Heart Rate Variability in Psychiatric Disorders

Albert C. Yang, M.D.[1,2,3], *Chen-Jee Hong, M.D.*[2,4,5], *Shih-Jen Tsai, M.D.*[2,5]

Objectives: The autonomic nervous system (ANS) dysregulation is a well known risk of adverse cardiovascular events. Analysis of heart rate variability (HRV) can give a valuable window into the ANS function being implicated in various medical diseases. But HRV analysis is not well established although psychiatric research findings have shown considerable association of psychopathology with cardiovascular comorbidity. In this review, we introduce the principle and technique of HRV analysis and illustrate how HRV analysis can shed light on neurobiology of psychiatric disorders. **Methods:** We present HRV methods and applications to quantify ANS dysregulation associated with psychiatric disorders. We will also highlight the novel approaches of HRV analysis to study mental illnesses in the context of genetic inferences and sleep physiology. **Results:** Symptoms of ANS disturbance are common in psychiatric disorders. HRV analysis has been used to quantify ANS dysregulation in depression, anxiety, and schizophrenia. Moreover, we reveal that some variations in genes, such as the genes encoding apolipoprotein-E and brain-derived neurotrophic factor, may have significant impact on cardiac dynamics which are implicated in psychopathology of psychiatric disorders. Finally, we introduce cardiopulmonary coupling analysis which is adopted from HRV analysis to show its application to quantify sleep stability. **Conclusions:** Investigating ANS functions may give insight into understanding neurobiology of psychiatric disorders. We need prospective studies of ANS dysregulation in various psychiatric disorders to evaluate their psychopathology connected with cardiovascular comorbidity.

Key words: autonomic dysregulation, heart rate variability, psychiatric disorder, genetic inference
(***Taiwanese Journal of Psychiatry* [Taipei] 2010;24:99-109**)

Introduction

Instantaneous heart rate in response to physiological perturbations often exhibits remarkable oscillations at multiple time scales. These oscillations are mainly mediated by the autonomic nervous system (ANS) through parasympathetic and sympathetic innervations and are known as "heart rate variability" (HRV). The analysis of HRV has provided a useful, noninvasive tool in clinical research to assess ANS function, and has generated considerable attention for over two decades because of its relatively low cost and widespread availability.

Loss of normal ANS control of cardiac dynamics is an important risk factor for adverse cardiovascular events. HRV is used to quantify cardiovascular risk in a wide range of medical diseases including hypertension, myocardial infarction, heart failure, stroke, diabetes, and renal failure [1]. The most important and validated application of HRV analysis is the risk stratification of myocardial infarction. Reduced HRV is significantly associated with increased risk of mortality in post myocardial infarction patients [2].

Intriguingly, the sense of emotion is often referred literally to heart, such as "broken heart" for feeling of sadness, or "pounding heart" for feeling of seeing a beloved person. Indeed, studies on cardiovascular diseases have been found that psychosocial risk factors (e.g., depression or hostility) are associated with ANS dysregulation [3].

Because the mental status also impacts on the ANS significantly, analysis of HRV in the mentally ill may shed light on the psychobiology of psychiatric disorders in relation to the cardiovascular physiology. In this article, we review the principle of HRV techniques and their applications to psychiatric disorders. We also highlight the novel approaches of HRV analysis to study the neurobiology of psychiatric disorders in the context of genetic inferences and sleep physiology.

Methods for Heart Rate Variability Analysis

Measurement of HRV is based on calculating the time interval between each heartbeat (interbeat interval or R-R interval) of the electrocardiogram. Many algorithms which have been proposed for being used to analyze interbeat interval time series, are generally categorized as: time-domain, frequency-domain and nonlinear methods. Each domain of HRV methods is based on distinct assumptions and approaches.

Time-domain methods: how much variability is there?

Time domain measures of HRV simply estimate the statistical variability of interbeat intervals. For long-term assessment, we measure the mean heart rate and standard deviation of the normal interbeat intervals (SDNN) [4]. For intermediate-term assessment, we record standard deviation of the averages of normal interbeat intervals in all five-minute segments of the entire recording (SDANN) [4]. And for short-term assessment, we calculate the root mean square successive difference between adjacent normal interbeat intervals (RMSSD) [4], and the percentage of adjacent intervals that varied by greater than 50 ms (pNN50) [5].

Frequency-domain methods: what are the underlying rhythms?

The methods commonly used to estimate underlying rhythm of the interbeat interval time series include Fourier transform, autoregressive procedures, or Lomb periodogram. Among those
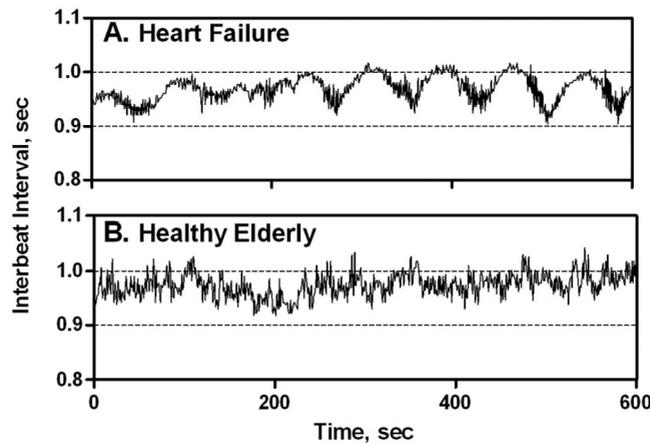
Figure 1. **A comparison of interbeat interval time series between (A) a patient with heart failure and (B) a healthy elderly subject. Each recording consists of 600 seconds of interbeat interval time series. They had different physiologic complexity but both had similar means and standard deviations of interbeat interval time series: 0.97 ± 0.02 second in panel A and 0.98 ± 0.02 second in panel B.**

methods, the most widely used one is Fourier transform, which is based on an assumption that any signal consists of an ensemble of sinusoidal waves with different frequencies and amplitude. The amplitude/frequency information can be mapped to a spectrum representing by amplitude/ power (on y-axis) as a function of frequency (x-axis).

Spectral HRV methods quantify frequency components of HRV that are expressed as the power (or energy) in three frequency regions or bands: high-frequency power (0.15-0.40 Hz), low-frequency power (0.04-0.15 Hz), and very-low-frequency power (0.003-0.04 Hz) [6]. Quantification of parasympathetic and sympathetic nervous system function can be estimated from spectral analysis of HRV. Low-frequency power is modulated by both sympathetic and parasympathetic activities and high-frequency power by parasympathetic activity alone [7]. The low-frequency/high-frequency ratio is computed as a measure of the sympathovagal balance toward

sympathetic activity [8]. The physiologic mechanism underlying very-low-frequency power is disputed, but possibly mediated partly by the renin-angiotensin-aldosterone system [6], and the parasympathetic modulation [1].

Nonlinear methods: what are complexity and self-similarity?

Complexity, the hallmark of healthy human function, is manifested physiologically and behaviorally in daily activities, heart rate, blood pressure, and brain electrical activities [9]. The term "complexity" is often confusing but does have rigorous physical definitions. Heart rate dynamics under healthy conditions typically exhibit "complex" oscillations, showing multi-scale variability, long-range correlations (or self-similarity), and non-linearity [10]. Time and frequency domain measures often cannot quantify important nonlinear properties [11]. Figure 1 is a comparison of interbeat interval time series from a healthy subject and a heart failure patient. It is important

to note that these two subjects with very different physiological conditions nevertheless had a similar statistical measure in mean and standard deviation of interbeat intervals. The complementary role of scaling or complexity analysis is, therefore, an important tool to quantify the nonlinear properties of physiological signals. Here we briefly describe two nonlinear HRV methods.

Detrended fluctuation analysis

Detrended fluctuation analysis (DFA) quantifies the presence of long-range (fractal) correlations [12]. In the DFA method, the root-mean-square fluctuation of integrated and detrended time series is measured at different observation windows and plotted against the size of the observation window on a log-log scale.

The scaling exponent α is then derived from the slope of line fitting to the obtained log-log plot. Low-exponent values represent reduced fractal property of heart rate dynamics and have been implicated in the risk of fatal cardiac arrhythmia, increased mortality, or poor prognosis in cardiovascular diseases [13].

Multiscale entropy

Traditional complexity measurements are based on the concept of entropy which quantifies the regularity (orderliness) of a time series. Entropy increases with the degree of disorder and becomes maximal for completely random systems. But an increase in entropy may not always be associated with an increase in dynamical complexity. For instance, heart rate rhythm of atrial fibrillation has higher entropy than that of sinus rhythm, yet the former is no more complex than the later. A biologically meaningful complexity measure is proposed to measure the entropy over multiple time scales inherent in physiological signals, termed multiscale entropy (MSE) [14].

The procedure and calculation of the MSE has three steps: (A) construction of coarse-grained time series, (B) quantification of the sample entropy of each coarse-grained time series, and (C) summation of the sample entropy values over a range of scales. Typically, the sum of a sample entropy over all scale factors from 1 to 20 is computed to represent the MSE measure.

Application of Heart Rate Variability in Psychiatric Disorders

Several signs and symptoms of psychiatric disorders are related to the ANS dysregulation. For example, depressed patients often complain of dryness of the mouth, constipation/diarrhea, or insomnia. Those clinical observations do not limit to depressed patients alone but also to a broad spectrum of mental illnesses. Altered ANS function assessed by analysis of HRV, has been investigated in the following psychiatric disorders.

Depressive disorders

The research of link between depression and ANS dysfunction have attracted the most attention in recent years. Epidemiological studies have shown that depression is an independent risk of cardiovascular morbidity and mortality [15]. Patients who are suffering from cardiovascular diseases (e.g., myocardial infarction or coronary heart disease) being comorbid with depression, are known to have a reduced short- and long-term HRV measures [3, 16]. One study further suggests that reduced HRV measures in ischemic heart disease patients with depression can be reversed by the use of antidepressants [17].

In studying HRV-measures in the depressive illness itself, conflicting results have been found [18], but many published articles suggest that the

depression itself is associated with reduced HRV [19, 20]. Nontheless, a recent report indicates that use of antidepressants may also contribute to reduced HRV in depressed individuals [21].

Anxiety disorders

Anxiety disorders are other typical mental illnesses that are commonly present with ANS disturbances. Anxiety symptoms are often associated with an increased cardiovascular mortality [15]. Patients with panic disorder or phobic anxiety are at increased risk of cardiovascular disease compared with control subjects [22, 23].

Stress has been known to alter sympathovagal balance toward sympathetic predominance [24]. Recent studies using HRV analysis suggest a decreased cardiac vagal function and a relatively increased sympathetic function in patients with anxiety disorders [25, 26]. One study also provides the link between trait anxiety and ANS dysfunction using HRV analysis [27]. Palpitation, a common symptom of the panic attack, are linked to reduced central parasympathetic activity, resulting in increased heart rate during panic attacks [28].

Schizophrenia

"Soft" neurological sign such as autonomic dysfunction is implicated in schizophrenia because the limbic system and associated subcortical brain areas are involved in higher-order control of ANS. Unmedicated schizophrenic patients show decreased RMSSD, pNN50, and spectral high-frequency power compared to healthy control subjects, suggesting a reduced vagal modulation [29, 30]. Other studies have been observed an association between decreased vagal tone in schizophrenic patients and an increased severity of psychotic symptoms [31, 32].

Certain antipsychotic drugs are found to have adverse effects on ANS functions. Patients treated with antipsychotic medications, especially clozapine, showed ANS dysregulation and abnormal cardiac repolarizations [33, 34]. Those data suggest that both the schizophrenic illness and its treatment may contribute to the increased risk of cardiovascular comorbidity. The association between the use of antipsychotics and adverse cardiovascular event is still not fully understood. Amisulpride has been found to protect ANS function compared to olanzapine after patients' medication being switched from first-generation antipsychotic drugs [35].

Other psychiatric disorders

Certain personality trait such as hostility, is known to be associated with ANS dysregulation. Men with hostility show decreased vagal modulation and sympathetic predominance as measured by spectral HRV indices [36].

ANS dysregulation has been implicated in other mental illnesses. Limited evidence suggests a possible association between bipolar disorder and ANS dysregulation but conflicting results have also been reported [37, 38]. Patients with bipolar disorder may be treated with antimanic agents such as lithium, valproate or carbamazepine, which show no significant effect on HRV. A recent study has been found that bipolar patients with declined heart rate complexity have more severe psychiatric symptoms, suggesting that ANS dysregulation in bipolar disorder may be dependent on the phase of the illness [39].

HRV is possibly implicated in attention deficit/hyperactivity disorder (ADHD), because the sympathetic tone is essential for the alertness and motivation. An early study has been found that ADHD patients have lower sympathetic-related spectral HRV measure compared to healthy sub-

jects [40]. But one recent study has been found to have contradicting results [41], and another study shows no association between ADHD and altered sympathovagal balance [42].

Dementia is another neuropsychiatric disorder which is comorbid with ANS dysregulation [43]. One study reports the findings of an association between reduced parasympathetic modulation and cognitive impairment in a sample of disabled, community-dwelling elderly women [44]. We also show that a sample of non-demented elderly veterans who have reduced cognitive functions, especially those related to short-term memory and attention, are found to be associated with decreased parasympathetic HRV indices, indicating a common pathophysiology underlying the cognitive and ANS dysfunction [45].

Genetic Inference on Heart Rate Variability

Analysis of HRV has been proposed to be a quantitative phenotypic marker of ANS activity [46]. Family and twin studies show a significantly genetic influence on various HRV measures, with heritability being estimated up to 65% [47]. Several genetic polymorphisms related to cardiovascular functions are found to affect HRV. For example, the high-frequency (vagal) spectral component of HRV is associated with a common polymorphism of the gene encoding angiotensin-converting enzyme [48]. The polymorphic variation in the choline transporter gene is significantly associated with vagal-related HRV indices [49]. A polymorphism in the gene coded for β2-adrenergic receptors is related to modulating sympathovagal balance [50]. More recently, a polymorphism in the C-reactive protein gene shows to contribute to both C-reactive protein levels and HRV in a healthy adult sample [47].

The evidences of the association between HRV and genes encoding neuropsychiatric disorders are limited. In our laboratory, we have recently identified two neuropsychiatry-related genes that are associated with changes in HRV measures: apolipoprotein E (APOE) gene [51] and brain-derived neurotrophic factor (BDNF) gene [52].

Apolipoprotein E gene and heart rate complexity

Aging and illness have been suggested to be associated with reduced behavioral or physiological complexity [9]. Little is known about the genetic predisposition to reduced physiological complexity among the elderly. We applied the MSE analysis (as shown in nonlinear HRV methods) to examine effects of the APOE genotypes on heart rate complexity in a cohort of robust elderly adults [51]. Our results show that the reduced physiological complexity is associated with the APOE ε4 allele in this elderly sample, suggesting a pivotal role of genetic inference in physiological aging and ANS dysregulation (Figure 2). Of interest, studies have shown that vagal tone-increasing procedures/exercise (e.g., meditation or Tai-Chi exercise) can protect heart functions [53]. Therefore, further research is warranted to examine if an appropriate treatment/prevention can compensate the adverse impact of APOE ε4 allele on physiological functions.

Brain-derived neurotrophic factor gene and sympathovagal balance

BDNF, a secretory protein in the neurotrophin family, is essential for the survival, development and maintenance of the neuronal system. A functional Val66Met polymorphism in the human BDNF gene has been found in studies of both humans and animals to affect anxiety traits and behaviors and that it may also have neurotrophic or
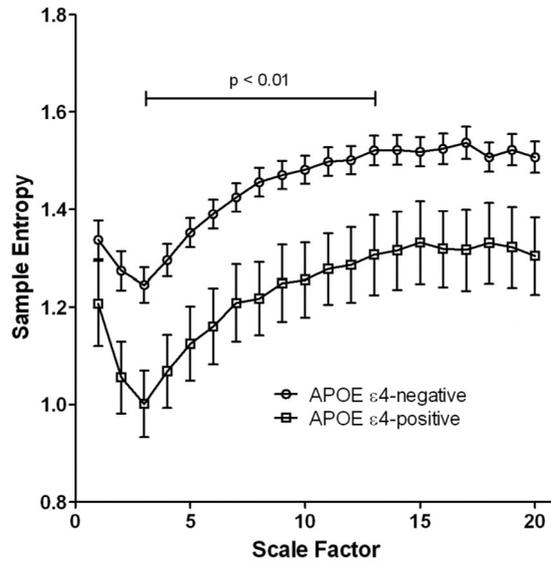
Figure 2.   Multiscale entropy analysis by APOE status. Reproduced from [51]
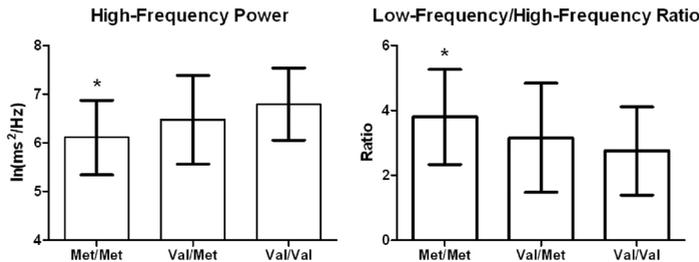

Figure 3.   Association of brain-derived neurotrophic factor polymorphism with spectral components of heart rate variability. The asterisk indicates that the p-value was less than 0.05 for the comparison between the Met/Met and Val/Val genotypic group. Reproduced from [52]

regulatory effects in neurons related to both the sympathetic and parasympathetic systems [54, 55]. We studied the association between BDNF Val66Met polymorphism and time/frequency components of HRV in healthy subjects [52]. We found that subjects bearing the BDNF Met/Met genotype had decreased RMSSD, pNN50, and high-frequency power and increased low-frequency/high-frequency ratio [52]. Those study findings suggest an altered sympathovagal balance with reduced parasympathetic modulation and possibly

increased sympathetic activity (Figure 3). This observation leads to further investigation of BDNF-associated ANS imbalance on incidence of anxiety disorders and cardiovascular diseases.

Sleep: A Special Application Adopted from Heart Rate Variability Analysis

ANS function is known to change from waking to sleep or during different sleep stages.

Generally, parasympathetic tone is predominant during sleep, but sympathovagal balance varies according to the depths of sleep stages and types [56]. Therefore, quantifying HRV during sleep, particularly those measures related to ANS functions, is useful in assessing sleep in the context of cardiovascular physiology.

Recently, a new method of quantifying sleep, termed cardiopulmonary coupling (CPC) analysis, was developed based on estimating the coupling of ANS and respiratory drives, using heart rate and respiratory modulation of QRS amplitude, respectively. Both informations can be read from a single channel of electrocardiogram [57]. Physiologically stable sleep is associated with high-frequency coupling between heart rate and respiration at frequencies of 0.1 to 0.4 Hz, whereas physiologically unstable sleep is associated with low-frequency coupling between heart rate and respiration over a range of 0.01 to 0.1 Hz. The presence of very-low-frequency coupling between heart rate and respiration below 0.01 Hz is correlated with waking or REM sleep.

The CPC analysis has been validated to detect sleep apnea based solely on the electrocardiogram signal [57, 58]. We have also shown the use of CPC method in evaluating sleep quality in patients with major depression [59]. The results showed that depressed patients had significantly increased unstable sleep compared to healthy controls, and that this increase in unstable sleep can be partially normalized using hypnotic drugs. Of interest, the spectral measures used in CPC analysis (i.e., low- or high-frequency coupling) are fundamentally different from conventional spectral HRV analysis. In CPC analysis, we incorporate both respiration and heart rate signals to measure the degree of coupling between them.

Limitations of Heart Rate Variability Analysis

Despite hundreds of publications on HRV analysis examining multiple measures, practical clinical application remains disappointing. This problem is mainly due to the lack of specificity of HRV analysis in diagnosis and outcome prediction. Arrhythmias and noise also significantly affect the accuracy of HRV estimation, even in the case of simple time-domain algorithms, thus hampering the use of HRV techniques in certain patients (e.g., medically ill or uncooperative, mentally ill patients). More sophisticated techniques, including frequency domain measures and those measures derived from nonlinear dynamics and complexity theory, are more difficult to validate and standardize [1].

Few resources exist to give freely available databases of cardiac physiology for testing, refinement, and validation of both older and newer algorithms. One of widely known resources is Physionet (http://physionet.org), which is a research resource for complex physiological signals. This website has been created under the National Center for Research Resources of the National Institutes of Health in the United States, intending to stimulate current research and new investigations in the study of cardiovascular and other complex biomedical signals [60].

Conclusion

Many uncharted areas still exist in the context of cardiovascular physiology and mental illnesses. Understanding the association between psychiatric disorders and fatal cardiovascular events, we can give appropriate managements for the mentally ill to lower their risk of cardiovascu-

lar diseases and their associated morbidity and mortality. Moreover, studying neuropsychiatric genetic inferences on cardiac dynamics may give more insight into neurobiology of psychiatric disorders. We need prospective studies of ANS dysregulation in various psychiatric disorders to evaluate a psychopathology in connection with cardiovascular comorbidity.

References

1. Kleiger RE, Stein PK, Bigger JT Jr.: Heart rate variability: measurement and clinical utility. *Ann Noninvasive Electrocardiol* 2005;10:88-101.

2. Huikuri HV, Seppanen T, Koistinen MJ, et al.: Abnormalities in beat-to-beat dynamics of heart rate before the spontaneous onset of life-threatening ventricular tachyarrhythmias in patients with prior myocardial infarction. *Circulation* 1996;93:1836-44.

3. Carney RM, Blumenthal JA, Stein PK, et al.: Depression, heart rate variability, and acute myocardial infarction. *Circulation* 2001;104:2024-8.

4. Task-Force: 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* 1996;93:1043-65.

5. Mietus JE, Peng CK, Henry I, Goldsmith RL, Goldberger AL: The pNNx files: re-examining a widely used heart rate variability measure. *Heart* 2002;88:378-80.

6. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ: Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* 1981;213:220-2.

7. Pomeranz B, Macaulay RJ, Caudill MA, et al.: Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985;248: H151-3.

8. Malliani A, Lombardi F, Pagani M: Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. *Br Heart J* 1994;71:1-2.

9. Vaillancourt DE, Newell KM: Changing complexity in human behavior and physiology through aging and disease. *Neurobiol Aging* 2002;23:1-11.

10. Bar-Yam Y: *Dynamics of Complex Systems.* Boulder Colorado, USA: Westview Press; 1997.

11. Goldberger AL, Peng CK, Lipsitz LA: What is physiologic complexity and how does it change with aging and disease? *Neurobiol Aging* 2002;23:23-6.

12. Peng CK, Havlin S, Stanley HE, Goldberger AL: Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos* 1995;5:82-7.

13. Huikuri HV, Makikallio TH, Peng CK, Goldberger AL, Hintze U, Moller M: Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. *Circulation* 2000;101: 47-53.

14. Costa M, Goldberger AL, Peng CK: Multiscale entropy analysis of complex physiologic time series. *Phys Rev Lett* 2002;89:068102.

15. Roose SP: Depression, anxiety, and the cardiovascular system: the psychiatrist's perspective. *J Clin Psychiatry* 2001;62 (Suppl) 8:19-22; discussion 23.

16. Gehi A, Mangano D, Pipkin S, Browner WS, Whooley MA: Depression and heart rate variability in patients with stable coronary heart disease: findings from the Heart and Soul Study. *Arch Gen Psychiatry* 2005;62:661-6.

17. Yeragani VK, Pesce V, Jayaraman A, Roose S: Major depression with ischemic heart disease: effects of paroxetine and nortriptyline on long-term heart rate variability measures. *Biol Psychiatry* 2002;52:418-29.

18. Jindal RD, Keshavan MS: Heart rate variability in patients with depression. *Arch Gen Psychiatry* 2007; 64:611-2.

19. Yeragani VK: Major depression and long-term heart period variability. *Depress Anxiety* 2000;12:51-2.

20. Yeragani VK, Pohl R, Balon R, et al.: Heart rate variability in patients with major depression. *Psychiatry Res* 1991;37:35-46.

21. Licht CM, de Geus EJ, Zitman FG, Hoogendijk WJ, van Dyck R, Penninx BW: Association between ma-

jor depressive disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). *Arch Gen Psychiatry* 2008;65:1358-67.

22. Kawachi I, Colditz GA, Ascherio A, et al.: Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation* 1994;89:1992-7.

23. Weissman MM, Markowitz JS, Ouellette R, Greenwald S, Kahn JP: Panic disorder and cardiovascular/cerebrovascular problems: results from a community survey. *Am J Psychiatry* 1990;147:1504-8.

24. Sloan RP, Shapiro PA, Bagiella E, et al.: Effect of mental stress throughout the day on cardiac autonomic control. *Biol Psychol* 1994;37:89-99.

25. Yeragani VK, Tancer M, Uhde T: Heart rate and QT interval variability: abnormal alpha-2 adrenergic function in patients with panic disorder. *Psychiatry Res* 2003;121:185-96.

26. Srinivasan K, Ashok MV, Vaz M, Yeragani VK: Decreased chaos of heart rate time series in children of patients with panic disorder. *Depress Anxiety* 2002;15:159-67.

27. Miu AC, Heilman RM, Miclea M: Reduced heart rate variability and vagal tone in anxiety: trait versus state, and the effects of autogenic training. *Auton Neurosci* 2009;145:99-103.

28. George DT, Nutt DJ, Walker WV, Porges SW, Adinoff B, Linnoila M: Lactate and hyperventilation substantially attenuate vagal tone in normal volunteers. A possible mechanism of panic provocation? *Arch Gen Psychiatry* 1989;46:153-6.

29. Bar KJ, Berger S, Metzner M, et al.: Autonomic Dysfunction in Unaffected First-Degree Relatives of Patients Suffering From Schizophrenia. *Schizophr Bull* 2009.

30. Boettger S, Hoyer D, Falkenhahn K, Kaatz M, Yeragani VK, Bar KJ: Altered diurnal autonomic variation and reduced vagal information flow in acute schizophrenia. *Clin Neurophysiol* 2006;117:2715-22.

31. Okada T, Toichi M, Sakihama M: Influences of an anticholinergic antiparkinsonian drug, parkinsonism, and psychotic symptoms on cardiac autonomic function in schizophrenia. *J Clin Psychopharmacol* 2003; 23:441-7.

32. Toichi M, Kubota Y, Murai T, et al.: The influence of psychotic states on the autonomic nervous system in schizophrenia. *Int J Psychophysiol* 1999;31:147-54.

33. Cohen H, Loewenthal U, Matar M, Kotler M: Association of autonomic dysfunction and clozapine. Heart rate variability and risk for sudden death in patients with schizophrenia on long-term psychotropic medication. *Br J Psychiatry* 2001;179:167-71.

34. Rechlin T, Claus D, Weis M: Heart rate variability in schizophrenic patients and changes of autonomic heart rate parameters during treatment with clozapine. *Biol Psychiatry* 1994;35:888-92.

35. Wang YC, Yang CC, Bai YM, Kuo TB: Heart rate variability in schizophrenic patients switched from typical antipsychotic agents to amisulpride and olanzapine: 3-month follow-up. *Neuropsychobiology* 2008; 57:200-5.

36. Sloan RP, Shapiro PA, Bigger JT Jr., Bagiella E, Steinman RC, Gorman JM: Cardiac autonomic control and hostility in healthy subjects. *Am J Cardiol* 1994;74:298-300.

37. Voss A, Baier V, Schulz S, Bar KJ: Linear and nonlinear methods for analyses of cardiovascular variability in bipolar disorders. *Bipolar Disord* 2006;8:441-52.

38. Cohen H, Kaplan Z, Kotler M, Mittelman I, Osher Y, Bersudsky Y: Impaired heart rate variability in euthymic bipolar patients. *Bipolar Disord* 2003;5:138-43.

39. Henry BL, Minassian A, Paulus MP, Geyer MA, Perry W: Heart rate variability in bipolar mania and schizophrenia. *J Psychiatr Res* 2009.

40. Borger N, van der Meere J, Ronner A, Alberts E, Geuze R, Bogte H: Heart rate variability and sustained attention in ADHD children. *J Abnorm Child Psychol* 1999;27:25-33.

41. Tonhajzerova I, Ondrejka I, Adamik P, et al.: Changes in the cardiac autonomic regulation in children with attention deficit hyperactivity disorder (ADHD). *Indian J Med Res* 2009;130:44-50.

42. Lackschewitz H, Huther G, Kroner-Herwig B: Physiological and psychological stress responses in adults with attention-deficit/hyperactivity disorder (ADHD). *Psychoneuroendocrinology* 2008;33:612-24.

43. Allan LM, Ballard CG, Allen J, et al.: Autonomic

dysfunction in dementia. *J Neurol Neurosurg Psychiatry* 2007;78:671-7.

44. Kim DH, Lipsitz LA, Ferrucci L, et al.: Association between reduced heart rate variability and cognitive impairment in older disabled women in the community: Women's Health and Aging Study I. *J Am Geriatr* Soc 2006;54:1751-7.

45. Yang AC, Tsai SJ, Hong CJ, Yang CH, Hsieh CH, Liu ME: Association between heart rate variability and cognitive function in elderly community-dwelling men without dementia: a preliminary report. *J Am Geriatr Soc* 2008;56:958-60.

46. Kupper NH, Willemsen G, van den Berg M, et al.: Heritability of ambulatory heart rate variability. *Circulation* 2004;110:2792-6.

47. Su S, Lampert R, Zhao J, et al.: Pleiotropy of C-reactive protein gene polymorphisms with C-reactive protein levels and heart rate variability in healthy male twins. *Am J Cardiol* 2009;104:1748-54.

48. Busjahn A, Voss A, Knoblauch H, et al.: Angiotensin-converting enzyme and angiotensinogen gene polymorphisms and heart rate variability in twins. *Am J Cardiol* 1998;81:755-60.

49. Neumann SA, Lawrence EC, Jennings JR, Ferrell RE, Manuck SB: Heart rate variability is associated with polymorphic variation in the choline transporter gene. *Psychosom Med* 2005;67:168-71.

50. Matsunaga T, Yasuda K, Adachi T, et al.: Association of beta-adrenoceptor polymorphisms with cardiac autonomic modulation in Japanese males. *Am Heart J* 2007;154:759-66.

51. Cheng D, Tsai SJ, Hong CJ, Yang AC: Reduced physiological complexity in robust elderly adults with the APOE epsilon4 allele. *PLoS One* 2009;4: e7733.

52. Yang AC, Chen TJ, Tsai SJ, et al.: BDNF Val66Met polymorphism alters sympathovagal balance in healthy subjects. *American Journal of Medical Genetics B* 2010: DOI:10.1002/ajmg.b.31069.

53. Yeh GY, Mietus JE, Peng CK, et al.: Enhancement of sleep stability with Tai Chi exercise in chronic heart failure: preliminary findings using an ECG-based spectrogram method. *Sleep Med* 2008;9:527-36.

54. Slonimsky JD, Yang B, Hinterneder JM, Nokes EB, Birren SJ: BDNF and CNTF regulate cholinergic properties of sympathetic neurons through independent mechanisms. *Mol Cell Neurosci* 2003;23:648-60.

55. Zhou X, Nai Q, Chen M, Dittus JD, Howard MJ, Margiotta JF: Brain-derived neurotrophic factor and trkB signaling in parasympathetic neurons: relevance to regulating alpha7-containing nicotinic receptors and synaptic function. *J Neurosci* 2004;24:4340-50.

56. Kuo TB, Shaw FZ, Lai CJ, Yang CC: Asymmetry in sympathetic and vagal activities during sleep-wake transitions. *Sleep* 2008;31:311-20.

57. Thomas RJ, Mietus JE, Peng CK, Goldberger AL: An electrocardiogram-based technique to assess cardiopulmonary coupling during sleep. *Sleep* 2005;28: 1151-61.

58. Thomas RJ, Mietus JE, Peng CK, et al.: Differentiating obstructive from central and complex sleep apnea using an automated electrocardiogram-based method. *Sleep* 2007;30:1756-69.

59. Yang AC, Yang CH, Hong CJ, et al.: Sleep state instabilities in major depressive disorder: detection and quantification with electrocardiogram-based cardiopulmonary coupling analysis. *Psychophysiology* 2010, in press.

60. Goldberger AL, Amaral LA, Glass L, et al.: PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. *Circulation* 2000;101:E215-20.