Meuse et al. 2004). Furthermore, unmedicated depressed women showed reduced respiratory sinus arrhythmia (RSA) compared to non-depressed controls (Cyranowski et al. 2011) although this is in contrast to other reports (Cacippo et al. 1994; Gianaros et al. 2005; Hawkey et al. 2001). Depressed women, the authors suggested may be less likely to demonstrate enhanced cardiac vagal control during acute stress. Sleep measures were not investigated in these studies.

Cardiopulmonary coupling (CPC) analysis detects and summarizes coupled modulation of respiration and HRV (Thomas et al. 2004; Thomas et al. 2005). CPC and polysomnography (PSG) sleep quality measures equally captured the worsening of sleep under the stress of the first night in a sleep lab in primary insomnia patients and matched control subjects (Schramm et al. 2012). Decreased sleep stability and increased unstable sleep in non-medicated depressive patients was recently reported suggesting this might indicate a long term risk for adverse cardiovascular risk in depressed patients (Yang et al. 2010). In the same study, medicated depressed patients using hypnotics had significantly improved CPC sleep quality measures compared to medication-free depressed patients demonstrating CPC's functionality to assess a pharmacological response.

Bupropion is an atypical antidepressant that influences central and autonomic nervous systems (Preskorn and Othmer 1984). In a study of 58 subjects with major depressive disorder, bupropion produced small increases in diastolic blood pressure suggesting that it may have mild cardiovascular side effects (Kiev et al. 1994). This study investigated a bupropion acute response in depressed patients. Our primary hypothesis is that the response to bupropion would be detectable using PSG and CPC variables of sleep quality.

The study was undertaken to determine: (1) possible differences in sleep quality between bupropion and placebo conditions measured by PSG and CPC variables in patients with major depressive disorder; and (2) if bupropion influenced changes would identify risk factors for cardiovascular disease.

Experimental Procedures

Design

The study had a randomized, double-blind, crossover design.

Subjects and setting

Nineteen subjects (1M/18F; aged 33.31 ± 7.66 years) with unipolar major depressive disorder defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (First et al. 1997) criteria were recruited. All participants provided written informed consent approved by the local Institutional Review Board before entering the study.

Inclusion criteria included: (1) age 21–55 years; (2) meeting diagnostic criteria for current major depressive disorder and/or dysthymic disorder (APA 1994). Patients were excluded if they had: (1) a lifetime diagnosis of bipolar disorder, primary anxiety disorder, eating disorder, schizophrenia or schizo-affective disorder; (2) suicidal ideation, with an active plan and/or a recent suicide attempt, or psychotic symptoms; (3) substance use disorder in the past 3 months; (4) using psychotropic medication(s), or alcohol and/or drugs, in the two weeks prior to entry into the study (8 weeks for fluoxetine and monoamine oxidase inhibitors) (urine was tested for occult drug use, and participants with a positive drug screen were excluded); (5) confirmed or suspected pregnancy, currently lactating females; (6) seizure or other neurological disorders, dermatological conditions, and unstable cardiac, pulmonary, endocrine or renal disorder; (7) history of failure to respond to bupropion, at a dose of 300 mg for at least 8 weeks; (8) irregular sleep-wake schedules, and/or clinical sleep disorders; (9) family history of narcolepsy; and (10) use of autonomic modulating medications, such as beta blockers, that might impact CPC.

The Beck Depression Inventory (BDI; a self-report) (Beck and Steer 1987) and the Hamilton Depression Rating Scale (HDRS; a clinician-rated scale) (Hamilton 1960) were used to determine depression severity.

Sleep Data Collection and Scoring

Sleep-wake schedules were regulated for 7–10 days prior to the laboratory study (with bedtimes between 9–11 pm and awake times between 6:30–7:30 am), and the participants were asked to refrain from caffeine intake after 4:00 pm during this period until the sessions were completed. The sleep-wake schedules were confirmed through sleep logs and wrist actigraphy. Sleep was recorded on two consecutive nights, with each 2-night session approximately one week apart. All subjects received a full overnight sleep assessment on Night 1 of the four-night protocol to rule out clinical sleep disorders. The group's mean apnea hypopnea index was 1.43 ± 3.17 . The clinical cutoff used was 10 events/hour. Scoring of breathing events used the 3% O₂ desaturation and 10s duration scoring rules (Iber et al. 2007). Oxygen desaturations ranged from 96–89%. On the morning following Night 1 sleep recording, participants received either placebo (baseline sleep) or a single dose of bupropion SR (150mg, PO). The study's paradigm follows the methodology and rationale described in Ott et al. (2002) for using an acute bupropion SR (150mg) dose. Since the bupropion XL formulation (300mg) blood concentration returned to baseline levels after 24 hours (Fave et al. 2005), a one-week washout period seemed an adequate timeframe to avoid potential medication effects. Only the PSG data from nights two and four were used for

analysis. The PSG protocol followed the standard overnight PSG procedures (AASM Task Force 1999) using commercially available equipment (Embla, Natus Medical, Santa Clara, CA, USA).

Sleep stage scoring was performed manually by a registered polysomnographer blind to the drug-placebo condition using the American Academy of Sleep Medicine's 2007 standard scoring criteria (Iber et al. 2007). Sleep stages for non-rapid eye movement sleep (NREM; sleep stage N1-N3), rapid eye movement (REM) and Wake were identified and summarized. Sleep onset (SO) was defined as the first minute of stage N2 or deeper sleep, followed by at least 9 minutes of stage N2 or deeper sleep, interrupted by no more than 1 minute of waking or stage N1. REM latency was defined as the time between SO and the first REM period 3 minutes in duration. The electrocardiogram (ECG) data were analyzed automatically using CPC analysis software (MyCardio, LLC, Broomfield, CO, USA).

ECG recording and processing with CPC analysis

The ECG was obtained from the PSG using lead II configuration. All ECG data were collected using a sampling rate of 200 Hz.

The CPC algorithm's detailed original methodology has been published (Thomas et al. 2005) and is available online at www.journalssleep.org. The CPC algorithm uses the continuous ECG data and extracts the heart rate variability and ECG-derived respiratory (EDR) activity from the ECG signal. Thoracic impedance differences between the 2 ECG chest leads oscillate with inhalation and exhalation resulting in amplitude changes in the QRS-complex allowing derivation of the EDR from the ECG signal. The time series data are filtered for outlying heart beats due to false or missed R-wave detection by rejecting central points >20% of the sliding window average filter and then the data are normalized (normal - normal intervals) and cubic spline resampled to 2 Hz.

The cross-spectral power and coherence of the heart rate variability and EDR signals are calculated using a 1024-sample (8.5 min) window using fast Fourier transformation. The calculation is performed on three overlapping sub-windows of 512 samples each and then advanced by 256-samples (approximately 2.1 minutes) where the calculation is repeated until the entire normal - normal intervals and EDR series are analyzed. The percent of high frequency coupling (HFC), low frequency coupling (LFC) and very low frequency coupling (VLFC) in their respective spectral band for each 8.5 minute window is determined from the product of the coherence and cross-spectral power. An average percent of each CPC variable within its frequency domain across the time series is determined. The CPC analyzer generates values for the following band widths of 0.1–0.4 Hz, 0.01–0.1 Hz, and 0.0039 – 0.01 Hz for HFC, LFC, VLFC, respectively. We do not present the results from frequency bands outside these ranges because their clinical significance has not been determined.

A simplistic way to approach this new terminology is to consider HFC as stable sleep and LFC as unstable sleep (Thomas et al. 2005). In this framework, VLFC can be associated with Wake or REM as the algorithm does not differentiate between these states. Transitions between stable and unstable sleep are expected within an intact system to modulate in 30 – 90 minute infraadian cycles that range from 5–16 cycles in an 8-hour sleep period and correspond to the alternating periods of NREM - REM sleep (Gianaros et al. 2005). Disease states may negatively impact this rhythm (Schramm et al. 2012; Thomas et al. 2004; Thomas et al. 2005). Stable-unstable sleep transitions defined as shifts from stable sleep to unstable sleep were automatically detected by the algorithm and summed manually for each recording.

Statistical Analysis

Summary measures of PSG and CPC variables are presented as means and standard deviations using summary statistics. Assessment of variables' suitability for parametric tests were determined by the Shapiro-Wilk test for normal distribution ($p > 0.05$). Logarithmic transformations were performed for sleep efficiency, wake after sleep onset, stage N1%, stage N1 minutes, sleep latency to stage N1 and sleep latency to stage N2 because these variables did not meet normal distribution prior to analyses. Separate multiple analyses of variance (MANOVA) for PSG and CPC variables were performed by treatment (placebo versus bupropion nights). When the ANOVA was significant ($p < 0.05$), paired and unpaired *t* tests were used and adjusted for multiple comparisons (Bonferroni method) to identify significant differences within and across groups respectively. Pearson correlations were used to determine associations between variables. Statistical Package for the Social Sciences (SPSS) software (ver. 8 for Windows; SPSS Inc. Chicago, Ill.) was used for the statistical analysis.

RESULTS

Demographic and clinical information is presented in Table 1. No statistical differences in age, weight, body mass index, BDI and HDRS scores were found.

PSG measures by treatment

Bupropion had no significant effect on sleep continuity or non-REM sleep measures. A significant lengthening of REM latency was an observed bupropion response ($F = 4.43$, $p = .043$). (Table 2)

CPC measures by treatment

Bupropion did not show a statistical effect on stable and unstable sleep duration. Bupropion demonstrated a statistical trend to increase VLFC duration ($p = 0.092$). (Table 2) We assessed the bupropion response on sleep quality stable-unstable transitions because of the VLFC trend and a previously reported association of VLFC with the ratio of low/high frequency (Yang et al. 2011).

Effects of bupropion on stable-unstable sleep transitions

Exploratory post hoc analyses were undertaken in an effort to further appreciate and integrate the effects of bupropion on stable-unstable sleep transitions. Summation of stable-unstable sleep transitions showed that the number of transitions increased for the study group on bupropion night (placebo: 13.00 ± 4.04 versus bupropion: 14.73 ± 4.43 , $p = 0.036$). (Figure 1)

Association between PSG and CPC variables

On placebo night, sleep efficiency and stage N3 % positively correlated with stable sleep. Wake after sleep onset, the number of awakenings, arousal index, and stage N1% negatively correlated with stable sleep. Unstable sleep correlated positively with Wake after sleep onset, the number of awakenings, arousal index, and stage N1%. Unstable sleep negatively correlated with sleep efficiency percent and stage N3 %. VLFC positively correlated with wake after sleep onset, the number of awakenings, arousal index, stage N1 latency, stage N2 latency and REM latency. A negative correlation between VLFC and sleep efficiency % was observed. (Table 3)

On bupropion night, stable sleep correlated negatively with stage N1%. Unstable sleep showed a positive and negative association with stage N1% and REM latency, respectively.

VLFC correlated positively with stage N1 latency and negatively with sleep efficiency %.
(Table 3)

DISCUSSION

This is the first report on the effect of bupropion in adult depressed patients using PSG and CPC variables. The key findings of our analysis are: (1) a bupropion response on REM sleep latency was observed but not for PSG sleep continuity, non-REM sleep architecture and CPC variables; (2) a trend towards increasing VLFC duration was detected; (3) bupropion increased the number of stable-unstable sleep transitions; and (4) moderate to strong correlations between PSG and CPC variables, particularly on placebo night, were found.

Although a ubiquitous bupropion response was not found by PSG sleep continuity, non-REM sleep architecture and CPC variables, lengthened REM latency was an observed effect on bupropion night supporting a similar finding in depressed patients treated chronically with bupropion. (Ott et al. 2004) The results partially validate previous findings (Ott et al. 2002) describing increased REM latencies in depressed patients after single-dose administration of bupropion who were responders to therapy measured by HDRS score reduction. The same study reported decreased REM latency in non-responders following 8-weeks of bupropion treatment. Shortening of REM latency and increases in REM sleep were observed responses to bupropion in a previous study using bupropion immediate-release form, (Nofzinger et al. 1995) A report by Nofzinger et al. (2001) found no change in REM latency following 12 weeks of treatment with bupropion SR which is in contrast to the same group's previous study.

However, a later report (Ott et al. 2004) described a REM latency increase of approximately 40% and no change on non-REM measures after approximately 8 weeks of twice daily bupropion treatment. Our current findings of REM latency increase and no non-REM sleep changes after acute drug intake is consistent with the Ott et al. (2004) report. Others reported a lack of REM sleep suppression with bupropion in patients with depression (Krystal et al. 2007). Reasons for the divergent results between reports could be related to differences in clinical and demographic characteristics between the study populations. It is possible that study groups may have various combinations of the two phenotypes described by Ott et al. (2004) resulting in some of the reported differences in bupropion response studies.

Bupropion effects on cardiopulmonary coupling variables

The CPC bupropion effects observed in this study compliment the standard PSG measures. The CPC results suggest that bupropion effects are not limited to central nervous system but also impact peripheral systems demonstrating an inter-linked physiological process that includes autonomic cardiac, respiratory and electrocortical systems. VLFC showed a statistical trend to be increased with bupropion and a negative association to sleep efficiency. Unmedicated depressed patients receiving hypnotics showed no difference in stable sleep, unstable sleep and VLFC compared to controls suggesting hypnotic use decreases VLFC and LFC and increases HFC. VLFC associates with REM and Wake (Thomas et al. 2005). REM sleep has the lowest cardiorespiratory phase synchronization indicating elevated cardiovascular risk. (Bartsch et al. 2012) Verrier et al. (1996) reported the highest occurrence of adverse cardiac events is found in REM sleep. Bupropion increases in VLFC may increase vulnerability to cardiovascular disease in some depressed patients. VLFC measures combined with other quantifiable physiological parameters may have implications for assessing pharmacological treatment of depressed patients with risk of cardiovascular disease.

Future research of time-scale development and resolution of cardiopulmonary decompensation co-varying with sleep quality variables using an end-point of cardiovascular disease will need to be investigated.

Bupropion effects on stable-unstable sleep transitions

Sleep continuity disturbances in individuals with depression are correlated with symptom severity (Thase et al. 2009; Yang et al. 2011). Increased stable-unstable sleep transitions following acute bupropion exposure suggests bupropion increased sleep stage transitions and disruption of sleep continuity although this was not reflected by PSG sleep continuity or architecture variables. It is likely that our current measures of objective sleep quality should be supplemented and supported with tools that capture core biological correlates. Our study results imply bupropion may increase sympathetic and reduced parasympathetic tone. Increased sympathetic and reduced parasympathetic tone was reported as risk factors for cardiovascular disease and cardiovascular mortality (Carney et al. 2001; Carney et al. 2003; Stein et al. 2000). Taken together, it is possible that the use of bupropion in some depressed patients and in those with cardiovascular vulnerability may place them at greater long-term risk for adverse cardiovascular events.

Relationship of polysomnography and CPC variables

Moderate to strong correlations were found between PSG and CPC variables under placebo conditions. Fewer correlations between standard PSG and CPC measures were seen on bupropion night, likely resulting from increased sleep fragmentation with bupropion administration since NREM sleep stage N3% correlated with stable sleep only on placebo night. The ECG-spectrogram strongly reflects bimodal oscillation (Thomas et al. 2005) and physiological synchronization (Bartsch et al. 2012) rather than the graded physiological characteristics of non-rapid movement sleep. Combining the pharmacological effect on the EEG and likely on subcortical structures influencing sleep transitions supports the dissociation observed between PSG and CPC variables response to bupropion. Additionally, stable sleep state is not dependent on conventional scored slow-wave sleep or delta EEG power although the two can be complimentary. (Thomas et al. 2005) Bupropion may have introduced sufficient additional variations in sleep (i.e. less synchronization between EEG power, heart rate variability dynamics and respiration sinus arrhythmia) in our group of subjects to produce a disassociation. It is likely that EEG sleep staging may not capture all of the sleep regulatory responses and the 'bimodal' switching detected by CPC analysis as a bupropion response.

Limitations

The current study has some limitations that include a modest sample size, female predominance that limits generalizability and lack of normal controls for comparison. Justification for not using a control group was based on previous work from two of the authors (REP, UR; Poland et al. 1997, Ott et al. 2002; Ott et al. 2004) The sample of depressed patients had placebo CPC sleep quality variable values that did not show the disturbed sleep quality reported in one other non-medicated group of depressed patients (Yang et al. 2011). The relatively good sleep quality on placebo in our group of depressed patients may have contributed to the lack of identifying a treatment effect. These higher values are likely related to our definition used to constrain the sleep onset to 10 minutes of continuous stage N2 or deeper sleep. Yang et al. (2012) obtained their data from 24hour Holter ECG data without associated EEG which could have biased their assessment of when subjects were actually asleep. We did not examine CAP and non-CAP relative to CPC measures as this was previously described under non-pharmacological conditions (Thomas et al. 2005). Our study did not specifically investigate HRV differences in assessing bupropion response. Assessment of HRV alone during sleep fails to identify the coupled or

synchronous periods with RSA. (Bartsch et al. 2012) The combination of HRV and RSA used by the CPC algorithm provides information beyond that obtained from each parameter therefore direct methodological comparisons cannot be made to previous investigations using HRV alone. Additionally, a discussion on HRV analysis limitations to assess sleep physiology has been described (Thomas et al. 2005).

Conclusions

The present study found complimentary results between PSG and CPC measures. CPC analysis identified a trend towards increasing VLFC duration and augmented stable-unstable sleep transitions in response to bupropion. Increased stable-unstable sleep transitions may indicate vulnerability to cardiovascular disease likely due in part to enhanced sympathetic and decreased parasympathetic tone. Our findings have important implications for clinical treatment of depression and whether the beneficial effects of antidepressant medication outweighs the impact on cardiopulmonary dynamics. Prospective studies should investigate the clinical paradigm of acute bupropion challenge, PSG measure of REM latency and CPC assessment of sleep quality and stable-unstable sleep transitions in identifying depressed patients who may be susceptible to developing heart disease.

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Placebo

Bupropion

Figure 1.

Sleep hypnogram, cardiopulmonary hypnogram and spectrogram (from top to bottom, respectively).

The black arrows show an example of the manually scored polysomnogram hypnogram during sleep stage N3 (top panel; placebo=28.8%, bupropion=20.6%). CPC hypnogram (middle panel) illustrates the stable-unstable sleep oscillations. The bottom panel arrow indicates the correlation of high frequency coupling peaks occurring at the same time as scored sleep stage N2 or N3.

Table 1

Demographic and clinical data of total sample (mean $\pm$ SD).

	Total sample
Age (years) (n=19)	33.31 $\pm$ 7.66
Gender (M/F) (n=19)	1/18
Weight (lbs., n =17)	182.35 $\pm$ 60.31
BMI (n =15)	29.97 $\pm$ 9.67
BDI (n=19)	29.33 $\pm$ 7.32
HDRS (n=19)	27.00 $\pm$ 5.23

Abbreviations: BDI = Beck Depression Inventory; HDRS= Hamilton Depression Rating Scale; BMI = Body mass index.

Table 2

Sleep polysomnography variables after placebo and bupropion-SR in depressed patients (n=19).

Sleep continuity	Placebo	Bupropion	<i>p</i> -value
Total sleep time (min)	422.23 ± 52.55	422.04 ± 53.43	0.909
Sleep efficiency (%)	89.42 ± 5.71	91.0 ± 5.67	0.501
WASO (min)	51.08 ± 30.97	42.47 ± 27.45	0.470
Number of awakenings	17.73 ± 7.99	16.78 ± 8.58	0.833
Sleep architecture			
Stage N1%	6.18 ± 3.46	6.30 ± 4.49	0.967
Stage N2%	47.73 ± 7.90	49.02 ± 8.11	0.652
Stage N3%	24.75 ± 9.52	23.70 ± 7.61	0.681
REM%	21.35 ± 5.23	21.04 ± 4.22	0.871
Stage N1 (min)	25.90 ± 17.39	26.10 ± 16.03	0.884
Stage N2 (min)	201.23 ± 42.03	208 ± 48.13	0.724
Stage N3 (min)	105.14 ± 42.90	98.5 ± 29.63	0.547
REM (min)	90.39 ± 26.71	88.78 ± 23.35	0.909
Stage N1 latency (min)	20.13 ± 20.32	16.86 ± 12.67	0.566
Stage N2 latency (min)	24.94 ± 21.44	33.42 ± 59.98	0.459
REM latency (min)	79.44 ± 33.64	107.78 ± 47.92	0.043
HFC (min)	253.15 ± 101.84	260.75 ± 69.71	0.452
LFC (min)	110.71 ± 73.07	128.64 ± 63.74	0.213
VLFC (min)	50.18 ± 45.05	63.41 ± 37.55	0.092

Abbreviations: WASO = Wake after sleep onset; SO = sleep onset; REM = rapid eye movement; HFC= high frequency coupling band (0.1 – 0.4 Hz); LFC= low frequency coupling band (0.01–0.1 Hz); VLFC= very low frequency coupling band (0.0039 – 0.01 Hz).

Table 3

Correlation of cardiopulmonary variables to all night standard PSG sleep variables following placebo and bupropion

Sleep variables	CPC variables (%)					
	Placebo (n = 19)			Bupropion-SR (n = 19)		
	HFC	LFC	VLFC	HFC	LFC	VLFC
Total sleep time (min)	0.331 (0.166)	-0.370 (0.119)	-0.134 (0.586)	-0.013 (0.958)	0.070 (0.777)	-0.084 (0.733)
Sleep efficiency (%)	0.654 (0.002)	-0.485 (0.035)	-0.655 (0.002)	0.327 (0.171)	-0.044 0.857	-0.615 (0.005)
Wake after sleep onset (WASO) (min)	-0.564 (0.012)	0.474 (0.040)	0.473 (0.041)	-0.277 (0.251)	0.138 (0.572)	0.350 (0.141)
Number of awakenings	-0.646 (0.003)	0.548 (0.015)	0.547 (0.015)	-0.392 (0.097)	0.440 (0.059)	0.039 (0.874)
Arousal index	-0.724 (< 0.001)	0.657 (0.002)	0.550 (0.015)	-0.432 (0.065)	0.453 (0.051)	0.095 (0.700)
Stage N1%	-0.658 (0.002)	0.661 (0.002)	0.417 (0.076)	-0.468 (0.043)	0.506 (0.027)	0.088 (0.719)
Stage N2%	-0.395 (0.094)	0.418 (0.075)	0.188 (0.440)	-0.151 (0.537)	0.111 (0.651)	0.143 (0.558)
Stage N3%	0.577 (0.010)	-0.559 (0.013)	-0.386 (0.103)	0.290 (0.229)	-0.273 (0.259)	-0.154 (0.529)
REM%	0.039 (0.873)	-0.103 (0.675)	-0.099 (0.688)	0.151 (0.538)	-0.142 (0.561)	-0.060 (0.807)
Stage N1 latency	-0.419 (0.074)	0.201 (0.410)	0.600 (0.007)	-0.126 (0.607)	-0.162 (0.507)	0.551 (0.015)
Stage N2 latency	-0.420 (0.073)	0.199 (0.414)	0.604 (0.006)	-0.277 (0.252)	0.181 (0.458)	0.290 (0.229)
REM latency	-0.229 (0.346)	-0.007 (0.978)	0.474 (0.040)	0.383 (0.106)	-0.525 (0.021)	0.138 (0.573)

Abbreviations: N1 = sleep stage 1% of TST; N2 = sleep stage 2% of TST; N3 = sleep stage 3% of TST; REM latency = the first consecutive 3 minutes of N2 or deeper sleep to the first 3 minutes of REM sleep. HFC% = high frequency coupling band (0.1 – 0.4 Hz); LFC% = low frequency coupling band (0.01–0.1 Hz); VLFC% = very low frequency coupling band (0.0039 – 0.01 Hz).