國立臺灣大學電機資訊學院生醫電子與資訊學研究所

博士論文

Graduate Institute of Biomedical Electronics and Bioinformatics
College of Electric Engineering and Computer Science
National Taiwan University

Doctoral Dissertation

腦波非線性訊號分析--以阿滋海默症為例

The application of non-linear signal processing of electroencephalography in Alzheimer's disease

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中華民國 103 年 6 月

June 2014

國立臺灣大學博士學位論文
口試委員會審定書

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本論文係蔡秉晃君（學號 D96945003）在國立臺灣大學生醫電子與資訊學研究所完成之博士學位論文，於民國 103 年 05 月 23 日承下列考試委員審查通過及口試及格，特此證明

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所　長：莊曜宇

致謝

在完成這一段修業後，心中只充滿著“感謝”兩字。對於一個從小懷著電機夢的我，大學時代選擇了從醫救人的路，本以為不再有機會踏入這電機的殿堂，感謝我的太太（之前的女朋友）維晟，讓我有機會認識了亦師亦友的羅孟宗博士，同時也激盪起了醫學與電機辯論火花。永遠記得台大電機二館前的一場玩笑似的辯論，電生理學的正負符號表示，及肌電圖的高頻濾波與電機低通濾波的衝突，孟宗的一句“不然你自己來念念看”，讓我重新燃起了一絲希望。

感謝劉秀枝主任與王署君主任肯為這不知天高地厚的後進小輩寫下了跨領域的推薦函，也感謝曹建和副教授的機會給予，讓我這一點電機基礎都沒有的神經內科醫師重新認識這廣大電機領域。

在學期間，感謝曹老師的寬容與細心教導，讓我從基礎重新認識了訊號的本質，並開始學習分析訊號與研究訊號，在這段期間，充分感受的台灣大學的自由學風，學生對學問的勇於發問，老師對學生天馬行空想法的廣大包容，讓我學會不受限制的思考模式，進而促進醫療與電機的結合。

並感謝研究進行期間，不熟悉程式編撰的我，靠著羅孟宗博士非線性理論的指導，林澂的討論，張儀中的程式撰寫教導與協助，與林佩芬醫師臨床想法的激盪，讓我心中的想法逐漸成熟與茁壯。

感謝口試委員，曹建和老師，王署君教授，尹彙文博士，羅孟宗博士，及王淵洪博士百忙之中抽空前來指導，讓我的論文研究增色許多並指明未來的研究方向。

最後，以此文獻給維晟，如果沒有妳在背後的默默支持，在我不順遂時聽我抱怨，在我開心時聽我炫耀，我想這一路會變得更加艱辛；也獻給我心愛的女兒昀杉，感謝妳的到來，給我最後完成的力量！並對於所有摯愛的家人，說聲感謝，感謝您們的體諒包容與默默的支持！

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中文摘要

在此研究中，我們試圖以渾沌(chaos)理論為基礎，Sampling entropy 為方法，來分阿滋海默症 Alzheimer's disease (AD)不同時期的腦波複雜度，以提供臨床新的客觀工具，以利 AD 的診斷與預後評估。

失智症是一認知功能逐漸惡化的疾病，且 AD 佔了其中最大部份，且隨著年齡的增長，其發生的機率也大幅上升，因此，隨著台灣人口老人化的現象，AD 病患也預期會增加。但是，AD 的臨床診斷，常因病情進展的緩慢，而延後了 2~3 年。因此，找到客觀方便的方式，來達到及早診斷及早治療的目的，變的刻不容緩。

目前，臨床上對於 AD 的診斷，是按照 DSM-IV（*Diagnostic and Statistical Manual of Psychiatric Disorders 4th ed*）診斷標準診斷。雖有如此詳盡的評估，早期 AD 依舊不容易在早期進行客觀的評估。雖然，有些功能性腦部影像檢查，如 functional MRI, positron emission tomography (PET), and single photon emission computed tomography (SPECT)，可以提供部分的訊息，以作為臨床診斷的參考，但是，限制於高單價，輻射暴露，及顯影劑注射引起的過敏反應，都使得這些檢查並非極度方便。而腦波圖(Electroencephalography, EEG)為一價格低廉，非侵入性的檢查方式，可以快速取得人類腦部活動的紀錄，且其臨床使用已超過五十年，為一安全性極高的檢查。

但由於過去，對於腦波圖的判讀，是需要倚靠有經驗的神經內科專科醫師，且其對於失智症的評估，只能提供局部慢波的訊息，對於診斷及追蹤，實無多大助益；但是，近年來，由於電腦的發達，及數位訊號處理的進步，數位腦波分析（quantitative EEG）的概念，例如使用傅立葉轉換（Fourier analyses），開始被提出並應用於臨床失智病人腦波的分析。但是，這些基於線性系統的數學模式分析方式，卻只能提供病人與正常人之間的差異，並無法有效提供進一步的應用。而基於非線性系統的近似熵（approximate entropy），可以分析訊號的複雜度，訊號越複雜，其值越高。是在數學模式上比較符合人類生理訊號的非線性特徵，在過去的研究中，也發現在 AD 的病人中，其雙側顳葉的近似熵會有下降的趨勢。但是，

單純的近似熵卻會受到資料的長短，及其潛在的趨勢，而得不到一個穩定的結果，而限制了其應用。在此方面，採樣熵（sampling entropy）則是避免了資料長短的誤差，再藉由此研究中，利用經驗解構模式，來去除潛在的趨勢，使得所得結果更能符合臨床資料，並有機會使腦波圖可以成為一客觀評估失智症的工具。

另一個問題為臨床醫生依舊無法在治療個別病人時，事前預見其治療效果。在這篇論文中，我們試圖用多尺度熵（multiscale entropy）來分析對於乙醯膽鹼酯酶抑製劑治療有效及無效病患腦波圖的差異。以期在治療的初期即能為病患訂定有效的治療方針。

腦波圖，通過非線性數位訊號處理的幫助下，腦波圖的潛藏信息可以被提取用於臨床評估，追蹤，甚至預測治療效果。

關鍵字: 阿滋海默症, 採樣熵, 多尺度熵, 腦波圖, 經驗解構模式

Abstract

In this dissertation, we will develop the computational tools, on the basis of sampling entropy, to evaluate different patterns of complexity activation of the electroencephalography (EEG) in longitudinal changes in the Alzheimer's disease (AD) after the acetylcholinesterase inhibitor (AChE inhibitor).

Alzheimer's disease is the most common form of dementia. The cause and progression of AD are not well understood. One hypothesis is that AD is caused by reduced synthesis of the neurotransmitter, acetylcholine (ACh). AChE inhibitors are proved as an effective therapy. The diagnosis and evaluation in the early stage dementia is challenging in clinical medicine. Quantitative electroencephalographs (qEEG) provide a potential method to objectively quantify the cortical activations in AD, but they are too insensitive to probe the alteration of EEG in the early AD.

The approximate entropy, which is a non-linear statistic and is able to quantify the irregularity of a time series, was significant lower in the bilateral temporal region in AD patients, in whom the basic pathology is hippocampus atrophy. But there were some bias in approximate entropy, such as inconsistent results, and depending on the data length. Therefore, in order to evaluate different patterns of complexity activation of the EEG in longitudinal changes in AD after the acetyl cholinesterase inhibitor therapy, it is necessary to develop a better method with the sampling entropy. However, a technical issue which has been ignored by most researchers is that the signal should be stationary. In order to resolve the non-stationarity of SaEn in EEG to improve the sensitivity, an empirical mode decomposition (EMD) was applied for detrending in this dissertation.

Twenty-seven AD patients (9M/18F; mean age 74.0±1.5 years) were included.

Their initial Minimal Mental Status Examination was 19.3±0.7. They received the first resting awake 30-mine EEG before the therapy. Five of them received a follow-up examination within 6 months after the therapy. The 30-s EEG data without artifacts were selected and analyzed with a new proposed method, " EMD-based detrended-SaEn" to attenuate the influence of intrinsic non-stationarity. The correlation factors in 27 AD patients showed a moderate correlation (0.361-0.523, $p < 0.05$) between MMSE and EMD-based detrended SaEn in Fp1, Fp2, F4 and T3. There was a high correlation (Correlation coefficient = 0.975, $p < 0.05$) between the changes of MMSE and the changes of EMD-based detrended-SaEn in F7 in 5 follow-up patients. The dynamic complexity of EEG fluctuations is degraded by pathological degeneration, and EMD-based detrended SaEn provides an objective, non-invasive and non-expensive tool for evaluating and following AD patients.

The other issue, for clinician, it is still not predictable effect in individual patient. In this dissertation, we tried to use multiscale entropy (MSE) in EEG to predict the efficacy of AChE inhibitor. Seventeen newly diagnosed AD patients (9M/8F; mean age 74.6±7.4 years) were enrolled in this study, with an initial MMSE of 18.8±4.5. After 12 months' therapy of AChE inhibitor, 7 patients (3M/4F; mean age 76.1±7.9 years) were responsive (responder) and 10 patients (6M/4F; 73.5±7.3 years) were non-responsive (non-responder). The major difference between two groups is Slope2 (MSE6 to 20). The area under curve (ROC curve) of Slope2 is 0.871(95% CI = 0.69 - 1). The sensitivity is 85.7% and the specificity is 60% while the cutoff value of Sloep2 is -0.024. MSE of EEG, especially Slope2, is able to be an objective tool to predict the efficacy of AChE inhibitor before the therapy.

By the assistance of non-linear digital signal processing, the embedded information

of EEG in AD could be extracted for the clinical evaluation, following up and even prediction the therapeutic effect.

Key Word: Alzheimer's disease, Sample entropy, Multiscale Entropy, Electroencephalography, Empirical mode decomposition

CHAPTER 1 Introduction

1.1 Background

1.1.1 Alzheimer's disease

Alzheimer's disease (AD) is characterized by a slowly progressing degenerative process of cognitive decline.[1, 2] It was first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906 and was named after him.[3] Most often, AD is diagnosed in people over 65 years of age.[4] In 2006, there were 26.6 million sufferers worldwide. Alzheimer's is predicted to affect 1 in 85 people globally by 2050.[5] Community studies in Taiwan,[6-8] Beijing,[9] Shanghai[10, 11] and Kinmen[12] have shown that AD is the leading cause of dementia among the ethnic Chinese, just as it is for whites.[13-19] The average annual conversion rate from mild cognitive impairment to AD has been reported as 10% to 15%,[20] but ranges from 4% to 41%. [21-30] The early diagnosis and treatment of AD would likely benefit from the proper identification of individuals at risk for developing AD.

Dementia is generally associated with a poor prognosis. [31-38] The Shanghai study[32] found a 2-year mortality rate of 34.6% and a 5-year mortality rate of 62.2% among AD patients. In Taiwan, the mean survival time for AD patients was 4.48 years (SD = 0.1 years) after the time of enrollment.[39]

In the early stages, the most common symptom is difficulty in remembering recent events. As the disease advances, symptoms can include confusion, irritability and aggression, mood swings, trouble with language, and long-term memory loss. Gradually, bodily functions are lost, ultimately leading to death.[1, 2]

The cause for most AD is still essentially unknown, and several competing hypotheses exist trying to explain the cause of the disease, such as beta-amyloid (βA) deposition, [40-42] neurofibrillary tangle [43-45] and cholinergic deficit. [46-48] There is still no definite therapy to cure or stop this disorder. Current treatments only help with the symptoms of the disease and it is generally accepted that many of its symptoms are related to a cholinergic deficit in the cerebral cortex and other areas of the brain. [46, 47, 49] Acetylcholinesterase inhibitors (AChE inhibitors) were proved as an effective therapy for AD. [50-55] Phamocoecnomic studies disclosed that therapies can postpone the progression of dementia to more severe stages and may offer economic benefit m patients' families, caregivers, and society. [56-60] However, clinicians often argue that AChE inhibitors have an effect in a subgroup of 25-50% of AD patients,[48, 61, 62] who cannot be identified objectively, and the effect is time-consuming.

1.1.2 Diagnosis of Alzheimer's disease

In clinical, the diagnosis of AD is dependent on DSM-IV criteria, as below. [63]

A. The development of multiple cognitive deficits manifested by both:

1. Memory impairment (impaired ability to learn new information or to recall previously learned information).

2. One (or more) of the following cognitive disturbances:

a. Aphasia (language disturbance).

b. Apraxia (impaired ability to carry out motor activities despite intact motor function.

c. Agnosia (failure to recognize or identify objects despite intact sensory function).

d. Disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting).

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:

1. Other central nervous systems, conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor).

2. Systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B12 or folic acid deficiency, neurosyphilis, HIV infection).

3. Substance-induced conditions.

E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another disorder (e.g., major depressive disorder, schizophrenia).

According to the criteria, AD is usually diagnosed clinically from the patient history. Neurological examination in early AD will usually provide normal results, except for obvious cognitive impairment, which may not differ from that resulting from other diseases processes, including other causes of dementia. Neurologists recorded medical and neurologic histories and performed neurologic examinations. Diabetes, hypertension, coronary artery disease, comorbid medical conditions, and drug histories were obtained from the subjects and their families. This information was confirmed by reviewing the medical charts if they were available. Either a neurologist or a neuropsychologist interviewed each subject and at least 1 caregiver (for those patients who suffered from dementia) on the subjects' memory, orientation, judgment, problem-solving abilities, participation in family and community affairs, engagement in hobbies, and competence in personal care. [64, 65] Individual participants and their caregivers were interviewed by the same psychiatrist at each visit to identify possible psychiatric symptoms. Delusions, depression, hallucinations, and misidentification were chosen as core psychiatric symptoms for study analysis. Delusion was considered present if the patient had thoughts of systematic or nonsystematic persecution, theft, infidelity, jealousy, or other delusional situations. Depression was diagnosed based on the results of the structured interview schedule of the DSM-IV criteria.[63] The degree of depression and the anxiety level were evaluated for all patients based on the Hamilton Depression Rating Scale (HDRS)[66] and the Hamilton Anxiety Rating Scale (HARS).[67] Hallucination was positive if the patient had formed or non-formed visual, auditory, olfactory, or tactile hallucinations. Patients with misidentification believed that someone was in their house when nobody was there, that their house was not their own, that a person was an impostor, that someone else was in the mirror, or that characters on television were real.

Medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI) and with single photon emission computed tomography (SPECT) or positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia. In the early stage, brain CT cannot provide any information to different between normal elderly and AD. In the late stage of AD, brain CT only discloses the brain atrophy. Volumetric MRI can detect changes in the size of brain regions. Measuring those regions that atrophy during the progress of AD is showing promise as a diagnostic indicator.[68] Functional imaging research , such as PET[69] and SPECT[70], suggests that AD typically have reduced brain cell activity in certain regions. For example, studies with fluorodeoxyglucose (FDG)-PET indicate that AD is often associated with reduced use of glucose in brain areas important in memory, learning and problem solving.[69] However, as with the shrinkage detected by structural imaging, there is not yet enough information to translate these general patterns of reduced activity into diagnostic information about individuals.

Neuropsychological screening tests can help in the diagnosis of AD. In the tests, people are instructed to copy drawings similar to the one shown in the picture, remember words, read, and subtract serial numbers. Neuropsychological tests such as the mini-mental state examination (MMSE) [71] are widely used to evaluate the cognitive impairments needed for diagnosis, which has a total score of 30. Clinical Dementia Rating (CDR) scales to rate the severity of the dementia was also evaluated after a neurologist conducted separate semi-structured interviews with the patient and a knowledgeable informant. The scores were as follows: 0 (normal), 0.5 (questionable), 1 (mild), 2 (moderate), and 3 (severe).[72]

Blood tests, such as thyroid function tests, Vitamin B12, syphilis test, HIV examination, renal function, liver function, electrolyte levels, and hemoglobin, can identify other causes for dementia than AD.[73]

1.1.3 Management of Alzheimer's disease

There is no cure for AD; available treatments offer only symptomatic benefit but remain palliative in nature. Reduction in the activity of the cholinergic neurons is a well-known feature of AD. [46-48, 74] AChE inhibitors were proved as an effective therapy for AD. [50-55] AChE inhibitors are employed to reduce the rate at which acetylcholine (ACh) is broken down, thereby increasing the concentration of ACh in the brain and combating the loss of ACh caused by the death of cholinergic neurons.[75, 76] Phamocoecnomic studies disclosed that therapies can postpone the progression of dementia to more severe stages and may offer economic benefit m patients' families, caregivers, and society. [56-60] The well-known AChE inhibitor is donepezil. [50-55]

Glutamate is a useful excitatory neurotransmitter of the nervous system, although excessive amounts in the brain can lead to cell death through a process called excitotoxicity which consists of the overstimulation of glutamate receptors. [77] Memantine is a noncompetitive N-methyl-d-aspartate (NMDA) receptor antagonist first used as an anti-influenza agent. It acts on the glutamatergic system by blocking NMDA receptors and inhibiting their overstimulation by glutamate. [77] Memantine has been shown to be moderately efficacious in the treatment of moderate to severe AD.[78-81]

1.2 Motivation

The early stages of AD are difficult to diagnose. A definitive diagnosis is usually made once cognitive impairment compromises daily living activities, although the person may still be living independently. The symptoms will progress from mild cognitive problems, such as memory loss through increasing stages of cognitive and non-cognitive disturbances, eliminating any possibility of independent living, especially in the late stages of the disease.[82-84]

Besides that, in clinical practice, the evaluation of memory decline is highly dependent on numerous neuropsychiatric tests that rely on testers and patients. Age and education compromise these neuropsychiatric tests[85-93] One of the major challenges is to identify the structural or functional changes of the brain. Some functional imaging techniques, such as functional MRI [94-96], PET[69], or SPECT[70], are useful in making objective evaluations of the severity of the dementia. The high cost, contrast-agent related allergies, and potential exposure to radionuclide irradiation limits clinical application.

1.3 Electroencephalography

Electroencephalography (EEG) is the recording of electrical activity along the scalp. EEG measures voltage fluctuations resulting from ionic current flows within the neurons of the brain.[97] In clinical, EEG refers to the recording of the brain's spontaneous electrical activity over a short period of time, usually 20–40 minutes, as recorded from multiple electrodes placed on the scalp. Diagnostic applications generally focus on the spectral content of EEG, that is, the type of neural oscillations that can be observed in EEG signals. The surface EEG signals are gained from the numerous

cortical neurons activations. The summation of inhibitory and excitatory post-synaptic potentials, after passing through at least three layers of boundaries, cerebrospinal fluid (CSF), dura and skull, are recorded at the surface of the scalp.[97] The action potential of the neuron cells is not through as the source of the surface EEG due to its short duration and the small amplitudes, compared with the post-synaptic potentials.[97] Because of this character, the sole neuron activation was not easily backwardly evaluated.[98, 99] It limited surface EEG spatial resolution, which is the major merit of the CT or MRI. But in the time resolution, surface EEG showed real time and high resolution, due to its high sampling rates, compared with the function MRI and PET or SPECT. In the other hand, surface EEG is a relative not expensive and a more portable tool in clinical. Overall, although the surface EEG could not provide the high spatial resolution, it could offer the real time and high time resolution signal for the evaluation of the neuron activations, which should be most important point in the function evaluation.

The surface EEG has been prescribed in clinical for years. Traditional surface EEG was applied in the diagnosis and the location of seizure majorly. In the other neurological disorders, such as dementia, [98, 100, 101],sleep disorder, [102] metabolic encephalopathy, [103] infective encephalopathy, [104-107] traumatic brain injury, [108] and numerous psychiatric disorders, like schizophrenia, [109] depression, [110] attention-deficient hyperactivation disorder, [111, 112] it played as an assistant tool for evaluation of the cortical function. However, because of the complexity of EEG, except seizure disorders, it could not disclose much robust information for clinical diagnosis.

In the surface EEG, the signals are composed of multiple oscillation components, whose mechanisms are still not clearly.[97] But in the traditional paper EEG, four major components, delta (0.5~4 Hz), theta (4~8Hz), alpha (8~12 Hz), beta (12~25 Hz) rhythm,

were recognized since Berger.[113] In clinical, to evaluate the locations, the amplitudes and the existence of their four components and to compare these findings with clinical diagnosis were performed for years with productive data. However, except in epilepsy, this information just provided as an assistant tools. [98, 100, 108, 110, 113]

CHAPTER 2 The non-linearity in Electroencephalography for Alzheimer' disease

2.1 Introduction

In recent years, by the assistance of digital EEG, much quantitative EEG methods were developed, including automatic detection and localization of epileptic discharges, topography displays and statistical analysis compared with the normative actives.[113] By the development of these quantitative EEG, clinicians would like to re-evaluate the role of EEG in clinical. In these methods, spectral analysis, which could easily extract these four familiar components in the frequency spectral analysis of the short-term EEG signals, due to its simplicity and non-invasiveness, has become one of the most commonly used objective tools for characterizing alternation of EEG changing from one state to another and the abnormalities related to pathological degeneration of the brain.

Numerous neurological and psychiatric disorders were evaluated by quantitative EEG, especially the alpha rhythm.[98, 100, 113] Although in human, the mechanism of the alpha rhythm is still not clear, by the many animal models, the alpha rhythm should be related to the interaction of cortical neurons and the thalamus,[114] and is though as the indication of consciousness level and cognitive function in surface EEG. Previous studies also confirmed that the powers of the alpha rhythms are associated with the aging and demented severity.[113] However, in these studies, only very severe disorders could be distinguished from the normal people, [98, 113] but exhibited non-significant difference between mild disorders and normal peoples. Because the power spectrum density in defined frequency band related to specific rhythms, it is typically used to

determine the severity of neuron disease. Although amplitudes of EEG signals are related to the degree of pathologies or age-related degenerations, but this seems not very reliable. Amplitudes of EEG signals can be attenuated by boundaries, such as thickness of the dura matter, skull and scalp or the amount of cerebrospinal fluid.[97] On the other hand, this Fourier transform based approach, however, assumed that signals are composed of superimposed sinusoidal oscillations of constant amplitude and period at a pre-determined frequency range. This assumption puts an unavoidable limitation on the reliability and application of the method, since EEG represents the output of the interactions between neural networks, it is not necessarily linear. Many deterministic chaos-based methods are applied to characterize the embedded intrinsic nonlinearity of EEG signals.[115, 116] However, most of these methods need a critical condition that the time series should be stationary.[117] Such constrain unfortunately becomes a major problem in the analysis of physiological signals since the nonstationarity (i.e. statistical properties such as mean and standard deviation vary with time) is an intrinsic feature of physiological data and persists even without external stimulation. The presence of nonstationarity makes conventional approaches not reliable. To resolve the difficulties related to nonlinear and nonstationary behavior, one of the innovative approaches applied to physiological studies is Hilbert Huang transform (HHT).[118] The HHT is based on nonlinear theories and has been designed to extract dynamic information from nonstationary signals at different time scales. The advantages of the HHT over traditional Fourier-based methods have been appreciated in many studies of different physiological systems such as blood pressure hemodynamics, [119] cerebral autoregulation, [120-125] cardiac dynamics, [126] respiratory dynamics, [127] and EEG activities [128]also included.

In this study, we focus on the comprehensive investigation of one of the common

EEG rhythms, alpha waves, to show how HHT can profile the nonlinear and nonstationary characteristics of such principal EEG rhythm. We also compare the performances of HHT and conventional methods used to analyze EEG fluctuations and then provide the strategies to extract certain features from HHT spectrum, which may be a potential noninvasive tool for the diagnosis of neuron disorders.

2.2 Material and Methods: Hilbert Huang Transform

The HHT algorithm requires two steps in analyzing data. The first step is to pre-process the data by the empirical mode decomposition (EMD) algorithm. [118] The decomposition is based on the simple assumption that any data consists of a finite number of intrinsic modes of oscillations. The first mode is obtained by tracing the envelope of local maxima and local minima in the repeat interval signal. The first mode is then subtracted from the repeat interval signal to obtain a first residual signal. The second mode is obtained by tracing the envelope of the maxima and minima in the first residual signal. The subsequent mode of oscillation, termed intrinsic mode functions (IMFs), is decomposed from the original time series following same procedures. Each IMF represents a certain frequency-amplitude modulation at a specific time scale, and therefore it can be used to analyze temporal or phase associations with comparable IMFs from other signals. For signals with intermittent oscillations, one essential problem in the EMD is that an intrinsic mode could comprise of oscillations with very different wavelengths at different temporal locations (i.e., mode mixing). The problem can cause certain complications for our analysis, making the results less reliable. To overcome the mode mixing problem, a noise assisted EMD algorithm, namely the Ensemble Empirical Mode Decomposition (EEMD) has been proposed. [122, 129] The EEMD applies the EMD to obtain an ensemble of decompositions of data with added

white noise, and uses the resultant means of the corresponding intrinsic mode functions from different decompositions as the final result. The second step is to apply the Hilbert transform to the decomposed IMFs and construct the energy-frequency-time distribution, designated as the Hilbert Spectrum. The biological fluctuations are not stationary and are better characterized by analytical methods that can quantify the amplitude and phase/frequency from time to time. [120, 125, 130] Hilbert transform provides a more informative and accurate tool to examine the nonlinear relationship between nonstationary signals. [126-128] Unlike the Fourier transform, the Hilbert transform does not assume that signals are composed of superimposed sinusoidal oscillations of constant amplitude and frequency. It provides the instantaneous amplitude and phase of an oscillation, instead. Physically, the necessary for us to define a meaningful instantaneous frequency/phase are that the functions are symmetric with respect to the local zero mean and have the same numbers of zero crossings and extrema. The intrinsic mode function derived from Empirical Mode Decomposed method satisfies the above conditions, since it holds the properties that (1) the total numbers of extrema and zeroes crossings must either equal or differ at most by one and (2) at any point, the mean value of the envelop defined by the local maxima and it defined by the local minima is zero. Thus, we can explore the instantaneous frequency and energy, rather than the global frequency and energy defined by the Fourier spectral analysis. These properties of the HHT make it ideal for quantitative analysis of complex biomedical signals that defy comprehensive analysis based on conventional spectral frequencies.

In this study, we attempt to specify whether the principal alpha waves will get altered under neuron disorder, in addition to the healthy control subject, we therefore included another two patients from the neurological outpatient department in National Yang Ming University Hospital, one is with mild AD (with MMSE of 26 score and

CDR of 1 score) and the other late stage of dementia at deep comatose state (with MMSE of 0 score and CDR of 5 score).

2.3 Results

2.3.1 Stationarity of temporal–spectral distribution

As alpha rhythms are best seen in the occipital region of the brain, in this study, signals at an occipital electrode (i.e. O1) will be examined at first. Figure 1 gives the raw O1 EEG signals recorded from three different subjects, who are normal control, mildly demented, and severe demented in deep coma. The investigation of raw data shows several facts that are (i) the EEG signals of the normal and the mildly demented subjects oscillate more quickly than that of the one in deep coma. (ii) The EEG morphologies of the normal and the mildly demented subjects look similar, difficult to distinguish one from the other by visual inspection. (iii) Sinusoidal wavelets appear intermittently rather than consistently in the EEG signals of the normal and the mildly demented subjects. Some of the above observations may be quantified by the linear Fourier analysis; however, the characteristics in visual inspection including irregular morphologies and intermittent/nonstationary sinusoidal wavelets could not be understood well by the Fourier spectra. Therefore, we propose some novel methods based on HHT to quantify such nonlinear and nonstationary characteristics of EEG signals.

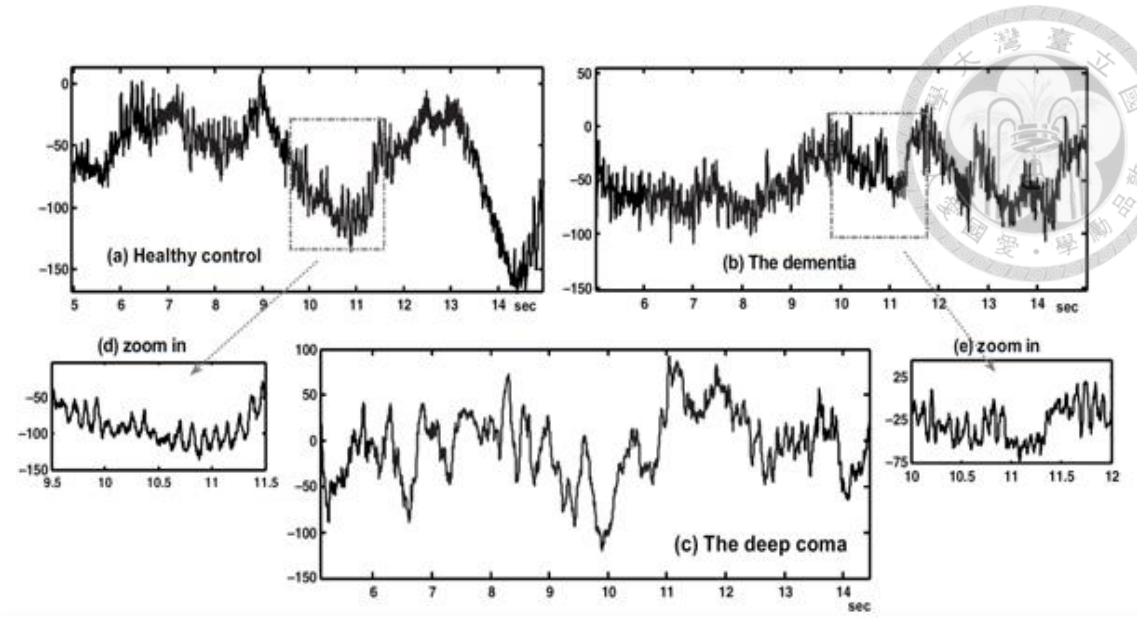


Figure 1 The comparison of EEG time domain signals recorded from three different subjects, who are (a) normal control, (b) mildly demented, and (c) severe demented in deep coma. We zoom in the time domain signals over 9.5-11.5 s for normal subject and over 10 – 12 s for mildly demented one and plot the details in (d) and (e).

In order to study the nonstationary characteristic of brain waves, time–frequency analyses are applied to the signals from different subjects, and we give the results of the normal control, the mild dementia, and the deep coma as shown in Fig. 2. Two conventional time frequency analyses including short-time Fourier transform (STFT) and continuous Morlet wavelet transform[130] are adopted to compare with the novel HHT. Each analysis shows a significant power in the frequency range of 8–12Hz (i.e. the alpha rhythms) in the normal control, and the mild dementia, while significantly reduced in the subject in deep coma. This agrees with the discovered fact that the appearance of alpha rhythm is an indicator of awareness.[131] The study of the temporal frequency that features from the results of STFT analysis shows concentrated energetic frequencies with no fluctuation over time in both normal control and the mildly demented subjects, which consequently leads to a misunderstanding that alpha rhythms in these two subjects are of consistent sinusoidal function. On the contrary, using the continuous Morlet-wavelet and the HHT, the frequency distributions fluctuate moderately with time in the normal control, and even more wildly in the mildly demented subject. In addition, the powers of alpha rhythm frequencies are not consistent over time. Obviously, many intermittent drops can be observed in both continuous Morlet-wavelet and Hilbert–Huang spectrums. Accordingly, the temporal frequency features from Morlet-wavelet and HHT analyses reveals that the "alpha rhythms" are not of pure sinusoidal functions, or rather, they are more similar to the combinations of many sinusoidal wavelets with varied amplitude and wavelength, which are stitched together one by one.

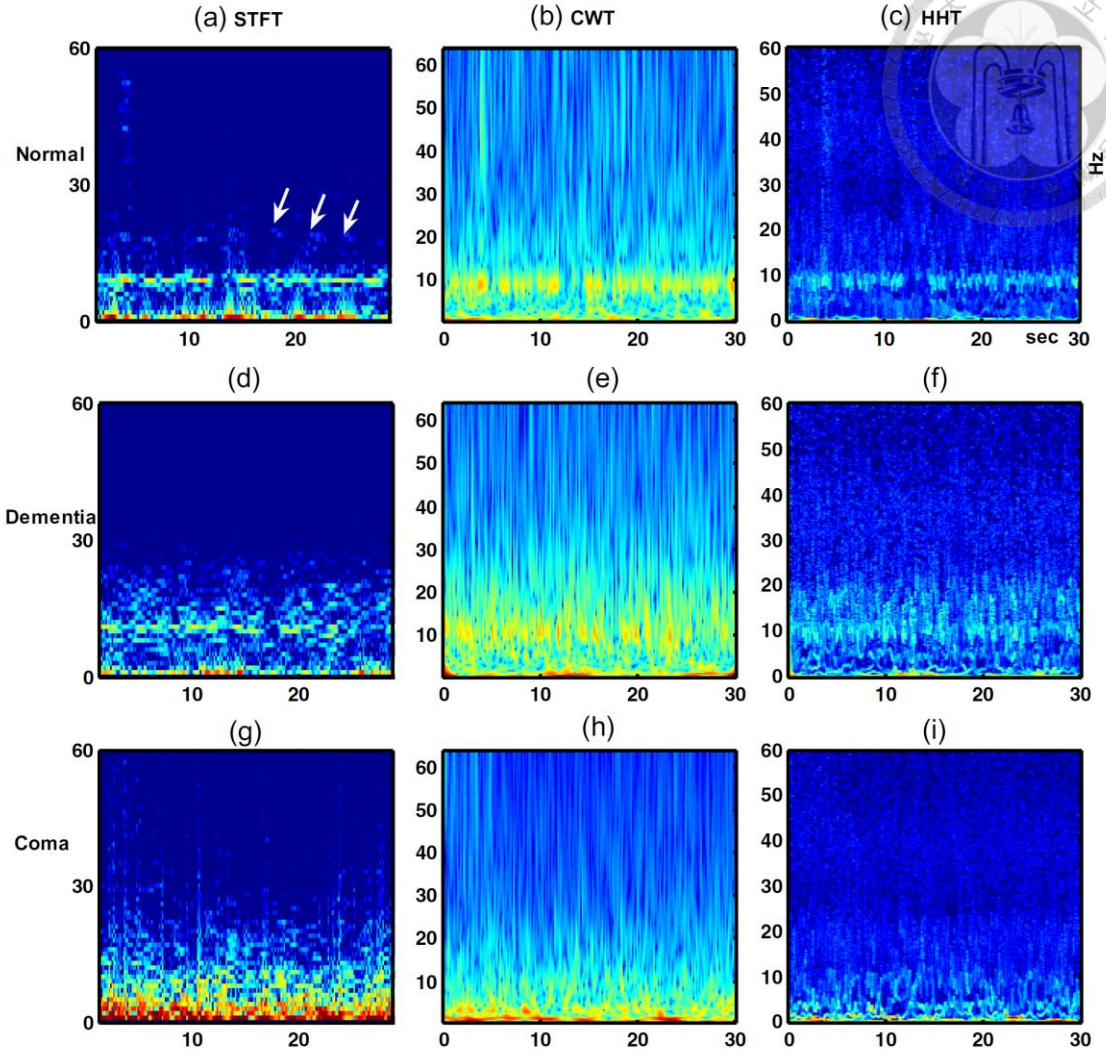


Figure 2 The comparison of the results between conventional time frequency analysis including short-time Fourier transform (STFT) and continuous Morlet wavelet transform, and the novel Hilbert-Huang transform from normal control (a-c), mildly demented subjects (d-f), and severe demented subject in deep coma (g-i).

We have demonstrated that the dominant frequency distribution in Hilbert–Huang spectrum varies with time, and in order to measure this inconsistency, two quantitative methods named "degree of stationarity",[118] developed by Huang et al ., and its extended method named "Shannon entropy of marginal spectrum" recently established by Tong et al .,[132] are introduced in this study. Degree of stationarity (DS), conceptually indicating the average deviation of frequency response over time from the mean marginal spectrum is given as

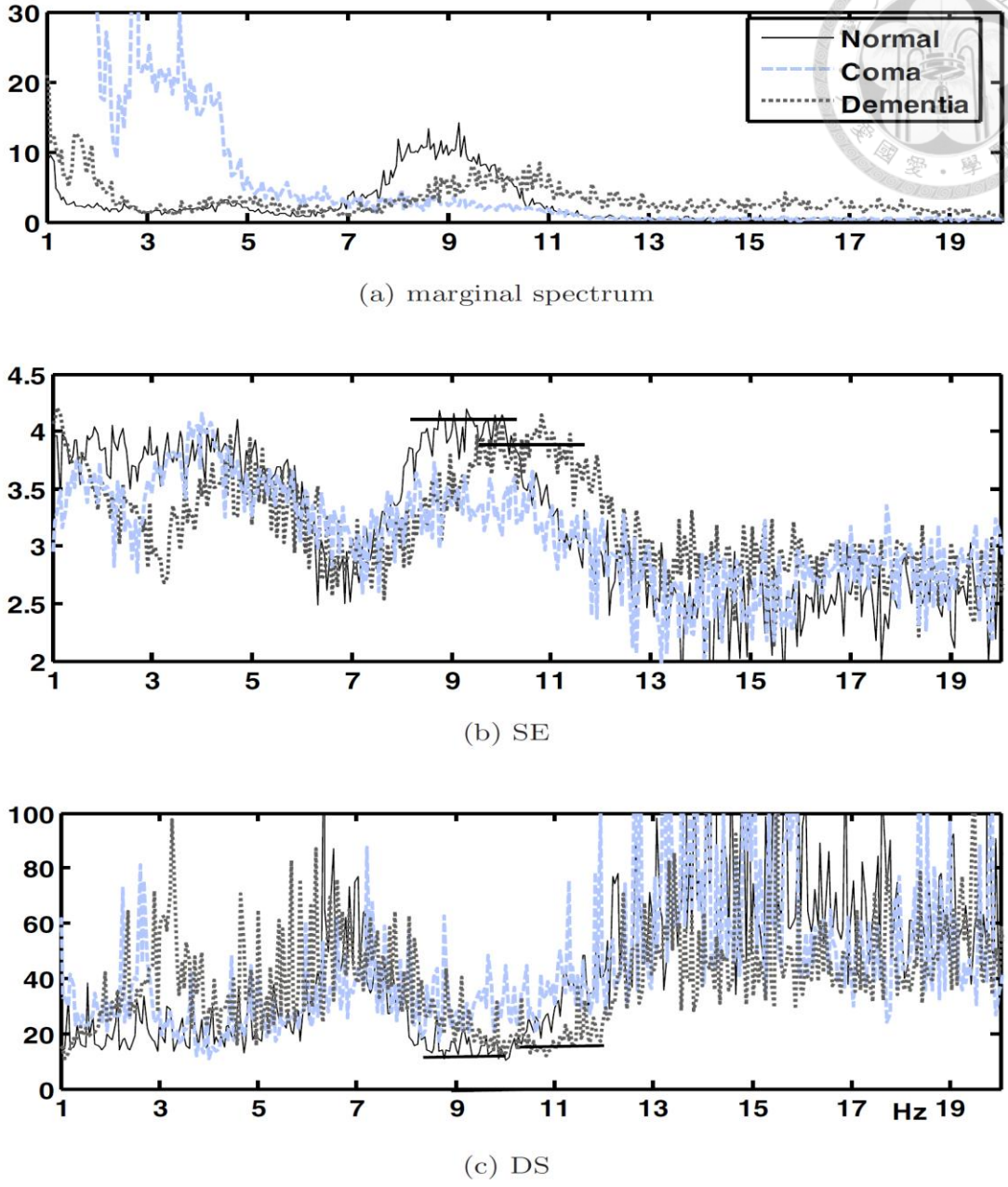
$$DS(w) = \frac{1}{T}\int_0^T (1 - \frac{H(w,t)}{n(w)})^2 dt \qquad \textbf{Equation 1}$$

where H (w, t) is the Hilbert spectrum of IMFs from EEMD except unwanted trends and n (w) is the mean marginal spectrum, defined as $\frac{1}{T}\int_0^T H(w,t)dt$. Different from the classic definition of stationarity, which gives only the qualitative description for the stochastic process, DS provides a quantitative index of stationarity for specific spectral components. According to Eq. (1), when the energy of the frequency, wi is invariant with time, that is H (wi, t) ≈ n (wi), apparently, DS (wi) will be close to zero. On the contrary, the DS will become larger as the energy distribution of wi diverse over time. Shannon entropy of marginal spectrum (SE) is an entropy-based measurement, also powerful at the quantification of the stationarity for specific frequencies in Hilbert–Huang spectrum like DS. Shannon entropy of marginal spectrum, which is ideally used to measure how uniform the distribution of the power for specific frequencies over time would be, is given as

$$SE(w) = -\int \frac{H(w,t)}{n(w)\cdot T} \cdot \log(\frac{H(w,t)}{n(w)\cdot T})dt \qquad \textbf{Equation 2}$$

According to Eq. (2), the SE will approach to its maximum value when the power for specific frequencies has a uniform distribution over time, and the SE for such frequencies will degrade substantially once these frequency components appear occasionally during recording, thus the larger SE indicates higher stationarity. The marginal spectrum, SE, and DS for three subjects are given in Fig. 3 from the top to the bottom panels. Note that the marginal spectrum is also used to indicate the constitutive frequency components of time series; nevertheless it is quite different from the Fourier spectrum. It can avoid including some broadened frequency components due to windowing effects.[133] For instance, a time series with zero value for the whole time but one sinusoidal wavelet localized at the center of the time series has a very narrow frequency distribution in the marginal spectrum in comparison with Fourier spectrum. Accordingly, the marginal spectrum provides more precision in studying the frequency components for intrinsically nonstationary signals. According to the marginal spectrum for the normal control, the substantial intensity of spectrum can only be observed within a specific frequency range (7.5– 11.5Hz), while for the mildly demented patient, high intensities of spectrum are shown in several frequency ranges such as 1–3, 3–7, and 9–19Hz. We compared the mean values of the DS and the SE in the frequency range of 8.5–10.5Hz for the normal subject with that in the frequency range of 9.5–11.5Hz for the mildly demented subject, and found that the DS is smaller (Fig. 3(c)) and the SE is larger (Fig. 3(b)) in the normal control. This shows that although the alpha rhythm frequencies in both cases exhibit significant high energy in the marginal spectrum, the stationarities of the two datasets are different, as the alpha rhythms of the normal subject seem more stationary than that of the mildly demented patient. Different from

the other two cases, the marginal spectrum for the patient in deep coma shows no significant intensity in the frequency band related to alpha rhythms. In the case of mildly demented patient, besides the alpha rhythms, the oscillations with frequencies over 13Hz have rather high intensity in the marginal spectrum with large DS and small SE measurements. It shows that such oscillations are only intermittently, not consistently exhibited in the whole recording in spite of the substantial power in frequency response. As to the other prominent slow oscillations with frequencies of 3–7 Hz, the corresponding intensity in the marginal spectrum is almost equal to that in high frequencies (13–19Hz), however, the slow oscillations are quite stationary since the values of the DS and the SE are at the same degree as the alpha rhythms.



(a) marginal spectrum

(b) SE

(c) DS

Figure 3 From the top to the bottom panels, there are (a) the marginal spectrum, (b) frequency function of SE, and (c) frequency function of DS for the three subjects who are normal control (solid line), mildly demented (gray dotted line), and severe demented in deep coma (gray dashed line).

The conventional visual findings of EEGs in AD (AD) reveal the slowing of the dominant posterior rhythms as well as the reduction in the alpha activities.[98, 100] In this study, the energetic frequencies of the mildly demented patient do not shift downwards compared with the normal subject, which might fail to express the slowing of EEG. However, recent clinical reports show that the slowing of the alpha rhythms are prominent in severe demented patients, but rarely seen in mild cases.[98, 113] In other words, the mildly demented patients do not necessarily exhibit the slowing of EEG. As a consequence, it limits the application of spectral analysis of EEG in the diagnosis of early stage dementia. On the other hand, conventional clinical studies have also reported an increase of diffuse slow (delta and theta) activities in AD patients.[134-136] According to the marginal spectrum in this study, the EEG signal recorded from the demented patient is not as monotonic as the normal subject; rather it consists of multiple frequency components, thus heightening the ratios of other waves to the alpha waves. The stationary tests give further evidence that the occurrence of slow oscillations (delta and theta waves) in demented patients are not intermittent, actually that are pretty consistent. According to some animal studies, a much wider dominant frequency range, theta rhythms (3–12Hz), generated from the hippocampus of lower mammals, are thought to be the equivalent of both alpha (8–12Hz) plus theta (4–8Hz) waves in human EEG.[137] Some hypothesis suggested that the development of the alpha rhythms results from the complex interactions between the cortical neurons in the highly developed cortex of the human brain; the sum of the synchronization of the postsynaptic potentials of these highly developed cortical neurons are the alpha waves.[113] We suppose that as people become demented, the complicated interaction between cortical neurons become less synchronized, therefore the power of the alpha rhythms decreases and that of the theta rhythms increases as the inhibition from alpha to theta decreases. Our study may

provide an alternative way to evaluate the relationship between the alpha and the theta rhythms. Do the alpha and the theta rhythms come from different sources of the EEG, or do they come from the same origin but representing different degrees of the synchronization of the neurons?

2.3.2 Brain topography

To function normally, the brain requires good mechanisms for the integration of many brain regions into specialized network for each particular task. Such sophisticated mechanisms of the integration in the human brain may project into many dominant frequency bands, which represent the synchronization of particular groups of the brain waves. It is difficult to describe or examine those integrations only by the traditional line format displays of EEG. Therefore, people have been searching for new methods to probe both temporal and spatial presentation of the electrical activities of the brain.[138] The most important thing is to combine all the channels of the EEG into a topographical map, which may easily present the spatial distribution of the brain activities. Namely, the locations of changes in rhythms, amplitudes, or any derived qEEG parameters (e.g. absolute or relative power in given frequency bands [138, 139] could be shown in a topographical map. In this study, we provide two EEG topographies which are built based on parameters acquired from the HHT, they are the power of oscillations related to alpha rhythms (see upper panels in Fig. 4) and the correlation index (CI) between the channels (see lower panels in Fig. 4). Since the alpha waves represent the activities of the visual cortex in a state called relaxed awareness, they are posterior dominant in the normal subject as shown in Fig. 4(a), whereas the demented patients have lost this dominance (see Figs. 4(b) and 4(c)). We hypothesize that some mechanisms for the integration of different brain regions to perform certain functions such as wakefulness

or cognition are disrupted in the pathological brains. It is worthy of notice that a highly bilateral symmetry is displayed in the topography of the alpha rhythms in the normal brain (see Fig. 4(a)), whereas the symmetry is lost in both demented patients with different clinical severities. It is generally believed that the loss of symmetry in EEG is pathological.

Nonstationarity leads the Fourier-based coherence to incorporate unwanted interferences, i.e. the discontinuity in amplitude or instantaneous frequency will induce the windowing effect in time domain, which broadens frequency components (i.e. the resulting frequency response turns out the true spectrum convolved with frequency response of time window). As a consequence, the spectral response of alpha rhythms would not be contributed solely from the waves oscillating within the frequencies of 8–13Hz; the windowing effect makes them blurred by mixing other brain oscillations like theta (4–7.5Hz), or beta (14–26Hz) rhythms. According to the simulations in our previous research,[140] EEMD, the HHT-based filter can attenuate nonstationary interferences substantially, and thus the cross correlation of extracted time domain EEG signals by means of EEMD is better to represent the relationship between two regions. Figure 4(b) demonstrates brain maps of the correlation coefficients between each channel and channel O1, which holds the maximum intensity of alpha rhythms in all the three subjects. Clearly, the correlation becomes weaker with the distance between the two channels, in addition, in the normal subject, the correlation between each channel in the right hemisphere and O1 is very similar to that acquired from channels in left hemisphere, thus the coherence (time domain correlation) shows a bilaterally symmetrical pattern. But this symmetry disappears in the brain maps of both demented patients. EEG coherence has been used as a measure for the synchronization of

electrical activities of the neurons.[141] The connection between neurons could be shown by two kinds of coherences, intrahemispheric, and interhemispheric coherences.

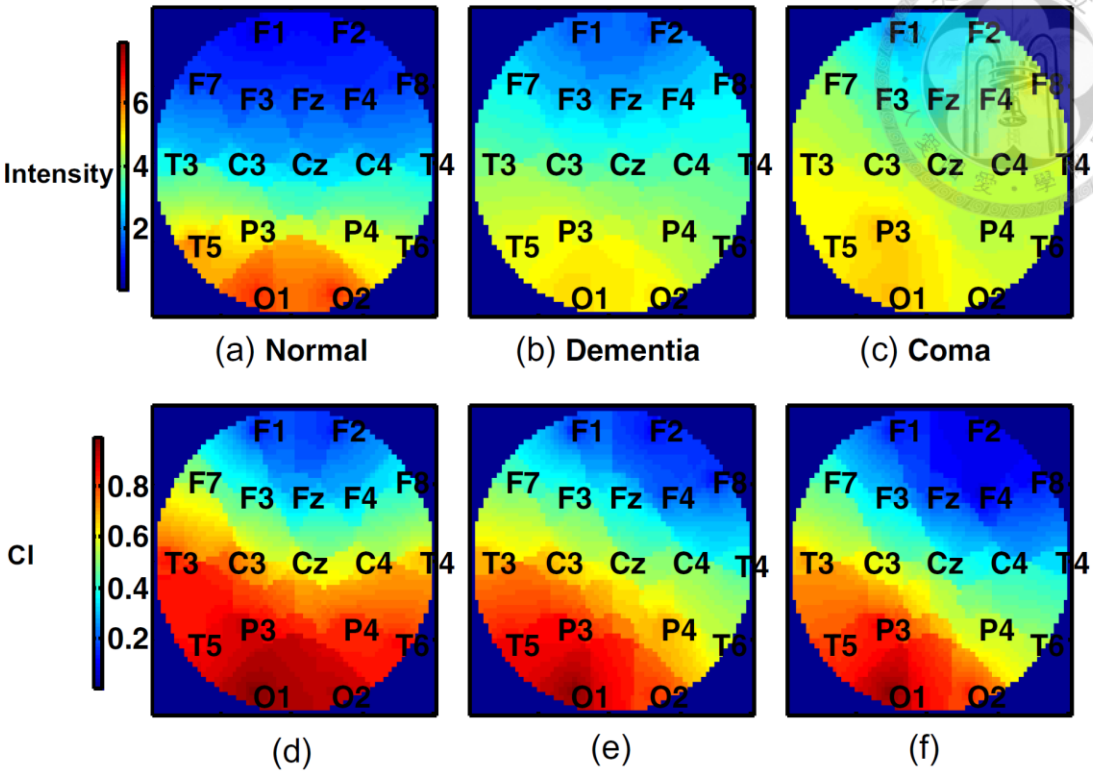


Figure 4 EEG topographies of the power of oscillations related to alpha rhythm (IMF mode 4) are illustrated in upper panel for the subjects who are (a) normal control (b) mildly demented (c) severe demented in deep coma. The subplots in lower panel demonstrate the EEG topographies of the correlation index (CI) of oscillations related to alpha rhythm (IMF mode 4) between the O1 and the other channels for each subject.

Anatomically, the tracts for the intrahemispheric electrical conduction are the intrahemispheric cortical–cortical or cortical–subcortical fibers, while the corpus callosum is the tract for the communication between the two hemispheres. The loss of interhemispheric coherences in both demented patients may indicate a failure of the connectivity through the corpus callosum, while the decrease of intrahemispheric coherences is the result of cortical deafferentation from the subcortical structures such as thalamus, the pacemaker of the alpha rhythms. Our study shows that the coherences in the mildly demented patient are of greater values compared to the comatose one. This may suggest that the degree of the loss of brain connectivity could be graded and correlated with the severity of the disease.

In some previous image studies of MRI,[142-147] corpus callosum atrophy is observed in the AD patients and is also severity-related. Because we did not perform MRI to record the thickness of their corpus callous of these three subjects, whether the loss of intrahemispherical symmetry in our coherence maps resulting from "atrophy of the corpus callosum" needs further studies to clarify.

2.4 Discussion and Remarks

In this study, based on HHT, we propose a novel analysis for the alpha rhythms of EEG, which are of nonlinear and nonstationary physiological data. The alpha rhythms are one of the dominant frequency components of the electrical activities detected at the surface of the brain. The pacemaker neurons of the alpha rhythms are believed to be distributed throughout the thalamus, which synchronously oscillate in the frequency range of 7.5–12.5Hz. Physiologically it represents a state called relaxed awareness and is mostly seen at the surface of visual cortex. Decrease of the frequency, the amplitude,

bilateral symmetry, and the regularity of the alpha rhythms are expected in aging or pathological degenerations. There are some feedback loops in the brain to control this system; they are loops between brain stem (i.e. the reticular activating system), thalamus, and visual cortex. We suppose these loops modulate at least one of the frequency, the degree of synchronization, or the location of the alpha rhythms.

In the present study, we use HHT analysis to define some features of the alpha rhythms as the followings:

(i) The stationary analysis based on Hilbert–Huang spectrum identifies the consistent and monotonic alpha rhythms as the dominant oscillations of EEG signal while acquired from the eye-closed normal subject.

(ii) The brain topography of the alpha rhythms for normal subject shows occipital predominant and bilateral symmetry, which are lost in both demented brain with a dose-response relationship. The topography of the coherences based on HHT seems to provide a more accurate and convenient way to compare the difference between different locations of the brain, which is important in the study of the mechanisms of those networks for different brain functions.

Throughout the study, we have been trying to clarify the physiological meanings and behaviors of the alpha rhythms, yet with only three subjects, many questions has left for the future study. For instance, there is a clinical condition called alpha coma, which means the patient is in a comatose state while the EEG shows relatively monotonous and much diffuse topographically.[148] This kind of alpha range rhythms is different from the normal in the unresponsiveness to any sensory input. Therefore, whether oscillations of similar frequency represent the same source is questionable.

This leads to our further plan to examine more waves on different frequency bands and in other physiological or pathological conditions.

2.5 Conclusion

In conclusion, we have established the differences of alpha rhythms in three different brains by several nonlinear quantitative methods. The EEG is a noninvasive and highly cost-effective clinical tool. Moreover, by using the HHT, the better understanding of the changes of frequencies, amplitudes, and phases is possible in both time and space domain. Finally, it might empower the studies in psychology, aging, or pathology of the brain.

CHAPTER 3 Empirical mode decomposition based detrended sample entropy in EEG for Alzheimer's disease

3.1 Introduction

Dementia is the progressive decline in the cognitive function due to damage or disease in the brain beyond that which may be expected from normal aging, and AD is the most common form of dementia. [1, 2] According to the criteria of the Diagnostic and Statistical Manual of Psychiatric Disorders, 4th ed., [63] memory decline is the major feature. However, in clinical practice, the evaluation of memory decline is highly dependent on numerous neuropsychiatric tests, which mainly rely on the testers and patients. Age and education particularly compromise these neuropsychiatric tests, [85, 87-92, 149] and although little is known of the actual cause of AD, it is generally accepted that many of its symptoms are related to a cholinergic deficit in the cerebral cortex and other areas of the brain.[46, 47, 49] Therefore, one of the major challenges is to identify the structural or functional changes of the brain. Some functional imaging techniques, such as functional MRI [94-96], PET [69], or SPECT [70], are useful particularly in making an objective evaluation of the severity of the dementia. However, the high cost, contrast agent related allergies, and the potential exposure to radionuclide irradiation limits their clinical application.

Conventional EEG may provide a non-invasive, simple and relatively low cost approach to characterizing the specific features of dementia, such as diffuse background slowing or an alpha wave anteriorization in the late stages of AD, but not in the early stages. [150] With the assistance of signal processing, numerous quantitative analyses have

analyzed the characteristics of EEG in order to improve its diagnostic power, and have been suggested to be an objective tool in evaluating AD. [140, 150-157] Fourier transform analysis is frequently utilized in these methods to identify the characteristics of frequency response in different frequency bands related to alpha, beta, theta and delta rhythms. [151, 152, 158] It can differentiate moderate to severe AD patients from normal subjects.[140] However, these linear signal analyses are limited because of the innumerable cortical neuron activations constructing the surface EEG, which fundamentally decide the non-linear pattern in the surface EEG and are not properly analyzed by a Fourier-based spectral analysis. Accordingly, non-linear based methods are more appropriate to explore EEG activities. [159] Recently, non-linear based analyses, such as correlation dimension, [160-162] fractal dimension,[163] synchronization likelihood,[164] and approximate entropy (ApEn)[165, 166] have been developed to evaluate the non-linear characteristics of EEG in AD patients. Among these methods, ApEn has been introduced as a quantification of the regularity of non-linear data sequences, and its simple algorithm has attracted attention in the clinical application of evaluating EEG in AD patients. [167, 168] In previous studies, the irregularity of the EEG signals measured by ApEn for moderate and severe AD patients (MMSE = 12.6±5.9) were significantly lower in the bilateral parietal region compared with normal subjects, which could be compatible with hippocampus atrophy [167, 168].

However, the complexity of the measurements from ApEn has not disclosed consistent results in a longitudinal follow-up and the correlations with the clinical symptoms, especially in early stage AD.[167, 168] ApEn has been found to have two potential problems: (1) ApEn is data length dependent, which may result in inconsistent results in clinical applications; [169] (2) stationarity is the fundamental requirement for entropy based methods, [170] but non-stationarity may compromise the measurement of

intrinsic complexity. [140, 171-173] Sample entropy (SaEn), based on the same concept of ApEn, is made, independent of record length, to reduce these biases,[169] and the non-stationarity issue is intuitively addressed by selecting a single short epoch with a stable background from the whole recordings by a visual examination of the researchers. [167, 168, 172] Nevertheless, sufficient data is another critical criterion for a nonlinear-based analysis to obtain reliable statistics. [174] Moreover, because of the presence of diurnal and circadian variations in EEG activations,[175] it is difficult to convince clinicians that a very small amount of recorded data can reflect the complex cortical activations.

Therefore, this study introduces a novel detrend method, empirical mode decomposition (EMD)[118] to elicit the intrinsic complexity. It demonstrates that in addition to its superiority over the traditional linear quantitative method, the SaEn calculated from the detrended EEG signals provides more sensitive results in early stage AD patients and consistent results in longitudinal individual follow-ups.

3.2 Materials and Methods

3.2.1 Subjects

All dementia patients were newly diagnosed and enrolled from the neurological clinic at National Yang Ming University Hospital. They were all screened for dementia and received further medical, neurological, neuropsychological, and psychiatric assessments as well as blood studies. The neurological assessments of all these patients included a CT to rule out intracranial pathology, such as brain tumors or stroke that may have contributed to cognitive decline. Trained research assistants administered the Chinese version of MMSE [71], which has a total score of 30. CDR scales to rate the severity of the dementia was also evaluated after a neurologist conducted separate

semi-structured interviews with the patient and a knowledgeable informant. The scores were as follows: 0 (normal), 0.5 (questionable), 1 (mild), 2 (moderate), and 3 (severe). [72] The diagnosis of AD was determined according to the diagnostic criteria of the Diagnostic and Statistical Manual of Psychiatric Disorders, 4th revised ed..[63] EEG was not part of the routine workup.

The inclusion criteria for participation in the EEG study meet both (1) a diagnosis of probable AD according to the DSM-IV criteria, [21] and (2) a rating of either 1 or 2 on the CDR scale. [72] The exclusion criterion included more than one possible cause of dementia existed as determined by history, neurological examination, imaging, and blood studies. The criteria for exclusion ensured that the changes of EEG were the results of AD in all participants. The research was approved by the institutional review board of National Yang Ming University Hospital, YiLan, Taiwan, a local community teaching hospital, and all patients provided written informed consent prior to the study.

Twenty-seven newly diagnosed AD patients (9M/18F; mean age 74.0±1.5 years) were enrolled in this study, with an initial MMSE of 19.3±0.7. Only four of the patients were moderately demented (CDR=2) with the other twenty-three patients mild (CDR=1). Four patients suffered from behavioral and psychological symptoms of dementia (BPSD); two of them were mild (CDR=1, depression, treated by citalopram), and the others were moderate (CDR=2, one patient with visual hallucinations and the other one suffered from delusions, treated by risperidone). None of the patients received any antipsychotics before the first EEG examination. Eleven patients suffered from hypertension, 5 from diabetes, and 2 had a history of hyperlipidemia. However, none of them suffered from cerebral vascular events and their brain images did not disclose vascular lesions or sub-cortical atherosclerosis encephalopathy. One patient suffered

from a thyroid goiter and had received thyroidectomy at a young age with supplements of thyroxin with euthyroidism. Every participating patient received either acetyl cholinesterase inhibitor therapy, donepezil hydrochloride (Aricept®) (24 mild AD patients), or N-methyl d-aspartate receptor antagonist, memantine (Witgen®) (1 mild and 2 moderate AD patients). Five patients (3M/2F) (3 mild and 2 moderate AD) received follow-up EEG examinations 6 months after therapy.

3.2.2 EEG Recordings

EEGs were recorded in all subjects. According to the International Federation of Clinical Neurophysiology (IFCN) standards for the digital recording of clinical EEG,[176] the surface EEG signals were recorded by a digital EEG recorder (NicoletOne®), from the 19 scalp loci of the international 10–20 system (channels Fp1, Fp2, F3, F4, C3, C4, P3, P4,O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz), with all electrodes referenced to the bilateral ear (A1, A2) for 30 minutes. Electrocardiograms (ECG) were recorded in a separate channel. The sample frequency was 256 Hz and the A/D digitalized resolution was 12 bits. All the patients remained awake with closed eyes and in a relaxed state to receive 30 minutes of eye-closed EEGs. The data was copied into a comma-separated values (CSV) file without any filtering. The EEG signals were analyzed by a self-designed program with MatLab 7.0© .

3.2.3 Signal Processing: Sample Entropy

The digitalized EEG signals, one artifact-free epoch of 30 seconds duration, were selected by an experienced neurologist. Sample entropy is a statistical result based on the information theory used to quantify the irregularity of a sequence of data. [165, 166, 169] Briefly, it examines a time series for similar epochs of a pre-determined length (m) and,

then, calculates the negative natural logarithm of the conditional probability that epochs similar for m points that will remain similar when one more point (m+1) is added to the subseries (i.e., the phase space distances are below the tolerance of r). [165, 166, 169] The higher the SaEn, the more unpredictable the data sequence is. Complicated systems typically generate highly irregular output. [177] Therefore, SaEn provides a promising way to quantify irregularities for physiological output. The detail of SaEn is as below. $\{x_i\} = \{x_1, x_2..x_i...x_N\}$ represents a time series of data length N. The m-length vector extracted from time series $\{x_i\}$ was defined by $u_m(i) = \{x_{i,} x_{i+1}, ..x_{i+m-1}\}$, where $n_i^m(r)$ represents the number of vectors, $u_m(j)$ that are close to the given vector, $u_m(i)$. To obtain $n_i^m(r)$, we first defined the distance, d $[u_m(i), u_m(j)]$ between the given vector $u_m(i)$ and $u_m(j)$ as the maximum absolute difference between their corresponding scalar elements, i.e., d $[u_m(i), u_m(j)] = \max_{k=0,m-1}[|x_{i+k} - x_{j+k}|]$. Then, $n_i^m(r)$ was defined by counting the number of $u_m(j)$ with d $[u_m(i), u_m(j)]$ $|_{j=1,\ n-m+1}$ smaller than the threshold, r, a given prior. Note that here $j \neq i$; i.e., self matches were not included to avoid the bias of ApEn. [169] The ratio of $n_i^m(r)$ to total number of m-vectors extracted from the time series, were evaluated, and the result was denoted as $C_r^m(i)$. The above steps were repeated to find $C_r^m(i)$ from i=1 to i=N-m+1, then the natural logarithm of each $C_r^m(i)$ was calculated and then averaged over i to obtain $\phi^m(r)$. Theoretically, sample entropy [165, 166] is defined as $SaEn(m,r) = \phi^m(r) - \phi^{m+1}(r)$. Note that the average of $C_r^m(i)$ can be regarded as the probability that any two vectors extracted from time series $\{x_i\}$ are similar in some sense, therefore, $\phi^m(r) - \phi^{m+1}(r)$, conceptually represents the average of the natural logarithm of the conditional

probability that the sequences that are close to each other for m consecutive data points will still be close to each other when one more point is given. In this analysis, we set m = 2 and r = 0.15 of the standard deviation for the processed signal.

3.2.4 Data Detrending Based on Empirical Mode Decomposition

Numerous non-linear analyses were developed to precisely analyze the true physiological signals. However, the fundamental assumption of the non-linear analyses is that data needs to be stationary, which is not often applicable for true physiological signals. The evaluation of SaEn counts the number of epochs within similar phase space distances, determined by the tolerance r. Thus, SaEn will be underestimated due to the exaggerated standard deviation when a trend or unstable background exists in the signal. For example, for a given 1/f fractal noise, an additional linear trend decreases SaEn and the decrement is in proportion to the slope of the trend (Figure 5). In order to minimize the effects of the heterogeneous non-stationarity on SaEn, prior to calculation of SaEn, the signal is preprocessed to remove unwanted trends such as using linear high pass filter or subtracting nonlinear polynomial fitting trend. Although single linear trends are easily removed by utilizing a traditional polynomial fitting [170], in physiological signals, the heterogeneous non-stationarity is of different multiple local trends, i.e. it is difficult to filter those trends out using traditional methods. [140, 153, 173] Figure 6 gives an example that shows that the surrogate data is composed of a pure sinusoidal oscillation and a non-stationary trends that are constructed by cascading several linear functions with random slopes and using a high-pass filter or, even, a 6th order polynomial fitting that cannot completely remove these trends.

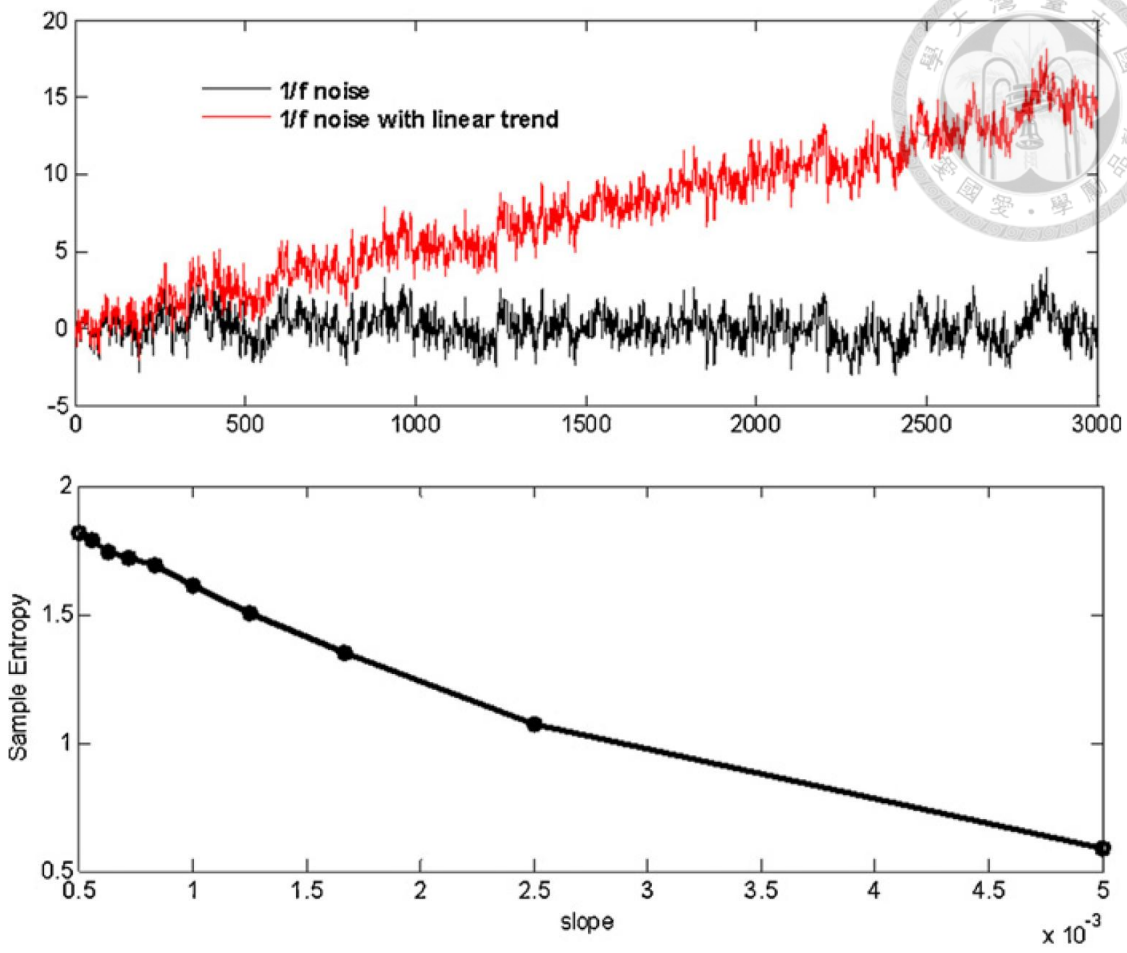


Figure 5 Upper panel is the demonstration of the original fractal noise (Black) and its combination with linear trends. Lower panel presents the sample entropy as the function of slope of linear trends. Greater slope, lower value of sampling entropy. It indicated that unsatisfied detrend procedure would under estimate the complexity of signals.

This study introduced the empirical mode decomposition (EMD) method [118] to detrend the signals. The EMD method is specifically developed to decompose the nonlinear, non-stationary signals into their intrinsic components. The decomposition is based on the simple assumption that any time series data $y(t)$ is composed of a finite number of intrinsic modes of oscillations. (i.e. $y(t) = \sum_{k=1}^{k=n} c_k(t) + r_n$) Each mode of the oscillation $c_k(t)$, termed intrinsic mode functions (IMFs), is decomposed sequentially from the original time series by identifying the intrinsic undulations at different time scales and sifting them out. Typically, different IMFs capture the properties of the original signal at different time scales, and are contributed from different physiological mechanisms rhythmically operating over different time scales. [125, 178-180] Figure 6D illustrates that, EMD separates the sinusoidal oscillations and trends completely. However, such trends are not perfectly fitted by polynomial equations. Thus, the residual is apparent (Figure 6C) even after utilizing high order polynomials. Obviously, after polynomial detrending, the residual trend still complicates entropy estimation. In this study, we use EMD to remove the unwanted background [173] before calculation of SaEn of the EEG raw data, termed EMD-based detrended SaEn. The IMFs with frequency distributions below 1 Hz were removed from the signal to preserve most of the EEG information such as delta waves (~1.5-3.5Hz) and the SaEn of the detrended signal was then calculated. Other than EMD, we also calculated SaEn after detrending the signal with polynomial fitting (polynomial fitting detrended SaEn) and high-pass filter (Conventional SaEn) for comparison.

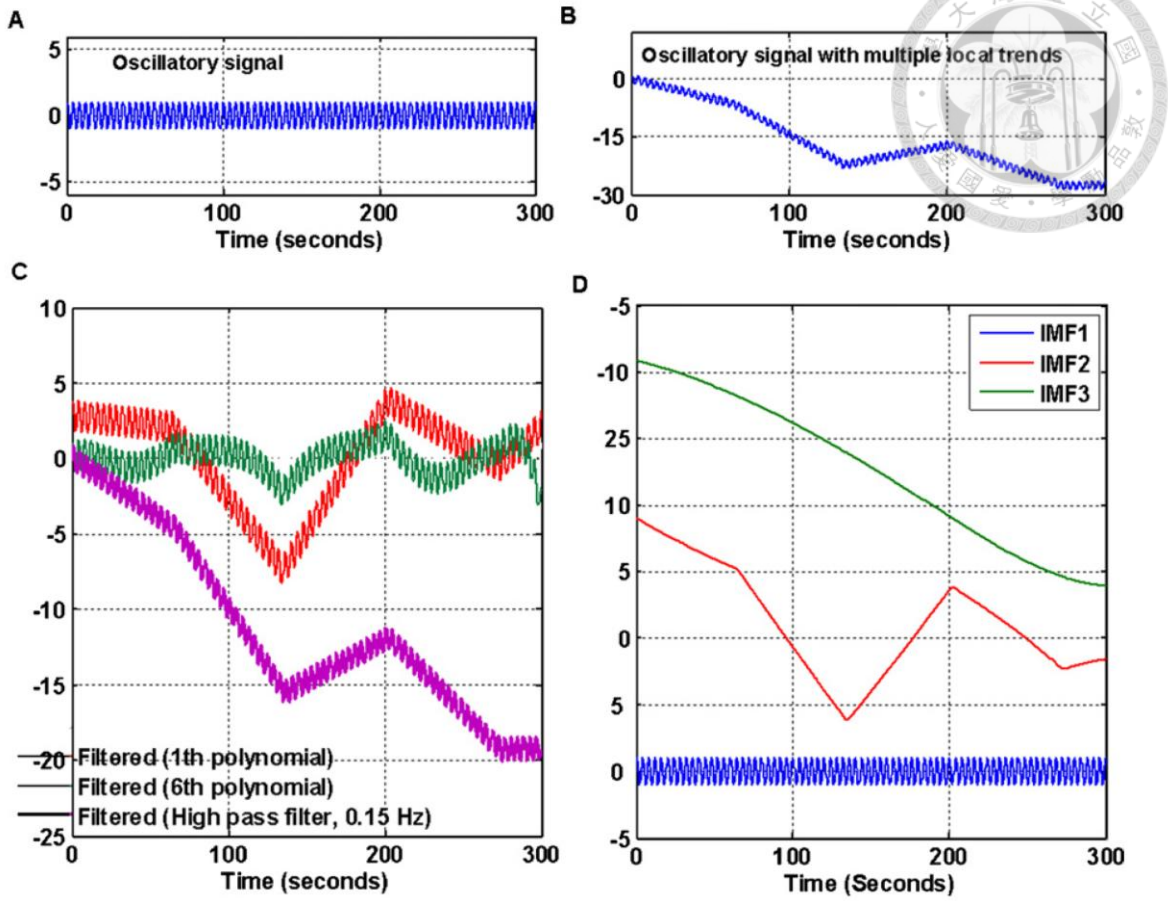


Figure 6 The example of detrend in a complicated signal. A and B disclose a pure sinusoidal oscillation with frequency of 0.2 Hz and the surrogate data, composition of a pure sinusoidal oscillation and a multiple-local trend, respectively. C shows three sets of detrended data (red and green) by the 1st and 6th polynomial fitting and high pass filter with cut frequency of 0.15 Hz (purple), which were different from the original signal (B). D shows the result of the surrogate data after signal processing with empirical mode decomposition, with three intrinsic mode functions (IMF); IMF 1 (blue) was compatible with the original signal. The summation of IMF 2 and 3 is the multiple-local trend.

3.2.5 Brain Topography

New methods have been studied to probe both temporal and spatial presentations of electrical activities of the brain because it is difficult to describe or examine integrations from a visual inspection of the raw EEG signals. [176] The most important feature of these methods is to combine all EEG channels into a topographical map to present the spatial distribution of brain activities. The location of changes in rhythms, amplitudes, or any derived qEEG parameters (e.g. absolute or relative power in given frequency bands)[109] [138] is shown in a topographical map. The brain topography of EMD-based detrended-SaEn was constructed for this study.

3.2.6 Statistical Analyses

Descriptive statistics were presented as means ± standard deviation (SD). SPSS (ver16.0) for Windows (SPSS Inc., Chicago, IL, USA) was used for analysis. The correlation between age and MMSE was calculated using Pearson's formula. Due to small sampling sizes, it is difficult to perform the multiple variants regressions, including MMSE and all electrodes directly. Factor analysis with a principal component analysis (PCA) was used to decide the number of major components because of the high correlation between the EEG leads. A multivariate backward stepwise regression was used to calculate the correlation factors between age, each lead EMD-based detrended-SaEn and MMSE. In the follow-up EEG study, the correlation between the changes of MMSE and the changes of the parameters in quantitative EEG (qEEG) for every lead were calculated using Spearman's formula. All the statistical tests were two-tailed and significance levels were set at p-values of less than 0.05.

3.3 Results

3.3.1 Initial EEG Findings

The correlation factor between MMSE and age was -0.4 (p=0.029), which was compatible with previous studies.[91, 181] In EMD-based detrended-SaEn, the factor analysis with PCA revealed high correlations between the leads, and the first component of PCA accounted for 82% variance. Therefore, in a multivariate backward stepwise regression, each lead needs to be calculated individually with age as a variant. The multivariate backward stepwise regression showed that the EMD-based detrended-SaEn was moderately correlated to the MMSE score in Fp1, Fp2, T3, and F4 leads (correlation factors = 0.361 ~ 0.523, $p < 0.05$), mild correlation to MMSE score in F7, F3, Fz, F8, and Cz ($p = 0.053 \sim 0.082$), which were not excluded from the backward stepwise regression. There were no correlations between the MMSE scores and EMD-based detrended-SaEn in C3, C4, T4, T5, P3, Pz, P4, T6, O1, and O2, which were excluded from the backward stepwise regression (Table 1).

The same statistical analyses as above were applied in conventional SaEn. The first component of PCA accounted for 80%; moderate correlation to MMSE score in F8 ($p = 0.044$), mild correlation to MMSE score in T5, and O1 ($p = 0.053$ & 0.088), which were not excluded from the backward stepwise regression and showed no significant correlations with MMSE for other leads (Table 1).

The same statistical analyses as above were applied in polynomial fitting of degree 3 based detrended SaEn (Polynomial fitting detrended SaEn). The first component of PCA accounted for 85.5%. The worst correlations between polynomial fitting detrended SaEn and MMSE were noted (with mild correlation in T3, $p = 0.056$) and were not

excluded from the backward stepwise regression and showed no significant correlations with MMSE for other leads (Table 1)

Table 1

EEG Leads	The Value of conventional SaEn	Standardized Correlation factors	The Value of polynomial fitting detrended SaEn	Standardized Correlation factors	The Value of EMD-based detrended-SaEn	Standardized Correlation factors	*p* Value for EMD-based detrended-SaEn
Fp1	0.60±0.46	0.277	0.54±0.41	0.161	1.90±0.06	0.464*	0.008
Fp2	0.56±0.32	0.181	0.61±0.49	0.074	1.72±0.07	0.422*	0.017
F7	0.54±0.37	0.145	0.58±0.46	0.259	1.60±0.08	0.43	0.057
F3	0.53±0.37	0.171	0.52±0.43	0.109	1.66±0.08	0.349	0.053
Fz	0.56±0.31	0.236	0.53±0.43	0.159	1.59±0.07	0.350	0.053
F4	0.56±0.39	0.282	0.63±0.51	0.205	1.73±0.06	0.361*	0.044
F8	0.51±0.32	0.361	0.53±0.43	0.306	1.62±0.07	0.316	0.082
T3	0.64±0.34	0.260	0.71±0.48	0.363	1.57±0.07	0.523*	0.002
C3	0.66±0.41	0.123	0.65±0.48	0.149	1.53±0.07	0.26	0.157
Cz	0.58±0.37	0.202	0.56±0.39	0.194	1.45±0.06	0.347	0.054
C4	0.59±0.34	0.233	0.60±0.42	0.265	1.51±0.07	0.264	0.150
T4	0.56±0.30	0.167	0.60±0.46	0.223	1.51±0.07	0.229	0.214
T5	0.62±0.30	0.310	0.66±0.36	0.258	1.37±0.06	0.215	0.243
P3	0.60±0.28	0.274	0.61±0.37	0.282	1.35±0.06	0.256	0.163
Pz	0.57±0.27	0.242	0.58±0.32	0.164	1.39±0.06	0.244	0.185
P4	0.59±0.29	0.239	0.57±0.37	0.169	1.35±0.06	0.213	0.248
T6	0.58±0.29	0.265	0.60±0.38	0.138	1.36±0.06	0.199	0.283
O1	0.56±0.28	0.350	0.58±0.32	0.284	1.34±0.06	0.121	0.515
O2	0.56±0.28	0.252	0.59±0.33	0.154	1.30±0.06	0.193	0.298

The correlation factors between Conventional SaEn, polynomial fitting detrended SaEn, EMD-based detrended-SaEn and MMSE; there was a moderate correlation between EMD-based detrended-SaEn and MMSE in Fp1, Fp2, F4 and T3; the star marker (*) indicates that the correlation is significant at the 0.025 level (2-tailed)

3.3.2 Follow-up EEG Findings

In the follow-up study, the correlation between the changes of the MMSE and the changes of EMD-based detrended-SaEn in each lead in 5 patients showed a high correlation coefficient, 0.975 ($p = 0.005$) in F7 lead, but not in the other leads. However, it was difficult to describe some information by statistical analyses. The brain topographies that were constructed by the values of 'EMD-based detrended-SaEn' in 19 scalp leads were demonstrated using spatial interpolation. The results for two patients, who received donepezil therapy only, with regular follow-up intervals of 6 months, are shown in Figures 7 and 8. In Figure 7, the patient received donepezil and improved clinically (MMSE from 23 to 25 and then to 26). In Figures 7A to 7C, EMD-based detrended-SaEn revealed a generally consistent pattern and the EMD-based detrended-SaEn in the bilateral parietal and temporal leads, especially in the left side, increased as the MMSE improved. Figure 8 demonstrates the results for another patient who received the same therapy, but whose cognitive function did not improve (i.e., MMSE scores decreased from 25 to 23). Figures 8A and 4B show the decreased EMD-based detrended-SaEn as a clinical change in the bilateral temporal and parietal leads. There was no correlation between the changes of the MMSE and the change of conventional SaEn in all leads.

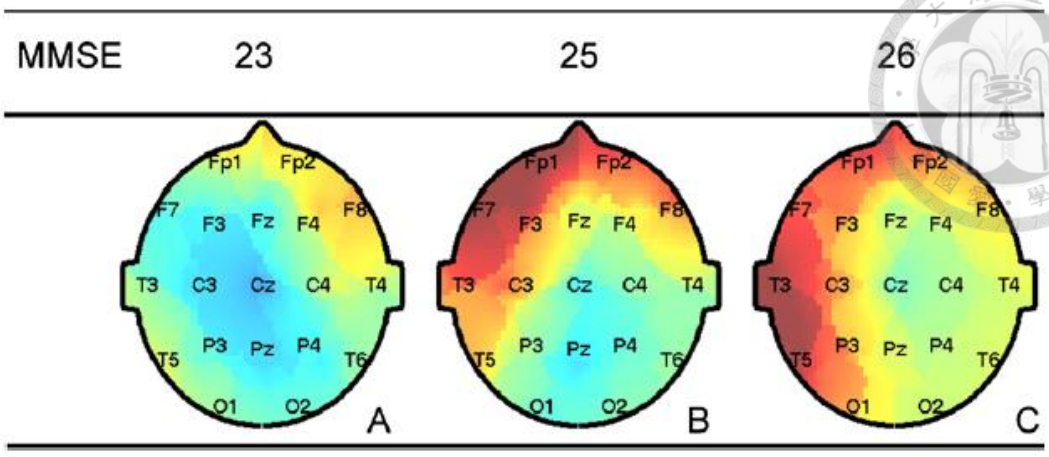


Figure 7 One set of topographies were constructed with the values in each lead with spatial interpolation. A-C were created with the exponential values of the EMD-based detrended SaEn. These figures disclosed a consistent pattern and changes associated with cognitive function improving in the left temporal region. The color map illustrates the relative powers from the lowest (blue) to the highest (red).

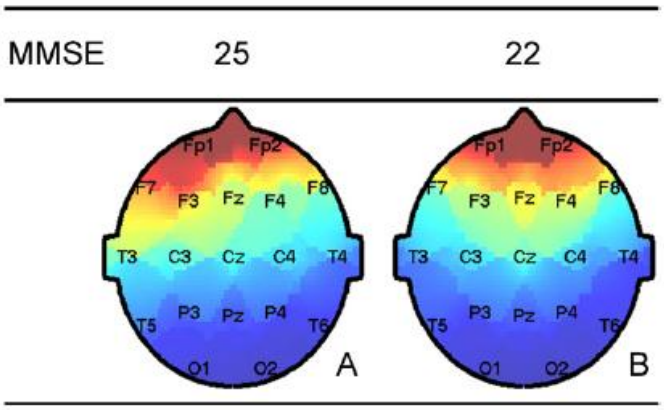


Figure 8 One set of topographies were constructed with the values in each lead with spatial interpolation. A and B were created with the exponential values of the EMD based detrended SaEn. These figures disclosed a consistent pattern and changes associated with cognitive function worsening in the left temporal region. The color map illustrates the relative powers from the lowest (blue) to the highest (red).

3.4 Discussion

This study applied an algorithm, sample entropy, to evaluate the irregularity of the EEG signals of AD patients and demonstrated that the irregularity of EEG signals is reduced in demented patients and is consistent with the results proposed by other studies.[69, 167, 168, 182, 183] However, most of the patients of those studies are limited to severe dementia and clinically acceptable performance for long-term follow-up of mildly demented patients remains controversial. This ambiguity can attribute to a technical issue for SaEn-the signals remaining stationary but not easily satisfied especially for biological signals .[175] As the simulation shown, SaEn can be underestimated if the signals were superimposed with local or global trends. Therefore, SaEn may have insufficient sensitivity to evaluate mild cognition function loss. Our previous studies had suggested that properly removing the trends in biological signals improved the performance of nonlinear signal analysis and only specifically designed detrending procedures to adaptively attenuate all unwanted influences (such as extrinsic non-stationarity).[140, 184] In this study, after the EEG signals were detrended by EMD, SaEn exhibited a moderate correlation (correlation factors = 0.361 ~ 0.523, $p < 0.05$) to the MMSE scores in the bilateral frontal, left temporal region, and mild correlation in bilateral frontal regions in the mild and moderate AD patients (Table 1) while conventional SaEn and polynomial fitting detrended SaEn failed to show any meaningful correlation. For the follow-up evaluation, the changes of MMSE scores were highly correlated with the changes of the EMD-based detrended SaEn in left frontal EEG signal. These results revealed that modified SaEn, detrended by EMD, is possibly regarded as a useful tool to evaluate demented patient objectivity.

Although neuropsychiatric examinations, especially MMSE, are able to provide

objective and acceptable evaluations for the mental function of AD patients, the reliability of those examinations may be compromised by numerous factors, such as age, degree of education [85-92, 174, 185], and the proficiency of the research assistants.[186] Moreover, recent functional imaging studies, such as functional MRI and PET, have revealed that most of the major categories of MMSE, including simple calculations, working memory and orientation are located in the bilateral frontal and left temporal regions. [187-190] Rather than an evaluation of global cortical function, MMSE reflects the bilateral frontal and left temporal function. The MMSE scores only correlated with the EMD-based detrended SaEn of EEG signals in the bilateral frontal and left temporal regions compatible with the findings of those functional imaging studies. Therefore, a quantitative EEG may be a potential candidate for objectively evaluating the brain function globally [140, 150, 152, 191] in addition to the regional information assessed by MMSE.

Treatment follow-up

The preliminary follow-up findings only revealed a high correlation coefficient factor (0.975) between the changes of MMSE scores and changes of EMD-based detrended SaEn in left frontal region (F7 lead), but not in other regions. The reason is two-fold. First, there were only a limited number of AD patients who finished their follow-up. Second, certain drugs have strong effects on bioelectric activity of the brain [192, 193] including antipsychotics or antidepressants. A total of 3 of the 5 patients presented at least one BPSD before the follow-up EEG examination and received antipsychotics or antidepressants. Nevertheless, a consistent pattern was found in the brain tomography for patients who did not receive antipsychotics or antidepressants. This was constructed by EMD-based detrended SaEn (Figures 7 and 8) and the

quantitative analysis of surface EEG may provide a useful way to evaluate the response to treatment without administering any contrasting medium or invasive procedure, especially in patients with poor communication skills.

The partial correlation analysis revealed that the EMD-based detrended SaEn positively correlated with the power of alpha waves and beta waves and negatively correlated with the power of theta and delta waves (Table2). This was compatible with the previous studies, severer dementia, slower EEG rhythms, and less complexity of EEG signals. It may indicate that the EMD-based detrended SaEn reflected the complex neuron interaction, and the Fourier analysis revealed the total summation of neuron activation. Therefore, a correlation was found between the non-linear EMD-based detrended SaEn and the linear Fourier analysis

Table 2

EEG Frequency	The absolute power (μV^2)	Correlation factors	*p* Value
Delta (1.5-3.5 Hz)	50.25±33.37	-0.396	0.093
Theta (3.5-7.5 Hz)	19.57±9.63	-0.485	0.035
Alpha (7.5-12.5 Hz)	21.04±6.19	-0.144	0.557
Beta (12.5-25.0 Hz)	9.14±3.21	-0.044	0.858
Alpha/Theta	2.63±1.04	0.295	0.220

The correlation factors between MMSE and mean values of absolute power in EEG frequency analysis

We did not include healthy age-matched subjects for two reasons. First, most of the studies have suggested that using spectral analysis to quantify the background EEG slowing can be an important indicator of AD. Although the biological signals should be better qualified and quantified by nonlinear analysis, few studies were done in patients with early AD. Recent studies[183] have showed SaEn can also be a fair tool to detect patients with mild AD, but none of them showed any correlation to the clinical relevant parameters which may due to the non-stationarity. Non-stationary properties of biological signals such as artifacts and trends can easily compromise the results of nonlinear analysis. The main purpose of this study, therefore, mainly focused on developing a novel method to overcome the undesired effects of unwanted artifacts and trends on SaEn and refine the algorithm especially to evaluate the subtle changes of EEG in patients with mild AD. Second, National Yang Ming University Hospital is a local community teaching hospital. It is relatively slow to recruit enough aged-matched healthy control subjects. In this pilot study, we followed up the patients with treatment instead to test if the proposed algorithm can be correlated to the improvement or deterioration of the disease after treatment. However, it should be cautious to extend our results to healthy control subjects and further study is warranted for investigating this issue.

The major limitations of this study are the small number of patients and pathology, which was not available under the principle of doing no harm to patients. For the follow-up studies, it was not possible to identify whether or not there was any influence from BPSD. Due to a lack of other types of dementia in this study, the application of brain tomography constructed by EMD-based detrended-SaEn in the pattern reorganization to different types of dementia is also uncertain.

3.5 Conclusion

This study showed that the improved quantitative EEG analysis by means of a combination of the EMD detrending procedure and sample entropy revealed that the changes in the complexity of EEG signals were correlated with the severity of the dementia. This could provide an alternative, non-invasive, low-cost, and objective tool in clinical evaluation and follow-up in dementia patients.

CHAPETR 4 Predict the efficacy of Acetylcholinesterase inhibitor in Alzheimer's disease by multiscale entropy in EEG

4.1 Introduction

Alzheimer's disease (AD) is the most common form of dementia [1, 2], with the dominant presentation of the progressive decline in cognitive function beyond what is expected from normal aging. Although little is known of the actual cause of AD, it is generally accepted that many of its symptoms are related to a cholinergic deficit in the cerebral cortex and other areas of the brain.[46, 47, 49] AChE inhibitors were proved as an effective therapy for AD.[50-55] Phamocoecnomic studies disclosed that therapies can postpone the progression of dementia to more severe stages and may be of economic benefit to patients' families, caregivers, and society.[56-60] However, clinicians often argue that AChE inhibitors have an effect in a subgroup of 25-50% of AD patients [48, 61, 62], who cannot be identified objectively, and the effect is time-consuming.

Recently, numerous studies try to find some prognostic predictor of AD by artificial network [194], brain MRI [61, 195], single-photon emission computed tomography (SPECT) [196] and cognitive function tests.[197] The technique dependence, high cost, contrast-agent related allergies, and potential exposure to radionuclide irradiation limits clinical application. On the other hand, numerous quantitative analyses, especially non-linear based method, have analyzed the characteristics of EEG to improve diagnostic power with the assistance of signal processing and suggest an objective tool in the evaluation of AD.[150-156, 160-163, 198, 199] Most of the studies utilizing non-linear

methods revealed that loss of the complexity of EEG signals were correlated with the severity of the dementia. [161-163, 198] However, it is hard to tell which specific physiology mechanism to degrade the EEG complexity, and could not provide clinicians enough information about the possible responder to AChE inhibitor in AD patients. In advance, multiscale entropy (MSE) analysis, proposed by Costa et al. [172, 200], is a possible method to check the signal complexity from system level, by means of an entropy-based measurement at different scales. The biological signal represents the outcome of the nonlinear interactions between different processes at multiple temporal or spatial scales. Thus, multiple scale complexity is regarded as a marker of healthy dynamics, and decreased complexity of MSE analysis at certain scales could respond to pathological degeneration.[172, 200] In addition to the MSE amplitude, other features of the MSE curve, such as the slope of the MSE, defined by sample entropy values between different time-scale factors, also has physiology meaning to assist with clinical classification.[201]

The present study was a pilot test via MSE in EEG analysis, depending on the ability of MSE to demonstrate different mechanisms with multiple temporal or spatial scales, to determine whether the feature of MSE in EEG is associated with the therapy efficacy of AChE inhibitor in AD patients.

4.2 Materials and Methods

4.2.1 Patients

All dementia patients were diagnosed and enrolled from the neurological clinic at National Yang Ming University Hospital. They were all screened for dementia and received further medical, neurological, neuropsychological, and psychiatric assessments as well as blood studies. The neurological assessments of all these patients included a

cerebral CT to rule out intracranial pathology, such as brain tumors or stroke that may have contributed to cognitive decline. Trained research assistants administered the Chinese version of Minimal Mental Status Examination (MMSE) [71], which has a total score of 30. CDR scale to rate the severity of the dementia was also evaluated after a neurologist conducted separate semi-structured interviews with the patient and a knowledgeable informant. The scores were as follows: 0 for normal, 0.5 for questionable, 1 for mild, 2 for moderate and 3 for severe.[72] The diagnosis of AD was determined according to the diagnostic criteria of the Diagnostic and Statistical Manual of Psychiatric Disorders, 4th revised ed..[63] EEG was not part of the routine workup.

The inclusion criteria for participation in the EEG study meet both (1) a diagnosis of probable AD according to the DSM-IV criteria [63] and (2) a rating of either 1 or 2 on the CDR scale.[72] The exclusion criterion included the existence of possible cause of dementia other than AD, determined by history, neurological examination, imaging and blood studies. The criteria for exclusion ensured that the alterations of EEG were the results of AD in all participants. The research was approved by the institutional review board of National Yang Ming University Hospital, YiLan, Taiwan, a local community teaching hospital, and written informed consent were given to all subjects prior to the study.

Seventeen newly diagnosed AD patients (9 men and 8 women, mean age of 74.6±7.4 years) were enrolled in this study, with an initial MMSE score of 18.8±4.5. Two of them were moderately demented (CDR=2), the others were mild (CDR=1). None of the patients received any antipsychotics before the first EEG examination. Every participating patient received AChE inhibitor therapy, donepezil hydrochloride

(Aricept®), 5mg/day, for 12 months, and received follow-up MMSE 12 months after therapy.

4.2.2 EEG Recordings

EEGs were recorded in all subjects. According to the International Federation of Clinical Neurophysiology (IFCN) standards for the digital recording of clinical EEG [176], the surface EEG signals were recorded using a digital EEG recorder (NicoletOne®) from the 19 scalp loci of the international 10–20 system (channels Fp1, Fp2, F3, F4, C3, C4, P3, P4,O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz and Pz), with all electrodes referenced to the bilateral ear (A1, A2) for 30 minutes. Electrocardiograms (ECG) were recorded in a separate channel. The sample frequency was 256 Hz and the A/D digitalized resolution was 12 bits. All the patients stayed awake in a relaxed state to have a 30-minute eyes-closed EEG test.

4.2.3 Signal Processing and Analysis: Multiscale Entropy Analysis

We adopt multiscale entropy (MSE) as a complexity measure to feature digitalized EEG signals. Before conducting the analysis, one artifact-free epoch of 30 seconds duration EEG signal were selected by an experienced neurologist. Further, empirical mode decomposition [118] was utilized to remove the trend from the signals. The MSE method comprises two steps: (i) coarse-graining the signals into different time scales; (ii) quantifying the degree of irregularity in each coarse-grained time series using sample entropy (SampEn) [165, 166]. SampEn is a statistical measure based on the information theory used to quantify the irregularity of a sequence of data. [165, 166, 169] Briefly, it examines a time series for occurrences of similar epochs of a pre-assigned length, where similarity is determined as whether the distance between epochs is under a tolerance r or

not. In detail, it calculates the negative natural logarithm of the conditional probability, those epochs similar for m points that will remain so when one more point is added to the subseries. [165, 166, 169] The higher the SampEn, the more unpredictable the data sequence is. However, complicated systems typically generate not only highly irregular output [177] but also exhibit dynamically diverse tendency on various time scales such as the coexistence of slow and fast phenomena. It turns out that SampEn alone, though provides an adequate way to quantify irregularities for physiological output, and is not sufficient to cope with the content of complexity in physiological interest. By contrast, multiscale entropy analysis, based on evaluating at multiple time scales the sample entropy, has been proved useful to this end. To recast a signal in another scale, the original series were segregated into blocks, where each block contains n data points. The mean value over each block then forms the coarse-grained time series at scale n. It is clear enough that the time series at coarse-grained scale 1 is identical to the original signal. Equipped with multiple scales, MSE method is readily capable of disclosing temporal structure as well as scale-dependent characteristics of signals.

In this study, the MSE value of each lead is calculated individually, which means 380 values for each patient. Slopes of the mean value of MSE, averaged out of all leads, over scales 1–5(Slope1) and 6-20(Slope2) were estimated using the least-squares method, i.e., one Slope1 and one Slope2 for each patient. Throughout the analysis, we set m = 2 and r = 0.15 times of the standard deviation of the processed signal.

4.3 Statistical Analyses

According to the difference between the follow-up and the initial MMSE scores, the patients were divided into two groups, one is responder and the other is

non-responder. The identification of responder is that whose follow-up MMSE score is greater than or equal to the initial, otherwise the non-responder.

Descriptive statistics were presented as means ± standard deviation (SD). SPSS (ver16.0) for Windows (SPSS Inc., Chicago, IL, USA) was used for analysis. Baseline demographic characteristics including age, MMSE-CE, CDR, MSE of each lead, Slope1 and Slope2 were coded as continuous variables. The other demographic characteristics, such as gender, were coded as dichotomous variables. All of these characteristics were treated as predicable variables for treatment response. Student's t-test was used at first to determine which factors were significant. A forward logistic regression was used to calculate the odds ratio in variants. All the statistical tests were two-tailed and significance levels were set at p-values of less than 0.05.

By the receiver operating characteristic (ROC) analysis and considering the optimal combination of sensitivity and specificity, we determined the best cut-off points. Likelihood ratios, positive and negative predictive values with 95% confidence intervals (CI) were assessed in each cut-off point levels.

4.4 Result

There are 7 patients (3M/4F, mean age of 76.1±7.9 years) in responder and 10 patients (6M/4F, 73.5±7.3 years) in non-responder. There was no significant difference in age and gender. The initial MMSE score in responder is 15.6±5.1, and in non-responder is 20.9±2.8 (p=0.042). The following MMSE score in the responder is 22.3±3.7, and in the non-responder is 16.8±6.3 (p=0.039). The MSE values in each lead showed significant higher in F4 MSE19, T3 MSE18, C3 MSE 19 and C3 MSE20 in responder, and significant higher in T4 MSE6, T4 MSE7, T4 MSE9 and Pz MSE8 in

non-responder (Table 3). The Slope1 in the responder is 0.063±0.038, and in the non-responder is 0.092±0.071 (p=0.333) (Table 3 and Figure 19). The Slope2 in the responder is -0.008±0.019, and in the non-responder is -0.03±0.009 (p=0.021) (Table 3 and Figure 9). After applying the forward logistic regression, it shows only Slope2 is preserved with odd ratio of larger than 100. The other factors, including initial MMSE, were excluded.

The area under the ROC curve of Slope2 (Figure 10) is 0.871(95% CI = 0.69 - 1). The sensitivity is 85.7% and the specificity is 60% while the cutoff value of Sloep2 is -0.024 (Figure 11).

Table 3

	Responder	Non-Responder	*p* Value
Age	76.1±7.9	73.5±7.3	0.669
Sex	3M/4F	6M/4F	0.601
MMSE	15.9±5.1	20.9±2.8	0.070
CDR	0.8±0.6	1.2±0.6	0.230
Slope1	0.063±0.038	0.092±0.071	0.475
Slope2	-0.008±0.019	-0.03±0.009	0.010*
F7 MSE7	1.85±0.15	1.98±0.10	0.043*
Fz MSE6	1.84±0.26	2.04±0.06	0.025*
Fz MSE7	1.87±0.23	2.04±0.08	0.043*
Fz MSE8	1.84±0.21	2.01±0.09	0.033*
C4 MSE5	1.84±0.25	2.05±0.10	0.043*

T4 MSE6	1.77±0.21	1.99±0.10	0.019*
T4 MSE7	1.79±0.20	1.99±0.12	0.033*
T4 MSE9	1.79±0.22	2.00±0.16	0.019*
Pz MSE7	1.92±0.20	2.13±0.10	0.010*
Pz MSE8	1.95±0.17	2.13±0.10	0.007*
O1 MSE7	1.89±0.23	2.08±0.10	0.033*

Demographic characteristics of two groups, including age, sex, MMSE, CDR, Slope 1, Slope 2, and MSE values of each lead with significant differences in Mann-Whitney U test. * Indicates that the correlation is significant at the 0.05 level (2-tailed).

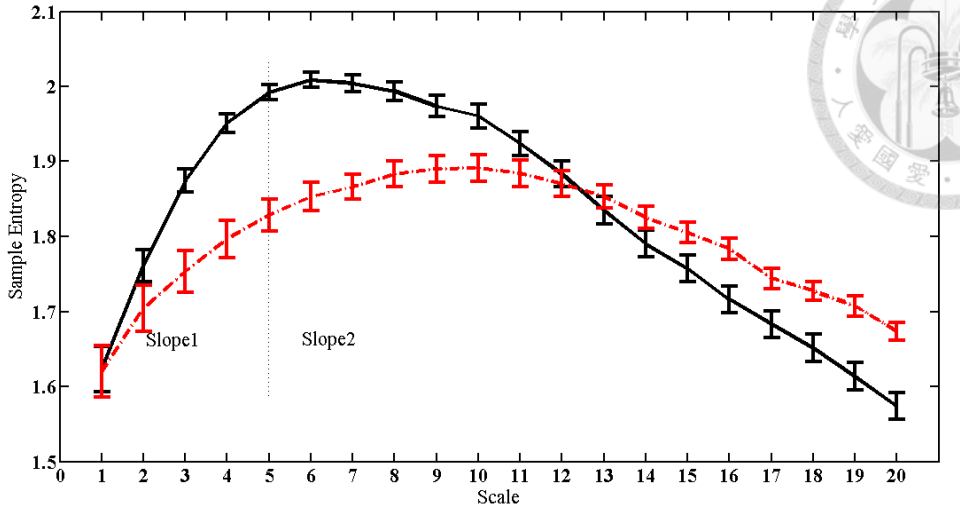


Figure 9 The red dash line was mean value of MSE in each lead in responder and the black solid line was result in non-responder.

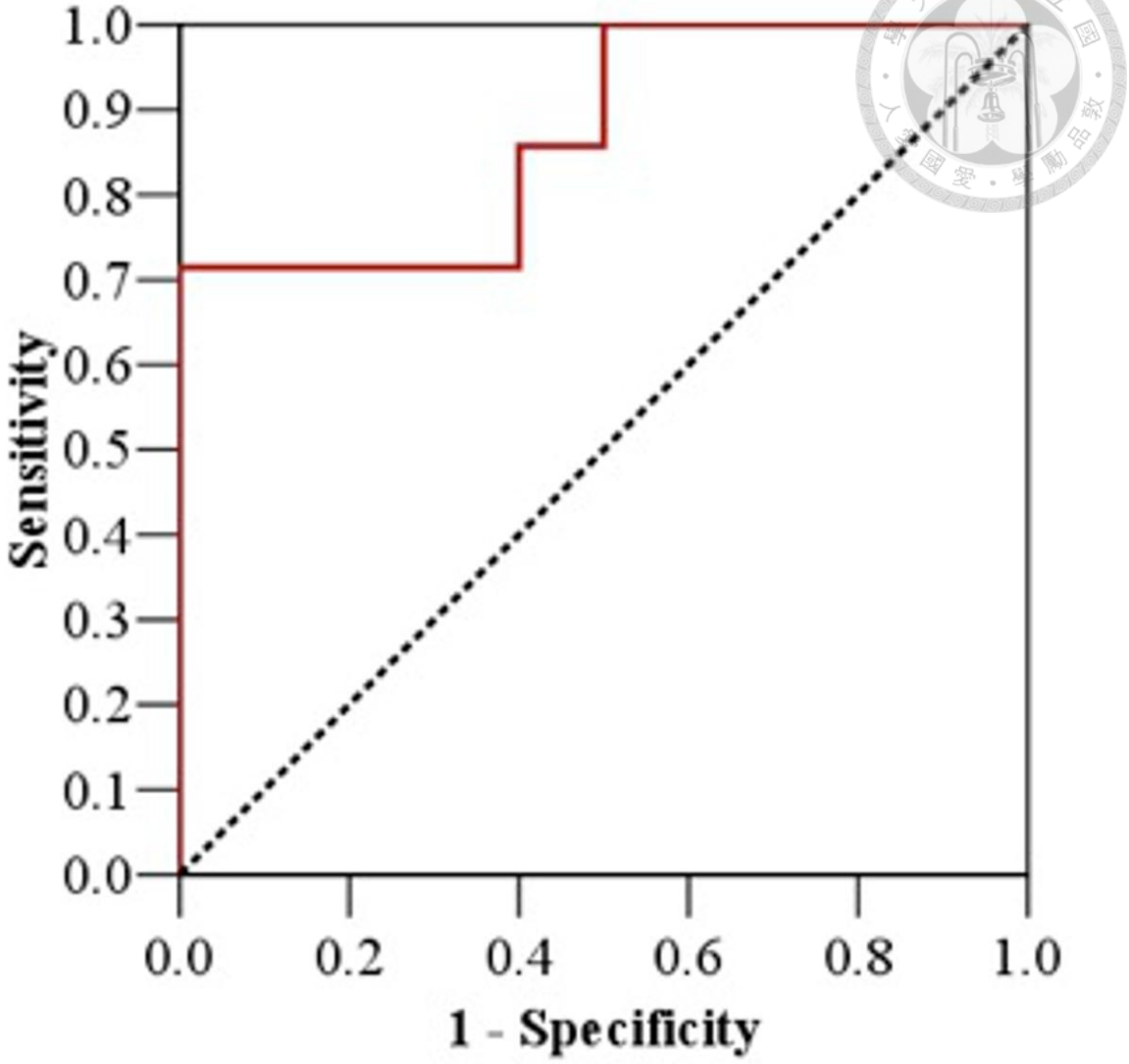


Figure 10 The ROC curve of Slope2, with the area under curve of 0.871(95% CI = 0.69 - 1). The sensitivity is 85.7% and the specificity is 60% while the cutoff value of Sloep2 is -0.024.

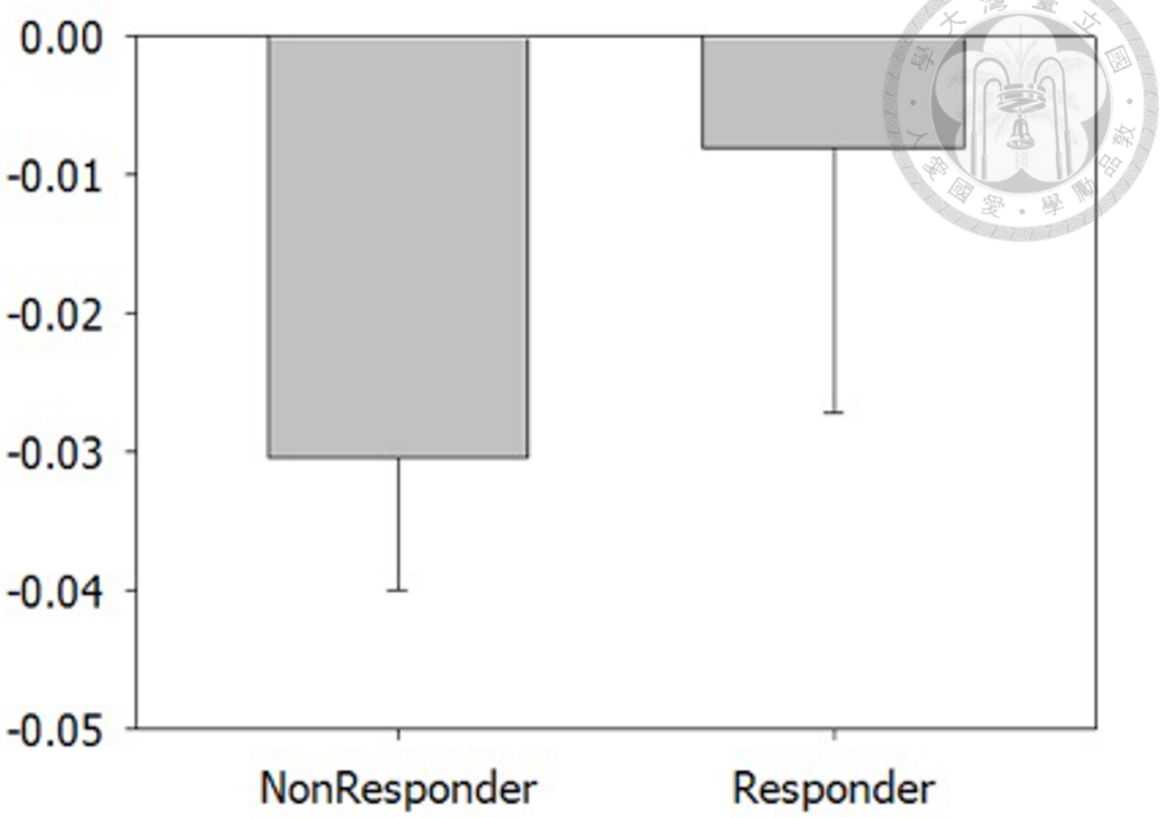


Figure 11 The figure discloses the distributions of Slope2 in responder and non-responder. The sensitivity is 85.7% and the specificity is 60% while the cutoff value of Sloep2 is -0.024.

4.5 Discussion

This pilot study disclosed the potential of quantitative EEG, multiscale entropy, to predict the efficacy of AChE inhibitor in AD. When the Slope2 (MSE 6 to 20) is less than -0.024, the therapy efficacy is relative poor, with sensitivity of 85.7% and specificity of 60%. However, the efficacy of AChE inhibitor in AD was affected by so many factors, such as anti-psychiatric agents for behavior and psychiatric syndromes, other systemic disorder, hypertension, diabetic, etc. It is very difficult to predict the efficacy using single biomarker, such as multiscale entropy in this study. However, this study could provide another idea, weather the dose of AChE inhibitor is enough, or combined other mechanism therapy, such as NMDA receptor antagonist is better.

The innumerable cortical neurons constructing surface EEG that fundamentally decide the complicate pattern, which indicating interactions between different mechanisms with multiple temporal or spatial scales, and is not able to explain the underlying neurophysiology mechanism easily. [177, 202] In other fields, some studies proposed the idea of carefully examining the change of non-linear indices with scales. The most well-known is crossover phenomenon of the fractal correlation exponents between short and long time scales in the detrended fluctuation analysis (DFA)[171] of heart rate dynamics and the short-term exponent is appreciated to be mostly determined by the cardiorespiratory coupling. [171, 203] Recently, the studies of activity fluctuation with aging and in AD [204, 205] find fractal correlations at certain scales (i.e., 1.5~8h) declined with age and an age-independent AD effect further reduced the correlations at these scales leading to the greatest reduction of the correlations in very old people with late-stage AD—resembling closely the loss of correlations at long time scales in SCN-lesioned animals.[206] In addition to DFA, multiscale entropy (MSE) is a possible

method to check the complexity at different temporal scales by means of an entropy-based algorithm. Our previous study, which proposed a detrending process [184, 198]to attenuate the spurious influence caused by nonstationarity in the real world, then revealed many features of the MSE curve, including the slope of the MSE, equivalent to the correlation between sample entropy values and different time-scale factors, could assist with clinical classification[201]. For instance, 1) sympathetic and parasympathetic activity are correlated with MSE in different scales of heart beat sequence (scales 3~5 and 1~4 for sympathetic and parasympathetic activity, respectively);[184] 2) The patients without β-blocker therapy exhibits very negative slope of MSE1~5, indicating the lack of cardiorespiratory coupling.[203]

Understanding the complexity at certain scales may correspond to the illness of specific physiology processes, MSE analysis of EEG signals is a possible way to profile the cholinergic effect in cortex. The figure 1 discloses the maximum value of MSE occurred at MSE6 (about 20msec in time scale) in non-responder and a nearly plateau from MES5 to MSE10 (about 20msec to 40msec in time scale) in responder, that time scales are compatible with the transfer time from the pre-synapse to post-synapse, where the membranes are separated by a synaptic cleft that averages 20 nm (0.02 μm) in width[207], is about 15msec[208] and the ACh molecules broken time from then binding receptor sites is about 20msec. [208] From the view of time scales, we could assume that the MSE of short time scales (1~5) is related to the process of transfer time, and that of long time scales (6~20) is associated with the binding time of ACh molecules. Therefore, the value of MSE1 to MSE5 is responsive to the amount of ACh being released. In addition, the higher value in T4 MSE6, T4 MSE7, T4 MSE9 and Pz MSE8 in non-responder could be considered as the compensative releasing of ACh and the higher MSE value in F4 MSE19, T3MSE18, C3 MSE19 and C3 MSE20 could be

considered as preserved the binding ability of ACh receptor. Hence, the non-responder has lower ACh molecular binding ability or binding count, and has poor effect for AChE inhibitor; they may need higher dose of AChE inhibitor or other mechanism therapy, such as NMDA receptor antagonist.

The previous studies [177, 202] disclosed higher complexity in demented patients in long time scales, which challenge the above hypothesis, the long time scales are related to the ACh molecular binding ability or binding counts. However, there were some differences in method and study design, such as empirical mode decomposition as a preprocessing to detrend the signals, which would have better results in nonstationary physiology signals[198], and the severity of demented patients in this study. Nevertheless, other neurophysiology mechanisms maybe exist to explain both conditions.

The initial MMSE in the responder showed lower scales than the non-responder, and that condition may provide a potential better response rate to AChE inhibitor in responder. However, the usefulness of MMSE was excluded by following forward logistic regression. The previous study [197] showed no significant difference in pretreatment MMSE scores between responder and non-responder, which was similar to our study. The study [197] also showed better visual-spatial motor ability, clock drawing and tracking test in responder. Therefore, the lower MMSE score in responder in this study could not explain the difference between responder and non-responder.

This study is limited by small sample size. Even though the sample size was small, the statistical power was still high enough to support our findings. It still requires more rigorous study to elucidate the physiological meaning of the values and slopes of MSE. Due to a lack of other types of medication in this study, the application of predicating the efficacy to different type's AChE inhibitors or NMDA antagonist is also uncertain.

4.6 Conclusion

Sampling entropy, especially the EMD-based sampling entropy, is introduced as a better method to evaluate the embedded information in EEG, and as an objective, non-invasive and non-expensive tool for evaluating and following AD patients. [198] However, it still could not provide clinicians enough information about the possible responder to AChE inhibitor in AD. MSE analysis on EEG recording could reveal characteristics both at short and long time scales and provide another potential tool to predict the efficacy of AChE inhibitor in AD.

CHAPTER 5 Conclusion and Future work

In this dissertation, we demonstrate the improvement of the sensitivity of EEG signals, by the non-linear detrending, EMD, under the fundamental condition, the EEG signal is non-linear. In clinical practice, the quantitative EEG, on the basis of sampling entropy and multiscale entropy, demonstrates the application of evaluation, following up, and prediction of therapeutic effect in AD patients. The improved quantitative EEG analysis by means of a combination of the EMD detrending procedure and sample entropy revealed that the changes in the complexity of EEG signals were correlated with the severity of the dementia. More, MSE analysis on EEG recording could reveal characteristics both at short and long time scales and provide another potential tool to predict the efficacy of AChE inhibitor in AD.

However, the diagnosis of the AD in this dissertation depends on DSM-IV criteria, which has both sensitivity and specificity only 70 to 80%. Newer bio-marker, such as plasma amyloid, should be included to improve the diagnosis power. In the future, if we could collect the AD patients, been diagnosed by newer biomarker, the similar digital signal results, such as EEG, could be more consistent.

We tried to connect the transport of neurotransmitter, Ach, to the results of MSE in EEG; however, there is no direct evidence. The pharmacodynamics study in health candidate with cholinergic effect and anticholinergic effect drugs should be performed to evaluate the effect in EEG signal changes. Moreover, the combination of pharmacodynamics study and animal mode to prove the connection is necessary.

Moreover, the evaluation of drug effect in this study is 12 months later. In the future, immediate responsive after taking medication, and acute effect, hours or days,

should be carefully evaluated to find which time is the change occurs in signal processing.

In other aspect, diurnal change of EEG was noted evaluated carefully in the dissertation. Especially, the EEG change during sleep may be another point for the degeneration disease.

In order to evaluate continually the patient for long time, such as days or weeks, a portable EEG device with signal lead should be evaluated to determine which lead is most meaningful for the evaluation of EEG in dementia. In the method, to improve the speed of signal processing in MSE of EEG combined with EMD, is another critical point for clinical application. The combination of easy device and fast signal processing would translate the application to population, and to particle in clinical, not limited in study.

Generally, there were still some limitations. First, the patient number is small, due to the limitation of National Yang Ming University Hospital, a local community teaching hospital. Second, the subtypes of dementia, such as fronto-temporal dementia, dementia with Lewy's body or Parkinson's disease with dementia, are not evaluated by the same method to prove that the method is able to be used un every kind of dementia. Beside of subtypes of dementia, patients, who suffering from delirium after anesthesia, are another possible candidate for this study. Third, the degree of education, which was not evaluated carefully in this dissertation, has huge effect in evaluation of the severity of dementia. Therefore, in the further work, more patient numbers, more subtype of dementia, should be included. The degree of education also should be evaluated carefully.

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