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Cardiopulmonary coupling analysis predicts early treatment response in depressed patients: A pilot study

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ABSTRACT

This pilot study evaluated the effect of anti-depression treatment on sleep quality and symptoms of depression in patients with major depressive disorder, and identified cardiopulmonary coupling (CPC) indices for predicting early response. Forty-one Han Chinese patients with major depressive disorder were assessed for objective sleep quality before treatment (baseline) and at 2 weeks using CPC. Subjective sleep quality and depression levels were measured at baseline and 2 and 4 weeks after treatment, using the 24-item Hamilton Rating Scale for Depression (HAMD-24), Epworth Sleepiness Scale (ESS), and Pittsburgh Sleep Quality Index (PSQI). Objective and subjective sleep quality, and depression symptoms, improved after treatment. Significant correlations were found between CPC variables at baseline and depression symptom improvement after 2 weeks of treatment. Total sleep time at baseline significantly correlated with somnipathy score reduction at week 2. Total in-bed time at week 2 significantly correlated with reductions in anxiety/somatic symptoms and retardation score, and total HAMD-24 score at week 4. In binary logistic regression, the total in-bed time at baseline was significantly associated with treatment response. Our findings suggest that objective sleep quality measured by CPC analysis is useful for predicting treatment response to antidepressant treatment in patients with major depressive disorder.

1. Introduction

Major depressive disorder (MDD) is a heterogeneous condition with various responses to any given treatment (Cuijpers et al., 2012). It is difficult for physicians to predict the effectiveness of antidepressant therapy (Insel and Wang, 2009), given that there are no biomarkers to reliably predict a response (Thase, 2014). It is important to identify markers that can predict treatment outcomes in patients with MDD.

Sleep disorders are a major symptom in patients with MDD (Cheng et al., 2015). Persistent sleep symptoms, particularly insomnia, independently contribute to the non-remission of depression (Chan et al., 2014). Patients with MDD commonly have a characteristic sleep electroencephalography (EEG) (Fenzl et al., 2011; Steiger and Kimura, 2010) with reduced slow-wave activity that reflects an overall decrease in restorative sleep (Armitage, 2007; Cheng et al., 2015). Numerous polysomnographic sleep studies have shown that changes in sleep structure in MDD include early onset of rapid eye movement (REM), increased phasic REM activity, and impaired sleep efficiency (Armitage, 2007; Steiger and Kimura, 2010; Thase et al., 1997; Tsuno et al., 2005). Pharmacotherapy, as well as psychotherapy, can partially improve sleep architecture in these patients (Thase, 2006; Tsuno et al., 2005). Most antidepressants decrease REM sleep by reducing REM time and increasing REM latency (Sharpley and Cowen, 1995; Thase, 2006).

Objective assessments of sleep physiology currently rely primarily on EEG-based polysomnography (PSG) (Buysse et al., 2006; Sylvia et al., 2014; Yang et al., 2011). However, EEG-based PSG is difficult to conduct and costly. A cyclic alternating pattern is considered a biomarker of fragmented sleep associated with microarousals, and has also been used to evaluate sleep stability (Schramm et al., 2016; Terzano et al., 2002).

The cardiopulmonary coupling (CPC) is a spectrographic method that was developed as an alternative to PSG to quantify sleep quality. CPC analysis uses a continuous single-lead electrocardiogram (ECG) signal to track changes in cardiac inter-beat (R-R) intervals and QRS amplitude during sleep (Bianchi and Thomas, 2013; Thomas et al., 2005). Through ECG-based CPC analysis, Yang et al. (2011) demonstrated that patients with MDD experienced reduced stable sleep, increased unstable sleep, and increased wakefulness/REM-sleep, which were restored by medication. CPC analysis was also used to detect sleep quality in chronically depressed patients after applying the cognitive behavioral analysis system of psychotherapy (Schramm et al., 2016).

The present study evaluated sleep quality changes and improvement

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of depressive symptoms after 4 weeks of anti-depression medication, using CPC analysis. In addition, associations between CPC indices and psychometrics for depression and subjective sleep quality were investigated; and possible CPC indices were identified for predicting treatment response.

2. Methods

2.1. Materials and study design

This single-group, unblinded cohort study is a pilot study that evaluated the effects of antidepressants on sleep quality and depressive symptoms in Han Chinese patients with MDD. The study was conducted between 1 November 2016 and 30 May 2017 at Second Affiliated Hospital of Xinxiang Medical University (Xinxiang, Henan Province), a health center that predominantly serves patients with mental disorders. The Institutional Review Board of Xinxiang Medical University approved this study, and all subjects gave written informed consent.

The power calculation and effect size determination were conducted using the G*Power 3.1.9.2 program (http://www.softpedia.com/get/Science-CAD/G-Power.shtml). At the power of 0.9 ($\beta = 0.1$) and a significance of 0.05 ($\alpha = 0.05$), the effect size number was calculated at 43 patients (Yang et al., 2011). The following equation was applied: effect size $= (m_1 - m_2)/\mathrm{SD}_{\mathrm{pooled}}$ (Yang et al., 2011) where m is the mean of the sample and $\mathrm{SD}_{\mathrm{pooled}}$ is the pooled standard deviation. Two patients were excluded due to inpatient days of less than 4 weeks. Finally, 41 patients were included in the study. All participants were referred by their supervising physician.

2.2. Inclusion and exclusion criteria

All the patient subjects conformed to the following inclusion criteria: Han Chinese ethnicity; aged 18–65 years; met the 10 criteria of the International Classification of Diseases for MDD as diagnosed by 2 psychiatrists; a baseline score of 17–35 on the 24-item Hamilton Rating Scale for Depression (HAMD-24); and inpatient status for 4 weeks or more.

Patients with any of the following were excluded from this study: any comorbid psychiatric diagnosis; history of psychosis or mania; alcohol or substance abuse or dependence in the last 6 months; neurological, cardiac, pulmonary, endocrine, or renal disorders; current pregnancy; or cardiac fibrillation or an implanted pacemaker. Also excluded were patients with current active suicidal or self-injurious potential, as assessed by the clinical judgment of their supervising physicians.

2.3. Psychometrics

In-person outcome measurements were assessed at baseline (before treatment), and 2 and 4 weeks after treatment by a trained estimator, using the HAMD-24, the Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI). The HAMD-24 and ESS were determined at baseline and 2 and 4 weeks after treatment. The PSQI was measured at baseline and 4 weeks after treatment.

2.4. HAMD-24

The HAMD-24 is an interview scale that is widely used in the clinic to identify the indications and severity of depression, and evaluate recovery of depression symptoms. The simplified Chinese version of HAMD has good reliability and validity: the total Cronbach's a1pha is 0.714, and the parallel validity and the construct validity are ideal (Sun et al., 2017). We assessed the HAMD-24 scores for anxiety/somatic symptoms, cognition, retardation, somnipathy, and despair, as well as the total HAMD-24 score. An anti-depression response to treatment was defined as a decrease in the HAMD-24 score by more than 50%.

2.5. PSQI and ESS

PSQI was used to assess subjective sleep disturbance over the previous month. PSQI is a 19-item self-report questionnaire, comprising scores of 7 components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleep medication, and daytime dysfunction. Each component score ranges from 0 to 3, and a total score (from 0 to 21) was determined by the summation of each component score. Higher scores indicated greater sleep difficulties (Buysse et al., 1989). The simplified Chinese version of PSQI has good internal consistency, test-retest reliability, and high consceiving and criterion-related validity (Liu et al., 1996).

The ESS was used to evaluate subjective daytime sleepiness, and consists of 8 self-report questions. Each item score ranges from 0 to 3 (0 for never doze; 3 for high chance of dozing), and a total score (0 to 24) was determined by the summation of each item score. Higher scores indicated increased daytime sleepiness (Johns, 1992). The reliability and validity of the simplified Chinese version of ESS is high, with a total Cronbach's alpha of 0.814, and good discriminant validity and construct validity (Peng et al., 2011).

2.6. Cardiopulmonary coupling analysis

A CPC device (Nanjing Fengsheng Yongkang Software Technology, Nanjing, China) was used to study sleep quality and stability. The CPC device has several advantages over the traditional laboratory PSG, including low cost. Furthermore, it is less intrusive, allows ambulation and multiple nights of monitoring, and automated scoring. The CPC device was connected to the patient's chest to record the single-lead ECG signal during sleep and analyze ECG data (Thomas et al., 2005). The CPC measurements were conducted on the first and fourteenth night of hospital stays.

The CPC device collected data for sleep time, respiratory events, actigraphy, and body position. The CPC analysis included the following: total sleep and in-bed times; stable time latency and stable sleep time by high-frequency coupling; unstable sleep time by low frequency coupling; REM, wake-up and get-up times (episodes) per night; sleep stages; and sleep efficiency (ratio of total sleep time to total in-bed time).

2.7. Statistical analysis

Statistical analyses were performed with SPSS version 23.0 software. Descriptive data are shown as mean ± standard deviation. The Kolmogorov-Smirnov one-sample test was used to test the normal distribution of the data. For data with normal distribution, a paired *t*-test was applied to compare the CPC variables and psychological tests pre- and post-treatment. For data without normal distribution, the Wilcoxon test was used. Spearman's correlation was employed to examine the association between CPC measurements and psychometrics. Exploratory logistic regression analysis was conducted to determine the attribution of CPC indices to the treatment response using a stepwise regression model. Multiple regression analysis was conducted to control covariates of BMI, antidepressant types and PSQI scores at baseline. A *P*-value < 0.05 (2-tailed) was considered statistically significant.

3. Results

3.1. Demographics

The study population comprised 41 patients with MDD (Table 1). The average age of the patients was 49.8 ± 14.2 y (range, 17–73 y) with an average education of 8.5 ± 3.8 y (range, 0–16 y). The majority of the patients were women (68.3%, 28/41). The average BMI was 24.8 ± 3.2. The average disease duration was 55.6 ± 66.0 months. Nine patients had disease relapse. Of the 41 patients, 27 received

Table 1
Demographic data of the 41 patients and their correlation with response after 4 weeks *.

S		Response after 4 weeks	
		r	P
Age, y	49.8 ± 14.2	0.157	0.326
Gender, male/female	13/28	–0.126	0.431
BMI, kg/m^2	24.8 ± 3.2	0.273	**0.085**
Education, y	8.5 ± 3.8	0.088	0.585
Family history, positive/negative	9/32	0.019	0.908
Relapse, yes/no	15/26	0.191	0.231
Disease course, mo	55.6 ± 66.0	0.211	0.184
Antidepressants, SSRI/non-SSRI	27/14	0.394	**0.011**
PSQI	17.1 ± 2.2	0.319	**0.042**

* Data reported as *n*, unless noted otherwise. Values that are associated with a *P* value <0.1 are given in bold.

selective serotonin reuptake inhibitors (SSRIs) including escitalopram (20 mg/d), sertraline (150–200 mg/d), fluoxetine (20 mg/d), paroxetine (20 mg/d), and fluvoxamine (150 mg/d). Fourteen patients received non-SSRI treatment, including venlafaxine (150–225 mg/d), duloxetine (60–90 mg/d), mirtazapine (30 mg/d), and agomelatine (50 mg/d). Table 1 also shows the correlations between demographic characteristics, PSQI score at baseline and response to antidepressant treatment.

Compared with the pre-treatment baseline data, the following were significantly less at 2 weeks after the beginning of treatment (Table 2): unstable sleep time, total sleep time, and sleep efficiency ($P = 0.027$, 0.013, and 0.016, respectively). At 2 weeks after the start of anti-depression treatment, the following were comparable with the baseline data: stable sleep latency, stable sleep time, REM sleep time, wake-up time, sleep score, sleep quality ratio (stable sleep time/unstable sleep time), wake-up episodes, and get-up time.

3.2. Psychometrics changes by treatment

There were no significant changes from baseline in self-reported sleepiness at 4 weeks after treatment, as reflected by ESS scores ($Z = –0.16$, $P = 0.87$). The following scores were significantly lower at 4 weeks after treatment relative to the baseline values: PSQI; total HAMD-24; and HAMD-24 for anxiety somatic symptoms, cognition, retardation, somnipathy, and despair ($P < 0.001$, all; Table 3).

3.3. Associations between baseline sleep indices and improvement in depression at week 2

We investigated whether sleep indices derived from the CPC analysis at baseline were related to the questionnaire scores 2 weeks after treatment. Total sleep time significantly correlated with the reduction in somnipathy score ($r = –0.329$, $P = 0.036$). The number of unstable sleep episodes significantly correlated with reduction in the retardation factor score ($r = –0.429$, $P = 0.005$). REM sleep episodes significantly correlated with reductions in cognitive and retardation factor scores ($r = –0.375$, $P = 0.016$ and $r = 0.014$, $P = 0.380$, respectively), and total score reduction ($r = –0.311$, $P = 0.048$; Table 4) at 2 weeks.

Table 2
CPC-based sleep quality before and at 2 weeks after beginning treatment.

	Week 0	Week 2	t/Z	P (2-tailed)
Total sleep time, min	496.0 ± 70.4	452.8 ± 104.3	2.585	0.013*
Stable sleep latency, min	65.0 ± 87.9	64.6 ± 89.9	–0.237	0.812
Stable sleep time, min	196.2 ± 107.8	184.8 ± 111.3	–0.251	0.802
Unstable sleep, min	191.1 ± 93.0	159.0 ± 71.7	2.297	0.027*
REM sleep time, min	96.1 ± 51.2	98.2 ± 44.5	–0.181	0.856
Wake-up time, min	20.8 ± 28.3	20.5 ± 14.2	–0.912	0.362
Sleep quality ratio	1.7 ± 2.6	1.6 ± 1.9	–0.538	0.591
Sleep efficiency,%	88.2 ± 10.9	82.2 ± 13.6	–2.410	0.016 *
Wake-up episodes, *n*	7.3 ± 5.2	9.1 ± 4.9	–1.891	0.059
Get-up time, min	7.9 ± 12.8	12.1 ± 17.1	–1.705	0.088

* $P < 0.05$.

Table 3
Subjective sleep assessments and HAMD-24 item scores.

		Week 0	Week 4	Z	P (2-tailed)
PSQI		17.1 ± 2.2	9.1 ± 2.0	–5.533	<0.001
ESS		3.6 ± 1.0	3.7 ± 1.1	–0.160	0.873
HAMD-24	Anxiety/somatic	4.0 ± 1.8	1.7 ± 1.5	–5.138	<0.001
	Cognition	2.9 ± 1.6	0.6 ± 0.9	–5.261	<0.001
	Retardation	5.9 ± 1.0	2.5 ± 1.0	–5.615	<0.001
	Somnipathy	4.9 ± 1.4	1.7 ± 1.1	–5.611	<0.001
	Despair	3.0 ± 1.2	1.3 ± 0.9	–4.935	<0.001
	Total	24.7 ± 3.1	9.9 ± 4.1	–5.581	<0.001

3.4. Association between depression improvement at 4 weeks and sleep indices at 2 weeks

The correlations between objective sleep variables at 2 weeks and questionnaire scores at 4 weeks after the start of treatment were investigated. Total in-bed time positively correlated with reductions in scores for anxiety/somatic symptoms ($r = 0.401$, $P = 0.009$), retardation factor ($r = 0.319$, $P = 0.042$), and total score ($r = 0.362$, $P = 0.020$). Total sleep time positively correlated with reductions in scores for anxiety/somatic symptoms ($r = 0.426$, $P = 0.006$), and despair ($r = 0.326$, $P = 0.037$). Unstable sleep episodes positively correlated with reduction in the despair score ($r = 0.328$, $P = 0.036$). Get-up episodes negatively correlated with the PSQI total score ($r = –0.389$, $P = 0.012$). Get-up time negatively correlated with the PSQI total score ($r = –0.392$, $P = 0.011$; Table 5).

3.5. CPC indices to predict early response to treatment

Exploratory regression analysis was performed to identify predictors of response to treatment (Table 6). The total in-bed time and stable sleep latency at baseline were significantly associated with treatment response (OR = 0.978, $P = 0.004$ and OR = 0.982, $P = 0.023$, respectively). Reduction in total in-bed time and stable sleep latency at 2 weeks after treatment were also attributed to anti-depression response (OR = 0.984, $P = 0.004$ and OR = 0.975, $P = 0.012$). Using the input model of logistic regression, unstable sleep episodes and stable sleep latency at week 2 was significantly associated with treatment response (OR = 0.455, $P = 0.007$ and OR = 1.019, $P = 0.027$).

In multiple logistic regression models (Table 7), after adjusting for BMI, antidepressant types and PSQI scores at baseline, the total in-bed time and stable sleep latency at baseline were significantly associated with treatment response (OR = 1.024, $P = 0.010$ and OR = 1.024, $P = 0.032$, respectively). Reduction in total in-bed time and stable sleep latency at 2 weeks after treatment were also attributed to anti-depression response (OR = 1.034, $P = 0.023$ and OR = 1.040, $P = 0.031$). However, after applying the multiple logistic regression, the predicting effects of CPC indices at week 2 disappeared ($P > 0.05$).

4. Discussion

In this pilot study, we investigated associations between CPC variables and depression symptoms and sleep quality in patients with MDD after antidepressant therapy. The subjective assessment methods consisted of the HAMD-24, ESS, and PSQI. It was found that after 2 weeks of antidepressant therapy, the total sleep time, unstable sleep time, and sleep efficiency were significantly lower compared with the baseline values. Total sleep time, unstable sleep episodes, and REM sleep

Table 4
Correlations between HAMD scores reduction at week 2 and CPC-Based sleep variables at baseline, reported as *r* (*P*).

	HAMD-24 scores reduction at week 2				
	△Cog1	△Ret1	△Som1	△Tol1	PSQI (baseline)
Total sleep time, min	0.073 (0.649)	–0.023 (0.888)	–0.329 (0.036*)	–0.043 (0.790)	–0.010 (0.950)
Stable sleep latency, min	–0.291 (0.064)	–0.099 (0.537)	–0.058 (0.721)	–0.110 (0.493)	0.076 (0.636)
Unstable sleep episodes	–0.197 (0.218)	–0.429 (0.005**)	0.117 (0.466)	–0.244 (0.125)	0.048 (0.766)
REM sleep episodes	–0.375 (0.016*)	–0.380 (0.014*)	–0.166 (0.299)	–0.311 (0.048*)	–0.100 (0.534)
Wake-up episodes	–0.301 (0.056)	–0.153 (0.340)	–0.292 (0.064)	–0.282 (0.074)	–0.156 (0.330)

Abbreviations: △Cog1, the cognitive factor score reduction at week 2; △Ret1, retardation factor score reduction at week 2; △Som1, somnipathy factor score reduction at week 2; △Tol1, total score reduction at week 2.

* $P < 0.05$;.

** $P < 0.01$.

Table 5
Correlations between HAMD score reduction at week 4 and CPC-based sleep variables at week 2, reported as *r* (*P*).

	HAMD-24 scores reduction at week 4				
	△An × 2	△Ret2	△Des2	△Tol2	PSQI (wk 4)
Sleep score	–0.010 (0.953)	–0.294 (0.062)	0.035 (0.827)	–0.080 (0.620)	–0.033 (0.836)
Stable sleep time, min	0.281 (0.075)	0.030 (0.851)	0.085 (0.595)	0.142 (0.375)	–0.060 (0.712)
Total in-bed time, min	0.401 (0.009**)	0.319 (0.042*)	0.303 (0.054)	0.362 (0.020*)	–0.148 (0.357)
Total sleep time, min	0.426 (0.006**)	0.197 (0.218)	0.326 (0.037*)	0.281 (0.075)	–0.161 (0.316)
Unstable sleep episodes	0.140 (0.382)	–0.126 (0.432)	0.328 (0.036*)	0.042 (0.796)	–0.146 (0.361)
Get-up episodes	–0.050 (0.756)	–0.013 (0.936)	0.121 (0.453)	0.033 (0.837)	–0.389 (0.012*)
Get-up time, min	–0.079 (0.624)	–0.048 (0.765)	–0.026 (0.871)	–0.027 (0.869)	–0.392 (0.011*)

Abbreviations: △Anx2, anxiety/somatic factor score reduction at week 4; △Ret2, retardation factor score reduction at week 4; △Des2, despair factor score reduction at week 4; △Tol2, total score reduction at week 4.

* $P < 0.05$;.

** $P < 0.01$.

Table 6
Logistic regression analysis to identify the variables contributing to response to antidepressant treatment.

	Variable	B	SE	WALD	*P*	OR (95% CI)
Baseline	Total in-bed time, min	–0.022	0.008	8.218	0.004	0.978 (0.964–0.993)
	Stable sleep latency, min	–0.018	0.008	5.139	0.023	0.982 (0.968–0.998)
Reduction	△Total in-bed time, min	–0.016	0.006	8.111	0.004	0.984 (0.973–0.995)
	△Stable sleep latency, min	–0.025	0.010	6.338	0.012	0.975 (0.957–0.995)
Week 2 *	Unstable sleep episodes	–0.788	0.293	7.232	0.007	0.455 (0.256–0.808)
	Stable sleep latency, min	0.019	0.009	4.866	0.027	1.019 (1.002–1.036)

* Logistic regression with input method.

Table 7
Multiple logistic regression analysis results after adjusting for co-variables.

		B	SE	WALD	*P*	OR (95% CI)
Baseline	Total in-bed time, min	0.023	0.009	6.670	0.010	1.024 (1.006–1.042)
	Stable sleep latency, min	0.024	0.011	4.594	0.032	1.024 (1.002–1.047)
Reduction	△Total in-bed time, min	0.033	0.015	5.151	0.023	1.034 (1.005–1.064)
	△Stable sleep latency, min	0.039	0.018	4.626	0.031	1.040 (1.003–1.078)

β and *p* values of multiple logistic regression models were calculated after adjusting for BMI, antidepressant types, PSQI scores at baseline.

episodes at baseline were significantly associated with depression levels, as assessed by the HAMD-24 at 2 weeks after treatment. The total in-bed time and stable sleep latency were significantly associated with the response to therapy, evaluated at 4 weeks. These findings suggest that CPC variables can be used to predict the effect of early treatment of antidepressants on sleep quality in patients with MDD.

The mechanisms that underlie the response of CPC parameters to antidepressant treatment in MDD are unknown. However, these responses may help inform our understanding of the pathophysiology of sleep instability in depression. The present findings that patients with MDD experience longer stable sleep latency and total in-bed time before treatment are consistent with the excessive wakefulness-facilitating factors found in depressed patients (Adrien, 2002). Longer stable sleep latency and total in-bed time may reflect hyperarousal caused by increased activity of the hypothalamic-pituitary-adrenal axis and central negative affective process, which increases the possibility of depression (Adrien, 2002). It is well accepted that the activity of brain regions that are responsible for higher order autonomic control and regulate heart rhythm and respiratory rate are altered in depression, and thus may influence the CPC analysis. These brain regions include the anterior cingulate, ventromedial prefrontal cortex, insular cortex, and amygdala (Bae et al., 2006; Drevets et al., 2008; Liotti et al., 2001; van Eijndhoven et al., 2009; von Leupoldt et al., 2008).

EEG-based PSG is the standard technology for studying sleep quality. However, the EEG-based PSG focuses on brain activities and reflects only the macrostructure of sleep, and can be easily affected by

endogenous and exogenous factors (Terzano and Parrino, 2000). Since sleep is a physiological process in which multiple organs and systems are involved (Bianchi and Thomas, 2013), ECG-based CPC to study sleep quality has been developed to supplement PSG (Thomas et al., 2005, 2017). CPC analysis couples respiratory oscillations during sleep using an ECG signal. Stable sleep and unstable sleep are characterized by high- and low-frequency coupling between heart rate and respiration, respectively (Thomas et al., 2005; Thomas et al., 2017). Thus, ECG-based CPC analysis provides information regarding sleep quality as well as sleep-disordered breathing (Harrington et al., 2013; Thomas et al., 2005).

Despite all these advantages, the CPC analysis has some disadvantages. Detection of stable and unstable sleep with CPC analysis reflects only an approximation of the EEG cyclic alternating pattern (CAP) and non-CAP (Thomas et al., 2005). The CPC analysis is based on the recorded ECG signal, which is influenced by arrhythmia and other environmental factors (Guo et al., 2014; Zhu et al., 2016).

Patients with MDD have sleep problems such as insomnia, and CPC analysis has been used to study sleep quality in these patients. Yang et al. (2011) used CPC analysis to conclude that medication-free patients with MDD had reduced stable sleep, increased unstable sleep, and increased wakefulness/REM sleep, whereas medicated patients experienced restored sleep stability. This suggests that CPC can be used to analyze the response to antidepressants in patients with MDD. Consistent with this, Schramm and colleagues (Schramm et al., 2014) determined that the antidepressant bupropion increased the stable-unstable sleep transitions in depressed patients, based on CPC analysis. This suggests that CPC analysis is useful for evaluating the response to antidepressants in depressed patients.

In addition, using ECG-based CPC analysis, Schramm et al. (2016) found that the sleep quality of chronically depressed patients improved with cognitive behavioral psychotherapy, and Ma et al. (2018) reported that Tai Chi decreased stable sleep latency, increased stable sleep percentages, and decreased unstable sleep percentages in depressed individuals. In the present study, we used ECG-based CPC analysis to evaluate the effect of an antidepressant on sleep quality, and found that patients with MDD experienced a reduction in unstable sleep. Taken together, these studies indicate that CPC analysis is valuable for evaluating the effect of antidepressants on sleep quality in patients with MDD.

Sleep disturbance has been used to predict the risk of depression, and is a major symptom in patients with MDD. For example, Troxel et al. (2012) reported that objectively measured sleep disturbances were associated with an increased risk of non-remission of depression in patients with MDD. In addition, Peters van Neijenhof et al. (2018) reported that sleep disturbance independently correlated with the severity of depression in depressed elderly persons.

Sleep quality can be used to predict the treatment response in patients with MDD. For example, Troxel et al. (2012) found that objectively measured sleep disturbance predicted treatment outcomes in depressed patients after psychotherapy. Manglick et al. (2013) reported that persistent sleep disturbances were associated with poorer treatment responses in adolescents with depression.

EEG-based methods have been used to measure sleep disturbances for predicting treatment outcome in patients with MDD. For example, Thase et al. (1998) reported that the EEG sleep profile (REM latency, REM density, and sleep efficiency) of remitted patients with MDD improved after cognitive behavior therapy. Khodayari-Rostamabad et al. (2013) found that a machine learning approach based on pre-treatment EEG data effectively predicted the treatment response to SSRIs in patients with MDD.

In the present study, we used ECG-based CPC analysis to measure sleep quality, and found that CPC-based sleep variables such as total sleep time, unstable sleep episode, and REM sleep episodes were significantly associated with improvement in depression at 2 and 4 weeks after beginning antidepressant treatment in patients with MDD. Our findings suggest that ECG-based CPC analysis may be a valuable method for predicting the treatment outcome in patients with MDD.

This study has the following limitations. First, this pilot study included a relatively small sample of 41 participants, which may affect the statistical power of the results. Future studies with a large sample size are required to confirm the findings of this study. Second, this study did not include a control group who did not receive antidepressant treatment. Therefore, although we found that the antidepressant treatment improved subjective and objective sleep quality in patients with MDD, we cannot exclude the possibility that these effects were caused by the passage of time, and are not due to the drug treatment. Further case-control studies will investigate the effect of antidepressant treatment on sleep quality using ECG-based CPC analysis. Third, in this study all the patients were treated with personalized medication and psychotherapy, and the treatments varied. Future studies will focus on the predictive effects of CPC indices when specific drugs or types of psychotherapy are used that target MDD.

Fourth, in this study the follow-up after beginning antidepressant treatment was relatively short (4 weeks). In our hospital, patients with MDD are generally discharged after the 4 weeks of treatment. To avoid the influences of environmental change and refusal to take medication, a follow-up of 4 weeks was selected as our ending point. Future studies will investigate the effect of antidepressants with a longer follow-up period (>6 weeks).

Fifth, this study recruited all patients from a single site, which may cause a potential sample bias. A recall bias may result from the use of self-reported questionnaires such as PSQI and ESS. A future multicenter study will may confirm the findings of this study, using objective assessment means such as PSG.

Sixth, the age range of the patients in this study was quite wide (18 to 65 years). Since age is a significant factor that affects sleep quality, in a future study with a large sample size, we will examine the effect of antidepressant treatment on sleep quality using ECG-based CPC analysis in patients with a narrower age range.

A final limitation is that the results of the current study were inconsistent over time. Total sleep time and REM sleep episodes at baseline were associated with the HAMD-24 score reduction at week 2, whereas total in-bed time at week 2 was associated with the HAMD-24 score reduction at week 4. This may be due to a number of reasons, such as small sample size and short follow-up time. Only one night of CPC analysis may also be unreliable, and may cause a type I error.

In summary, this study investigated the CPC variables that may predict the therapeutic response to antidepressants in patients with MDD. It was determined that objective and subjective sleep quality and symptoms of depression improved after antidepressant treatment. CPC variables such as total in-bed time and stable sleep latency, measured before and 2 weeks after beginning treatment, are associated with improvements of depression symptoms at 4 weeks in patients with MDD.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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References

Adrien, J., 2002. Neurobiological bases for the relation between sleep and depression. Sleep Med. Rev. 6, 341–351.
Armitage, R., 2007. Sleep and circadian rhythms in mood disorders. Acta Psychiatr. Scand. Suppl. 433, 104–115.
Bae, J.N., MacFall, J.R., Krishnan, K.R., Payne, M.E., Steffens, D.C., Taylor, W.D., 2006. Dorsolateral prefrontal cortex and anterior cingulate cortex white matter alterations

in late-life depression. Biol. Psychiatry 60, 1356–1363.
Bianchi, M.T., Thomas, R.J., 2013. Technical advances in the characterization of the complexity of sleep and sleep disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry 45, 277–286.
Buysse, D.J., Ancoli-Israel, S., Edinger, J.D., Lichstein, K.L., Morin, C.M., 2006. Recommendations for a standard research assessment of insomnia. Sleep 29, 1155–1173.
Buysse, D.J., Reynolds 3rd, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 28, 193–213.
Chan, J.W., Lam, S.P., Li, S.X., Yu, M.W., Chan, N.Y., Zhang, J., Wing, Y.K., 2014. Eveningness and insomnia: independent risk factors of nonremission in major depressive disorder. Sleep 37, 911–917.
Cheng, P., Goldschmied, J., Deldin, P., Hoffmann, R., Armitage, R., 2015. The role of fast and slow EEG activity during sleep in males and females with major depressive disorder. Psychophysiology 52, 1375–1381.
Cuijpers, P., Reynolds 3rd, C.F., Donker, T., Li, J., Andersson, G., Beekman, A., 2012. Personalized treatment of adult depression: medication, psychotherapy, or both? A systematic review. Depress Anxiety 29, 855–864.
Drevets, W.C., Price, J.L., Furey, M.L., 2008. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct. Funct. 213, 93–118.
Fenzl, T., Touma, C., Romanowski, C.P., Ruschel, J., Holsboer, F., Landgraf, R., Kimura, M., Yassouridis, A., 2011. Sleep disturbances in highly stress reactive mice: modeling endophenotypes of major depression. BMC Neurosci. 12, 29.
Guo, D., Ma, Y., Peng, C.K., Sun, S.C., Wu, H.L., Sun, R.S., Liu, Y.H., 2014. Application of cardiopulmonary coupling(CPC) in pediatric sleep. World J. Sleep Med. 2, 75–81.
Harrington, J., Schramm, P.J., Davies, C.R., Lee-Chiong Jr., T.L., 2013. An electrocardiogram-based analysis evaluating sleep quality in patients with obstructive sleep apnea. Sleep Breath. 17, 1071–1078.
Insel, T.R., Wang, P.S., 2009. The STAR*D trial: revealing the need for better treatments. Psychiatr. Serv. 60, 1466–1467.
Johns, M.W., 1992. Reliability and factor analysis of the epworth sleepiness scale. Sleep 15, 376–381.
Khodayari-Rostamabad, A., Reilly, J.P., Hasey, G.M., de Bruin, H., Maccrimmon, D.J., 2013. A machine learning approach using EEG data to predict response to SSRI treatment for major depressive disorder. Clin. Neurophysiol. 124, 1975–1985.
Liotti, M., Brannan, S., Egan, G., Shade, R., Madden, L., Abplanalp, B., Robillard, R., Lancaster, J., Zamarripa, F.E., Fox, P.T., Denton, D., 2001. Brain responses associated with consciousness of breathlessness (air hunger). Proc. Natl. Acad. Sci. USA 98, 2035–2040.
Liu, X.C., Tang, M.Q., Hu, L., Wang, A.Z., Wu, H.X., Zhao, G.F., Gao, C.N., Li, W.S., 1996. Reliability and validity of the Pittsburgh sleep quality index. Chin. J. Psychiatry 29, 103–107.
Ma, Y., Yeung, A., Yang, A.C., Peng, C.K., Clain, A., Alpert, J., Fava, M., Yeung, A.S., 2018. The effects of Tai Chi on sleep quality in Chinese American patients with major depressive disorder: a pilot study. Behav. Sleep Med. 16, 398–411.
Manglick, M., Rajaratnam, S.M., Taffe, J., Tonge, B., Melvin, G., 2013. Persistent sleep disturbance is associated with treatment response in adolescents with depression. Aust. N. Z. J. Psychiatry 47, 556–563.
Peng, L.L., Li, J.R., Sun, J.J., Li, W.Y., Sun, Y.M., Zhang, R., Yu, L.L., 2011. Reliability and validity of the simplified Chinese version of Epworth sleepiness scale. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 46, 44–49.
Peters van Neijenhof, R.J.G., van Duijn, E., Comijs, H.C., van den Berg, J.F., de Waal, M.W.M., Oude Voshaar, R.C., van der Mast, R.C., 2018. Correlates of sleep disturbances in depressed older persons: the Netherlands study of depression in older persons (NESDO). Aging Ment. Health 22, 233–238.
Schramm, P.J., Poland, R.E., Rao, U., 2014. Bupropion response on sleep quality in patients with depression: implications for increased cardiovascular disease risk. Eur. Neuropsychopharmacol. 24, 207–214.
Schramm, P.J., Zobel, I., Monch, K., Schramm, E., Michalak, J., 2016. Sleep quality changes in chronically depressed patients treated with mindfulness-based cognitive therapy or the cognitive behavioral analysis system of psychotherapy: a pilot study. Sleep Med. 17, 57–63.
Sharpley, A.L., Cowen, P.J., 1995. Effect of pharmacologic treatments on the sleep of depressed patients. Biol. Psychiatry 37, 85–98.
Steiger, A., Kimura, M., 2010. Wake and sleep EEG provide biomarkers in depression. J. Psychiatr. Res. 44, 242–252.
Sun, X.Y., Li, Y.X., Yu, C.Q., Li, L.M., 2017. Reliability and validity of depression scales of Chinese version: a systematic review. Zhonghua Liu Xing Bing Xue Za Zhi 38, 110–116.
Sylvia, L.G., Salcedo, S., Bianchi, M.T., Urdahl, A., Nierenberg, A.A., Deckersbach, T., 2014. A novel home sleep monitoring device and brief sleep intervention for bipolar disorder: feasibility, tolerability, and preliminary effectiveness. Cognit. Ther. Res. 38, 55–61.
Terzano, M.G., Parrino, L., 2000. Origin and significance of the cyclic alternating pattern (CAP). REVIEW ARTICLE. Sleep Med. Rev. 4, 101–123.
Terzano, M.G., Parrino, L., Smerieri, A., Chervin, R., Chokroverty, S., Guilleminault, C., Hirshkowitz, M., Mahowald, M., Moldofsky, H., Rosa, A., Thomas, R., Walters, A., 2002. Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep. Sleep Med. 3, 187–199.
Thase, M.E., 2006. Depression and sleep: pathophysiology and treatment. Dialogues Clin. Neurosci. 8, 217–226.
Thase, M.E., 2014. Using biomarkers to predict treatment response in major depressive disorder: evidence from past and present studies. Dialogues Clin. Neurosci. 16, 539–544.
Thase, M.E., Fasiczka, A.L., Berman, S.R., Simons, A.D., Reynolds 3rd, C.F., 1998. Electroencephalographic sleep profiles before and after cognitive behavior therapy of depression. Arch. Gen. Psychiatry 55, 138–144.
Thase, M.E., Kupfer, D.J., Fasiczka, A.J., Buysse, D.J., Simons, A.D., Frank, E., 1997. Identifying an abnormal electroencephalographic sleep profile to characterize major depressive disorder. Biol. Psychiatry 41, 964–973.
Thomas, R.J., Mietus, J.E., Peng, C.K., Goldberger, A.L., 2005. An electrocardiogram-based technique to assess cardiopulmonary coupling during sleep. Sleep 28, 1151–1161.
Thomas, R.J., Wood, C., Bianchi, M.T., 2017. Cardiopulmonary coupling spectrogram as an ambulatory clinical biomarker of sleep stability and quality in health, sleep apnea and insomnia, Sleep. https://doi.org/10.1093/sleep/zsx196. [Epub ahead of print].
Troxel, W.M., Kupfer, D.J., Reynolds 3rd, C.F., Frank, E., Thase, M.E., Miewald, J.M., Buysse, D.J., 2012. Insomnia and objectively measured sleep disturbances predict treatment outcome in depressed patients treated with psychotherapy or psychotherapy-pharmacotherapy combinations. J. Clin. Psychiatry 73, 478–485.
Tsuno, N., Besset, A., Ritchie, K., 2005. Sleep and depression. J. Clin. Psychiatry 66, 1254–1269.
van Eijndhoven, P., van Wingen, G., van Oijen, K., Rijpkema, M., Goraj, B., Jan Verkes, R., Oude Voshaar, R., Fernandez, G., Buitelaar, J., Tendolkar, I., 2009. Amygdala volume marks the acute state in the early course of depression. Biol. Psychiatry 65, 812–818.
von Leupoldt, A., Sommer, T., Kegat, S., Baumann, H.J., Klose, H., Dahme, B., Buchel, C., 2008. The unpleasantness of perceived dyspnea is processed in the anterior insula and amygdala. Am. J. Respir. Crit. Care Med. 177, 1026–1032.
Yang, A.C., Yang, C.H., Hong, C.J., Tsai, S.J., Kuo, C.H., Peng, C.K., Mietus, J.E., Goldberger, A.L., Thomas, R.J., 2011. Sleep state instabilities in major depressive disorder: detection and quantification with electrocardiogram-based cardiopulmonary coupling analysis. Psychophysiology 48, 285–291.
Zhu, Y.Q., Long, Q., Wang, C., Shuai, X.J., Chen, B., Kong, J., Wei, Y.L., 2016. Relationship between sleep architecture and blood pressure dynamic change in patients with sleep apnea syndrome. Zhonghua Yi Xue Za Zhi 96, 2220–2223.