



## Research report

## Reduced physiologic complexity is associated with poor sleep in patients with major depression and primary insomnia

Albert C. Yang<sup>a,b,c,\*</sup>, Shih-Jen Tsai<sup>c,d</sup>, Cheng-Hung Yang<sup>c,d</sup>, Chung-Hsun Kuo<sup>c,d</sup>,  
Tai-Jui Chen<sup>e</sup>, Chen-Jee Hong<sup>c,d,f,\*</sup>

<sup>a</sup> Department of Psychiatry, Chu-Tung Veterans Hospital, Hsin-Chu County, Taiwan

<sup>b</sup> Center for Dynamical Biomarkers and Translational Medicine, National Central University, Chungli, Taiwan

<sup>c</sup> Division of Psychiatry, School of Medicine, National Yang-Ming University, Taipei, Taiwan

<sup>d</sup> Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan

<sup>e</sup> I-Shou University and E-DA Hospital, Kaohsiung, Taiwan

<sup>f</sup> Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan

## ARTICLE INFO

## Article history:

Received 9 June 2010

Received in revised form 29 November 2010

Accepted 29 November 2010

Available online 31 December 2010

## Keywords:

Depression

Insomnia

Physiologic complexity

Heart rate variability

## ABSTRACT

**Background:** Depression is known to be associated with altered cardiovascular variability and increased cardiovascular comorbidity, yet it is unknown whether altered cardiac autonomic function in depression is associated with insomnia, a common symptom comorbid with depression. This study aimed to investigate the long-term diurnal profile of autonomic function as measured by heart rate variability (HRV) in both major depression and primary insomnia patients.

**Method:** A total of 52 non-medicated patients with major depression, 47 non-medicated patients with primary insomnia, and 88 matched controls without insomnia were recruited. Each subject was assessed by means of sleep and mood questionnaires and underwent twenty-four-hour ambulatory electrocardiogram monitoring. Standard HRV analysis and a well-validated complexity measure, multiscale entropy, were applied to comprehensively assess the diurnal profiles of autonomic function and physiologic complexity in our study sample.

**Results:** Compared with the controls, the patients with major depression and those with primary insomnia exhibited significant reductions in parasympathetic-related HRV indices, and this association was mainly driven by the presence of poor sleep. Both groups of patients also exhibited significant reductions in physiologic complexity during the sleep period as compared with the healthy controls. Alterations in HRV indices were correlated with perceived sleep questionnaire scores but not with depression scales.

**Conclusions:** Our findings suggest a pivotal role of sleep disturbance in regulating cardiovascular variability in major depression and primary insomnia patients. These findings could highlight the importance of treating insomnia as an independent disease rather than a symptom.

© 2010 Elsevier B.V. All rights reserved.

### 1. Introduction

Insomnia, which is characterized by a perception of poor sleep quality, is a common symptom comorbid with major

depression. Studies have found that both insomnia and depression are independent risks of cardiovascular morbidity and mortality (Mallon et al., 2002; Roose, 2001; Schwartz et al., 1999), suggesting potential cardiac autonomic dysregulation in depression and insomnia.

Using heart rate variability (HRV) as a non-invasive means of assessing autonomic function, reduced HRV measures have been observed in patients suffering from cardiovascular

\* Corresponding authors.

E-mail addresses: [ccyang@physionet.org](mailto:ccyang@physionet.org) (A.C. Yang),  
[cjhong@vghtpe.gov.tw](mailto:cjhong@vghtpe.gov.tw) (C.-J. Hong).

diseases comorbid with depression (Carney et al., 2001; Gehi et al., 2005). One study further suggested that reduced HRV indices in ischemic heart disease patients with depression could be reversed by the use of anti-depressants (Yeragani et al., 2002). Considering depressive illness itself, conflicting results have been reported (Bar et al., 2004; Jindal and Keshavan, 2007; Moser et al., 1998), but majority of the literature suggests that depression itself is associated with reduced HRV indices, particularly those related to vagal activity (Boettger et al., 2008; Guinjoan et al., 1995; Kemp et al., 2010b; Nahshoni et al., 2004; Tonhajzerova et al., 2010; Udupa et al., 2007; Yeragani, 2000).

Patients with primary insomnia may have no significant symptoms of depression, but insomnia itself has been suggested to be an important risk factor for onset of depression in later life (Sateia and Nowell, 2004). Insomnia has been linked to altered heart rate or autonomic function (Bonnet and Arand, 1998; Jurysta et al., 2009; Monroe, 1967; Nilsson et al., 2001), yet it is unclear how insomnia may affect cardiac autonomic regulation in patients with depression and those with primary insomnia. Furthermore, despite a growing body of clinical research regarding the association of HRV and depression, the factors contributing to altered cardiovascular variability in depressed patients remain largely unknown.

The majority of previous studies investigating autonomic function in depressed patients have utilized short-term electrocardiogram (ECG) recordings, for periods ranging from five minutes to a few hours, with a limited number of studies regarding depression and autonomic function having used long-term ECG monitoring (Boettger et al., 2008; Carney et al., 2001; Yeragani, 2000). In order to elucidate the role of autonomic dysfunction in depression and its relationship with insomnia, twenty-four-hour ECG monitoring covering the sleep period was employed in a sample of non-medicated patients suffering from major depression and another group of subjects with primary insomnia.

We hypothesized that insomnia, as measured by perceived sleep questionnaires, may contribute to altered HRV in the patient group, and applied both standard HRV analysis and a well-validated complexity measure, multiscale entropy (MSE), to comprehensively assess the diurnal profiles of autonomic function and physiologic complexity in our study sample.

## 2. Methods

### 2.1. Subjects

The study sample consisted of three groups of adult medication-free subjects: patients with major depressive disorder ( $n = 52$ ; age,  $42.7 \pm 10.2$  years; range, 25–63 years), patients with primary insomnia ( $n = 47$ ; age,  $43.9 \pm 10.4$  years; range, 23–63 years), and healthy controls ( $n = 88$ ; age,  $41.6 \pm 11.7$  years; range, 22–64 years). Informed consent was received from all subjects prior to commencement of the study, and the protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital.

The psychiatric diagnosis of major depression or primary insomnia in each patient was verified by a psychiatrist using criteria based on the *Diagnostic and Statistical Manual*

*of Mental Disorders*, 4th Edition, and each subject's history of medical disease, psychiatric illness, and medication use was evaluated by the interview and medical charts carefully. Subjects were screened and excluded if they had (1) a comorbid substance-related disorder, (2) hypertension (presence of systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg) or diabetes (fasting glucose  $\geq 126$  mg/dL), (3) an acute medical illness within 3 months of the start of the study, or (4) cardiovascular disease, severe cardiac arrhythmia, or a frequent ectopic heartbeat. Subjects were also excluded if they were taking any medication that has a documented effect on the autonomic nervous system (e.g.,  $\beta$ -blockade and anticholinergics drugs).

Depression severity was evaluated by the self-reported Beck Depression Inventory (BDI) (Beck et al., 1961) and the psychiatrist-rated Hamilton Depression Rating Scale (HAM-D, 17 items) (Hamilton, 1960). Subjective sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and daytime sleepiness by the Epworth Sleepiness Scale (ESS) (Johns, 1991).

### 2.2. Twenty-four-hour ECG monitoring

Holter recordings (MyECG E3-80 Portable Recorder, Microstar Inc., Taipei, Taiwan) were used to obtain continuous 24-hour ECG data. The majority of subjects underwent ECG monitoring at home, with the exception of eight depressed patients, who were monitored on an acute psychiatric ward. Participants were asked to maintain their usual daily activities and to avoid smoking and drinking alcoholic beverages during testing. All patients were off medication for a week and agreed to undergo ECG monitoring before initiating medication treatment and, therefore, were medication-free on the day of ECG evaluation. Bedtime ECG was defined as the recording obtained from the time at which subjects went to bed until the time they got out of bed, and awake ECG as that obtained during the rest of day. The ECG signals were automatically processed and analyzed by open-source HRV algorithms (Goldberger et al., 2000).

### 2.3. Analysis of standard heart rate variability

Standard HRV analysis has been well-reviewed (Task-Force, 1996). Time domain measures of HRV include the mean heart rate and standard deviation of the normal interbeat intervals (SDNN), the root mean square successive difference between adjacent normal interbeat intervals (RMSSD), and the percentage of adjacent intervals that varied by greater than 50 ms (pNN50) (Mietus et al., 2002). The SDNN assesses the overall variability of interbeat intervals, while the RMSSD and pNN50 measure the short-term variation of interbeat intervals, which reflects parasympathetic innervation (Goldberger et al., 2001). Spectral HRV measures include high-frequency power (HF; 0.15–0.40 Hz), low-frequency power (LF; 0.04–0.15 Hz), and very-low-frequency power (VLF; 0.003–0.04 Hz). LF power is thought to be modulated by both sympathetic and parasympathetic activities, whereas HF power is mainly modulated by parasympathetic activity. The LF/HF ratio was computed as

a measure of the sympathovagal balance towards sympathetic activity.

#### 2.4. Analysis of physiologic complexity

Heart rate time series typically exhibit multi-scale variability, long-range correlations, and non-linearity (Bar-Yam, 1997) in healthy conditions. The working definition of physiologic complexity is based on the degree of unpredictability in heart rate dynamics, and was assessed in this study using MSE, a well-validated entropic measure (Costa et al., 2002). Typically, entropy quantifies the regularity (orderliness) of a time series, increasing with greater degrees of irregularity, and is at a maximum for completely random systems. However, this approach has certain limitations, in that an increase in entropy may not always be associated with an increase in biologically meaningful complexity: for instance, beat-to-beat variation in atrial fibrillation has a higher entropy than that of a sinus rhythm, yet the former is no more “complex” than the latter in terms of cardiovascular physiology (Goldberger et al., 2002). MSE has therefore been proposed to be conducted by measuring the entropy over multiple time scales inherent in physiologic signals.

The procedure for calculation of the MSE is summarized in three steps as follows: 1) construction of coarse-grained time series according to a scale factor; 2) quantification of the sample entropy of each coarse-grained time series; and 3) summation of the sample entropy values over a range of scales. The length of each coarse-grained time series is equal to the length of the original time series divided by the scale factor: e.g., for scale one, the time series is simply the original time series. In the present study, sample entropy was calculated using a pattern length ( $m$ ) of 2 and a similarity factor ( $r$ ) of 0.15. The sum of entropy over all scale factors from 1 to 20 was computed for each subject and used to represent the single MSE measure in subsequent analyses. The computational algorithms for the MSE are available publicly at [www.physionet.org](http://www.physionet.org).

#### 2.5. Statistical analysis

The spectral HRV indices were log-transformed to produce normalized distributions. Chi-squared tests were used to compare categorical variables, and between-group differ-

ences in diurnal HRV variables were compared using analysis of variance followed by the Bonferroni post hoc test for corrections of multiple between-group comparisons. Backward linear regression with  $p < 0.05$  was used to identify significant factors contributing to HRV differences between groups (if any). Student's  $t$ -test was used to assess the diurnal differences in HRV indices between awake and bedtime periods. Partial correlation analysis was applied, controlling for age and BMI, to identify associations between HRV indices and mood/sleep assessments. Statistical Package for the Social Sciences (SPSS version 15.0, Chicago, IL) software was used for statistical analyses. A  $p$  value of less than 0.05 (two-tailed) was considered to indicate significance for all statistical comparisons.

### 3. Results

#### 3.1. Demographic data

The demographic and clinical data are presented in Table 1. The patient groups and control subjects did not differ in terms of the age, BMI, and gender ratio. The depression group rated higher on the PSQI than the insomnia group ( $p = 0.008$ ), and both patient groups had significantly higher PSQI scores than the control subjects (both  $p < 0.001$ ). The three groups did not differ in terms of daytime sleepiness, as measured by the ESS.

#### 3.2. Diurnal variation of heart rate variability between groups

For the awake HRV (Table 2), significant between-group differences were detected in most standard HRV measures (with the exception of the LF/HF ratio). Post hoc comparisons showed that the depression and insomnia groups had comparable measures of standard HRV indices, whereas most HRV indices were significantly reduced in both patient groups as compared with the control subjects, particularly those indices related to parasympathetic activity (e.g., RMSSD, pNN50, and HF power). Backward linear regression showed that age and PSQI were significantly associated with the parasympathetic-related HRV indices.

Between-group differences in bedtime HRV (Table 3) were similar to awake HRV. In comparison with the controls,

**Table 1**

Clinical and demographic characteristics of the subjects.

Measure	Major depression $n = 52$	Primary insomnia $n = 47$	Controls $n = 88$	$p$
Age (years)	42.7 ± 10.2	43.9 ± 10.4	41.6 ± 11.7	0.482
Gender, M/F	20/32	16/31	33/55	0.891
Body mass index, kg/m <sup>2</sup>	23.3 ± 3.0	22.3 ± 3.7	22.8 ± 2.0	0.397
Beck Depression Inventory	26.4 ± 13.7	10.9 ± 6.5	4.5 ± 4.7	<0.001
Hamilton Depression Rating Scale	16.8 ± 7.5	5.8 ± 5.0	1.0 ± 2.3	<0.001
Pittsburgh Sleep Quality Index	12.8 ± 4.0	10.7 ± 3.9	4.3 ± 2.2	<0.001
#1 Subjective sleep quality	2.4 ± 0.7	2.4 ± 0.7	1.0 ± 0.7	<0.001
#2 Sleep latency	2.0 ± 0.8	1.8 ± 1.0	0.6 ± 0.8	<0.001
#3 Sleep duration	1.3 ± 1.2	1.1 ± 1.3	0.6 ± 0.7	0.001
#4 Sleep efficiency	1.6 ± 1.4	1.0 ± 1.3	0.1 ± 0.4	<0.001
#5 Sleep disturbance	1.7 ± 0.8	1.5 ± 0.5	1.0 ± 0.4	<0.001
#6 Use of sleep medication	2.1 ± 1.2	1.4 ± 1.4	0.1 ± 0.5	<0.001
#7 Daytime dysfunction	1.5 ± 0.9	1.2 ± 0.8	0.7 ± 0.7	<0.001
Epworth Sleepiness Scale	10.7 ± 6.2	9.1 ± 5.4	9.5 ± 4.3	<0.001

**Table 2**

Heart rate variability characteristics during the awake period.

Measure	Major depression <i>n</i> = 52	Primary insomnia <i>n</i> = 47	Controls <i>n</i> = 88	<i>p</i>
<i>Time domain</i>				
Mean heart rate, beats/min	83.0 ± 11.3	83.3 ± 12.7	78.6 ± 9.5	0.023
SDNN, ms	93.1 ± 27.5 <sup>a</sup>	92.4 ± 28.2 <sup>a</sup>	107.9 ± 32.3	0.005
RMSSD, ms	23.7 ± 9.4 <sup>a</sup>	26.9 ± 12.7 <sup>a</sup>	34.1 ± 19.2	0.001
pNN50, %	5.2 ± 5.7 <sup>a</sup>	7.0 ± 7.7 <sup>a</sup>	11.8 ± 12.6	0.001
<i>Frequency domain</i>				
VLF power, ln(ms <sup>2</sup> /Hz)	8.38 ± 0.69 <sup>a</sup>	8.52 ± 0.60 <sup>a</sup>	8.81 ± 0.69	0.001
LF power, ln(ms <sup>2</sup> /Hz)	6.79 ± 0.87 <sup>a</sup>	7.04 ± 0.70 <sup>a</sup>	7.38 ± 0.76	<0.001
HF power, ln(ms <sup>2</sup> /Hz)	5.93 ± 0.87 <sup>a</sup>	6.14 ± 1.04 <sup>a</sup>	6.59 ± 0.99	0.001
LF/HF ratio, normalized unit	3.87 ± 1.71	3.82 ± 2.25	3.27 ± 1.74	0.126
<i>Complexity measure</i>				
Multiscale entropy	21.2 ± 5.1	22.1 ± 5.3	22.6 ± 5.1	0.297

<sup>a</sup> *p* < 0.05, compared with controls by Bonferroni post-hoc tests.

significant increases in the mean heart rate and decreases in LF power were observed in the patient groups. Furthermore, RMSSD, pNN50, and HF power were significantly lower in the depression group than in the control subjects. These reductions in parasympathetic-related HRV measures were not seen in the insomnia group. As was the case for the awake HRV, age and PSQI were identified as significant predictors of parasympathetic-related HRV indices.

With regards to complexity measurement, significantly lower MSEs in both the depression and insomnia groups were detected, exclusively during the bedtime period, as compared with the healthy controls (*p* < 0.001 and *p* = 0.012, respectively). There were no differences in the MSE between the three groups during the awake periods.

### 3.3. Diurnal variation of heart rate variability within subjects

Significant increases in the mean heart rate and LF/HF ratio and reductions in parasympathetic-related HRV indices during the awake period as compared with the bedtime

period were observed in all groups (data not shown). With regards to complexity measure, significant diurnal variation (awake vs. bedtime period) in MSE was detected only in the control subjects (*p* = 0.002) and not in either of the patient groups.

### 3.4. Correlation of heart rate variability with psychopathology

There was no association between any of the HRV indices and sleep/mood assessment in the control group, while different correlative profiles of HRV with psychopathology were identified in the patient groups.

In the depression group, PSQI was correlated positively with LF/HF ratio in the awake HRV (*r* = 0.345, *p* = 0.057) and negatively with awake RMSSD (*r* = -0.404, *p* = 0.024), pNN50 (*r* = -0.359, *p* = 0.047) and HF power (*r* = -0.376, *p* = 0.037), whereas daytime sleepiness (assessed by the ESS) and depression severity (assessed by BDI and HAMD) were not found to be associated with any of the HRV indices.

**Table 3**

Heart rate variability characteristics during the bedtime period.

Measure	Major depression <i>n</i> = 52	Primary insomnia <i>n</i> = 47	Controls <i>n</i> = 88	<i>p</i>
<i>Time domain</i>				
Mean heart rate, beats/min	69.2 ± 10.2 <sup>a</sup>	69.1 ± 14.3 <sup>a</sup>	63.2 ± 6.5	0.001
SDNN, ms	88.8 ± 33.7	88.3 ± 27.9	93.3 ± 24.7	0.542
RMSSD, ms	32.6 ± 15.8 <sup>a</sup>	35.6 ± 17.8	42.6 ± 21.1	0.009
pNN50, %	12.7 ± 12.5 <sup>a</sup>	14.4 ± 14.5	20.1 ± 18.2	0.019
<i>Frequency domain</i>				
VLF power, ln(ms <sup>2</sup> /Hz)	8.37 ± 0.83 <sup>a</sup>	8.48 ± 0.63	8.78 ± 0.54	0.002
LF power, ln(ms <sup>2</sup> /Hz)	6.75 ± 0.99 <sup>a</sup>	7.04 ± 0.81 <sup>a</sup>	7.45 ± 0.65	<0.001
HF power, ln(ms <sup>2</sup> /Hz)	6.41 ± 1.07 <sup>a</sup>	6.69 ± 0.99	7.07 ± 0.87	0.001
LF/HF ratio, normalized unit	2.07 ± 1.08	1.88 ± 1.13	1.91 ± 1.10	0.632
<i>Complexity measure</i>				
Multiscale entropy	21.0 ± 4.1 <sup>a,b</sup>	22.6 ± 4.7 <sup>a</sup>	24.6 ± 3.4	<0.001

<sup>a</sup> *p* < 0.05, compared with controls by Bonferroni post-hoc tests.<sup>b</sup> *p* < 0.05, comparison between the depression and insomnia groups by Bonferroni post-hoc tests.

For the insomnia group, ESS was correlated positively with LF/HF ratio in both the awake and bedtime HRV ( $r=0.353$ ,  $p=0.061$ ;  $r=0.399$ ,  $p=0.032$ , respectively) and negatively with RMSSD ( $r=-0.446$ ,  $p=0.015$ ;  $r=-0.362$ ,  $p=0.054$ , respectively) and HF power ( $r=-0.488$ ,  $p=0.007$ ;  $r=-0.402$ ,  $p=0.031$ , respectively). PSQI and depression severity were not found to be associated with any of the HRV indices in the insomnia group.

#### 4. Discussion

The principle findings of this study were as follows: 1) in comparison with the controls, both the patients with major depression and those with primary insomnia exhibited significant reductions in parasympathetic-related HRV indices; 2) both the patients with major depression and those with primary insomnia exhibited significant reductions in physiologic complexity during the bedtime period as compared with the healthy controls; and 3) alterations in HRV indices were correlated with perceived sleep questionnaire score but not with depression scales scores. These results suggest that altered cardiac autonomic control and physiologic complexity is associated with poor sleep in patients with major depression and primary insomnia.

The underlying cause of diminished HRV in depression has generated considerable interest in recent years. A large-scale report suggested the association of diminished HRV with depression was driven by the use of psychotropics (Licht et al., 2008), but this finding was criticized by controversially using analysis of covariance (Kemp et al., 2010a). While impact of antidepressants on HRV remains elusive, our findings based on a direct comparison of awake and bedtime HRV among non-medicated sample may strengthen the previous observation that HRV was reduced in depressed individuals. Recently, we also observed decreased sleep-related cardiopulmonary coupling dynamics in the respiratory frequency range in depressed patients, which was able to be reversed by the use of hypnotics (Yang et al., 2010). Hence the impact of hypnotics on HRV in depression or insomnia could be a focus of future research.

The pathogenesis of primary insomnia is largely unknown (Becker, 2006), but may cause predisposition to major psychiatric disorders such as depression, anxiety, substance abuse, and other chronic medical disorders (Sateia and Nowell, 2004). Hyperarousal model with increased sympathetic nervous system activity may well explain our HRV results in both depression and insomnia group (Bonnet and Arand, 2010). Of note, anxiety has been attributed to reduced HRV in depressive patients (Rottenberg, 2007). Despite this study did not employ a specific anxiety questionnaire, we did not find significant correlations between HRV indices and anxiety-related components of HAMD and BDI (data not shown). Furthermore, contrary to a recent meta-analysis reporting significant correlations between depression severity and HRV (Kemp et al., 2010b), we found the association between diminished HRV and poor sleep. It is noteworthy that most of prior depression/HRV studies did not involve sleep-related measures or assessments. Our findings may therefore provide new insights into the depression and cardiac autonomic dysregulation.

This study employed a nonlinear method termed MSE, which is adapted from complexity theory, to detect changes in physiological complexity in patients with depression and primary insomnia. Alteration in physiologic complexity may reflect underlying autonomic dysregulation, which is known to be associated with increased comorbidity and poor outcomes of cardiovascular diseases (Goldberger et al., 2002). Recent evidence suggests that reduced MSE is associated with mortality in trauma patients (Norris et al., 2008; Norris et al., 2009) and is potentially a novel, sensitive marker for predicting outcomes of cardiovascular disease (Valencia et al., 2009). Our findings show that reduced physiologic complexity in depression and insomnia was observed exclusively during the bedtime period, indicating a pivotal role of sleep disturbance in the pathophysiology of cardiac autonomic controls in these patients. Moreover, we found the correlations between MSE and standard HRV measures to be weak in general (Table A1), suggesting an independent role of MSE in the quantification of cardiovascular physiology.

Several limitations influence the interpretation of the findings presented in this study. First, as this was a case-control study, the possibility of selection bias cannot be excluded due to various confounders (e.g., smoking status). Second, we were unable to evaluate hyperarousal state based solely on ECG signal, and patients with insomnia may misinterpret their sleep. Our findings may be biased due to subjective sleep reports and this limitation may be compensated by the aid of objective sleep assessment in the future research. Of interest, we have shown previously that depressed patient with insomnia was associated with unstable sleep based on cardiopulmonary coupling analysis using ECG signals (Yang et al., 2010). Third, evaluation of medical condition was based on interviews with patients and reviews of medical charts, and we cannot exclude the possibility that subjects may have had undiagnosed medical conditions that could have affected the HRV analysis. For example, sleep apnea has known effects on HRV measures (Narkiewicz et al., 1998). Despite these limitations, our findings may have important implications in clinical practice. Appropriate management of insomnia may lower the risk of cardiovascular disease and minimize associated morbidity and mortality. Comparison of the different treatments available for insomnia and investigation of their effects on cardiac autonomic function in these patients could be a focus of future research.

#### Role of funding source

This work was supported by the National Science Council (NSC) of Taiwan (NSC 95-2314-B-075-111); NSC support for Center for Dynamical Biomarkers and Translational Medicine, National Central University, Taiwan; Taipei Veterans General Hospital, Taiwan (V96C1-083, V97C1-132, V97F-005); and the Joint Projects of the Veterans General Hospitals University System of Taiwan (Grant VGHUST100-G1-4). These organizations had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

#### Conflict of interest

All authors declare that they have no conflicts of interest.

#### Acknowledgements

The authors wish to thank Zi-Hui Lin, Shan-Ing Chen and Chen-Ru Wang for their excellent technical assistance.

## Appendix A

Table A1

Partial correlations between multiscale entropy and standard heart rate variability.

Relationship with HRV indices $n = 187$	Multiscale entropy awake period		Multiscale entropy bedtime period	
	$r$	$p$	$r$	$p$
Mean heart rate, beats/min	−0.254	0.012	−0.052	0.615
SDNN, ms	−0.016	0.873	−0.015	0.884
RMSSD, ms	0.148	0.147	0.198	0.051
pNN50, %	0.103	0.317	0.229	0.024
VLF power, $\ln(\text{ms}^2/\text{Hz})$	0.276	0.006	0.186	0.067
LF power, $\ln(\text{ms}^2/\text{Hz})$	0.333	0.001	0.270	0.007
HF power, $\ln(\text{ms}^2/\text{Hz})$	0.229	0.024	0.286	0.004
LF/HF ratio, normalized unit	−0.004	0.970	−0.137	0.181

Abbreviations:

- $r$ : partial correlation coefficient, controlled for age and BMI.  
 SDNN: standard deviation of the normal interbeat intervals.  
 RMSSD: root mean square successive difference between adjacent normal interbeat intervals.  
 pNN50: percentage of adjacent intervals that varied by greater than 50 ms.  
 VLF: very-low-frequency component of heart rate variability (0.003–0.04 Hz).  
 LF: low-frequency component of heart rate variability (0.04–0.15 Hz).  
 HF: high-frequency component of heart rate variability (0.15–0.4 Hz).  
 LF/HF: ratio of low-frequency to high-frequency.

The absolute values of spectral heart rate variability indices were log-transformed.

## References

- Bar, K.J., Greiner, W., Jochum, T., Friedrich, M., Wagner, G., Sauer, H., 2004. The influence of major depression and its treatment on heart rate variability and pupillary light reflex parameters. *J. Affect. Disord.* 82, 245–252.
- Bar-Yam, Y., 1997. Dynamics of complex systems. Westview Press.
- Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. *Arch. Gen. Psychiatry* 4, 561–571.
- Becker, P.M., 2006. Insomnia: prevalence, impact, pathogenesis, differential diagnosis, and evaluation. *Psychiatr. Clin. North Am.* 29, 855–870 abstract vii.
- Boettger, S., Hoyer, D., Falkenhahn, K., Kaatz, M., Yeragani, V.K., Bar, K.J., 2008. Nonlinear broad band dynamics are less complex in major depression. *Bipolar Disord.* 10, 276–284.
- Bonnet, M.H., Arand, D.L., 1998. Heart rate variability in insomniacs and matched normal sleepers. *Psychosom. Med.* 60, 610–615.
- Bonnet, M.H., Arand, D.L., 2010. Hyperarousal and insomnia: state of the science. *Sleep Med. Rev.* 14, 9–15.
- Buysse, D.J., Reynolds III, 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.
- Carney, R.M., Blumenthal, J.A., Stein, P.K., Watkins, L., Catellier, D., Berkman, L.F., Czajkowski, S.M., O'Connor, C., Stone, P.H., Freedland, K.E., 2001. Depression, heart rate variability, and acute myocardial infarction. *Circulation* 104, 2024–2028.
- Costa, M., Goldberger, A.L., Peng, C.K., 2002. Multiscale entropy analysis of complex physiologic time series. *Phys. Rev. Lett.* 89, 068102.
- Gehi, A., Mangano, D., Pipkin, S., Browner, W.S., Whooley, M.A., 2005. Depression and heart rate variability in patients with stable coronary heart disease: findings from the Heart and Soul Study. *Arch. Gen. Psychiatry* 62, 661–666.
- Goldberger, A.L., Amaral, L.A., Glass, L., Hausdorff, J.M., Ivanov, P.C., Mark, R.G., Mietus, J.E., Moody, G.B., Peng, C.K., Stanley, H.E., 2000. PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. *Circulation* 101, E215–E220.
- Goldberger, J.J., Challapalli, S., Tung, R., Parker, M.A., Kadish, A.H., 2001. Relationship of heart rate variability to parasympathetic effect. *Circulation* 103, 1977–1983.
- Goldberger, A.L., Amaral, L.A., Hausdorff, J.M., Ivanov, P., Peng, C.K., Stanley, H.E., 2002. Fractal dynamics in physiology: alterations with disease and aging. *Proc. Natl. Acad. Sci. USA* 99 (Suppl 1), 2466–2472.
- Guinjoan, S.M., Bernabo, J.L., Cardinali, D.P., 1995. Cardiovascular tests of autonomic function and sympathetic skin responses in patients with major depression. *J. Neurol. Neurosurg. Psychiatry* 59, 299–302.
- Hamilton, M., 1960. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 23, 56–62.
- Jindal, R.D., Keshavan, M.S., 2007. Heart rate variability in patients with depression. *Arch. Gen. Psychiatry* 64, 611–612.
- Johns, M.W., 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 14, 540–545.
- Jurysta, F., Lanquart, J.P., Sputaels, V., Dumont, M., Migeotte, P.F., Leistedt, S., Linkowski, P., van de Borne, P., 2009. The impact of chronic primary insomnia on the heart rate–EEG variability link. *Clin. Neurophysiol.* 120, 1054–1060.
- Kemp, A.H., Quintana, D.S., Gray, M.A., 2010a. Is heart rate variability reduced in depression without cardiovascular disease? *Biol. Psychiatry*. doi:10.1016/j.biopsych.2010.1007.1030.
- Kemp, A.H., Quintana, D.S., Gray, M.A., Felmingham, K.L., Brown, K., Gatt, J.M., 2010b. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. *Biol. Psychiatry* 67, 1067–1074.
- Licht, C.M., de Geus, E.J., Zitman, F.G., Hoogendijk, W.J., van Dyck, R., Penninx, B.W., 2008. Association between major depressive disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). *Arch. Gen. Psychiatry* 65, 1358–1367.
- Mallon, L., Broman, J.E., Hetta, J., 2002. Sleep complaints predict coronary artery disease mortality in males: a 12-year follow-up study of a middle-aged Swedish population. *J. Intern. Med.* 251, 207–216.
- Mietus, J.E., Peng, C.K., Henry, I., Goldsmith, R.L., Goldberger, A.L., 2002. The pNNx files: re-examining a widely used heart rate variability measure. *Heart* 88, 378–380.
- Monroe, L.J., 1967. Psychological and physiological differences between good and poor sleepers. *J. Abnorm. Psychol.* 72, 255–264.
- Moser, M., Lehofer, M., Hoehn-Saric, R., McLeod, D.R., Hildebrandt, G., Steinbrenner, B., Voica, M., Liebmann, P., Zapotoczky, H.G., 1998. Increased heart rate in depressed subjects in spite of unchanged autonomic balance? *J. Affect. Disord.* 48, 115–124.
- Nahshoni, E., Aravot, D., Aizenberg, D., Sigler, M., Zalsman, G., Strasberg, B., Imbar, S., Adler, E., Weizman, A., 2004. Heart rate variability in patients with major depression. *Psychosomatics* 45, 129–134.
- Narkiewicz, K., Montano, N., Cogliati, C., van de Borne, P.J., Dyken, M.E., Somers, V.K., 1998. Altered cardiovascular variability in obstructive sleep apnea. *Circulation* 98, 1071–1077.
- Nilsson, P.M., Nilsson, J.A., Hedblad, B., Berglund, G., 2001. Sleep disturbance in association with elevated pulse rate for prediction of mortality – consequences of mental strain? *J. Intern. Med.* 250, 521–529.
- Norris, P.R., Anderson, S.M., Jenkins, J.M., Williams, A.E., Morris Jr., J.A., 2008. Heart rate multiscale entropy at three hours predicts hospital mortality in 3, 154 trauma patients. *Shock* 30, 17–22.
- Norris, P.R., Canter, J.A., Jenkins, J.M., Moore, J.H., Williams, A.E., Morris Jr., J.A., 2009. Personalized medicine: genetic variation and loss of physiologic complexity are associated with mortality in 644 trauma patients. *Ann. Surg.* 250, 524–530.
- Roose, S.P., 2001. Depression, anxiety, and the cardiovascular system: the psychiatrist's perspective. *J. Clin. Psychiatry* 62 (Suppl 8), 19–22 discussion 23.
- Rottenberg, J., 2007. Cardiac vagal control in depression: a critical analysis. *Biol. Psychol.* 74, 200–211.
- Sateia, M.J., Nowell, P.D., 2004. Insomnia. *Lancet* 364, 1959–1973.
- Schwartz, S., McDowell Anderson, W., Cole, S.R., Cornoni-Huntley, J., Hays, J.C., Blazer, D., 1999. Insomnia and heart disease: a review of epidemiologic studies. *J. Psychosom. Res.* 47, 313–333.
- Task-Force, 1996. Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 93, 1043–1065.
- Tonhajzerova, I., Ondrejka, I., Javorka, K., Turianikova, Z., Farsky, I., Javorka, M., 2010. Cardiac autonomic regulation is impaired in girls with major depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 34, 613–618.
- Udupa, K., Sathyaprabha, T.N., Thirhalli, J., Kishore, K.R., Lavekar, G.S., Raju, T.R., Gangadhar, B.N., 2007. Alteration of cardiac autonomic functions in patients with major depression: a study using heart rate variability measures. *J. Affect. Disord.* 100, 137–141.
- Valencia, J.F., Porta, A., Vallverdu, M., Claria, F., Baranowski, R., Orłowska-Baranowska, E., Caminal, P., 2009. Refined multiscale entropy: application

- to 24-h Holter recordings of heart period variability in healthy and aortic stenosis subjects. *IEEE Trans. Biomed. Eng.* 56, 2202–2213.
- 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., 2010. Sleep state instabilities in major depressive disorder: detection and quantification with electrocardiogram-based cardiopulmonary coupling analysis. *Psychophysiology*. doi:10.1111/j.1469-8986.2010.01060.
- Yeragani, V.K., 2000. Major depression and long-term heart period variability. *Depress. Anxiety* 12, 51–52.
- Yeragani, V.K., Pesce, V., Jayaraman, A., Roose, S., 2002. Major depression with ischemic heart disease: effects of paroxetine and nortriptyline on long-term heart rate variability measures. *Biol. Psychiatry* 52, 418–429.