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Heart rate variability changes in major depressive disorder during sleep: Fractal index correlates with BDI score during REM sleep

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ABSTRACT

We investigated the relationship between autonomic nervous system activity during each sleep stage and the severity of depressive symptoms in patients with major depressive disorder (MDD) and healthy control subjects. Thirty patients with MDD and thirty healthy control subjects matched for sex, age, and body mass index completed standard overnight polysomnography. Depression severity was assessed using the Beck Depression Inventory (BDI). Time- and frequency-domain, and fractal HRV parameters were derived from 5-min electrocardiogram segments during light sleep, deep sleep, rapid eye movement (REM) sleep, and the pre- and post-sleep wake periods. Detrended fluctuation analysis (DFA) alpha-1 values during REM sleep were significantly higher in patients with MDD than in control subjects, and a significant correlation existed between DFA alpha-1 and BDI score in all subjects. DFA alpha-1 was the strongest predictor for the BDI score, along with REM density as a covariate. This study found that compared with controls, patients with MDD show reduced complexity in heart rate during REM sleep, which may represent lower cardiovascular adaptability in these patients, and could lead to cardiac disease. Moreover, DFA alpha-1 values measured during REM sleep may be useful as an indicator for the diagnosis and monitoring of depression.

1. Introduction

Major depressive disorder (MDD) is a common mental disease and the leading cause of disease burden and disability worldwide (Thornicroft et al., 2017). MDD is associated with an increased risk of cardiovascular morbidity and mortality (Taylor, 2010; Yeh et al., 2015). Yet, the precise mechanisms underlying this association are unknown.

Several studies have suggested that autonomic dysfunction is a common pathophysiological mechanism linking depression and cardiovascular disease (Hare et al., 2014; Sgoifo et al., 2015; Thayer and Lane, 2007). Several studies have reported autonomic imbalances during specific mental tasks (Sun et al., 2016) and under stress conditions (Lambert and Lambert, 2011). Altered autonomic nervous system (ANS) activity has also been related to an increased risk of cardiovascular disease (Carney et al., 2005; Malpas, 2010).

Analyses of heart rate variability (HRV) provide a quantitative assessment of the ANS in clinical patients. Accordingly, various studies have used HRV to compare ANS activity among patients with psychiatric, affective, or mood disorders and healthy control subjects during the waking or resting states (Alvares et al., 2016; Henje Blom et al., 2010; Kemp et al., 2010). Previous studies of cardiac function in depression suggest that overall HRV (standard deviation of normal R-R intervals [SDNN]) is decreased and vagal tone (the root mean square differences of R-R [RMSSD] and power in high frequency range [HF]) is inhibited in patients with depression compared to non-depressed control subjects (Carney et al., 2005; Sgoifo et al., 2015; Van der Kooy et al., 2006; Yeh et al., 2015). Nevertheless, few studies have analyzed HRV during sleep in patients with MDD. Analyses of HRV during sleep eliminate confounding factors in the external environment and changes in emotional status that may influence cardiac activity. Additionally, sleep stages are specifically associated with distinct mechanisms of autonomic control (Bartsch et al., 2012). Polysomnographic findings have demonstrated sleep continuity disturbances, slow wave sleep

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deficits, and rapid eye movement (REM) sleep abnormalities in patients with MDD (Ansseau et al., 1985; Berger and Riemann, 1993; Cartwright et al., 2003; Franzen and Buysse, 2008; Kupfer, 2006; Palagini et al., 2013; Paunio et al., 2015). Therefore, a better understanding of HRV during sleep in patients with MDD can inform the relationship between depression and ANS dysfunction.

Migliorini (2012) compared HRV between a patient with bipolar disorder in the depressed state and healthy control subjects across 4 different nights. The results indicated decreased time-domain HRV in the patient with bipolar disorder compared to healthy subjects and a correlation between HRV complexity and depression severity; however, this research evaluated a single patient and did not evaluate polysomnographic findings which requires a more study for extensive statistical analysis. Pawlowski et al. (2017) investigated time- and frequency-domain HRV as well as prefrontal theta cordance during 3-min periods of REM sleep in patients with a depressive episode who were treated with antidepressants for 4 weeks to examine HRV and prefrontal theta cordance as potential biomarkers of antidepressant treatment response (Pawlowski et al., 2017). Despite significant differences in time- and frequency-domain HRV in patients with depression compared to healthy control subjects, these parameters failed to discriminate responders from non-responders.

Detrended fluctuation analysis (DFA) quantifies the presence of fractal correlation properties in R-R intervals which characterize complexity of fluctuations in cardiovascular dynamics. The DFA value α indicates the autocorrelation properties of the signal: $\alpha < 0.5$, anti-correlated signal; $\alpha = 0.5$, uncorrelated signal (white noise); $\alpha > 0.5$, positive autocorrelation in the signal; $\alpha = 1$, 1/f noise; $\alpha = 1.5$, Brownian noise or random walk (Schmitt and Ivanov, 2007). DFA distinguish nonlinear behavior in heart rate time series better than time- and frequency-domain HRV indices (Antônio et al., 2014; Voss et al., 1996). Accordingly, the fractal HRV indices detect R-R interval changes more sensitively than conventional analyses and discriminate (Carvalho et al., 2011; De Souza et al., 2014; Krishnam et al., 2005) and estimate the severity of altered physiology (Da Silva et al., 2015). In fact, the complexity of heart rate has been reported to be reduced in patients with depression compared to healthy control subjects (Boettger et al., 2008; Yang et al., 2011; Yeragani et al., 2002). Moreover, REM sleep, which shows abnormal characteristics such as REM latency, REM duration, and REM density in patients with MDD, also has been characterized by high DFA values in comparison with other sleep stages in both control subjects and patients with sleep apnea (Bunde et al., 2000; Ivanov, 2007; Penzel et al., 2003). The goal of the present study was first, to investigate the HRV indices during each sleep stage in patients with MDD; second, to compare them with those of healthy controls; and third, to elucidate whether the HRV indices are associated with depression severity.

2. Methods

2.1. Subjects

The Institutional Review Board of Seoul National University Hospital approved this retrospective study and waived the requirement for informed patient consent (IRB no. 1608-150-787). We enrolled 30 patients with MDD and 30 healthy control subjects matched for sex, age, and body mass index from our previous study (Kwon et al., 2017). Patients with MDD were interviewed by a certified psychiatrist and diagnosed with MDD as per DSM-5 criteria (American Psychiatric Association, 2013) but a structured interview, such as SCID or CIDI, was not conducted. The diagnosis was current, and subjects were excluded in case of any other psychiatric comorbidity, such as schizophrenia spectrum disorder, bipolar disorder, anxiety disorder, obsessive compulsive disorder, and trauma related disorder. In this study, only 3 patients had a history of insomnia or daytime sleepiness, although sleep quality ratings using the Pittsburgh Sleep Quality Index (PSQI) revealed mild habitual sleep disturbances in 10 patients and moderate habitual sleep disturbances in 5 patients (Buysse et al., 1989). None of the patients with MDD used any antidepressant on the PSG night. In addition, none of the patients had taken long-acting medication including fluoxetine and depot neuroleptics. Depression severity was assessed using the Beck Depression Inventory (BDI). Subjects were free of any other medical or neurological disorders, cardiovascular disorders, and medication use or substance use disorders. Moreover, any patient with respiratory sleep disorders such as sleep apnea was excluded. It was done because sleep apnea has been reported to have a strong association with sleep-related events during sleep (Yoon et al., 2018).

2.2. Polysomnography

All subjects underwent overnight diagnostic polysomnography (PSG) at the Center for Sleep and Chronobiology of Seoul National University Hospital. Nocturnal polysomnographic recordings were performed as per the standard PSG manual, scored in 30-s epochs by certified sleep technologists, and verified by sleep physicians in accordance with the 2012 AASM manual (Berry et al., 2012). The following data were collected: electroencephalography (EEG) at C3-A2 and O2-A1; bilateral electrooculography (EOG); electromyography at the chin and anterior tibialis muscles; electrocardiography (ECG) at lead II; body posture using a tri-axis accelerometer; nasal pressure using a nasal cannula/pressure transducer; oronasal airflow using a thermistor; thoracic and abdominal volume changes using piezoelectric-type belts; audible snoring using a microphone; and blood oxygen saturation using a pulse oximeter. All signals were collected at a 250-Hz sampling frequency.

2.3. REM detection

REM events during REM sleep period were detected using a semi-automatic algorithm and bilateral EOG recordings. First, the 2 EOG signals were band-pass filtered between 1 and 5 Hz using a fourth-order digital Butterworth filter to attenuate fast background activity (Agargun and Cartwright, 2003). A detection threshold was set at the mean + 2*standard deviation of the EOG signals and epochs with absolute amplitude > 1 mV were discarded from the computation (Andrillon, 2012). REM candidates surpassing the detection threshold were further inspected for 3 criteria: maximal slope > 1 μV/ms; duration of signal above the threshold < 1.5 s; and opposite polarity and synchronization (within 70 ms) of both eye signals, intended to prevent the detection of transmitted EEG potentials from the frontal lobes. Finally, to ensure the accuracy of this semi-automatic method, REMs and rejected candidates were visually inspected for confirmation. The mean REM density index was defined as the average ratio of 3-s mini epochs of REM sleep, including REMs, to the total number of 3-s mini epochs of REM sleep (Lauer et al., 1995).

2.4. HRV analysis

The HRV analysis included time domain, frequency domain, and fractal analyses. Computations were performed for each sleep stage: light sleep (N1 + N2); deep sleep (N3); and REM sleep. Pre-sleep wake and post-sleep wake periods were also included for baseline HRV comparisons. HRV indices during light sleep and deep sleep were investigated by calculating the HRV for all non-overlapping 5-min segments. Calculations for the pre-sleep wake, post-sleep wake, and REM sleep periods used data in 5-min time windows shifted by 30 s as these periods were shorter than the other sleep periods.

2.4.1. Time- and frequency-domain HRV

Measurements for the time domain analysis as follows: mean heart rate (MHR); standard deviation of normal R-R intervals (SDNN); and percentage of adjacent normal R-R intervals differing by more than

50 ms (pNN50). A power spectral analysis was performed using a fast Fourier transformation; power in the low frequency range (LF, 0.04–0.15 Hz) indicated sympathetic activity, power in the high frequency range (HF, 0.15–0.4 Hz) indicated parasympathetic activity, and the LF/HF ratio (LFHF) represented the ratio of sympathetic to parasympathetic activity (Gentili et al., 2017). For the spectral analysis, we resampled R–R time series with the interpolation method in an attempt to distribute the non-equally spaced R–R time series so that they are equidistant (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

2.4.2. DFA

A DFA was applied to time series of the R-R intervals extracted from sleep recordings in order to generate a fractal analysis of heart rate. The DFA calculation was performed as follows (Carvalho et al., 2011; Antônio et al., 2014):

First, the R-R intervals were integrated:

$$Y(k) = \sum_{i=1}^{k} [RR(i) - RR_{\text{ave}}] \quad (1)$$

where Y(k) indicates the kth term of the integrated series (k = 1, 2, …, N) and RR(i) indicates the ith value of the R-R intervals. RR_{ave} is the mean of R-R intervals in the original series with N length, given as the equation below.

$$RR_{\text{ave}} = \frac{1}{N} \sum_{i=1}^{N} RR(i) \quad (2)$$

Second, the Y(k) was divided into non-overlapping segments with a length of n, where n = 1, 2, 3, …, N. Then, the local trend of each segment (Yn (k)) was calculated by linear fitting with each segment and the local tendency was removed from the time series Y(k). Third, for a given segment of size n, the size characteristic of the fluctuation for the integrated and detrended series was determined by:

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^{N} [Y(k) - Yn(k)]^2} \quad (3)$$

Lastly, the above calculation for obtaining F(n) from intervals of size n was repeated. A linear relationship representing log (F(n)) versus log (n) was identified using the formula:

$$F(n) \approx n^{\alpha} \quad (4)$$

The slope of the curve (α) is the scaling exponent. Scaling exponents obtained with the DFA are self-similarity parameters (i.e., characteristics for fractal behavior) (Beckers, 2006). The DFA included a short-term fractal exponent (alpha-1), which represented periods of $10 \le n \le 30$ (around 1 epoch in duration). For the purpose of this study, a long-term fractal exponent (alpha-2), which can be properly calculated only with R-R series of about 8000 beats, was excluded from the analysis (Peng et al., 1995). The range of alpha-1 was determined as 10 to 30 beats considering that the fluctuation is quite random in very short time scales (n < 10 beats) (Yeh et al., 2006).

2.5. Statistical analysis

Statistical analyses were performed using SPSS statistics software (v.21.0, SPSS Inc., Chicago, IL). All data were tested for normality using the Shapiro-Wilk test. Student's t-tests were performed on normally distributed data and Mann–Whitney U tests (non-parametric) were performed on data with a non-normal distribution. The threshold for statistical significance was a 2-sided p-value < 0.05. In order to manage Type I errors in the face of multiple comparisons while maintaining statistical power, we used the false discovery rate (FDR) framework (Benjamini and Hochberg, 1995) to compute a single p-value threshold for each test. Possible associations between BDI score and HRV indices in each sleep stage and in the pre- and post- sleep wake periods were tested by Pearson correlation coefficients. If a significant correlation was detected, a stepwise regression analysis with BDI score as the criterion variable and all HRV indices as potential predictive variables was performed for confirmation. Standardized errors were tested for a normal distribution using the Kolmogorov-Smirnov test and visually inspected for homoscedasticity. The stepwise regression analysis identified the model with the smallest number of predictive variables explaining the maximum amount of variance in the data.

Table 1
Comparison of anthropometric and sleep parameters between patients with major depressive disorder (MDD) and healthy control subjects.

Characteristics	Patients with MDD	Control subjects	p-value
Sex	15M + 15F	15M + 15F	
Age (years)	50.5 (14.5)	50.0 (17.5)	0.338
BMI (kg/m^2)	24.5 (4.0)	24.6 (3.5)	0.267
AHI (h^{-1})	1.3 (1.8)	0.8 (1.0)	0.513
BDI score	26.4 (5.6)	8.6 (4.1)	0.000
TIB (min)	498.1 (37.6)	502.7 (29.8)	0.259
TST (min)	390.7 (63.1)	410.8 (70.4)	0.421
SE (%)	80.8 (17.4)	88.3 (16.6)	0.108
SOL (min)	23.8 (21.6)	12.8 (16.8)	0.087
REML (min)	77.9 (41.6)	98.5 (37.4)	0.073
WASO (min)	57.6 (61.5)	42.9 (42.8)	0.214
N1 sleep (%)	15.2 (9.8)	20.5 (6.7)	0.141
N2 sleep (%)	53.4 (13.2)	52.3 (12.9)	0.327
N3 sleep (%)	5.9 (7.9)	7.7 (6.7)	0.284
REM sleep (%)	25.5 (6.2)	19.5 (3.2)	0.032
REMD (min^{-1})	37.1 (7.5)	27.3 (5.8)	0.007

BDI, Beck's Depression Inventory; BMI, body mass index; AHI, apnea hypopnea index; N1, non-REM stage 1; N2, non-REM stage 2; N3, non-REM stage 3; REMD, REM density; REML, rapid eye movement latency; SE, sleep efficiency; SOL, sleep onset latency; TIB, time in bed; TST, total sleep time; WASO, wake after sleep onset.

3. Results

3.1. Anthropometric and sleep parameters

Anthropometric and sleep parameters for all participants are summarized in Table 1. Polysomnographic results showed sleep continuity disturbances and REM sleep abnormalities in patients with MDD. Patients with MDD in this study had marginally longer sleep onset latencies than healthy control subjects (p = 0.087). Patients with MDD also exhibited REM sleep abnormalities including shorter REM sleep latencies (p = 0.073), increased REM sleep (p = 0.032), and increased REM density (p = 0.007) compared to healthy control subjects.

3.2. HRV indices during sleep

Data for all HRV indices during each sleep stage and the pre- and post-sleep wake periods are presented in Fig. 1. There were significant between-group differences during the pre-sleep wake period; SDNN and HF were lower and LFHF was higher in the MDD group compared to the control group (MDD group vs. control group; SDNN, 41.2 ± 19.3 vs. 34.6 ± 15.2; HF, 38.3 ± 15.5 vs. 31.7 ± 12.8; LFHF, 2.8 ± 1.5 vs. 3.6 ± 2.3; all p < 0.05; Fig. 1b, e, and f). There were no significant between-group differences in the post-sleep wake period. During sleep, there were significant between-group differences during REM; DFA alpha-1 was higher in the MDD group than in the control group (DFA alpha-1, 1.3 ± 0.2 vs. 1.2 ± 0.1, respectively; p < 0.05; Fig. 1g).

3.3. Relationship between HRV indices and BDI score

There was a significant correlation between the BDI score and DFA alpha-1 during REM sleep in all subjects (BDI score range: 2–40, r = 0.36, p = 0.005; Table 2 and Fig. 2). A stepwise regression analysis revealed that, as a predictor, DFA alpha-1 explained 12.9% (R2) of

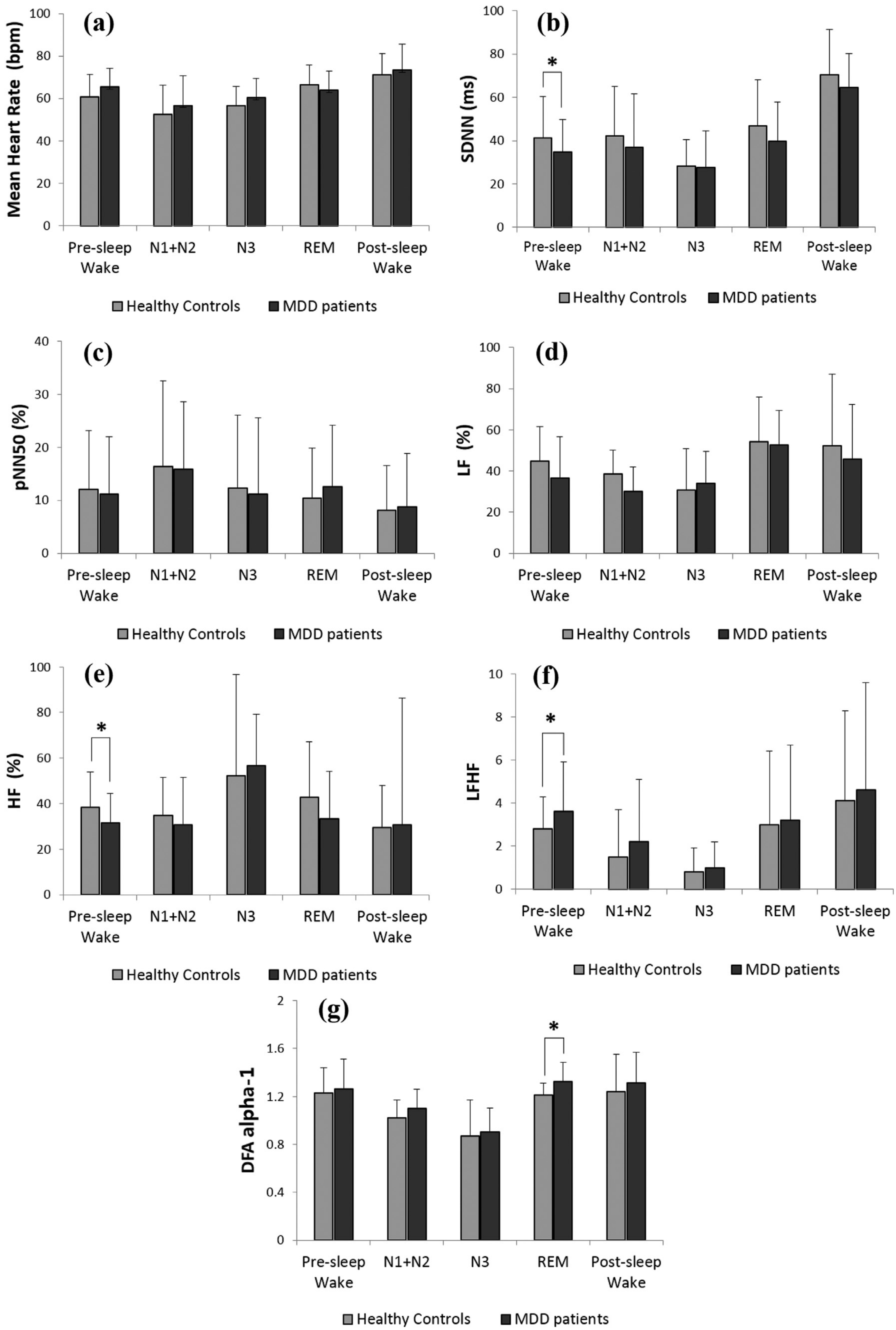

Fig. 1. Averaged measures of (a) mean heart rate (MHR), (b) standard deviation of normal R-R intervals (SDNN), (c) percentage of adjacent normal R-R intervals differing by more than 50 ms (pNN50), (d) low frequency heart rate variability (LF), (e) high frequency heart rate variability (HF), (f) the LFHF ratio, and (g) detrended fluctuation analysis (DFA) alpha-1 during each sleep stage and the pre- and post-sleep wake periods in patients with major depressive disorder (MDD) and control subjects. Error bars indicate the standard deviation. * $p < 0.05$, ** $p < 0.01$.

Table 2
Correlations between DFA alpha-1 indices during rapid eye movement (REM) sleep and Beck Depression Inventory (BDI) score in patients with major depressive disorder (MDD) and overall subjects.

HRV indices	MDD group		MDD group + control group	
	r	*p*-value	*r*	*p*-value
Alpha-1	0.22	0.239	0.36	0.005

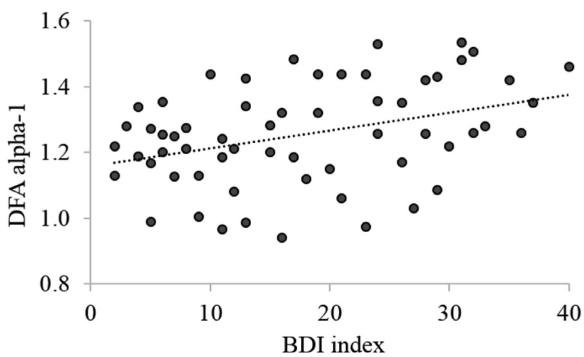

Fig. 2. Relationship between detrended fluctuation analysis (DFA) values during rapid eye movement sleep and Beck Depression Inventory (BDI) score in all subjects.

Table 3
Stepwise regression analysis.

Criterion variable: Beck Depression Inventory score	Regression coefficient	*t*	*p*-value
(Constant) intercept	−11.74	−1.169	0.247
DFA alpha-1	23.31	2.931	0.005
$R = 0.359$; $R^2 = 0.129$; corrected $R^2 = 0.114$			

DFA, detrended fluctuation analysis.

variance of the BDI score (Table 3). The effect size of the regression analysis was small ($f^2 = R^2/[1 - R^2] = 0.148$).

It is well known that eye movement influences ANS activity during sleep (Hoshiyama and Hoshiyama, 2007). Kuo and Yang (2009) reported a positive correlation between eye movements extracted from EOG during nighttime sleep and HRV indices representing sympathetic activity. Pawlowski et al. (2017) also identified a negative correlation between REM density and HRV indices in patients with MDD and control subjects. Additionally, several studies have suggested a correlation between mood disorder severity and REM-related sleep parameters (Agargun and Cartwright, 2003; Cartwright, 1983; Mellman et al., 2002). In our study, patients with MDD had significantly higher REM density than control subjects ($p = 0.007$; Table 1) and there was a correlation between REM density and DFA alpha-1 ($r = 0.258$; $p = 0.047$). Thus, we performed a 1-factorial analysis of covariance to determine the association of each HRV index during REM sleep with BDI score after adjusting for REM density. Moreover, partial correlation coefficients were calculated to control for the effects of REM density in overall subjects. The results showed a significant between-group difference in DFA alpha-1 during REM sleep, indicating that DFA alpha-1 is the only variable significantly influenced by MDD (Table 4). There was a significant correlation between DFA alpha-1 during REM sleep and depressive symptoms (BDI) in the controlled group ($r = 0.280$; $p = 0.032$; Table 4).

4. Discussion

The current study investigated the relationship between MDD and ANS activity assessed by HRV during each sleep stage. Our study yields

Table 4
One-factorial analysis of covariance (ANCOVA).

Factor	ANCOVA Dependent variable: Group covariate: REM density		Partial correlation analysis dependent variable: BDI score covariate: REM density	
	F	*p*-value	*r*	*p*-value
DFA alpha-1	5.32	0.025	0.280	0.032

BDI, Beck Depression Inventory; DFA, detrended fluctuation analysis; REM, rapid eye movement.

2 main findings: DFA alpha-1 values during REM sleep separate the patients with MDD from healthy control subjects; DFA alpha-1 values during REM sleep correlate positively with depression severity evaluated using BDI score.

Polysomnographic results in this study showed REM sleep abnormalities in patients with MDD (Table 1). These alterations in structure of REM sleep are in agreement with previous studies of MDD (Ansseau et al., 1985; Cartwright et al., 2003; Franzen and Buysse, 2008; Palagini et al., 2013). The results in HRV analysis indicated significant between-group differences in HRV indices during the pre-sleep wake period and REM sleep. Decreased HF and SDNN in patients with MDD during pre-sleep wake period indicate reduced parasympathetic tone and overall ANS activity, respectively. Moreover, increased LFHF in patients with MDD suggests a shift in sympathovagal balance to sympathetic dominance during the waking period. These results are consistent with studies demonstrating reduced HRV (Agenlink et al., 2002; Alvares et al., 2016; Carney et al., 2005; Van der Kooy et al., 2006) and ANS imbalance (Koschke et al., 2009; Sgoifo et al., 2015; Yeh et al., 2015) in patients with MDD compared to control subjects.

To the best our knowledge, this is the first study to compare fractal HRV in different sleep stages between patients with MDD and healthy control subjects. A short-term scaling alpha-1 value close to 1.0 indicates a complex (non-linear) system while a value > 1.0 indicates decreasing complexity (linearity) and pathological states (Javorka et al., 2008; Lipsitz and Goldberger, 1992; Poon and Merrill, 1997; Virtanen et al., 2007). Considering this relationship, our study can be interpreted as that patients with MDD shows reduced heart rate complexity during REM sleep compared to healthy control subjects and the reduction correlates with depression severity. This result is in line with previous studies reporting reduced heart rate complexity in patients with MDD during the resting state using autonomic Lyapunov exponents (Yeregani et al., 2002), information flow (Boettger et al., 2008), and multi-scale entropy (MSE) (Yang et al., 2011). Additionally, other studies have reported correlations between depression severity and HRV indices (Henje Blom et al., 2010; Kemp et al., 2010).

In HRV analysis, MSE also can be used to quantify the complexity of heart rate fluctuations. MSE measures the regularity of a complex RR interval series on multiple time scales, whereas the DFA method is used to quantify the scaling behavior of a time series and to quantify the fractal-like scaling properties of the RR interval data. Based on the framework of sample entropy (Richman and Moorman, 2000), which is estimated at multiple coarse-grained scales, MSE calculates entropy over multiple scales and has identified impaired cardiovascular control and increased cardiovascular risk in various pathological conditions (Costa et al., 2002; Costa et al., 2005). However, studies have suggested that at least 1,000 points are necessary to reliably estimate entropy (Pincus, 1991; Pincus and Goldberger, 1994). Therefore, in this study, we judged that MSE is not appropriate to investigate the complexity of the relatively short time series during each sleep stage (5-min heartbeat).

DFA alpha-1 was the strongest predictor of BDI score, with the REM density as a covariate. Multiple regulatory processes that act during different time scales influence beat-to-beat changes in heart rate resulting in complex patterns in the R-R intervals (Kaplan et al., 1991;

Schubert et al., 2009). Numerous studies have proposed that there is a loss in the complexity of various physiological systems of the body with disease (Gottschalk et al., 1995; Javorka et al., 2008; Mestivier et al., 1997, Migliorini, 2012). These changes occur because of alterations in the structural and functional properties of multiple macro and micro physiological systems of the organism (Vaillancourt and Newell, 2002). These changes reduce the capacity of the systems to adapt to internal or external environmental challenges (Goldberger et al., 2002; Lipsitz and Goldberger, 1992). Thus, the reduction in the complexity of heart rate during REM sleep in patients with MDD may represent a lower cardiovascular adaptability. Therefore, a stronger regularity and decreased responsiveness of the cardiac system to changing conditions in patients with MDD may lead to reduced flexibility of the cardiovascular system and increased susceptibility to stressors in the long-term (Schubert et al., 2009; Viola et al., 2011). Moreover, considering that all subjects in this study were free of any cardiovascular disease, we speculate that the reduced complexity of heart rate during REM sleep in MDD might cause altered cardiovascular risk.

DFA quantifies the fractal scaling properties of a time series, providing a sensitive approach for characterizing autonomic control mechanisms. Previous studies have shown that a higher short-term scaling exponent DFA alpha-1 is accompanied by attenuation of both sympathetic and vagal modulation (Beckers, 2006; Willson et al., 2002). The mean value of SDNN and HF, which reflect overall ANS activity and parasympathetic modulation respectively, was decreased during REM sleep in the MDD group compared to the control group with marginal significance (MDD group vs. control group; SDNN, 39.6 ± 18.2 vs. 46.8 ± 21.3, $p = 0.081$; HF, 42.7 ± 24.6 vs. 33.4 ± 20.8, $p = 0.079$), suggesting the possibility of impaired autonomic control of heart rate during REM sleep in patients with MDD. These results present evidence for a relationship between depression pathophysiology and ANS/cardiac abnormalities. REM sleep HRV is regulated the central autonomic network (CAN) (Benarroch, 1993). The CAN is critically involved in regulating physiological responses in the services of emotional expression (Appelhans and Luecken, 2006). The CAN is composed of medial prefrontal cortex, insula and amygdala, which have a strong relationship with MDD (Desseilles et al., 2006; Perlman et al., 2012). Thus, the altered activity of the CAN may lead to impaired autonomic control of heart rate during REM sleep. Therefore, our study suggests that MDD influences both the physiological characteristics during REM sleep as well as the structure of REM sleep.

DFA alpha-1 showed a significant difference between patients with MDD and healthy controls in REM sleep stage whereas it did not in non-REM sleep and pre- and post- sleep wake. Viola et al. (2011) evaluated the HRV complexity during sleep in young and older subjects. In the older group, HRV complexity was reduced during REM sleep compared to light sleep, deep sleep, and pre-sleep wake. Moreover, compared to young subjects, HRV complexity was reduced in REM sleep, light sleep, and pre-sleep wake. The most noticeable aspect is that the decrease of HRV complexity was more evident during REM sleep. Thus, they suggested that REM sleep is a condition characterized by a marked reduction in cardiovascular control complexity more than that in NREM sleep and wake. Numerous studies have shown that REM sleep plays a fundamental role in stress response (Mellman and Hipolito, 2006; Suchecki et al., 2012). In this context, we can speculate that REM sleep is more vulnerable to reduction in complexity of heart rate by emotional stressors than NREM and wake. However, this hypothesis needs further research.

Although HRV is traditionally quantified using time- and frequency-domain indices, fractal HRV seemed to provide additional diagnostic information in patients with MDD. Recent automatic sleep monitoring studies have utilized ECG alone that are applicable in our daily life or for clinical purposes (Xiao et al., 2013; Yoon et al., 2017). Using such monitoring methods, the evidence for reduced complexity of autonomic regulation in patients with MDD may be a useful indicator of depression in daily healthcare systems; this system is neither cost- nor labor-intensive. Furthermore, this parameter may also have utility for monitoring therapeutic responses given an ability to predict depression severity.

The present study had several limitations. First, only the self-reported BDI questionnaire was used to assess depression severity in this retrospective study. Although the BDI provides global indices of depression severity, assessment by attending psychiatrists using clinician-rated scales such as the Hamilton Depression Rating Scale would have strengthened the present findings. Second, it is necessary to evaluate the effects of antidepressant interventions on HRV parameters in order to validate the correlation between the short-term fractal HRV and depression severity observed in this study. Previous studies assessing HRV in MDD have reported significant effects of antidepressant treatment on HRV (Kemp et al., 2010; Van Zyl et al., 2008; Yeh et al., 2015). Moreover, studies about the effects of antidepressants on sleep have demonstrated REM suppression including prolonged REM latency, decreased REM time, and decreased REM density (Armitage, 2000; Gursky and Krahn, 2000; Mayers and Baldwin, 2005; Steiger and Kimura, 2010). Third, our study is based on a relatively small sample size ($N = 60$) compared to recent studies on HRV and depression (Chang et al., 2015; O'Regan et al., 2015). However, in contrast to our work, the studies did not include PSG data, because their aim was not HRV analysis during sleep. However, considering the heterogeneity of depression, the sample size in our study might limit the generalizability of our results.

In this study, we showed imbalanced autonomic nervous system activity and reduced complexity in heart dynamics during REM sleep in patients with MDD. Moreover, this reduction in complexity positively correlated with the BDI score. These findings provide evidence for reduced cardiovascular adaptability to a changing environment in these patients, which may relate to an increased cardiac risk in patients with MDD. Therefore, our results support, replicate, and extend previous findings of reduced overall HRV and inhibited vagal tone in patients with MDD and suggest that MDD affects not only the sleep structure, but also neurophysiological characteristics of sleep in MDD. Further, the results presented here indicate that DFA alpha-1 values in REM sleep may be a good index for screening and estimating the severity of depression.

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Conflict of interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.11.021.

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