Heart Rate Variability in Psychiatric Disorders

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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

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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

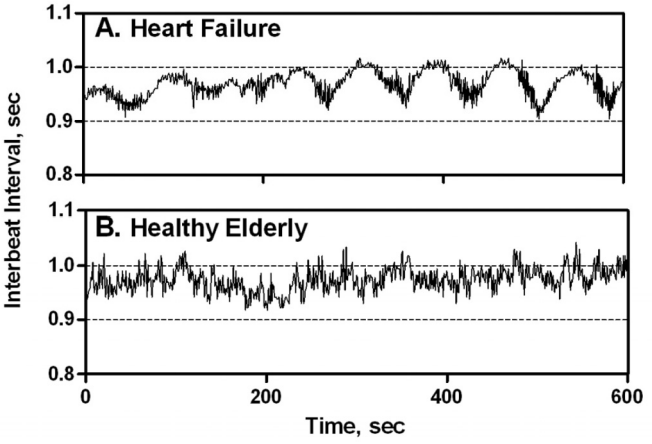

Figure 1. A comparison of interbeat interval time series between (A) a patient with heart failure and (B) a healthy elderly subject. Each recording consists of 600 seconds of interbeat interval time series. They had different physiologic complexity but both had similar means and standard deviations of 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

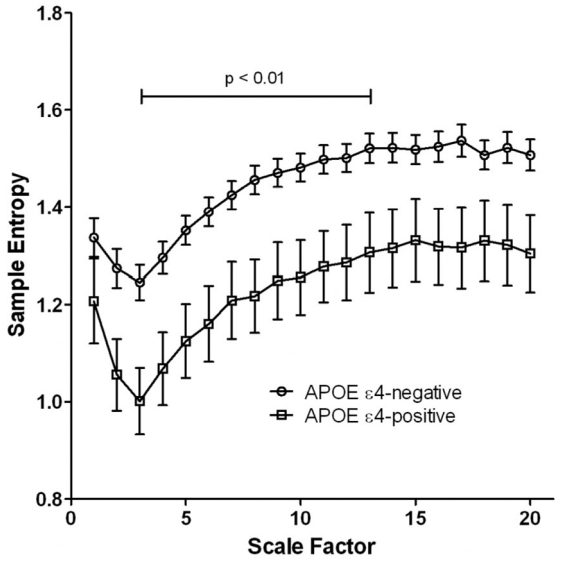

Figure 2. Multiscale entropy analysis by APOE status. Reproduced from [51]

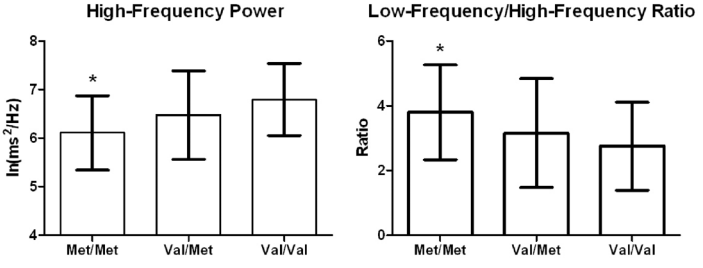

Figure 3. Association of brain-derived neurotrophic factor polymorphism with spectral components of heart rate variability. The asterisk indicates that the p-value was less than 0.05 for the comparison between the Met/Met and Val/Val genotypic group. Reproduced from [52]

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.

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2010 年 TSSCI 資料庫收錄期刊名單

行政院國家科學委員會人文及社會科學發展處（簡稱國科會人文處）於2010年10月8日召開期刊評審委員會聯席會議，依據2009年10月9日修訂之「臺灣社會科學引文索引資料庫期刊收錄實施方案」，調整2010年TSSCI資料庫收錄期刊名單。

2010年期刊收錄名單相較於**2009**年名單如下表，新增期刊以「★」標示：

99年度TSSCI期刊收錄名單
（各學門依刊名筆劃順序排列）共87種

學門	期刊名稱
人類學	民俗曲藝 Journal of Chinese Ritual, Theatre and Folklore
	臺灣人類學刊 Taiwan Journal of Anthropology
社會學	文化研究 ★ Router: A Journal of Cultural Studies
	中華傳播學刊 Chinese Journal of Communication Research
	台灣社會學 Taiwanese Sociology
	社會政策與社會工作學刊 Social Policy & Social Work
	新聞學研究 Mass Communication Research
	臺大社會工作學刊 ★ NTU Social Work Review
	臺灣社會學刊 Taiwanese Journal of Sociology
教育學	科學教育學刊 Chinese Journal of Science Education
	特殊教育研究學刊 Bulletin of Special Education
	特殊教育學報 ★ Journal of Special Education
	教育政策論壇 Educational Policy Forum
	教育研究集刊 Bulletin of Educational Research
	教育科學研究期刊 Journal of Research in Education Sciences
	教育資料與圖書館學 Journal of Educational Media and Library Sciences
	教育實踐與研究 ★

學	教育實踐與研究 ★ Journal of Educational Practice and Research
	教育學刊 Educational Review
	當代教育研究 Contemporary Educational Research Quarterly
	圖書資訊學研究 ★ Journal of Library and Information Science Research
	臺灣教育社會學研究 Taiwan Journal of Sociology of Education
	課程與教學 Curriculum & Instruction Quarterly
	藝術教育研究 Research in Arts Education
心理學	中華心理學刊 Chinese Journal of Psychology
	中華輔導與諮商學報 Chinese Journal of Guidance and Counseling
	台灣精神醫學 Taiwanese Journal of Psychiatry
	本土心理學研究 Indigenous Psychological Research in Chinese Societies
	教育心理學報 Bulletin of Educational Psychology
	測驗學刊 Psychological Testing
法律學	National Taiwan University Law Review
	公平交易季刊 Fair Trade Quarterly
	中原財經法學 ★ Chung Yuan Financial & Economic Law Review
	東吳法律學報 Soochow Law Review
	東海大學法學研究 Tunghai University Law Review
	政大法學評論 Chengchi Law Review
	國立臺灣大學法學論叢 National Taiwan University Law Journal
	臺北大學法學論叢 Taipei University Law Review
	公共行政學報 Journal of Public Administration
	台灣政治學刊 Taiwanese Political Science Review
	行政暨政策學報 Public Administration & Policy
	東吳政治學報

政治學	Soochow Journal of Political Science
	政治科學論叢 (註一) Taiwanese Journal of Political Science
	政治與社會哲學評論 SOCIETAS: A Journal for Philosophical Study of Public Affairs
	政治學報 Chinese Political Science Review
	問題與研究 Issues & Studies
	臺灣民主季刊 Taiwan Democracy Quarterly
	遠景基金會季刊 Prospect Quarterly
	選舉研究 Journal of Electoral Studies
經濟學	經濟研究 Taipei Economic Inquiry
	經濟論文 Academia Economic Papers
	經濟論文叢刊 Taiwan Economic Review
	農業經濟叢刊 Taiwanese Agricultural Economic Review
	農業與經濟 Agriculture and Economics
	臺灣經濟預測與政策 Taiwan Economic Forecast and Policy
	應用經濟論叢 Taiwanese Journal of Applied Economics
管理學	Asia Pacific Management Review
	International Journal of Information and Management Sciences
	工業工程學刊 Journal of the Chinese Institute of Industrial Engineers
	中山管理評論 Sun Yat-Sen Management Review
	交大管理學報 Chiao Da Management Review
	財務金融學刊 Journal of Financial Studies
	會計評論 International Journal of Accounting Studies
	資訊管理學報 Journal of Information Management
	電子商務學報 Journal of E-Business
	管理評論 Management Review
	管理與系統

	管理與系統 Journal of Management & Systems
	管理學報 Journal of Management
	臺大管理論叢 NTU Management Review
	證券市場發展季刊 Review of Securities and Futures Markets
區域研究及地理學	戶外遊憩研究 Journal of Outdoor Recreation Study
	台灣土地研究 Journal of Taiwan Land Research
	地理學報 Journal of Geographical Science
	住宅學報 Journal of Housing Studies
	建築學報 Journal of Architecture
	都市與計劃 City and Planning
	運輸計劃季刊 Transportation Planning Journal
	運輸學刊 Journal of the Chinese Institute of Transportation
	觀光休閒學報 Journal of Tourism and Leisure Studies
綜合類	The Journal of Nursing Research 護理研究
	人口學刊 Journal of Population Studies
	人文及社會科學集刊 Journal of Social Sciences and Philosophy
	中國大陸研究 Mainland China Studies
	中華心理衛生學刊 Formosa Journal of Mental Health
	台灣公共衛生雜誌 Taiwan Journal of Public Health
	台灣社會研究季刊 Taiwan: A Radical Quarterly in Social Studies
	教育與心理研究 Journal of Education & Psychology
	歐美研究 EurAmerica
＊註一：於2009年3月第39期開始，英文刊名由《Political Science Review》改為《Taiwanese Journal of Political Science》。	