國立交通大學

多媒體工程研究所

碩 士 論 文

以休息狀態腦磁波進行情感性疾病之分類

Classification of Mood Disorders from Resting MEG Signals

研 究 生：黃詠恬

指導教授：陳永昇　博士

中 華 民 國　九 十 七　年 九 月

以休息狀態腦磁波進行情感性疾病之分類
Classification of Mood Disorders from Resting MEG Signals

研 究 生：黃詠恬　　Student：Yung-Tien Huang

指導教授：陳永昇　　Advisor：Yong-Sheng Chen

國 立 交 通 大 學

多 媒 體 工 程 研 究 所

碩 士 論 文

A Thesis

Submitted to Institute of Multimedia Engineering

College of Computer Science

National Chiao Tung University

in partial Fulfillment of the Requirements

for the Degree of

Master

in

Computer Science

September 2008

Hsinchu, Taiwan, Republic of China

中華民國九十七年九月

摘　要

近年來，受情感性疾病（Mood Disorder）所苦的病患日益增加，此類疾患嚴重擾亂病人的情緒，進而對日常生活層面造成不良影響，而其中又屬躁鬱症(Bipolar Disorder）以及重鬱症（Major Depressive Disorder）最廣為所知。情緒性疾病已漸漸成為現代人的主要疾病之一，關於此類疾病的各方面研究也在近數十年內蓬勃發展，其中，患者腦部結構與功能的異常被認為是情感性疾病的重要病因之一。

關於情感性疾病在腦部異常的研究，主要分為腦結構影像與腦波訊號兩方面。然而現今對於患者腦波的研究仍顯不足，最主要的困難之一在於如何自腦波訊號中擷取具有鑑別力的訊號特徵。在本篇論文當中，我們和台北榮民總醫院合作，取得情緒性疾病患者在休息狀態的腦磁波（Magnetoencephalography）訊號量測資料。受試者包含二十六位躁鬱症患者、二十二位重鬱症患者以及二十五位做為對照組的健康受試者。在本篇研究中我們分析研究這三個群組的腦磁波訊號，提出具有鑑別力的訊號特徵並且對此三群組加以分類。

在本篇論文中我們使用三種類型的特徵擷取方法，其一是從功率頻譜密度(Power Spectrum Density)中所擷取的特徵，其次為時序訊號上的複雜度，包含Lempel-Ziv Complexity 以及 Sample Entropy，最後再總合前兩類型特徵以取得左右半腦非對稱性的特徵。針對所擷取的特徵，我們使用統計學中的 T 檢定(t-test)以及線性判別分析(Linear Discriminant Analysis)的方法，挑出有鑑別力的訊號特徵並藉以將特徵空間的維度降至合理的範圍。在本篇論文中我們對所擷取的特徵做了詳細的分析與探討，此外並使用支援向量機(Support Vector Machine)作為分類器。最後，在任兩群組以及三個群組的分類中得到良好的分類正確率，證明用於本篇論文中的訊號特徵對於情感性疾病具有一定程度的鑑別能力。

誌　謝

感謝陳永昇與陳麗芬老師，除了在學術上的成就，也在為人處事上豎立典範，兩年間不只有學業上的指導，更有生活上的鼓勵與關心。也要感謝我的父母二十多年來對我的養育與栽培、兄長朋友的關心以及男朋友的鼓勵，一切都是因為有你們的支持。

Classification of Mood Disorders from Resting MEG Signals

A thesis presented

by

Yung-Tien Huang

to

Institute of Multimedia Engineering

College of Computer Science

in partial fulfillment of the requirements

for the degree of

Master

in the subject of

Computer Science

National Chiao Tung University

Hsinchu, Taiwan

2008

Classification of Mood Disorders from Resting MEG Signals

Abstract

Recently, more and more people are suffering from mood disorders such as Bipolar Disorder(BD) and Major Depressive Disorder(MDD). These mood disorders have become one of the major illness of modern people. Therefore, researchers are attempting to study these disorders in different areas, including the abnormality of brain structure and brain signals.

However, studies about the abnormality of brain signals are still insufficient and inconsistent. One of the main difficulties is to obtain significant features for further analysis. In this work, we studied three groups of resting Magnetoencephalographic signal data collected by Taipei Veterans General Hospital, including 26 patients with BD, 22 patients with MDD, and 25 normal controls. We then proposed a procedure to classify the three study groups from each others.

In this work, we studied features obtained from power spectrum density, Lempel-Ziv complexity, sample entropy, multi-scale entropy, and hemispheric asymmetry. After the feature extraction, t-test and Linear Discriminant Analysis were applied as feature selection and also to reduce the features to a reasonable number. We provided methodical analysis of the selected features. Furthermore, we applied Support Vector Machine to classify the three groups. The results showed an almost 100% accuracy in the classification, verifying the significance of our features.

Contents

List of Figures v

List of Tables vii

1 Introduction 1
- 1.1 Mood Disorders . . . 2
  - 1.1.1 Bipolar Disorder . . . 2
  - 1.1.2 Major Depressive Disorder . . . 3
- 1.2 Relative Researches . . . 4
  - 1.2.1 Structural Abnormalities of Mood Disorder Patients . . . 4
  - 1.2.2 Brain Signal Abnormalities of Mood Disorder Patients . . . 6
  - 1.2.3 Hemispheric Asymmetry . . . 6
- 1.3 Magnetoencephalographic studies of mood disorders . . . 7
- 1.4 Thesis Scope . . . 8

2 Feature Extraction 9
- 2.1 ROI . . . 10
- 2.2 PSD features . . . 10
  - 2.2.1 Band Powers . . . 10
  - 2.2.2 Spectral Measures . . . 11
  - 2.2.3 Spectral Ratio Measures . . . 12
  - 2.2.4 Spectral Entropy . . . 14
- 2.3 Temporal Complexity . . . 15
  - 2.3.1 Lempel-Ziv Complexity . . . 15
  - 2.3.2 Sample Entropy . . . 17
  - 2.3.3 Multi-Scale Entropy . . . 18
- 2.4 Hemispheric Asymmetry . . . 20

3 Classification 23
- 3.1 Linear Discriminant Analysis . . . 25
  - 3.1.1 Introduction to LDA . . . 25

3.1.2 Feature Selection . . . 26
3.2 Support Vector Machine . . . 28

4 Experiment Results **33**
4.1 Materials . . . 34
4.1.1 Subjects . . . 34
4.1.2 MEG Device . . . 34
4.1.3 MEG Data Collection . . . 36
4.2 Data Preprocessing . . . 36
4.3 Features of Power Spectrum . . . 37
4.3.1 band power . . . 37
4.3.2 MF and SEF90 . . . 41
4.3.3 Spectral Ratio Measures . . . 43
4.3.4 Spectral Entropy . . . 46
4.4 Temporal Complexity . . . 47
4.4.1 LZC . . . 47
4.4.2 SampEn . . . 52
4.5 Hemispheric Asymmetry . . . 57
4.5.1 Band Power . . . 57
4.5.2 Spectral Measures . . . 59
4.5.3 Spectral Ratio Measures . . . 61
4.5.4 Spectral Entropy . . . 65
4.5.5 Lempel-Ziv Complexity . . . 65
4.5.6 Sample Entropy . . . 69
4.6 Classification Results . . . 73
4.6.1 Normal Control vs. Bipolar Disorder . . . 73
4.6.2 Normal Control vs. Major Depressive Disorder . . . 75
4.6.3 Bipolar Disorder vs. Major Depressive Disorder . . . 78
4.6.4 The three groups classificaiton . . . 80
4.7 Correlation Between Rating and Features . . . 83

5 Discussion **91**
5.1 Suitable Spectral Ratios for Mood Disorders . . . 92
5.2 Spectral Entropies . . . 92
5.3 The Parameters in Multi-scale Sample Entropy . . . 94
5.4 Features for Classification . . . 97

6 Conclusions **99**

Bibliography **103**

List of Figures

1.1 Framework 8

2.1 Schematic illustration of the MEG sensor layout and the ROIs. 11
2.2 Schematic representation of MF and SEF90. 12
2.3 LZC concept. 17
2.4 the concept of sample entropy. 19
2.5 Schematic illustration of the MEG sensor layout and the ROIs for asymmetric analysis. 21

3.1 Classification procedures. 24
3.2 An idea of LDA projection. 25
3.3 The weighting of LDA projection matrix. 27
3.4 The idea of selecting separating hyperplain in SVM. 28
3.5 Margin and support vectors of SVM. 29

4.1 MEG device 35
4.2 Preprocessing procedures for MEG recordings 37
4.3 Relative band power 38
4.4 MF and SEF90 41
4.5 Spectral Ratios. 44
4.6 Spectral Entropies. 46
4.7 Multi-scale LZC. 48
4.8 Multi-scale entorpy (SampEn). 53
4.9 Hemispheric asymmetry of relative band power. 58
4.10 Hemispheric asymmetry of MF and SEF90. 60
4.11 Hemispheric asymmetry of spectral ratios. 63
4.12 Hemispheric asymmetry of spectral entropies. 64
4.13 Results of the NC and BD classification. 75
4.14 Results of the NC and MDD classification. 75
4.15 Results of the BD and MDD classification. 78
4.16 Results of the 3-groups classification. 80

5.1 The influence of different r in multi-scale sample entropy. 95
5.2 The influence of different m in multi-scale sample entropy. 96

List of Tables

1.1 Brain structural changes reported in mood disorders. 5

4.1 Demographic data of subjects. 35
4.2 The p-values of band power between NC and BD. 39
4.3 The p-values of band power between NC and MDD. 39
4.4 The p-values of band power between BD and MDD. 40
4.5 The p-values of mean frequency (MF). 42
4.6 The p-values of the 90% spectral edge frequency (SEF90) 42
4.7 The p-values of spectral ratios between NC and BD. 43
4.8 The p-values of spectral ratios between NC and MDD. 45
4.9 The p-values of spectral ratios between BD and MDD. 45
4.10 The p-values of spectral antropy 1 (SE1). 46
4.11 The p-values of spectral antropy 2 (SE2). 47
4.12 The p-values of Lempel-Ziv complexity (LZC) between NC and BD in multiple scales. 49
4.13 The p-values of Lempel-Ziv complexity (LZC) between NC and MDD in multiple scales. 50
4.14 The p-values of Lempel-Ziv complexity (LZC) between BD and MDD in multiple scales. 51
4.15 The p-values of sample entropy (SampEn) between NC and BD in multiple scales. 54
4.16 The p-values of sample entropy (SampEn) between NC and MDD in multiple scales. 55
4.17 The p-values of sample entropy (SampEn) between BD and MDD in multiple scales. 56
4.18 The p-values of band power asymmetry between NC and BD. 57
4.19 The p-values of band power asymmetry between NC and MDD. 59
4.20 The p-values of band power asymmetry between BD and MDD. 59
4.21 The p-values of MF asymmetry. 60
4.22 The p-values of SEF90 asymmetry. 60
4.23 The p-values of spectral ratio asymmetry between NC and BD. 61

4.24 The p-values of spectral ratio asymmetry between NC and MDD. 62
4.25 The p-values of spectral ratio asymmetry between BD and MDD. 62
4.26 The p-values of spectral entropy 1 (SE1) asymmetry. 64
4.27 The p-values of spectral entropy 2 (SE2) asymmetry. 64
4.28 The p-values of LZC asymmetry between NC and BD in multiple scales. . . 66
4.29 The p-values of LZC asymmetry between NC and MDD in multiple scales. 67
4.30 The p-values of LZC asymmetry between BD and MDD in multiple scales. 68
4.31 The p-values of SampEn asymmetry between NC and BD in multiple scales. 70
4.32 The p-values of SampEn asymmetry between NC and MDD in multiple scales. 71
4.33 The p-values of SampEn asymmetry between BD and MDD in multiple scales. 72
4.34 The features used in NC and BD classification. 74
4.35 The features used in NC and MDD classification. 76
4.36 The features used in NC and MDD classification. 77
4.37 The confusion matrix of the BD and MDD classification. 78
4.38 The features used in BD and MDD classification. 79
4.39 The features used in 3-groups classification. 81
4.40 The features used in 3-groups classification. 82
4.41 Demographic data of subjects. 83
4.42 The significance of correlation between ratings and features in the BD case. 84
4.43 The significance of correlation between ratings and features in the BD case. 85
4.44 The significance of correlation between ratings and features in the MDD case. 86
4.45 The significance of correlation between ratings and features in the MDD case. 87
4.46 The significance of correlation between ratings and features in the MDD case. 88
4.47 The significance of correlation between ratings and features in the MDD case. 89

5.1 Comparison of different spectral ratios. 93

Chapter 1

Introduction

The first chapter is a brief introduction about some background knowledge of this thesis. Nowadays mood disorders have been common diseases which effect daily life ill. We first briefly introduce the mood disorders in section 1.1 and then focus on bipolar disorder and major depressive disorder. Both bipolar disorder and major depressive disorder are reported intently relating to brain abnormalities, and are described in the section 1.2.

1.1 Mood Disorders

Nowadays many people suffer from mood disorders. Mood disorders, also known as affective disorders, are a grouping of psychiatric diseases where the primary symptom is a disturbance in mood. The patients with mood disorders not only suffer from the abnormalities of mood, but also the differences of biological, behavioral, and social aspects.

According to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders 4th Edition), which was published by the American Psychiatric Association in 1994, four disorders are included in the category of mood disorders: bipolar disorder, cyclothymic disorder, dysthymic disorder and major depressive disorder. Bipolar disorder and major depressive disorder are the most well-known disorders among them, and what follows is a brief introduction of the two disorders.

1.1.1 Bipolar Disorder

Bipolar disorder (BD), also known as manic-depressive disorder and bipolar affective mood disorder, is a kind of mood disorder that causes unusual shifts in a person's mood. And the influences of BD also extend many aspects like sleep, energy, and ability to function.

People with bipolar disorder periodically exhibit mood episodes including depressive episodes, manic episodes and mixed episodes. During depressive episodes, individuals usually experience low mood, feel sad, diminished interest in usual activities and disturbances in sleep, appetite, energy, and concentration. Manic episodes typically involve either extremely happy or irritable mood, accompanied by other changes in behavior, such as increased activity, decreased need for sleep, flight of ideas, and racing thoughts. Mixed

episodes include the features of both mania and depression episodes presented at the same time. The duration of mood episodes typically lasts from a couple of hours to many months. Between episodes people with BD often return to their usual functioning and personality.

There are two diagnostic types in bipolar disorder according to the type and severity of mood episodes experienced. Bipolar I disorder is characterized by severe mania episodes and depression. For a diagnosis of bipolar I disorder, a person must have at least one manic episode. Bipolar II disorder is characterized by hypomania episodes and often followed by periods of severe depression.

Up to now, the clinical causes of bipolar disorder are still unknown. Studies suggest that there may be many contributory factors acting together to produce the illness, such as genetics, stress, environmental factors, neurobiology, and psychological and social processes. In recent decades, many studies have attempted to clarify the neural substrates of bipolar disorder, and inferred that bipolar disorder has been associated with abnormalities of brain structure and function.

1.1.2 Major Depressive Disorder

Major depressive disorder (MDD) is also known as major depression, unipolar depression, or clinical depression. This may be compared with bipolar depression which has the two poles of depressed mood and mania (i.e., euphoria, heightened emotion and activity). It is a kind of mood disorders which is characterized by a pervasive and recurrent low mood or loss of interest or pleasure in usual activities.

Different from patients of bipolar disorder, patients with major depressive disorder experience at least one major depressive episodes but without manic episodes. A major depressive episode has been defined as a severely depressed mood that persists for at least two weeks. The patients suffer from recurrent depressive moods, and may feel sad, worthless, guilty or empty, lose energy and interests in daily life. Some of them also suffer from sleep disturbances (sleeplessness or too much sleeping). There are also difficulties in concentrating, social life, and even working. For some, the pain from MDD effects life so deeply that MDD becomes a major risk factor of suicide.

Causes of major depressive disorder can be roughly classified into two categories, the

psychological and the biological. In the psychological aspect, the causes may be stress, environment or life experiences. In the biological aspect, researches have shown that depression is influenced by genetic and brain abnormalities.

1.2 Relative Researches

Although mood disorders affect daily life so significant and have become common diseases nowadays, the specific cause of these disorders are still a mystery. In recent years, scientists and clinicians have reached general agreement that these disorders are strongly correlated with brain dysfunction. The researches about brain abnormalities can be roughly divided to two categories, brain structural changes and brain signal abnormalities.

1.2.1 Structural Abnormalities of Mood Disorder Patients

In the past decades, the development of neuroimaging techniques has produced a proliferation of studies that have attempted to clarify the brain abnormalities responsible for mood disorders. The modalities such as positron emission tomography (PET), computed X-ray tomography (CT), and particularly magnetic resonance imaging (MRI) have contributed to found the structural abnormalities in mood disorders undoubtedly. And Table 1.2.1 summarizes the studies which reported structural changes in bipolar disorder and major depressive disorder [36, 37, 39, 40].

In the BD case, some apparent abnormalities were found. Researchers examined whole brain volumes and found that although the overall brain volumes of BD patients do not different from volumes of healthy controls, but a global decrease in cortical gray matter was conclusive, especially in prefrontal cortex (PFC). The temporal cortex was also reported to be abnormal for many times, but the volume changes are not consistent in these researches. In the subcortical level, abnormalities of enlargements were reported in amygdala, thalamus, and striatum including caudate nucleus and putamen. Besides cortical and subcortical findings, enlargements of ventricles were found, and be obvious in lateral ventricle and the third ventricle. Moreover, abnormal reduction was found in cerebellar vermis, which is generally thought to modulate movement.

Table 1.1: **Brain structural changes reported in mood disorders.** The table summarizes some reviews of neuroimaging studies reporting structural abnormalities of mood disorders. The black triangle ▲ represents the increase of volumn size, and black inverted triangle ▼ stands for decrease of volumn size on the contrary. Besides, some structures have been widely reported to different from healthy subjects, but there were no consistant opinions on enlargement or atrophy. We represent these changes as ∗.

Research	Bipolar Disorder				Major Depressive Disorder		
	Strakowski [39]	Strakowski [40]	Sheline [36]	Soares [37]	Strakowski [39]	Sheline [36]	Soares [37]
Cerebellum				▼			
Cerebellar vermis	▼	▼			▼		▼
Ventricular							
3rd Ventricular	▲	▲	▲	▲	▲		
Lateral Ventricular	▲	▲	▲	▲	▲		▲
Cortical							
PFC	∗	▼			▼	▼	▼
Temporal Lob	∗		∗	∗			
Subcortical							
Limbic System							
Amygdala	∗	▲	∗		∗	∗	
Hippocampus					▼	▼	▼
Basal Ganglia					▼	▼	▼
striatum		▲					
Caudate Nucleus		▲		▲	▼	▼	▼
Putamen		▲			▼	▼	▼
Thalamus	▲	▲		∗			

In the MDD case, prefrontal cortex atrophy, cerebellar vermis atrophy and ventricular enlargements were also found. Contrast to BD patients, the subcortical abnormalities of MDD patients are decreasing volumes of basal ganglia and hippocampus. The structural change of amygdala was also discussed, but there is no conclusion about atrophy or enlargement.

1.2.2 Brain Signal Abnormalities of Mood Disorder Patients

Conpare with neuroimaging, the number of studies relative to brain signal abnormalities about mood disorder is small, and the study results disagree with each others, especially in the BD case.

In the MDD case, most researches in resting brain signals are with EEG. These researches indicated that MDD patients had decreased relative delta band power and increased relative theta and alpha band powers [16, 34]. Some indicated increased relative beta band power [16, 26], but some indicated decreased power [34]. Besides band powers, coherence was also reported to decrease [26, 34], the correlation of left temporocentral is related to the severity of depression, and the theta band correlation disappears in MDD patients [28].

1.2.3 Hemispheric Asymmetry

Hemispheric asymmetry is the relative imbalance of cerebral activities. Resting frontal EEG asymmetry in the alpha frequency band is believed to reflect certain emotions and behaviors. It has been proposed that individuals with greater left than right frontal brain activity are more likely to have the behaviors with approach motivation and positive affect, while individuals with greater right versus left frontal brain activity are more likely to behave with withdrawal and negative affect [45]. Besides, Graae found an abnormality of EEG asymmetry in female adolescent suicide attempters, and suicidal adolescents had a greater alpha power over left than right hemisphere [20].

Many studies tried to found out the relationship between asymmetry and mood disorders. Asymmetrical resting frontal EEG not only distinguishes currently depressed individuals from nondepressed individuals, but also distinguishes previously depressed eu-

thymic individuals from individuals without a history of depression [22]. Some indicated that frontal EEG asymmetry is sensitive to mood disorder in adults and may characterize adolescents at risk for mood disorder [43]. Some studies measuring EEG asymmetry in depressed subjects found the greater left than right alpha band power [9] and reduced left hemisphere activation [26]. In the BD case, it was reported that increased relative right frontal activity has been observed in bipolar depression, whereas increased relative left frontal activity has been observed in mania [4].

1.3 Magnetoencephalographic studies of mood disorders

For Human beings, brain a ruler of our body. It not only coordinates all parts of our body, also control human consciousness such as memory, though and feeling. Researchers have devoted themselves to discover the accurate brain functionalities for a long time. Then various non-invasive techniques to monitor the brain activity, such as the modalities of Electroencephalography (EEG), Magnetoencephalography (MEG), functional Magnetic Resonance Imaging (fMRI), come into being.

MEG and EEG are used to measure the magnetic fields and the scalp electric potentials produced by the ensemble of neuronal activities inside the brain. And the major advantage of both MEG and EEG is the high temporal resolution (on the order of milliseconds) rather than fMRI which has a high spatial resolution. Besides, MEG is less affected by the irregular distortions caused by the skull and tissue compared to EEG.

Although MEG is an excellent modality to study the brain function directly, the amount of EEG researches about mood disorder is much more than MEG studies. It may be limited by both the complexity and expense of the technology.

In the studies about mood disorders, many discoveries are found by the structural neuroimaging, but the researches relative to EEG and MEG are relatively rare, especially in MEG. However, more and more evidences show that the mood disorders are correlating with the abnormal brain function. In this work, we aim to find the differences of brain activities between patients with mood disorders and healthy subjects with the excellent modality of MEG.

1.4 Thesis Scope

The objective of this thesis is to differentiate the patients with mood disorders from the healthy controls by the resting MEG signals. Fig. 1.1 illustrates the framework of this thesis. We preprocess the MEG signals and then extract features from them. There are three kind of features. The first is the PSD features which extract from the power spectral density, the second is about temporal complexity, and the other one is hemispheric asymmetry. The features of hemispheric asymmetry are calculated from the features of PSD and temporal complexity. Finally, those features are used to differentiate the BD patients, MDD patients and normal controls by classification.

In the following chapters, we will bring up our methods, experiment results and some discussions about this work. The methods of feature extraction will be introduced in Chapter 2. The classification procedure and the method to select features are introduced in Chapter 3. In Chapter 4, we will analyze the individual features and then show the classification results. Then, we will have some discussions and conclusions in Chapter 5 and Chapter 6.

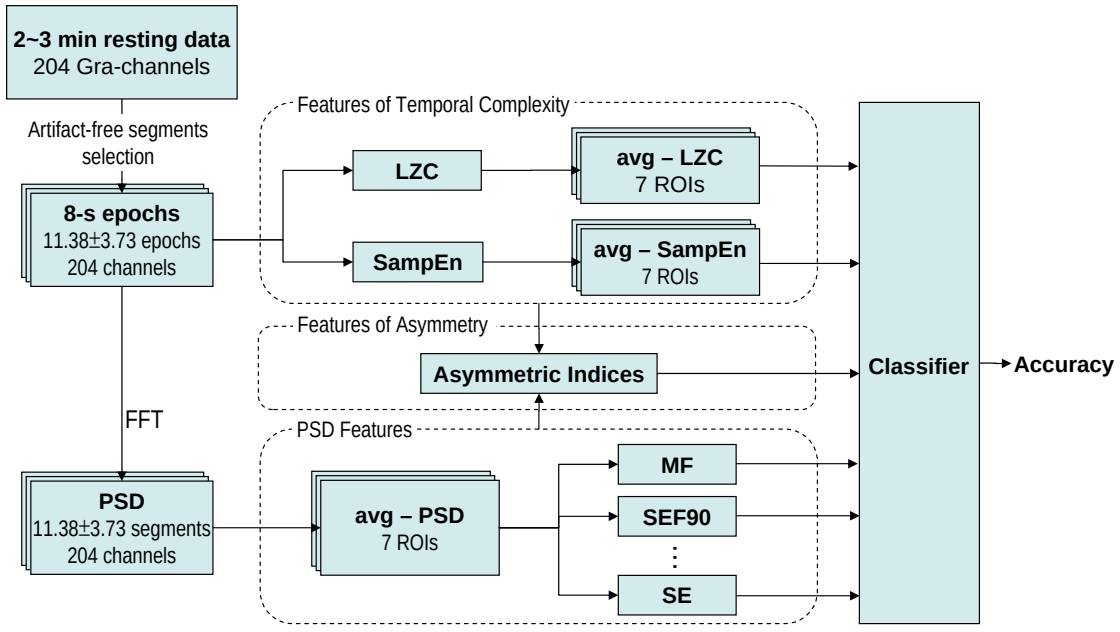


Figure 1.1: **Framework.**

Chapter 2

Feature Extraction

This chapter is concerning how we extract features to differentiate different groups based on some abnormalities of brain function. There are three kind of features used in this work. The first is the PSD features in section 2.2, the second is the features about temporal complexity in section 2.3, and the last is about the hemispheric asymmetry of the brain.

2.1 ROI

According to the function of brain, we divided the brain into seven areas: frontal, central, occipital, left frontotemporal, right frontotemporal, left temporal and right temporal.

Discarding the channels in the suburbs of the brain where the activities are rarely weak, we divided the MEG channels into seven groups according to the seven areas mentioned above. The seven groups of MEG channels are shown in Fig. 2.1. Besides the seven channels groups, we also observe the whole brain activities by the union of the seven channel groups. In another word, we analysis the brain in eight different ROIs: the seven areas separately and the union of the seven areas.

2.2 PSD features

In this work, we used several spectral based measures to summarize the information of the power spectral density (PSD).

2.2.1 Band Powers

The frequency bands are defined as delta (2-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (30-50 Hz). The power spectrum density is first normalized by the total power, the areas under PSD curve. And then each band power is calculated from the average of the power bins within the same frequency band.

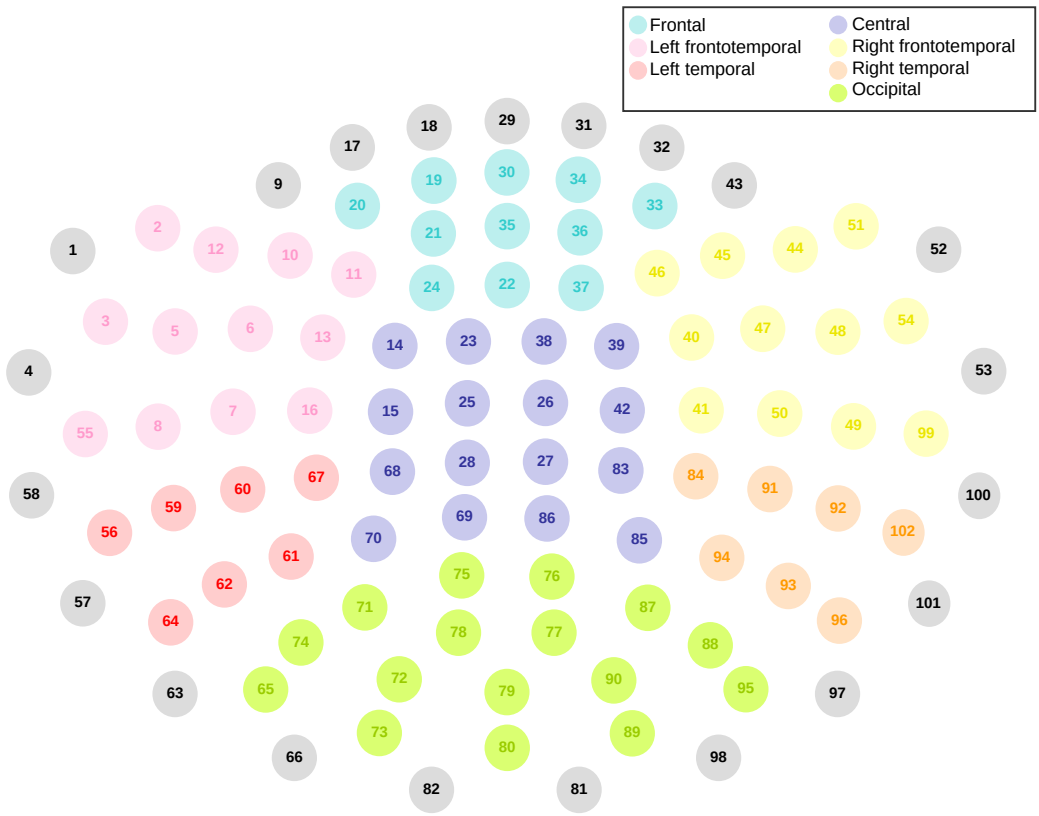


Figure 2.1: **Schematic illustration of the MEG sensor layout and the ROIs.** In this work, we devide the brain into 7 areas: frontal, central, occipital, left frontotemporal, right frontotemporal, left temporal and right temporal. The illustration shows the channel groups corresponding to the 7 areas. Different colors are used to distinguish different areas, and the gray channels in the suburbs of the brain are discarded due to the weak activitis.

2.2.2 Spectral Measures

Mean frequency (MF) offers a simple means which summaries the whole power spectrum. It is defined as the frequency which contains 50% of the PSD power. As a frequency which divides PSD into equal powers, the mean frequency can roughly present the trend of band power distribution. The mean frequency is represented in Eq. 2.1, where MF is calculated from the PSD between 2 Hz and 50 Hz.

It has been used to study the spectrum of Alzheimer's disease, mild cognitive impairment or vascular dementia patients' EEG or MEG signals [15, 31].

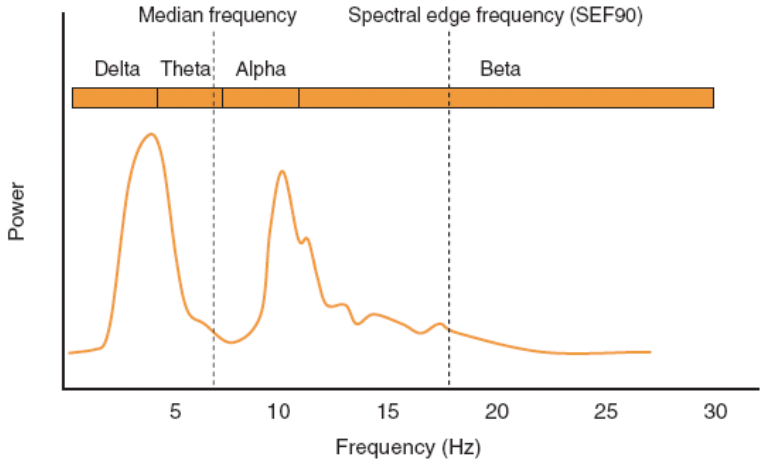


Figure 2.2: **Schematic representation of MF and SEF90 [44].** The median frequency (MF) is the freqeuncy that divides the area under the curve in half, and the 90% spectral edge frequency (SEF90) is the frequency which divides the area area into 90% and 10%.

$$0.5 \sum_{f=2Hz}^{50Hz} \mathbf{PSD}(f) = \sum_{f=2Hz}^{MF} \mathbf{PSD}(f). \tag{2.1}$$

Similar to the mean frequency, the 90% spectral edge frequency (SEF90) is defined as the frequency which separates 90% of the PSD power from 10%. It has been used to study monitor depth of anaesthesia and Alzheimer's disease.

Eq. 2.2 represents the calculation of SEF90 which is analogous to the mean frequency shown in Eq. 2.1.

$$0.9 \sum_{f=2Hz}^{50Hz} PSD(f) = \sum_{f=2Hz}^{SEF90} PSD(f). \tag{2.2}$$

Fig. 2.2 shows the concept of MF and SEF90. The MF divides the area under the PSD curve into equal parts, and the SEF90 divides the area into 90% and 10% parts.

2.2.3 Spectral Ratio Measures

To calculate the spectral ratio measures is a method to emphasize the difference between the powers of high and low frequency bands.

Some previous EEG studies successfully used the spectral ratio measures to distinguish between patients of cognition disorders and Alzheimer's disease [24,27]. Some other studies also use the ratio to emphasize the difference between Alzheimer's disease and elderly normal controls [8,32,38].

Poza used four spectral ratios to differentiate the patients of Alzheimer's disease from the normal controls. And the spectral ratios reveal the higher correlation with severity of dementia than individual relative band powers. According to the characteristics of the Alzheimer's disease, Poza evaluate the power ratio of high frequency to low frequency bands shown in Eq. 2.3 to Eq. 2.6 where relative power was calculated in the frequency bands: δ (1-4 Hz), θ (4-8 Hz), α (8-13 Hz), β_1 (13-19 Hz), β_2 (19-30 Hz) and γ (30-64 Hz) [32].

$$r_1 = \frac{RP(\alpha)}{RP(\theta)}. \tag{2.3}$$

$$r_2 = \frac{RP(\alpha) + RP(\beta_1) + RP(\beta_2) + RP(\gamma)}{RP(\delta) + RP(\theta)}. \tag{2.4}$$

$$r_3 = \frac{RP(\beta_1) + RP(\beta_2)}{RP(\delta)}. \tag{2.5}$$

$$r_4 = \frac{RP(\beta_2)}{RP(\delta)}. \tag{2.6}$$

Due to the different characteristics of mood disorders, we designed different spectral ratio measures in this work. Based on the observed band power abnormalities of MDD patients, we used five spectral ratio measures defined in Eq. 2.7 to Eq. 2.11.

$$r_{\beta\gamma 2\theta\alpha} = \frac{RP(\beta) + RP(\gamma)}{RP(\theta) + RP(\alpha)}. \tag{2.7}$$

$$r_{\beta 2\theta} = \frac{RP(\beta)}{RP(\theta)}. \tag{2.8}$$

$$r_{\beta 2\alpha} = \frac{RP(\beta)}{RP(\alpha)}. \tag{2.9}$$

$$r_{\gamma 2\theta} = \frac{RP(\gamma)}{RP(\theta)}. \tag{2.10}$$

$$r_{\gamma 2\alpha} = \frac{RP(\gamma)}{RP(\alpha)}. \tag{2.11}$$

2.2.4 Spectral Entropy

Spectral Entropy is a method to quantify the flatness of the power spectral density (PSD). It applies the Shannon's entropy computed over the normalized PSD. The entropy was first defined as a measure for information theory by Shannon [10], and it is a measure of the spread of the data. A data with a wider and flatter probability distribution will have higher entropy. On the contrary, a data with a narrower and pecked probability distribution will have lower entropy.

As applying Shannon entropy to EEG and MEG signals, it quantifies the regularity and the spectral complexity of the time series. In the first, the PSD of the signal is computed. And then, the spectral entropy is calculated by using the amplitude components of the PSD of the signal as the probabilities in Shannon entropy calculations.

In this work, we adopt two spectral entropies. The first type of spectral entropy is defined as Eq. 2.12 where $\mathbf{PSD_n(f)}$ denotes the normalized PSD of the total power between 2 Hz and 50 Hz.

$$SE = -\sum_{f=2Hz}^{50Hz} PSD_n(f) ln[PSD_n(f)]. \tag{2.12}$$

This definition of spectral entropy has been used to study anaesthesia monitor [7], the spectrum of Alzheimer's disease [15, 31], and the detection of epilepsy [25].

The above-mentioned SE calculates all frequency bins of power spectral density, and it will be influenced by the different bandwidth. In other words, it brings about a bias in the frequency band with larger range. For example, the beta band (13-30 Hz) will have lager weight than theta band (4-8 Hz) due to the bandwidth. Poza brought up the second type of spectral entropy to analyze Alzheimer's disease [30].

To calculate the second type of spectral entropy (**SE2**), we denote the average power at each frequency band as $\mathbf{P_j}, \mathbf{j} = \{\delta, \theta, \alpha, \beta, \gamma\}$. Then we normalize the average power by the sum of them as Eq. 2.13 where $\mathbf{p_j}$ represent the probability distribution of each band.

$$p_j = \frac{AP(j)}{\sum_j AP(j)}. \tag{2.13}$$

Afterwards, we apply Shannon's entropy as Eq. 2.14 .

$$SE2 = -\sum_j p_j \cdot ln[p_j]. \tag{2.14}$$

2.3 Temporal Complexity

2.3.1 Lempel-Ziv Complexity

The Lempel-Ziv complexity (LZC) proposed by Lempel and Ziv is a nonparametric method to evaluate complexity (randomness) of finite sequences [3]. The LZ complexity measures the number of distinct substrings and the rate of their occurrence along the given sequence. The more complex data will have larger values.

Lempel-Ziv complexity has been widely used to solve information theoretic problems and applied to data compression [1,23] and coding [5,42]. In recent years, the LZC has been applied to biomedical signal analysis as a measurement of the complexity of discrete time signals. For example, the LZC was used to evaluate the complexity of DNA sequences [21], and to differentiate different kinds of stimuli [41]. Besides, LZC has also been used to study the Alzheimer's disease [14, 19], epileptic seizure time-series data [33], the depth of anesthesia [46], and the intracranial pressure signals with acute intracranial hypertension episodes [2].

LZ complexity analysis is based on a coarse-graining of the measurements [46]. In other words, before calculating the LZ complexity, the signal must be transformed into a sequence whose elements are only a few symbols. In this work, we convert the MEG signal $x = [x_1, x_2, \ldots, x_N]$ into a binary sequence. By comparison with the threshold T_d, the original signal x is converted to a binary sequence $P = [s_1, s_2, \ldots, s_N]$ where s_i is defined by:

$$s_i = \begin{cases} 0 & \text{if } x_i < T_d \\ 1 & \text{otherwise} \end{cases} \tag{2.15}$$

We use the median as the threshold T_d because of it is robust to outliers [29].

To calculate the LZ complexity, the sequence P is scanned from left to right, and the subsequence number $c(N)$ is increase by one while a new substring was found. The algorithm of Lempel-Ziv complexity analysis is as follows.

Let S and Q denote subsequence of the sequence $P = [s_1, s_2, \ldots, s_N]$, and SQ be the concatenation of S and Q. Let π be a operation which deletes the last character in a sequence, and then $SQ\pi$ is a substring derived from sequence SQ with its last character deleted. And then, let $\nu(SQ\pi)$ denote the vocabulary of all different subsequences of $SQ\pi$.

Initially, we set the subsequence number $c(N) = 1$, $S = s_1$, $Q = s_2$, and therefore $SQ\pi = s_1$. In general, we suppose $S = s_1, s_2, \ldots, s_r$, $Q = s_{r+1}$, and $SQ\pi = s_1, s_2, \ldots, s_r$. And then, there are two cases:

1. If $Q \in \nu(SQ\pi)$, then Q is a subsequence of $SQ\pi$. In other words, Q is not a new sequence. In this case, S dose not change and Q is renewed to be $s_{r+1}, s_{r+2}, \ldots, s_{r+i}$ until $Q \notin \nu(SQ\pi)$.

2. If $Q \notin \nu(SQ\pi)$, then Q is not a subsequence of $SQ\pi$. In this case, $c(N)$ increases by one and S is renewed by combining original S with Q. At this time, S is $s_1, s_2, \ldots, s_r, s_{r+1}, \ldots, s_{r+i}$ and Q is renewed with $Q = s_{r+i+1}$.

Repeat the procedure until Q is the last character. At this time, the number of different subsequences $c(N)$ is the measurement of LZ complexity.

The last step of the procedure is to normalize $c(N)$ in order to obtain a complexity measure independent of the sequence length. Suppose the number of different symbols is α and the sequence length is N. It has been proved that the upper bound of $c(N)$ [3] is

$$\lim_{N\to\infty} c(N) = b(N) = \frac{N}{\log_\alpha N} \tag{2.16}$$

For a binary sequence, $\alpha = 2$, therefore

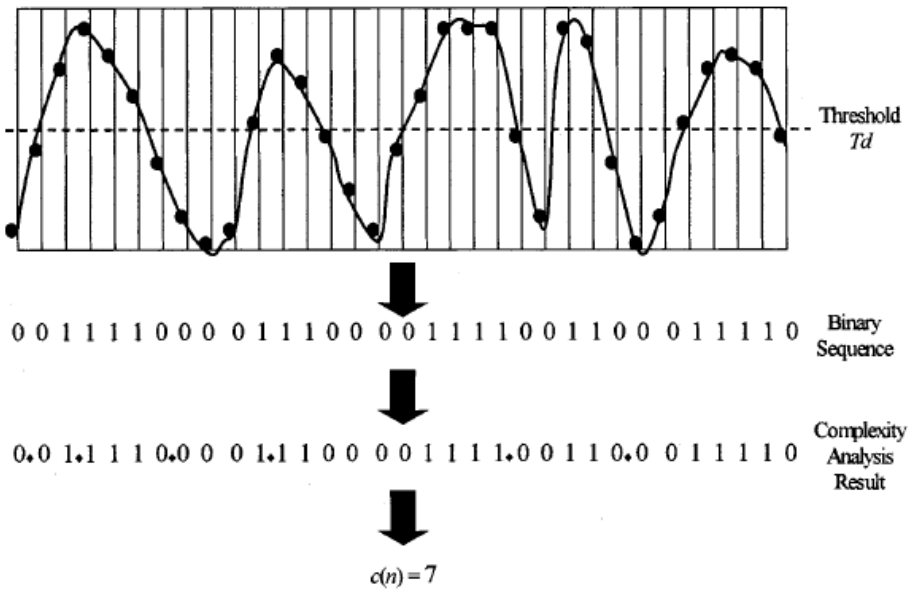


Figure 2.3: **LZC concept.** An example showing how to transform a segment of time series into a binary sequence by threshold and the results of LZC calculation [46].

$$b(N) = \frac{N}{\log_2 N} \tag{2.17}$$

and $c(N)$ can be normalized by the upper bound $b(N)$ as

$$C(N) = \frac{c(N)}{b(N)} \tag{2.18}$$

Fig. 2.3 illustrates the example of calculating LZC. The time series will first trnasform into a binary series and then a LZC procedure is appled to calculate the LZC values.

2.3.2 Sample Entropy

Sample Entropy (SampEn) quantifies the regularity of a time series by evaluation the appearance of repetitive patterns. It has already been widely used to study some biomedical signals. For example, it was applied to representative interbeat interval time series and differentiate subjects with congestive heart failure and atrial fibrillation from healthy subjects [13].

To calculate the sample entropy of x, there are two parameters: m and r. m is the length of sequences to be compared, and r is the tolerant range of match. Given a time series $x = [x_1, x_2, \ldots, x_N]$ with length N. First form vectors $X_m(1), X_m(2), \ldots, X_m(N - m + 1)$ with length of m, and let $X_m(i) = [x_i, x_{i+1}, \ldots, x_{i+m-1}]$. Then define the distance $d[X_m(i), X_m(j)]$ between vectors $X_m(i)$ and $X_m(j)$ as the maximum difference in their respective scalar components

$$d[X_m(i), X_m(j)] = \max_{k=1,2,\ldots,m} (\|x_{i+k-1} - x_{j+k-1}\|). \tag{2.19}$$

Define $B_i^m(r)$ as $1/(N-m-1)$ times the number of vectors $X_m(j)$ within r of $X_m(i)$ (the distance between $X_m(j)$ and $X_m(i)$ is less than or equal to r) where $1 \leq j \leq N - m(j \neq i)$ to exclude self-matches. Then define $B_m(r)$ as:

$$B_m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} B_i^m(r) \tag{2.20}$$

Similarly, define $A_i^m(r)$ as $1/(N-m-1)$ times the number of $X_{m+1}(j)$ such that the distance between $X_{m+1}(j)$ and $X_{m+1}(i)$ is less than or equal to r. And then set $A_m(r)$ as:

$$A_m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} A_i^m(r) \tag{2.21}$$

Finially, $SampEn(m, r)$ is defined by:

$$SampEn(m, r) = \lim_{N \to \infty} [-\ln \frac{A_m(r)}{B_m(r)}] \tag{2.22}$$

which is estimated by the statistic

$$SampEn(m, r, N) = -\ln \frac{A_m(r)}{B_m(r)} \tag{2.23}$$

2.3.3 Multi-Scale Entropy

The entropy-based measurements quantify the regularity of a time series. In theory, an increase in entropy represents the increase of complexity. However, it may not always be

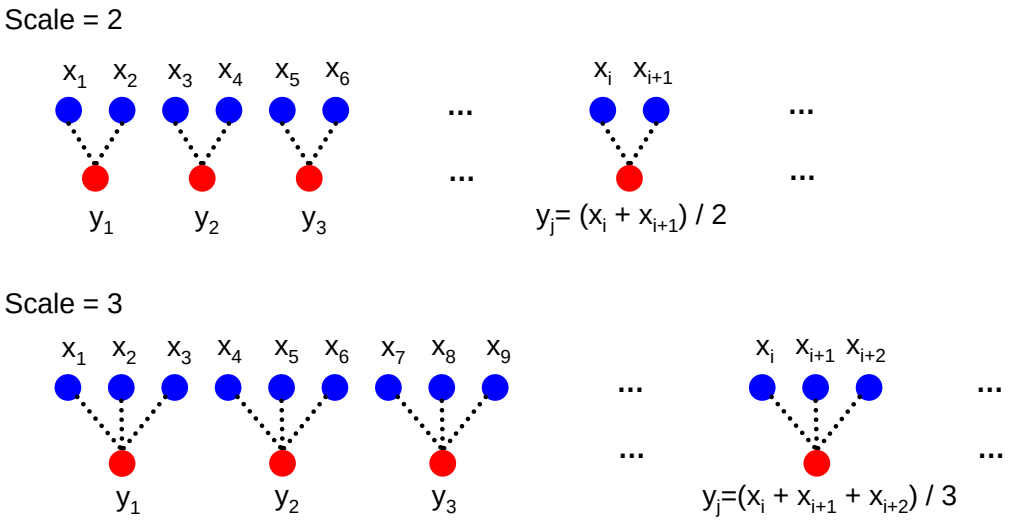


Figure 2.4: **the concept of sample entropy.** xzz.

true in real case. One possible reason may be the fact that these measures are based on a single scale [12].

Costa brought up a multiscale method based on the sample entropy, and it is a non-linear method to measure complexity over a range of scales [12].

The MSE procedure is as follows [12,18]. Given a discrete time series $x = [x_1, x_2, \ldots, x_N]$, consecutive coarse-grained time series $y^\tau = [y_1^\tau, y_2^\tau, \ldots, y_{N/\tau}^\tau]$ is constructed corresponding to the scale factor τ. In the first place, the original time series x is divided into nonoverlapping windows of length τ. Second, we average the data points within the same window according to Eq. 2.24. Fig. 2.24 illustrates this coarse-grained method. Afterwards, sample entropy for each coarse-grained sequences is calculated and plotted as a function of the scale factor.

$$y_j^\tau = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_1, \; 1 \leq j \leq \frac{N}{\tau} \tag{2.24}$$

2.4 Hemispheric Asymmetry

Hemispheric EEG activation asymmetry in the patients with mood disorders has been frequently observed in recent years as mentioned in section 1.2.3.

Knott measured the inter-hemispheric absolute power asymmetry for each band in eight homologous sites (Fp1-Fp2, F7-F8, F3-F4, C3-C4, P3-P4, O1-O2, T3-T4, T5-T6) [26]. In Knott's method, the activity asymmetric indices of left hemisphere (L) and right hemisphere (R) were calculated with the formula:

$$\frac{L-R}{L+R} \tag{2.25}$$

In this work, we follow the basic comparison method as Eq. 2.25 but change the site-based comparison. Unlike the EEG channels, the amount of MEG channels is bigger and the channels are closed to each other. For this reason, differ from EEG studies, we compare the brain asymmetry region by region shown in Fig. 2.5. Based on the ROIs mentioned in section 2.1, we slightly modify the ROI design. In the middle areas (frontal, central and occipital), we discard the channels directly on the midline of the brain and divide the other channels into left and right groups. The left and right temporal areas are in pairs, but we subdivide frontotemporal areas into lateral and interior parts due to the bigger channel number. In other words, the left lateral- and interior- frontotemporal areas are corresponding to right lateral- and interior- frontotemporal areas respectively.

Besides the band power asymmetry, we also extend the asymmetric indices to other features described in section 2.2 and section 2.3.

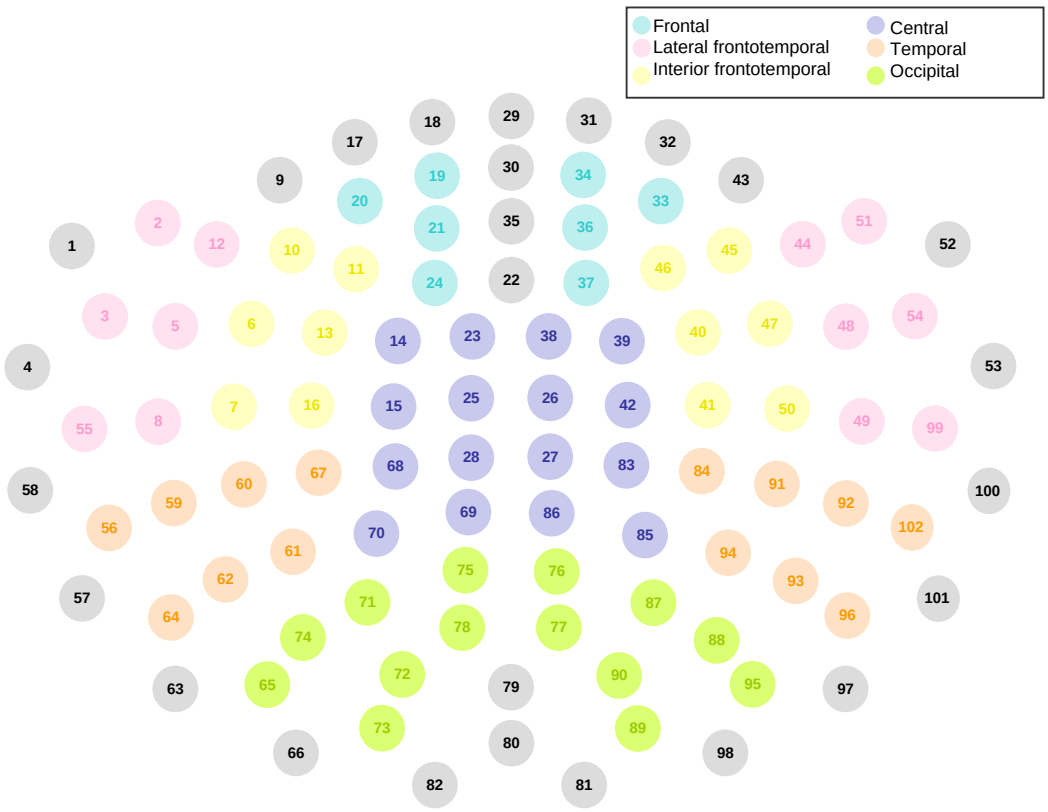


Figure 2.5: **Schematic illustration of the MEG sensor layout and the ROIs for asymmetric analysis.** There are six areas for observation: frontal, central, occipital, lateral-frontotemporal, interior-frontotemporal and temporal. The illustration shows the channel groups corresponding to the six areas, and the same colors stand for the areas in pairs. The gray channels were excluded due to the week activitis or right in the middle of the brain.

Chapter 3

Classification

This chapter is concerning how we select the features with differentiability and design the classifier. In the following sections, the methods of t-test and Linear Discriminant Analysis (LDA) are applied to select beneficial feature for classification. And then the classification will be brought out by Support Vector Machine (SVM) described in section 3.2.

Fig. 3.1 shows the classification procedures in this work.

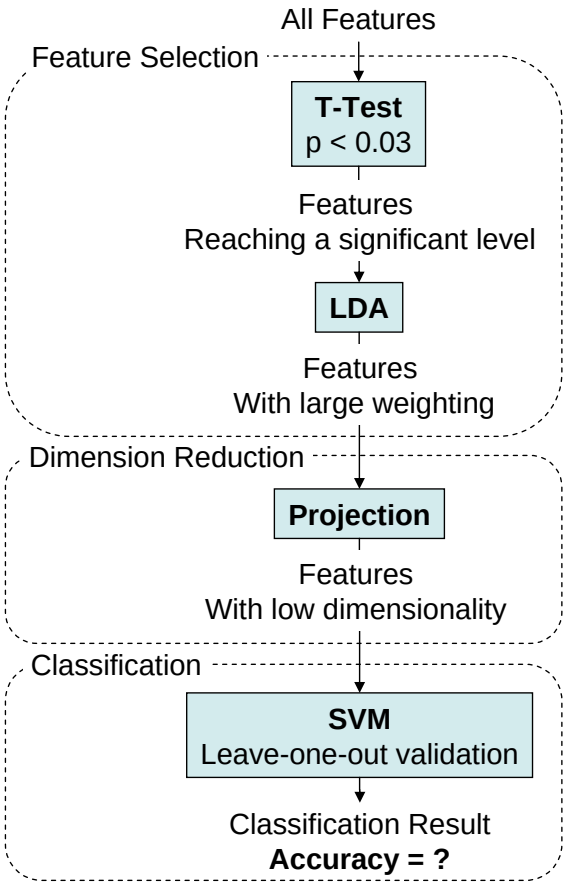


Figure 3.1: **Classification procedures.** The figure shows the classification procedures in this work. The significant level of t-test is set to be the first threshold to select features in the first place. And then the features selected from t-test are selected again by LDA method. To reduce the dimensionality of feature set, we then project the selected features to a subspace with low dimension by LDA projection matrix. Finally, SVM is applied to classify the final features.

3.1 Linear Discriminant Analysis

3.1.1 Introduction to LDA

Linear discriminant analysis (LDA) is one of the most popular techniques for data classification and dimensionality reduction. It was originally developed in 1936 by R.A. Fisher [17], and has been widely applied in the areas of classification, face recognition, marketing researches. The LDA method finds the linear combination of features which best separate two or more classes and the resulting combination may be used as a linear classifier or for dimensionality reduction before classification.

Fig. 3.2 illustrates a simple idea for LDA projection. It is an example of two dimensional data, and the data is unable to be separated by neither $dimension1$ nor $dimension2$ in Fig. 3.2(a). However, in Fig. 3.2(b) we can find a projection matrix and project the data into a new axis where the projected data are more separable than $dimension1$ and $dimension2$.

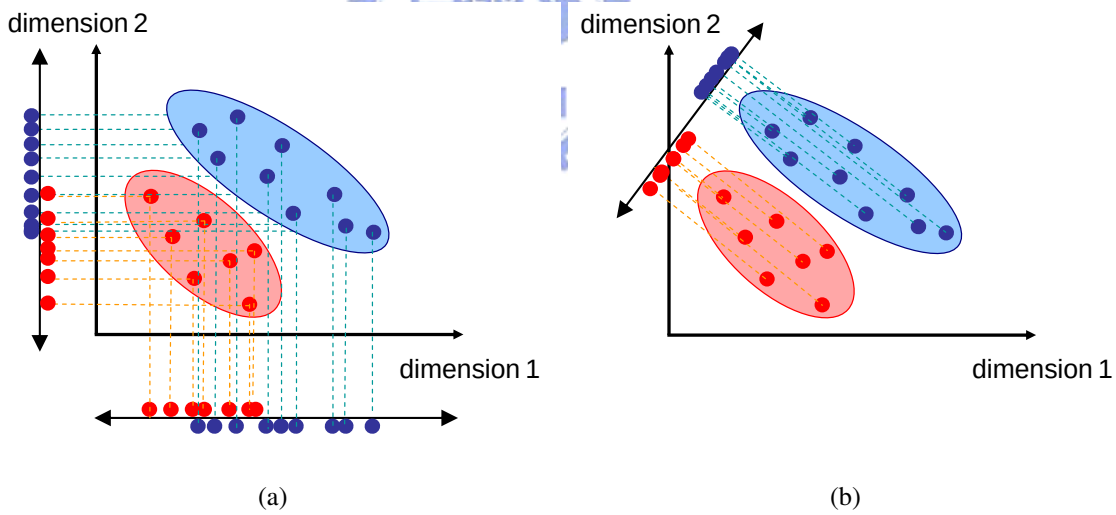


Figure 3.2: **An idea of LDA projection.** The figure shows an example of LDA in two dimensions. The data can not be separate from each other in any of the two axes in (a). However we may project data into another one dimension axis which is the combination of the original axes and the projected data is be more separable in (b).

Let K be the number of classes, N be the number of all samples where N_k is the number

of samples in the kth class. The within-class scatter matrix S_w and the between-class scatter matrix S_b are defined as

$$S_w = \sum_{k=1}^{K} \sum_{x \in Class\ k} (x - \mu_k)(x - \mu_k)^T, \tag{3.1}$$

and

$$S_b = \sum_{k=1}^{K} N_k(\mu_k - \mu_0)(\mu_k - \mu_0)^T, \tag{3.2}$$

where μ_k is the mean vector of the kth class, and μ_0 is the global mean vector defined as

$$\mu_0 = \frac{1}{N} \sum_{k=1}^{K} N_k \mu_k. \tag{3.3}$$

The objective of LDA is to find a projection matrix P which projecting the feature vectors onto a l-dimensional subspace of the original m-dimensional feature space and the projected feature vectors maximizes the Fisher's discriminant ratio. The Fisher's discriminant criterion is

$$J = tr\{{S_w}^{-1} S_b\}. \tag{3.4}$$

Thus the objective function can be written as

$$P_{LDA} = \arg\max_P J = \arg\max_P \frac{P^T S_b P}{P^T S_w P} \tag{3.5}$$

According to the linear algebra, we get

$${S_w}^{-1} S_b P = \lambda P, \tag{3.6}$$

where the column vectors of projection matrix P_{LDA} are the eigenvectors of ${S_w}^{-1} S_b$. In case of K classes, LDA can reduce dimensionality to $1, 2, \ldots, K-1$ dimensions. In the 2-classes case, the vector $S_b P$ is always along the $(\mu_1 - \mu_2)$ direction, and we can then obtain P_{LDA} as ${S_w}^{-1}(\mu_1 - \mu_2)$.

3.1.2 Feature Selection

The performance of classifier depends on the interrelationship between the training sample size and the number of the features. To achieve an acceptable performance, the

number of training samples grows exponentially with the dimensionality of features [35]. This phenomenon is termed as curse of dimensionality, which leads to the peaking phenomenon in classifier design and impacts on the performance of the classifier. In practice, it has been observed that the added features may degrade the performance of a classifier if the number of the training samples is small relative to the number of the features used for clasification [6]. Therefore, for a fixed sample size, it is necessary to reduce the number of features to a sufficient minimum. In this work, we use t-test to select the most discrepant features and apply LDA to reduce the dimensionality of feature set.

Fig. 3.3 is an example of different importances in different dimensions. With LDA, we can project data to a subspace with low dimension and it is obviously that dimension 2 contribute more than dimension 1 to the projection. It means that dimension 2 is probably more important than dimension 1 for classification. Thus we select the features with larger weightings in the projection matrix of LDA in order to get the features favorable for classification.

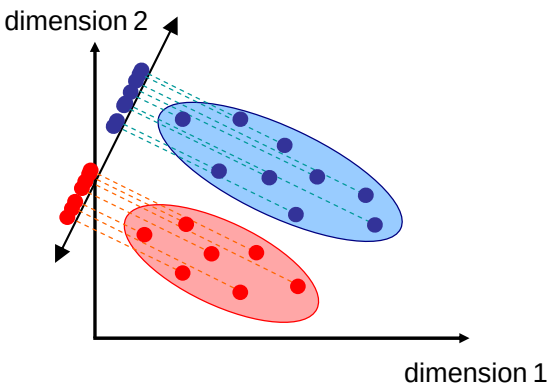


Figure 3.3: **The weighting of LDA projection matrix.**

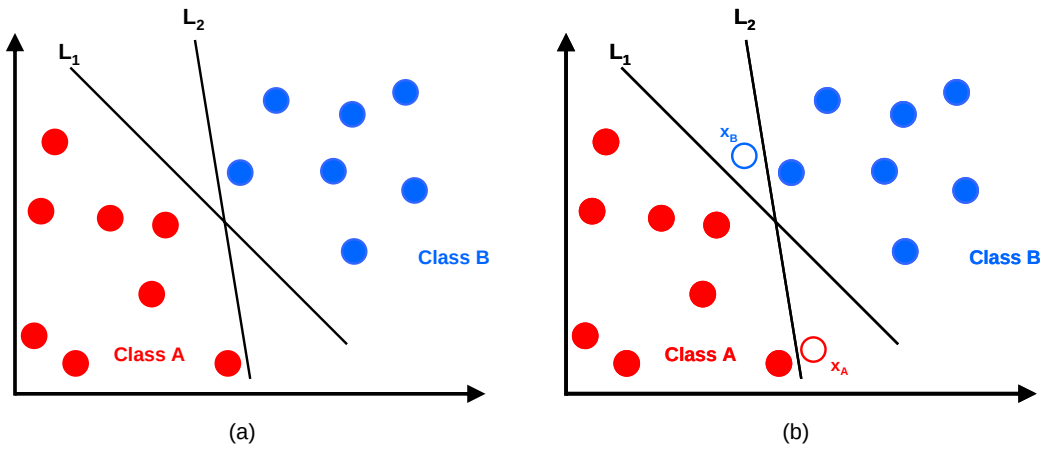


Figure 3.4: **The idea of selecting separating hyperplain in SVM.** The circles represent the samples, and different color represent for different groups. In (a), both L_1 and L_2 can separate class A from class B successfully. In (b), L_1 can separate two classes correctly but L_2 does not, while considering with new sample x_A in class A and x_B in class B.

3.2 Support Vector Machine

Support Vector Machine (SVM) is a powerful method of classification. In recent years, SVM has been applied to diverse problems very successfully, such as face recognition.

The main idea of SVM is to determine a decision hyperplane which not only separates different groups, but also be as far as possible from all samples. Fig. 3.4 depicts this idea. When considering only the training set just like Fig. 3.4(a), both the two hyperplane L_1 and L_2 can separate class A from class B well. However, when considering with the new testing sample x_A and x_B in Fig. 3.4(b), L_2 fail to classify x_A to class A even though x_A is close to one of the samples in class A and so does x_B and class B. The SVM method decides which hyperplane separates classes generally, that is, the hyperplane with largest margin, which is as far as possible from all samples like L_1 in Fig. 3.4.

The margin is defined as twice the absolute value of distance of the closest samples to the separating hyperplane as Fig. 3.5. The samples closest to the separating hyperplane are defined as support vectors and which completely define the optimal hyperplane. Let the separating hyperplane be $w^T x + w_0$, and then the distance between sample x and the

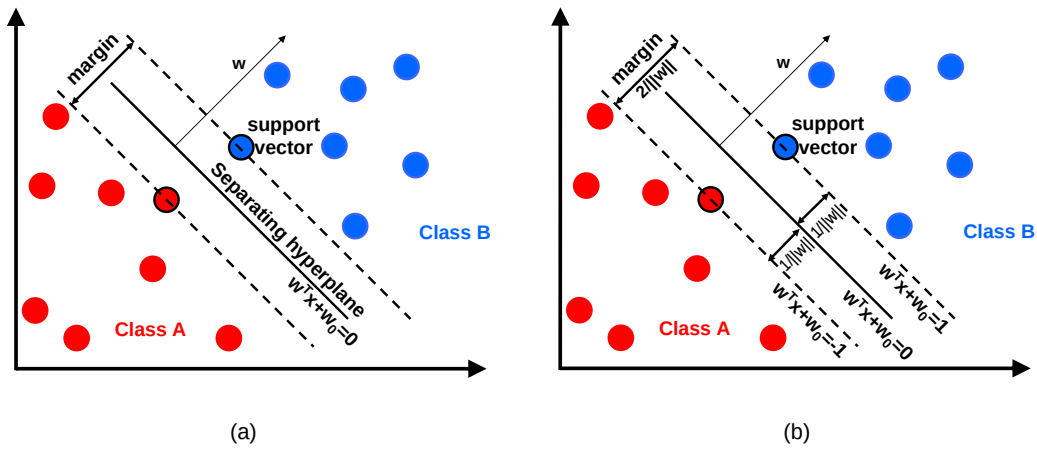


Figure 3.5: **Margin and support vectors of SVM.** The figure shows an example of a linear SVM for two classes. (a)The samples with black edges are the support vectors, which are the closest samples to the separating hyperplane. (b)The distance from support vectors to the largest margin hyperplane is $1/||w||$, and the margin is $2/||w||$.

hyperplane is given by

$$\frac{|w^T x + w_0|}{||w||}. \tag{3.7}$$

The distance is unchanged after scaling w and w_0. Thus to make the largest margin hyperplane is unique, we add the requirement to support vectors:

$$|w^T x + w_0| = 1. \tag{3.8}$$

And then, the distance from support vectors to the largest margin hyperplane is $1/||w||$, and the margin is given by $2/||w||$ as depicted in Fig. 3.5(b).

The objective of SVM is to maximize the margin $2/||w||$ subject to the constraints

$$\begin{cases} w^T x_i + w_0 \geq 1 & \text{if } x_i \text{ is a positive example.} \\ w^T x_i + w_0 \leq -1 & \text{if } x_i \text{ is a negative example.} \end{cases} \tag{3.9}$$

Let

$$\begin{cases} y_i = 1 & \text{if } x_i \text{is a positive example.} \\ y_i = -1 & \text{if } x_i \text{is a negative example.} \end{cases} \tag{3.10}$$

Then can convert the problem to minimize

$$J(w) = \frac{1}{2}||w||^2 \tag{3.11}$$

constrained to

$$y_i(w^T x_i + w_0) \geq 1, \forall i. \tag{3.12}$$

Using Lagrange multipliers λ_i to include the constraints:

$$L = \frac{1}{2}||w||^2 - \sum_{i=1}^{N} \lambda_i [y_i(w^T x_i + w_0) - 1], \tag{3.13}$$

then minimize L relative to w and w_0 by setting the partial derivatives to zero and get

$$w = \sum_{i=1}^{N} \lambda_i y_i x_i \tag{3.14}$$

$$\sum_{i=1}^{N} \lambda_i y_i = 0 \tag{3.15}$$

Substitude Eq. 3.14 an Eq. 3.15 into Eq. 3.13, then the problem is transformed to maximize

$$L = \sum_{i=1}^{N} \lambda_i - \frac{1}{2} \sum_{i=1}^{N} \sum_{j=1}^{N} \lambda_i \lambda_j y_i y_j {x_i}^T x_j. \tag{3.16}$$

Subject to the constraints

$$\sum_{i=1}^{N} \lambda_i y_i = 0 \text{ and } \lambda_i > 0, \forall i. \tag{3.17}$$

By Cover's Theorem, a pattern classification problem cast in a high dimensional space nonlinearly is more likely to be linearly separable than in a low-dimensional space. If we apply a transformation ϕ to all samples so as to lift the original feature spaces to a high dimensional spaces where the discriminability is stronger, then we can find a linear discriminant function for transformed data $\phi(x)$. Substitute ϕ into Eq. 3.16

$$L = \sum_{i=1}^{N} \lambda_i - \frac{1}{2} \sum_{i=1}^{N} \sum_{j=1}^{N} \lambda_i \lambda_j y_i y_j [\phi(x_i)^T \phi(x_j)]. \tag{3.18}$$

We define the kernal function $K(x_i, x_j)$ as

$$K(x_i, x_j) = \phi(x_i)^T \phi(x_j). \tag{3.19}$$

To substitute kernal function into Eq. 3.18, and we obtain

$$L = \sum_{i=1}^{N} \lambda_i - \frac{1}{2} \sum_{i=1}^{N} \sum_{j=1}^{N} \lambda_i \lambda_j y_i y_j K(x_i, x_j). \tag{3.20}$$

Various kernal function choices have been brought up such as Gaussian radial basis kernal. Gaussian radial basis kernal is

$$K(x_i, x_j) = \exp(-\frac{||x - z||^2}{2\sigma^2}). \tag{3.21}$$

where the σ adjusts the smoothness of the boundary. Such kernal based support vector machine is often a nonlinear SVM method.


E S A
1896

Chapter 4

Experiment Results

In this chapter, we show the experiment results in this work. We first introduce the materials used in the experiment, and than show the differences between three groups about every feature. According to the analysis of each feature, a corresponding classifier was designed and trained with real data. Finally we show the classification accuracy of these groups. Further discussions and conclusions will be provided in the next chapter.

4.1 Materials

4.1.1 Subjects

In this work, three study groups are collected, including normal controls (NC), bipolar disorder (BD), and major depressive disorder (MDD). Patients with BD and MDD were selected from the outpatients of psychiatric department of Taipei Veterans General Hospital, and the clinical diagnosis was made by two independent psychiatrists according to DSM-IV criteria. Demographic data of all subjects are summarized in Table 4.1.

The BD group consisted of 26 patients suffering from bipolar disorder, and the MDD group consisted of 22 patients with major depressive disorder. 25 healthy subjects, matched by age and without history of any psychiatric disorders and neurological disorders, were recruited through advertisement from the community. Besides, all of the normal controls underwent Mini International Neuropsychiatric Interview (M.I.N.I.) before the experiments to exclude the possible morbidity of major psychiatric illness. All subjects provided written informed consent to participate in the experiment and study according to the guidelines approved by the Institutional Committees of Medical Ethics and Radiation Safety.

4.1.2 MEG Device

The minute magnetic field generated by electrical activity within the living human brain was measured with a whole-head MEG system at Integrated Brain Research Unit of Taipei Veterans General Hospital (Neuromag Vectorview 306, Neuromag Ltd., Helsinki, Finland.) The MEG system contains 204 gradiometer sensors and 102 magnetometer sensors which simultaneously record at 102 distinct sites covering the entire scalp. The system has the

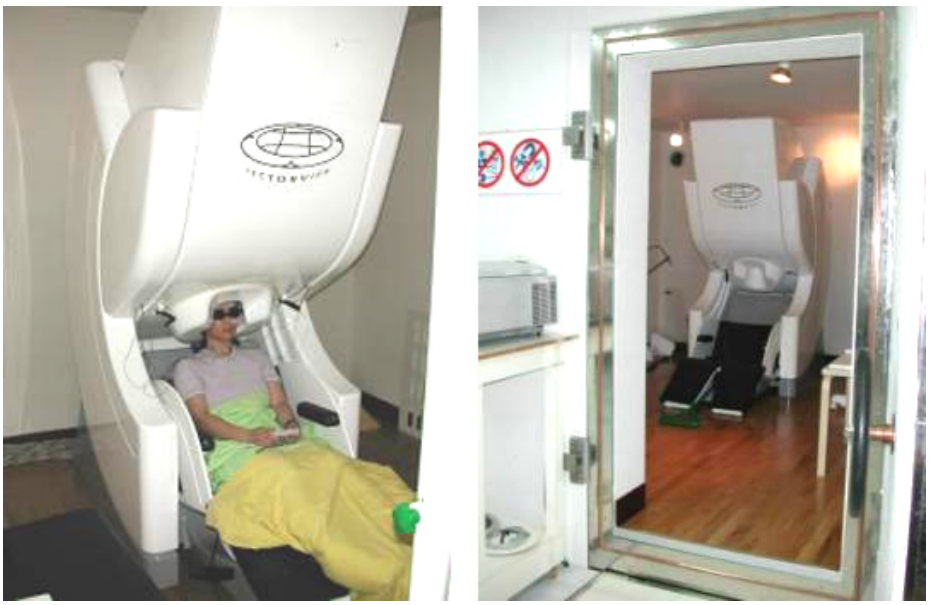


Figure 4.1: **MEG device.** The MEG device in Integrated Brain Research Unit of Taipei Veterans General Hospital.

capabilities of 24 bits analog to digital conversion and up-to-8 kHz sampling rate which is sufficient to probe the fast dynamic changes inside human brains. Figure 4.1 shows the MEG device.

Table 4.1: **Demographic data of subjects.** The table shows the demographic data of the three groups: normal controls (NC), patients with bipolar disorder (BD), and patients with major depressive disorder (MDD).

Variable	NC	BD	MDD
n	25	26	22
Gender, n(%), male	9 (36.00)	10 (38.46)	8 (36.36)
Age, mean (SD), years	36.04 (11.19)	34.62 (10.40)	34.18 (9.17)
Handedness, n(%), right	25 (100)	26 (100)	21 (95.45)

4.1.3 MEG Data Collection

Data recording was performed in a magnetically shielded room (Euroshield, Eura, Finland) at Integrated Brain Research Unit of Taipei Veterans General Hospital. The magnetic fields were recorded while subjects were seated comfortably and in a resting state, relax, awake, and with eyes closed for two to three minutes. The signals were recorded at a sampling rate of 1001.6 Hz and was filtered with a bandwidth of 0.03-330 Hz.

4.2 Data Preprocessing

The brain signal is relative weak as compared with environmental interference noises. To extract the weak brain signals, experiment should be in a magnetically shielded room. Besides, in order to enhance signal-to-noise ratio (SNR), some preprocessing procedure is necessary before the further processing.

The preprocessing steps we used for MEG recordings are as follows and shown in Figure 4.2. First, we eliminate bad channels which record abnormally. Second, while conducting experiment, eye movement and eye blinking may contaminate the MEG signals. To avoid the noise, we found out the abnormal scale of Electro-OculoGram (EOG) manually. Only the segments without eye blinking and eye movement were accepted for further analysis. Third, signal space projection (SSP) was applied to eliminate the ambient noise. Furthermore, because the MEG recording may drift along with time due to the device, a baseline correction was applied in each channel. The baseline is estimated by the mean of the whole segment. Besides eye movement and eye blinking, there are still some external artifacts like heartbeat, breath, and electromyographic(EMG). Therefore, finally we use bandpass filter of 2-50 Hz to minimize those unavoidable artifacts. Only the signals recorded from gradiometer sensors were used in this study, because gradiometer sensors detect less ambient noise and give the largest signal right above the source [28].

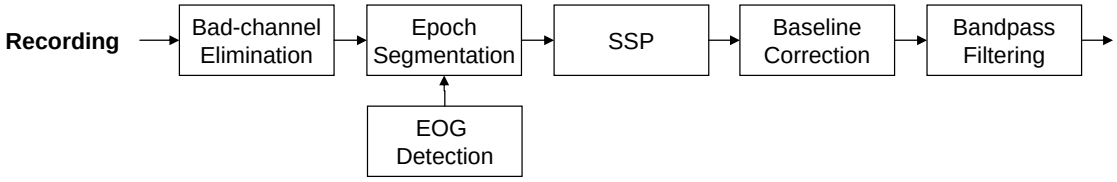


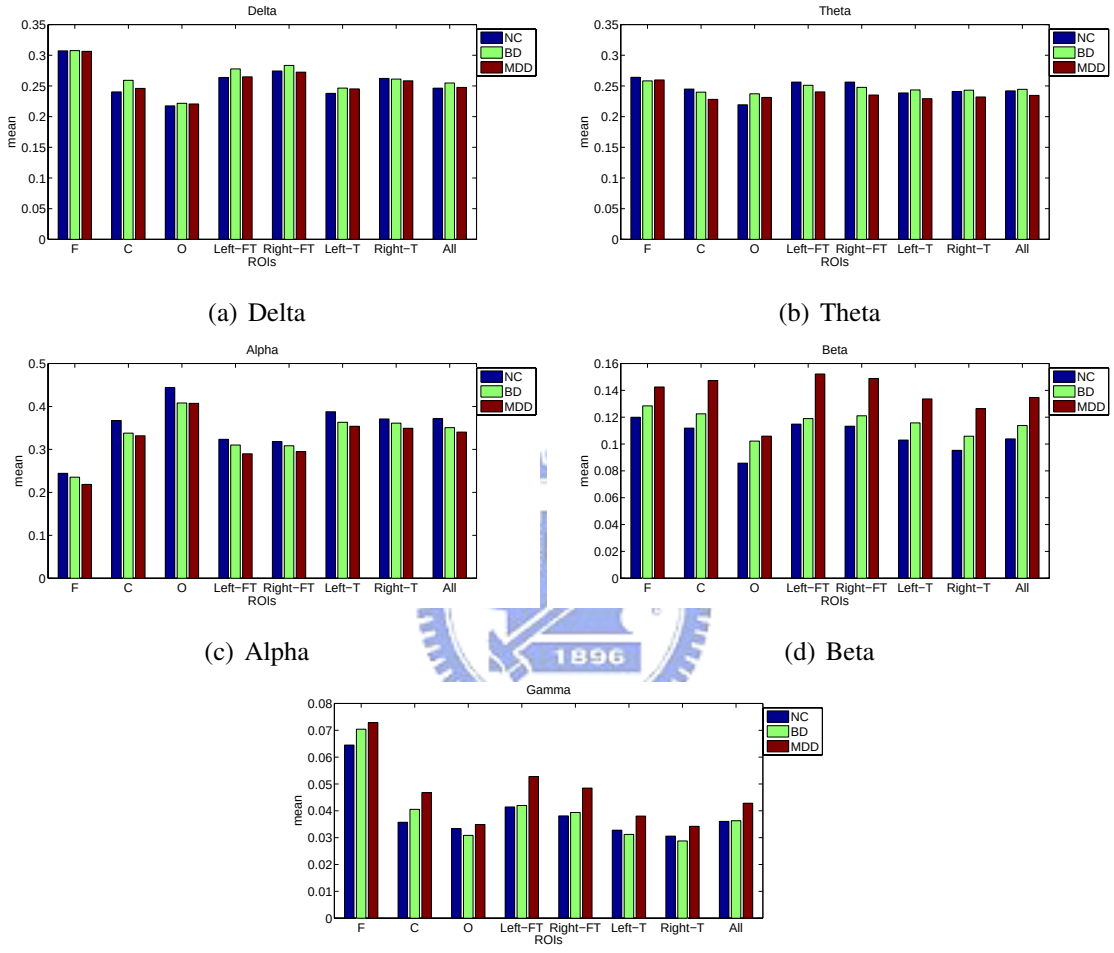
Figure 4.2: **Preprocessing procedures for MEG recordings.** In order to enhance SNR, preprocessing for the recordings is necessary before the further processing. First we eliminate the bad channels and choose the segmentations without eye movements for further analysis. Second, we apply signal space projection (SSP) to eliminate the unbalanced noise effect on different sensors. Then baseline correction is applied to eliminate the drift of recordings. Finally, a 2-50 Hz bandpass filter is used to eliminate other artifacts such as heartbeat and breath.

4.3 Features of Power Spectrum

To characterize the spectral content of each MEG recording, we used the Fourier transform and then extracted the features. Initially, we computed the power spectral density (PSD) for each epoch and then averaged the PSD for all epochs. To compare with different area of brain, we averaged the PSD of different channels based on the ROI showed in section 2.1.

4.3.1 band power

Fig. 4.3 shows the relative band powers of the five frequency bands, and Table 4.2, Table 4.3 and Table 4.4 show the p-value of two groups comparisons. Compared with the three groups, the delta band power of the patients with bipolar disorder are slightly stronger than others and so do the alpha band power of normal controls. However, these differences do not reach the significant level (p-value < 0.05). On the other hand, the beta and gamma band powers of patients with major depressive disorder are stronger significantly, especially than the normal controls.



(a) Delta

(b) Theta

(c) Alpha

(d) Beta

(e) Gamma

Figure 4.3: **Relative band power.** The bar chart shows the relative band power in the NC, BD and MDD groups.

Table 4.2: **The p-values of band power between NC and BD.** The differences between normal controls (NC) and patients with bipolar disorder (BD) are not significant in any frequency bands.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
Delta	0.979	0.417	0.853	0.566	0.675	0.718	0.961	0.696
Theta	0.452	0.754	0.367	0.734	0.561	0.783	0.898	0.874
Alpha	0.609	0.435	0.383	0.671	0.761	0.495	0.791	0.537
Beta	0.131	0.379	0.165	0.733	0.512	0.341	0.356	0.373
Gamma	0.126	0.239	0.549	0.883	0.765	0.663	0.566	0.942

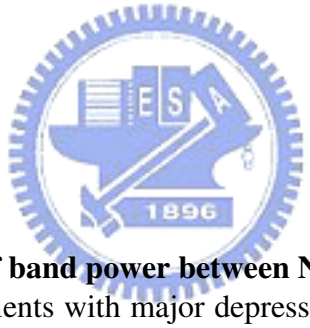
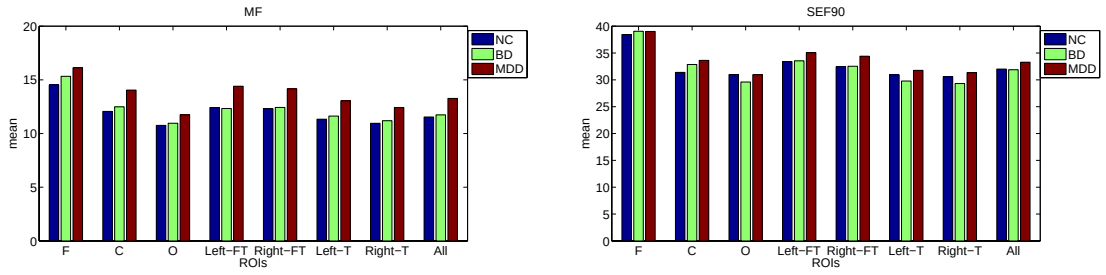


Table 4.3: **The p-values of band power between NC and MDD.** Compared with NC, the relative band power of patients with major depressive disorder (MDD) are quite different in beta and gamma band, especially in the beta band power of frontal, gamma band power of central and frontotemporal of brain.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
Delta	0.954	0.778	0.888	0.959	0.927	0.723	0.850	0.952
Theta	0.617	0.290	0.530	0.294	0.178	0.539	0.540	0.620
Alpha	0.127	0.334	0.362	0.233	0.452	0.318	0.519	0.321
Beta	**0.048**	0.056	0.065	0.077	0.063	0.069	0.056	0.059
Gamma	0.061	**0.016**	0.731	**0.023**	**0.023**	0.188	0.271	0.077

Table 4.4: **The p-values of band power between BD and MDD.** Compared BD with MDD, the significant difference of relative band power are in the gamma band of frontotemporal areas.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
Delta	0.915	0.564	0.963	0.585	0.575	0.956	0.903	0.730
Theta	0.830	0.386	0.772	0.466	0.331	0.375	0.464	0.491
Alpha	0.187	0.865	0.984	0.480	0.630	0.787	0.728	0.745
Beta	0.215	0.195	0.804	0.131	0.154	0.355	0.258	0.240
Gamma	0.544	0.178	0.370	**0.032**	0.061	0.113	0.130	0.096



(a) Mean Frequency

(b) 90% spectral edge frequency

Figure 4.4: **MF and SEF90.** The bar chart shows the MF and SEF90 in all ROIs whithin the three groups. MF of patients with MDD apparently higher than that of NC and BD in all ROIs. But MF of BD patients and NC are quite similar. Compared MDD with NC, patients with MDD are still have a little higher SEF90 in each ROIs. But in the case of BD and MDD, SEF90 of BD are higher in frontal, central, and frontotemporal, but lower in others.

4.3.2 MF and SEF90

Fig. 4.4 shows the bar chart of the mean frequency (MF) and the 90% spectral edge frequency (SEF90), and Table 4.5 and Table 4.3.2 show the detail of the p-value of the difference between any two groups. Roughly speaking, the MF and SEF90 of MDD are higher than NC and BD groups.

The MF differences between NC and BD are not clear, but are significantly different between NC and MDD. Except for the occipital of brain, each ROI reaches significant level (p-value < 0.05). Compare the MF of BD with MDD, the frontotemporal has clearer differences, but only the left frontotemporal reaches significant level. On the contrary, the features of SEF90 do not show any clearer difference between any two groups.

Table 4.5: **The p-values of mean frequency (MF).** The MF differences between NC and BD are unapparent, but significant between NC and MDD. Except for occipital, each ROI reaches significant level (p-value less than 0.05). Compare the MF of BD with MDD, the frontotemporal has clearer differences, but only the left frontotemporal reaches significant level.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
NC vs. BD	0.158	0.523	0.690	0.896	0.878	0.643	0.878	0.739
NC vs. MDD	**0.032**	**0.018**	0.549	**0.028**	**0.027**	**0.020**	**0.027**	**0.016**
BD vs. MDD	0.249	0.084	0.233	**0.034**	0.051	0.106	0.106	0.062

Table 4.6: **The p-values of the 90% spectral edge frequency (SEF90).** The significant differences of SEF90 are not found no matter what ROI is.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
NC vs. BD	0.261	0.233	0.356	0.882	0.938	0.364	0.341	0.912
NC vs. MDD	0.337	0.079	0.982	0.119	0.104	0.542	0.554	0.273
BD vs. MDD	0.981	0.501	0.377	0.132	0.101	0.135	0.123	0.195

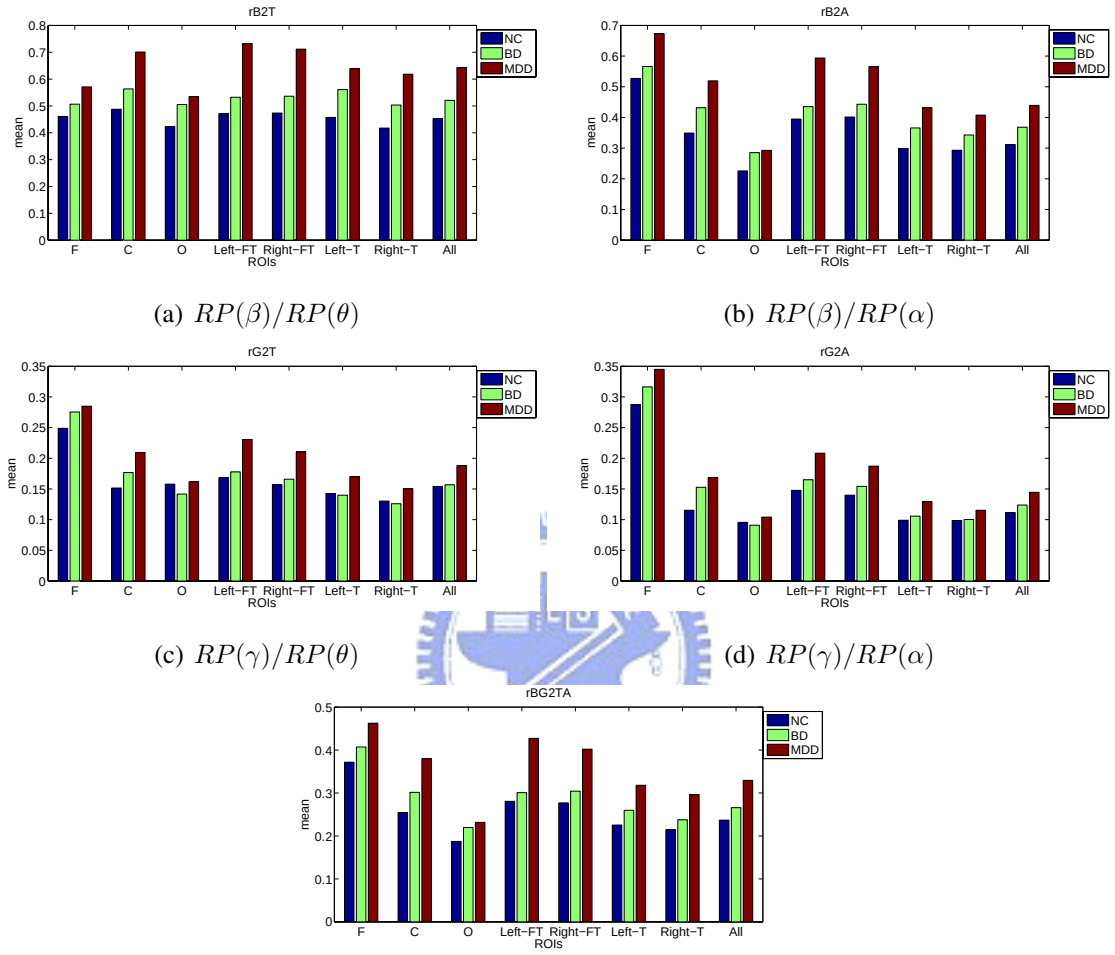
4.3.3 Spectral Ratio Measures

Fig. 4.5 illustrates the means of the five spectral ratios described in section 2.2.3. In the MDD case, all means of these spectral ratios are larger than those of BD patients and NC group no matter what ROI is. The mean spectral ratios of patients with BD are almost larger than those of NC but smaller than those of MDD patients, besides some areas. The ratios of gamma to theta band in occipital and temporal are the smallest in the three groups, and so does the ratio of gamma band to alpha band.

Table 4.3.3, Table 4.3.3 and Table 4.3.3 show the details of the p-values which show the degree of discrepancy between NC and BD, NC and MDD, and BD and MDD respectively. There are no obvious differences between NC and BD groups, but not between NC and MDD groups. The most different feature are the ratio of $(RP(\beta) + RP(\gamma))/(RP(\theta) + RP(\alpha))$ and the ROI of central of the brain. Ratio of $(RP(\beta)+RP(\gamma))/(RP(\theta)+RP(\alpha))$ in most ROIs are significant different between NC and MDD, besides occipital. Moreover, the ratio of gamma to theta band $(RP(\gamma)/RP(\theta))$ reaches the strong significant level of p < 0.01 in central and right temporal of brain. Besides, in the case of comparison of BD and MDD patients, only the ratio of gamma to theta band $(RP(\gamma)/RP(\theta))$ reach the significant level of p < 0.05.

Table 4.7: **The p-values of spectral ratios between NC and BD.** In the NC and BD case, the spectral ratios do not differentiate BD from NC in any ROIs.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
$\frac{RP(\beta)+RP(\gamma)}{RP(\theta)+RP(\alpha)}$	0.116	0.190	0.275	0.543	0.439	0.316	0.428	0.333
$\frac{RP(\beta)}{RP(\theta)}$	0.160	0.365	0.322	0.461	0.441	0.297	0.303	0.378
$\frac{RP(\beta)}{RP(\alpha)}$	0.307	0.168	0.163	0.458	0.461	0.203	0.320	0.227
$\frac{RP(\gamma)}{RP(\theta)}$	0.128	0.200	0.419	0.612	0.650	0.880	0.761	0.875
$\frac{RP(\gamma)}{RP(\alpha)}$	0.300	0.119	0.810	0.497	0.574	0.717	0.931	0.494



(a) $RP(\beta)/RP(\theta)$ (b) $RP(\beta)/RP(\alpha)$

(c) $RP(\gamma)/RP(\theta)$ (d) $RP(\gamma)/RP(\alpha)$

(e) $(RP(\beta)+RP(\gamma))/(RP(\theta)+RP(\alpha))$

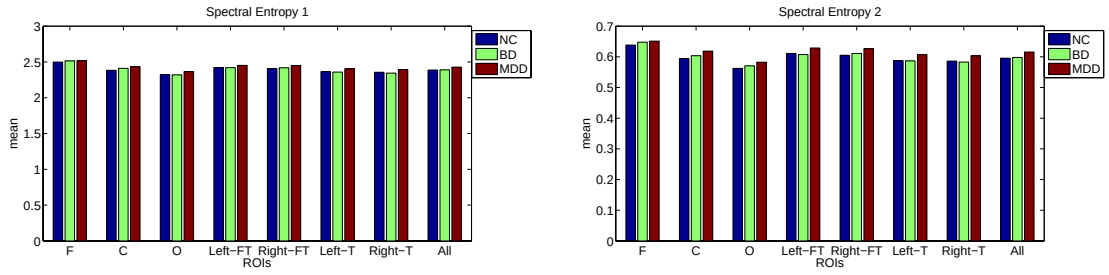
Figure 4.5: **Spectral Ratios.** The bar charts show five kinds of spectral ratios. For all spectral ratios, MDD patients have larger ratio means than NC and BD patients in all ROIs. All of the ratio means of BD patients are larger than those of NC and smaller than those of MDD, except for ratios of gamma to theta band in occipital and temporal areas and ratio of gamma to alpha band in occipital.

Table 4.8: **The p-values of spectral ratios between NC and MDD.** The differences of NC and MDD in spectral ratios are obvious. In all of the areas of brain, except for occipital area, the spectral ratios of beta and gamma band to theta and alpha band ($RP(\beta) + RP(\gamma)/RP(\theta) + RP(\alpha)$) reach the significant level of p less than 0.05. And then, four of the five ratios in central of brain also reach the significatn level. Moreover, the ratio of gamma to theta band ($RP(\gamma)/RP(\theta)$) reach the significant level of p less than 0.01 in central and right temporal of brain. Besides, the spectral ratio of beta to alpha band ($RP(\beta)/RP(\alpha)$) and the ratio of gamma to alpha band ($RP(\gamma)/RP(\alpha)$) also get well distinctions between NC and MDD groups.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
$\frac{RP(\beta)+RP(\gamma)}{RP(\theta)+RP(\alpha)}$	**0.018**	**0.020**	0.101	**0.028**	**0.024**	**0.030**	**0.037**	**0.027**
$\frac{RP(\beta)}{RP(\theta)}$	0.071	0.060	0.250	0.077	0.072	0.105	0.106	0.096
$\frac{RP(\beta)}{RP(\alpha)}$	**0.031**	**0.040**	0.111	0.056	0.061	**0.044**	0.066	**0.046**
$\frac{RP(\gamma)}{RP(\theta)}$	0.077	**0.005**	0.856	**0.012**	**0.009**	0.129	0.162	0.057
$\frac{RP(\gamma)}{RP(\alpha)}$	0.070	**0.043**	0.705	0.063	0.099	0.181	0.389	0.135

Table 4.9: **The p-values of spectral ratios between BD and MDD.** To differentiate BD from MDD using spectral ratios, the frontotemporal areas are more discriminable than other areas of brain, especially in the ratio of gamma to theta band ($RP(\gamma)/RP(\theta)$) the differences reach significant level.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
$\frac{RP(\beta)+RP(\gamma)}{RP(\theta)+RP(\alpha)}$	0.126	0.163	0.736	0.064	0.086	0.237	0.181	0.163
$\frac{RP(\beta)}{RP(\theta)}$	0.305	0.282	0.806	0.211	0.213	0.583	0.419	0.345
$\frac{RP(\beta)}{RP(\alpha)}$	0.095	0.333	0.883	0.139	0.178	0.376	0.356	0.310
$\frac{RP(\gamma)}{RP(\theta)}$	0.619	0.139	0.357	**0.043**	**0.041**	0.151	0.140	0.103
$\frac{RP(\gamma)}{RP(\alpha)}$	0.352	0.605	0.526	0.221	0.310	0.348	0.476	0.388



(a) Spectral Entropy 1.

(b) Spectral Entropy 2.

Figure 4.6: **Spectral Entropies.** The barchart illustrates the mean of spectral entropies for the three groups.

4.3.4 Spectral Entropy

Fig. 4.6 illustrates the means of the spectral entropies described in section 2.2.4. It shows that the SE1 of MDD patients are larger than NC and BD patients, so do SE2 in all ROIS.

Table 4.10 and Table 4.11 show the p-value of t-test between any tow of the three groups. In the case of SE1, although there is no features reaching significant level, the difference between NC and MDD patients are a little significant than NC and MDD. In the case of SE2, the NC and BD groups do not show any clear difference, but p-values of SE2 between NC and MDD groups reach the significant level in frontal and frontotemporal. Besides, in both SE1 and SE2 cases, the differences between BD and MDD patients are a little obvious in frontotemporal and temporal, especially SE2 in left frontotemporal.

Table 4.10: **The p-values of spectral antropy (SE1).** In the case of NC and MDD groups, the differences are more obvious than in the case of NC and BD groups, but the differences do not reach significant level. In the BD and MDD case, there are distinctions in frontotemporal and temporal areas, but also can not reach the significant level.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
NC vs. BD	0.082	0.376	0.934	0.958	0.651	0.862	0.702	0.918
NC vs. MDD	0.052	0.130	0.276	0.146	0.083	0.206	0.234	0.156
BD vs. MDD	0.663	0.364	0.183	0.101	0.109	0.108	0.073	0.109

Table 4.11: **The p-values of spectral antropy 2 (SE2).** The p-values between NC and BD groups do not show any differences. In the NC and MDD cases, differences are in the frontal and frontotemporal, especially in frontal and right frontotemporal. In the BD and MDD case, only SE2 in left frontotemporal can reach significant level.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
NC vs. BD	0.068	0.517	0.625	0.735	0.592	0.980	0.805	0.853
NC vs. MDD	**0.012**	0.125	0.235	0.059	**0.042**	0.124	0.171	0.121
BD vs. MDD	0.394	0.232	0.441	**0.022**	0.075	0.090	0.068	0.115

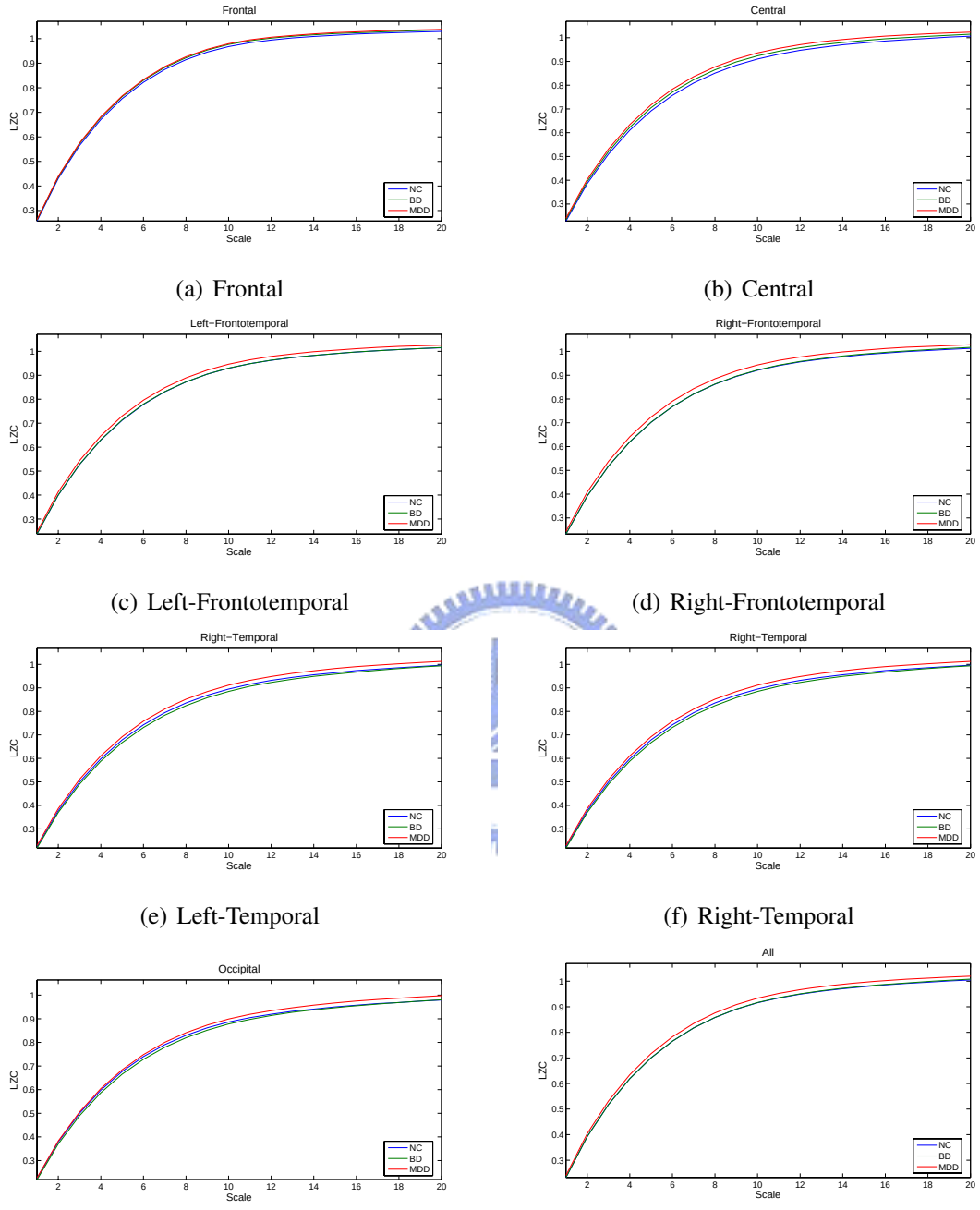
4.4 Temporal Complexity

To characterize the temporal signal content of MEG recordings, we calculate LZC and sample entropy (SampEn). The features were calculate for each channel and then we average the features within the same ROIs. To get a stable result, then we average them for all epochs. The method of multi-scale entropy described in sec 2.3.3 is applied to not only the sample entropy but LZC method, and the scale range of 1 to 20 is taken into account.

4.4.1 LZC

Fig. 4.7 shows the multi-scale LZ complexity of all ROIs. The values of LZC of MDD patients are larger than NC and BD patients in all scales and all ROIs. In the frontal, the three group are quite similar, especially BD and MDD. In frontotemporal, temporal, occipital, and all brain, LZC values of MDD patients are larger than NC and BD patients, and the NC and BD patients are quite similar, especially in frontotemporal. Besides, LZC values in central are separate between the three groups.

Table 4.4.1 to Table 4.4.1 show details of the p-values of t-test between two groups. LZ complexities of BD patients do not different from NC obviously, but different from the MDD patients. The differences between BD patients and MDD patients are significant in frontotemporal and temporal, especially in right hemesphere. The differences between MDD patients and NC are in the frontal, central and frontotemporal.



(a) Frontal (b) Central

(c) Left-Frontotemporal (d) Right-Frontotemporal

(e) Left-Temporal (f) Right-Temporal

(g) Occipital (h) All

Figure 4.7: **Multi-scale LZC.** The illustration shows the mean values of LZ complexity and corresponding to scale factors from one to twenty.

Table 4.12: **The p-values of Lempel-Ziv complexity (LZC) between NC and BD in multiple scales.** In the NC and BD case, the differences in frontal and central areas are slightly clearer than others, but there is no feature which reaches significant level.

Scale	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
1	0.236	0.246	0.376	0.909	0.996	0.460	0.373	0.975
2	0.216	0.264	0.414	0.913	0.984	0.476	0.371	0.980
3	0.205	0.274	0.421	0.917	0.980	0.495	0.391	0.978
4	0.208	0.279	0.448	0.942	0.970	0.507	0.405	0.989
5	0.208	0.281	0.470	0.889	0.964	0.540	0.390	0.996
6	0.216	0.298	0.493	0.905	0.994	0.512	0.411	0.992
7	0.214	0.298	0.521	0.946	0.979	0.516	0.440	0.999
8	0.229	0.292	0.551	0.959	0.968	0.609	0.421	0.981
9	0.195	0.302	0.561	0.991	0.933	0.619	0.465	0.970
10	0.152	0.310	0.618	0.960	0.921	0.669	0.478	0.931
11	0.140	0.322	0.656	0.996	0.883	0.627	0.534	0.922
12	0.139	0.365	0.739	0.972	0.872	0.686	0.511	0.905
13	0.171	0.355	0.780	0.971	0.839	0.723	0.548	0.882
14	0.156	0.420	0.831	0.995	0.760	0.856	0.608	0.858
15	0.118	0.388	0.841	0.996	0.801	0.918	0.623	0.836
16	0.180	0.394	0.864	0.957	0.732	0.917	0.602	0.831
17	0.179	0.411	0.894	0.967	0.741	0.917	0.736	0.824
18	0.166	0.412	0.988	0.994	0.656	0.970	0.732	0.759
19	0.153	0.445	0.999	0.988	0.674	0.973	0.827	0.767
20	0.061	0.404	0.937	0.894	0.595	0.933	0.810	0.689

Table 4.13: **The p-values of Lempel-Ziv complexity (LZC) between NC and MDD in multiple scales.** The differences in frontal, central and frontotemporal areas reach significant level.

Scale	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
1	0.072	**0.030**	0.697	**0.048**	**0.027**	0.231	0.246	0.083
2	0.071	**0.038**	0.686	0.061	**0.034**	0.245	0.268	0.096
3	0.078	**0.044**	0.687	0.073	**0.043**	0.257	0.281	0.110
4	0.087	**0.048**	0.643	0.086	**0.047**	0.270	0.295	0.116
5	0.101	0.051	0.649	0.092	0.055	0.255	0.292	0.124
6	0.101	0.058	0.610	0.113	0.061	0.251	0.260	0.128
7	0.082	0.057	0.554	0.118	0.063	0.243	0.262	0.122
8	0.078	0.061	0.517	0.120	0.065	0.234	0.252	0.121
9	0.082	0.064	0.500	0.126	0.064	0.205	0.269	0.122
10	0.066	0.065	0.447	0.117	0.064	0.201	0.219	0.112
11	**0.050**	0.067	0.383	0.112	0.058	0.200	0.230	0.103
12	**0.041**	0.074	0.342	0.100	0.064	0.165	0.207	0.098
13	0.057	0.062	0.329	0.100	**0.048**	0.161	0.177	0.090
14	**0.031**	0.080	0.253	0.079	**0.046**	0.129	0.177	0.080
15	**0.025**	0.074	0.241	0.090	0.061	0.111	0.133	0.076
16	**0.048**	0.080	0.198	0.079	**0.040**	0.096	0.159	0.071
17	**0.032**	0.080	0.208	0.076	**0.041**	0.096	0.137	0.069
18	**0.028**	0.083	0.159	0.077	**0.048**	0.100	0.147	0.064
19	**0.032**	0.103	0.165	0.097	0.056	0.136	0.133	0.076
20	**0.024**	0.108	0.143	0.123	0.054	0.103	0.127	0.071

Table 4.14: **The p-values of Lempel-Ziv complexity (LZC) between BD and MDD in multiple scales.** The most different areas between BD and MDD are frontotemporal and temporal, and reach significant level in right hemisphere in most scales.

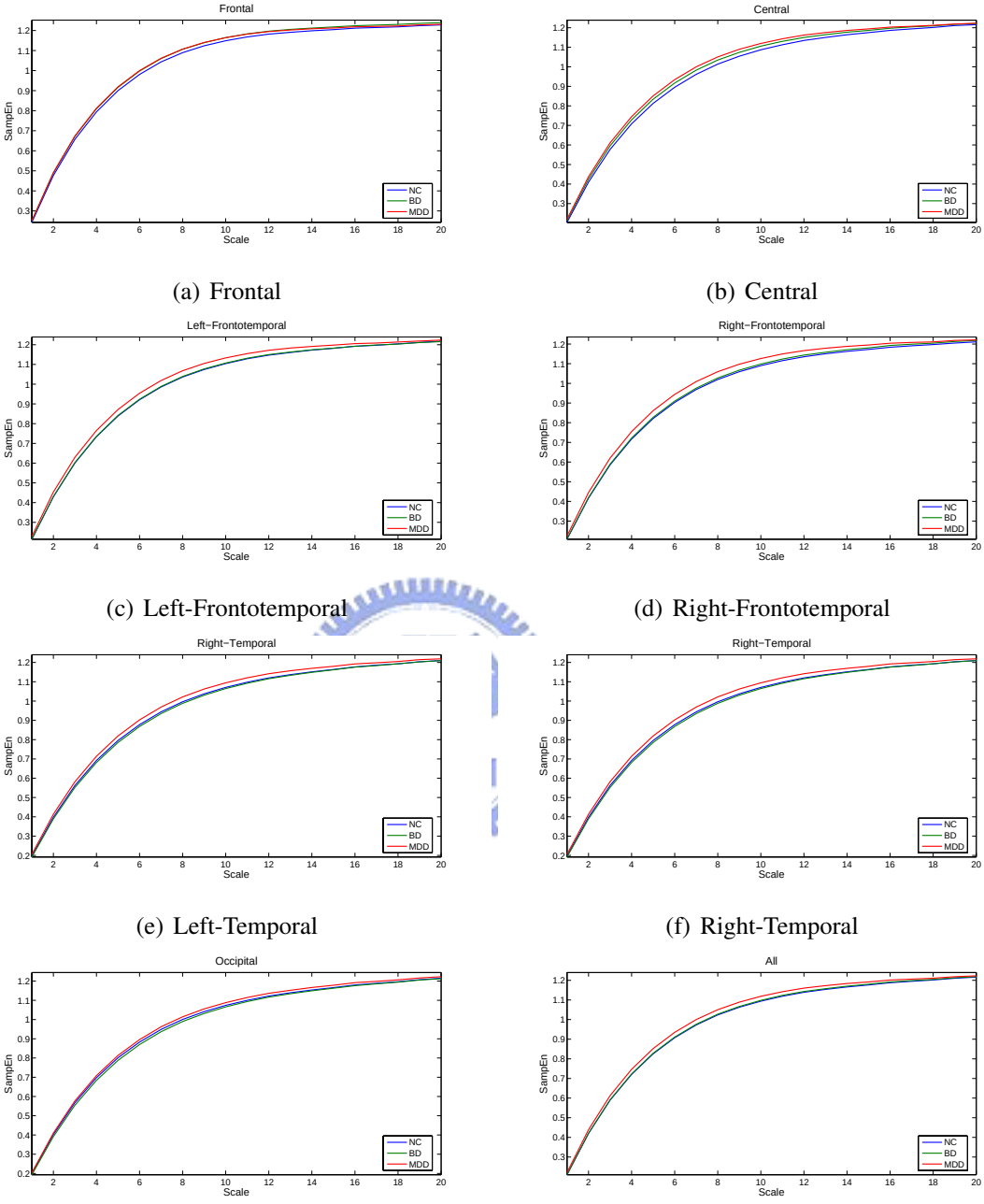
Scale	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
1	0.416	0.205	0.197	**0.050**	**0.016**	0.063	**0.040**	0.059
2	0.454	0.223	0.212	0.062	**0.019**	0.070	**0.042**	0.067
3	0.511	0.241	0.214	0.072	**0.022**	0.075	**0.047**	0.075
4	0.533	0.246	0.208	0.081	**0.027**	0.082	**0.050**	0.081
5	0.598	0.258	0.222	0.099	**0.032**	0.081	**0.046**	0.091
6	0.578	0.268	0.215	0.115	**0.032**	0.071	**0.041**	0.090
7	0.488	0.256	0.203	0.113	**0.033**	0.068	**0.046**	0.087
8	0.434	0.278	0.196	0.103	**0.035**	0.085	**0.039**	0.088
9	0.524	0.275	0.189	0.104	**0.034**	0.075	**0.048**	0.091
10	0.539	0.270	0.190	0.103	**0.035**	0.079	**0.039**	0.091
11	0.470	0.263	0.174	0.089	**0.034**	0.072	**0.048**	0.087
12	0.427	0.239	0.185	0.083	**0.039**	0.064	**0.039**	0.086
13	0.443	0.212	0.194	0.089	**0.030**	0.068	**0.034**	0.084
14	0.324	0.210	0.171	0.059	**0.034**	0.073	**0.040**	0.078
15	0.302	0.211	0.162	0.071	**0.038**	0.076	**0.029**	0.077
16	0.397	0.222	0.141	0.075	**0.031**	0.059	**0.032**	0.075
17	0.244	0.211	0.157	0.055	**0.031**	0.057	**0.038**	0.073
18	0.292	0.208	0.156	0.067	**0.048**	0.084	**0.042**	0.084
19	0.387	0.236	0.164	0.085	0.059	0.097	0.054	0.097
20	0.650	0.281	0.170	0.142	0.080	0.087	**0.047**	0.119

4.4.2 SampEn

The values of the parameters used to calculate sample entropy (SampEn) are m=1, and r=0.25 times of the standard deviation (SD) of the time series. While the scale factor is different, the r will also different due to the change of SD of the time series.

Fig. 4.8 shows the mean multi-scale entropy of sample entropies for all ROIs. The values of SampEn are larger than other groups in most ROIs and scales. SampEn of the three groups are similar in occipital, but are separate in central and. In left-frontotemporal, frontotemporal and the whole brain, the sampEn of NC and BD patients are quite similar, but sampEn of MDD patients are larger than NC and BD patients.

Table 4.4.2, Table 4.4.2, and Table 4.4.2 show the detail of the p-values of t-test between NC and BD patients, NC and MDD patients, and BD and MDD patients respectively. To compare with NC, sample entropies of BD patients are different in frontal, and the differences reach the significant level with larger scales. The sampEn differences between NC and MDD patients are mainly in frontotal, central, and frontotemporal. Those differences reach the significant level ($p < 0.05$) in central and frontotemporal with smaller scales, and some of them even reach the strong significant level of $p < 0.01$. The sampEn differences between BD and MDD patients are in the frontotemporal and temporal, and those sampEn with smaller scales reach the significant level.



(a) Frontal (b) Central

(c) Left-Frontotemporal (d) Right-Frontotemporal

(e) Left-Temporal (f) Right-Temporal

(g) Occipital (h) All

Figure 4.8: **Multi-scale entorpy (SampEn).** The illustration shows the mean values of sample entropies and corresponding to scale factors from one to twenty.

Table 4.15: **The p-values of sample entropy (SampEn) between NC and BD in multiple scales.** Sample entropy differences between NC and BD in frontal area reach significant level in larger scales.

Scale	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
1	0.130	0.208	0.409	0.891	0.842	0.346	0.444	0.916
2	0.114	0.199	0.426	0.887	0.812	0.351	0.469	0.905
3	0.102	0.195	0.449	0.879	0.779	0.366	0.494	0.884
4	0.096	0.191	0.469	0.874	0.740	0.376	0.523	0.863
5	0.086	0.190	0.486	0.854	0.705	0.384	0.539	0.842
6	0.076	0.191	0.517	0.862	0.676	0.395	0.585	0.819
7	0.068	0.193	0.535	0.843	0.656	0.399	0.594	0.806
8	0.054	0.192	0.569	0.822	0.625	0.411	0.628	0.776
9	0.057	0.205	0.604	0.806	0.585	0.400	0.657	0.765
10	**0.040**	0.207	0.640	0.822	0.569	0.433	0.693	0.740
11	**0.032**	0.209	0.700	0.818	0.530	0.445	0.708	0.712
12	**0.028**	0.251	0.718	0.800	0.499	0.417	0.762	0.714
13	**0.021**	0.275	0.735	0.847	0.521	0.439	0.805	0.713
14	**0.023**	0.282	0.772	0.887	0.448	0.452	0.841	0.700
15	**0.019**	0.326	0.810	0.935	0.456	0.464	0.876	0.704
16	**0.034**	0.345	0.795	0.994	0.373	0.448	0.936	0.715
17	**0.026**	0.365	0.829	0.872	0.414	0.413	0.830	0.708
18	**0.023**	0.455	0.864	0.902	0.446	0.384	0.997	0.751
19	**0.034**	0.540	0.874	0.943	0.380	0.382	0.934	0.766
20	**0.034**	0.558	0.872	0.790	0.393	0.330	0.959	0.802

Table 4.16: **The p-values of sample entropy (SampEn) between NC and MDD in multiple scales.** The differences of sample entropy between NC and MDD are apparent in frontal, central, and frontotemporal areas. Some features in these areas with smaller scales reach the significant level of p-value smaller than 0.05, and reach the significant level of p-value smaller than 0.01 in right frontotemporal in scale of 6 to 11.

Scale	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
1	0.063	**0.026**	0.616	**0.028**	**0.013**	0.259	0.197	0.056
2	0.065	**0.028**	0.604	**0.030**	**0.012**	0.265	0.192	0.059
3	0.065	**0.031**	0.583	**0.031**	**0.012**	0.271	0.184	0.061
4	0.065	**0.032**	0.564	**0.031**	**0.011**	0.274	0.171	0.061
5	0.062	**0.033**	0.543	**0.031**	**0.011**	0.267	0.164	0.059
6	0.058	**0.034**	0.516	**0.031**	**0.010**	0.262	0.145	0.057
7	0.061	**0.035**	0.483	**0.029**	**0.010**	0.262	0.139	0.056
8	0.057	**0.037**	0.472	**0.028**	**0.009**	0.260	0.125	0.055
9	0.060	**0.038**	0.422	**0.027**	**0.009**	0.273	0.114	0.053
10	0.058	**0.043**	0.406	**0.029**	**0.009**	0.243	0.114	0.054
11	0.064	**0.045**	0.354	**0.036**	**0.009**	0.263	0.111	0.054
12	0.076	0.055	0.343	**0.032**	**0.011**	0.291	0.104	0.058
13	0.087	0.065	0.346	**0.036**	**0.012**	0.298	0.106	0.063
14	0.112	0.079	0.302	0.061	**0.015**	0.361	0.119	0.074
15	0.163	0.106	0.305	0.074	**0.020**	0.360	0.142	0.089
16	0.260	0.140	0.292	0.110	**0.023**	0.465	0.136	0.106
17	0.288	0.216	0.343	0.122	**0.044**	0.530	0.217	0.148
18	0.386	0.294	0.344	0.227	0.084	0.686	0.200	0.200
19	0.421	0.422	0.374	0.308	0.071	0.843	0.238	0.251
20	0.553	0.464	0.401	0.410	0.184	0.911	0.319	0.341

Table 4.17: **The p-values of sample entropy (SampEn) between BD and MDD in multiple scales.** The sample entropies of BD are different from the sample entorpies of MDD in frontotemporal and temporal areas, and reach significant level in smaller scales.

Scale	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
1	0.623	0.246	0.196	**0.036**	**0.018**	0.057	**0.047**	0.066
2	0.690	0.267	0.200	**0.038**	**0.019**	0.059	**0.049**	0.071
3	0.740	0.288	0.203	**0.041**	**0.020**	0.064	**0.050**	0.077
4	0.756	0.303	0.207	**0.042**	**0.021**	0.068	0.051	0.082
5	0.779	0.310	0.209	**0.046**	**0.022**	0.068	0.052	0.087
6	0.792	0.313	0.216	**0.046**	**0.024**	0.071	0.055	0.092
7	0.862	0.317	0.213	**0.048**	**0.025**	0.073	0.054	0.096
8	0.900	0.339	0.231	0.052	**0.027**	0.078	0.056	0.107
9	0.902	0.332	0.228	0.058	**0.031**	0.082	0.057	0.112
10	0.994	0.368	0.246	0.061	**0.036**	0.081	0.069	0.128
11	0.876	0.386	0.253	0.083	**0.044**	0.096	0.073	0.148
12	0.782	0.384	0.264	0.088	0.060	0.100	0.084	0.165
13	0.607	0.415	0.286	0.092	0.070	0.110	0.097	0.188
14	0.566	0.471	0.282	0.138	0.114	0.137	0.120	0.230
15	0.348	0.523	0.311	0.155	0.142	0.140	0.156	0.271
16	0.322	0.593	0.303	0.180	0.217	0.170	0.166	0.310
17	0.230	0.761	0.358	0.287	0.300	0.178	0.203	0.405
18	0.134	0.795	0.384	0.270	0.414	0.207	0.261	0.460
19	0.138	0.880	0.413	0.363	0.477	0.262	0.235	0.516
20	0.100	0.909	0.434	0.345	0.738	0.337	0.334	0.598

4.5 Hemispheric Asymmetry

We applied the formula of asymmetric indices of Eq. 2.25 to all the features we described in section 4.3 and section 4.4.

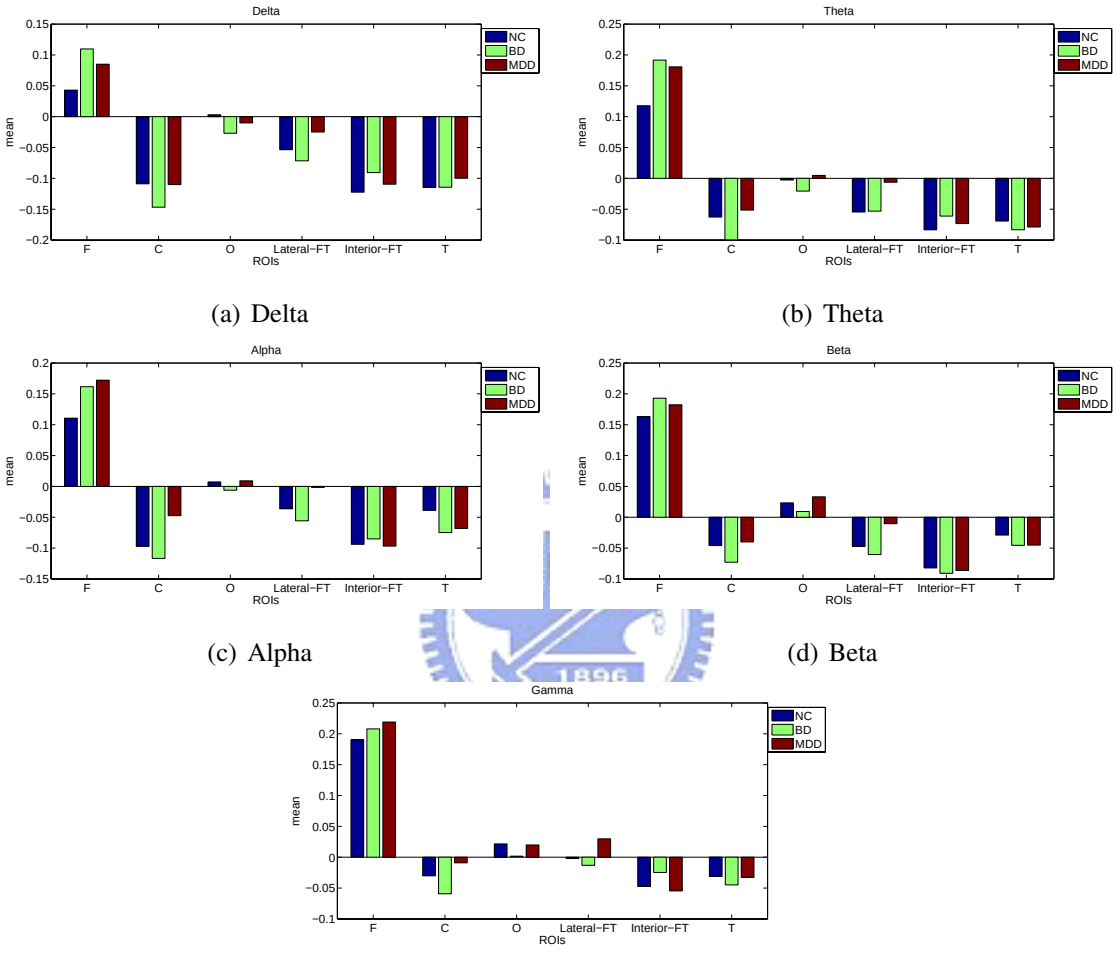
4.5.1 Band Power

Fig. 4.9 shows the mean hemisphere asymmetry of relative band powers of the three groups. The positive value of asymmetric indices mean that the power of left hemisphere is stronger than right. On the other hand, the negative values mean the power of left hemisphere is weaker than right. If the value is closer to zero, it means that the powers of left and right hemisphere are more symmetric.In the frontal, the relative band powers in left hemisphere are larger than in right hemisphere no matter what ROI is. Both BD and MDD patients have stronger relative power than NC in frontal in all frequency bands. Besides frontal and occipital, all ROIs have the characteristic of right stronger than left in all bands.

Table 4.5.1, Table 4.5.1 and Table 4.5.1 show the details of the p-values of t-test between two groups: NC and BD, NC and MDD, and BD and MDD. In the NC and BD case, the clear differences of power asymmetry are in the frontal and central, especially in delta and theta bands. In the NC and MDD case, the differences between them are the theta and alpha bands in the frontal. In the BC and MDD case, the differences of power asymmetry are significant in central.

Table 4.18: **The p-values of band power asymmetry between NC and BD.** Band power asymmetry shows the difference of delta and theta band in frontal and central, especially of theta band in frontal ($p < 0.01$).

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
Delta	**0.037**	0.055	0.207	0.683	0.222	0.995
Theta	**0.002**	**0.025**	0.480	0.975	0.467	0.635
Alpha	0.086	0.475	0.641	0.628	0.823	0.237
Beta	0.117	0.105	0.477	0.677	0.795	0.484
Gamma	0.326	0.053	0.143	0.700	0.324	0.508



(a) Delta

(b) Theta

(c) Alpha

(d) Beta

(e) Gamma

Figure 4.9: **Hemispheric asymmetry of relative band power.** The bar chart shows the mean hemisphere asymmetry of relative band power in the NC, BD and MDD groups. F:Frontal, C:Central, O:Occipital, FT:Frontotemporal, T:Temporal.

Table 4.19: **The p-values of band power asymmetry between NC and MDD.** The significant differences between NC and MDD patients are the theta and alpha band powers in the frontal.

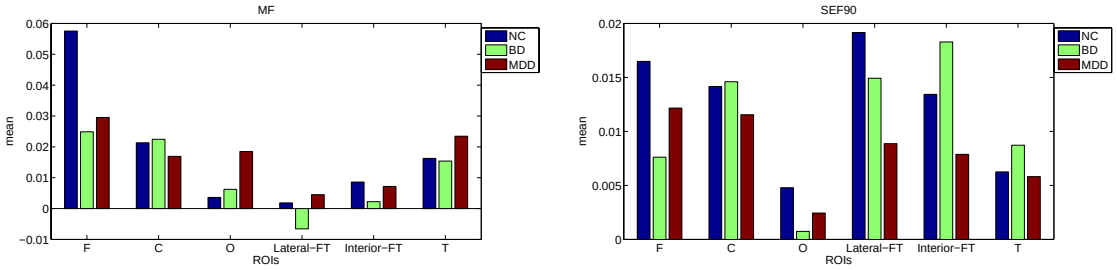
Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
Delta	0.225	0.957	0.598	0.501	0.633	0.657
Theta	**0.011**	0.572	0.808	0.269	0.738	0.786
Alpha	**0.040**	0.095	0.955	0.390	0.945	0.443
Beta	0.383	0.751	0.684	0.242	0.899	0.629
Gamma	0.111	0.179	0.898	0.166	0.766	0.936

Table 4.20: **The p-values of band power asymmetry between BD and MDD.** The differences of asymmetric band powers between BD and MDD patients appear in central, and reach the significant level.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
Delta	0.266	0.084	0.479	0.232	0.438	0.671
Theta	0.559	**0.017**	0.373	0.216	0.677	0.897
Alpha	0.704	**0.009**	0.651	0.200	0.757	0.863
Beta	0.532	**0.060**	0.335	0.150	0.892	0.992
Gamma	0.400	**0.003**	0.252	0.191	0.272	0.613

4.5.2 Spectral Measures

Fig. 4.10 illustrates the mean of MF and SEF90 asymmetry. The main difference is that the MF asymmetries of NC are stronger than both BD and MDD patients, especially BD patients. Table 4.5.2 and Table 4.5.2 are the p-values of t-test between the three groups. Only in the NC and BD case, there is significant difference of MF asymmetry in frontal.



(a) Mean Frequency

(b) 90% spectral edge frequency

Figure 4.10: **Hemispheric asymmetry of MF and SEF90.** The bar chart shows the mean of MF and SEF90 asymmetry in all ROIs whithin the three groups. F:Frontal, C:Central, O:Occipital, FT:Frontaltemporal, T:Temporal. In frontal, the MF and SEF90 asymmetry of NC are apparently stronger than BD and MDD patients.

Table 4.21: **The p-values of MF asymmetry.** Compared with BD patients and NC, the difference of MF asymmetry in frontal are significant. In the NC and MDD case, the differences do not reach the significant level.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
BD	**0.020**	0.895	0.678	0.622	0.476	0.909
MDD	0.067	0.599	0.077	0.852	0.883	0.413
BD vs. MDD	0.658	0.501	0.093	0.498	0.602	0.408

Table 4.22: **The p-values of SEF90 asymmetry.** The difference of SEF90 asymmetry between the three groups are not significant.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
BD	0.080	0.937	0.591	0.744	0.504	0.739
MDD	0.410	0.709	0.787	0.421	0.504	0.958
BD vs. MDD	0.355	0.646	0.860	0.596	0.173	0.757

4.5.3 Spectral Ratio Measures

Fig. 4.11 shows the bar chart of the mean of spectral ration asymmetry between the three groups. The spectral ratio asymmetries of NC are obviously larger than BD and MDD patients in the frontal. The hemispheric asymmetries of $RP(\beta)/RP(\alpha)$, $RP(\gamma)/RP(\alpha)$, and $(RP(\beta)+RP(\gamma))/(RP(\theta)+RP(\alpha))$ in the central are smaller in MDD case than NC and BD.

Table 4.5.3, Table 4.5.3 and Table 4.5.3 show the detail of the p-value of t-test between NC and BD, NC and MDD, and BD and MDD respectively. From the table, the differences between NC and BD patients are in the frontal. In the NC and MDD case, the differences of spectral ratio asymmetries are the $(RP(\beta)+RP(\gamma))/(RP(\theta)+RP(\alpha))$ in frontal, $RP(\beta)/RP(\theta)$ in frontal, and $RP(\beta)/RP(\alpha)$ in central. The only one difference of spectral ratio asymmetry between BD and MDD is the ratio of $RP(\beta)/RP(\alpha)$ in the central.

Table 4.23: **The p-values of spectral ratio asymmetry between NC and BD.** Spectral ratio differences between NC and BD patients are only in frontal.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
$\frac{RP(\beta)+RP(\gamma)}{RP(\theta)+RP(\alpha)}$	**0.037**	0.885	0.791	0.781	0.111	0.608
$\frac{RP(\beta)}{RP(\theta)}$	**0.021**	0.515	0.830	0.632	0.140	0.986
$\frac{RP(\beta)}{RP(\alpha)}$	0.320	0.723	0.982	0.834	0.349	0.466
$\frac{RP(\gamma)}{RP(\theta)}$	**0.013**	0.638	0.938	0.762	0.986	0.897
$\frac{RP(\gamma)}{RP(\alpha)}$	0.278	0.712	0.805	0.834	0.657	0.628

Table 4.24: **The p-values of spectral ratio asymmetry between NC and MDD.** Compared NC with MDD patients, the differences of spectral ratio asymmetry are only $(RP(\beta) + RP(\gamma))/(RP(\theta) + RP(\alpha))$ in frontal, $RP(\beta)/RP(\theta)$ in frontal, and $RP(\beta)/RP(\alpha)$ in central.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
$\frac{RP(\beta)+RP(\gamma)}{RP(\theta)+RP(\alpha)}$	**0.023**	0.105	0.698	0.802	0.675	0.874
$\frac{RP(\beta)}{RP(\theta)}$	**0.030**	0.681	0.886	0.695	0.473	0.765
$\frac{RP(\beta)}{RP(\alpha)}$	0.071	**0.026**	0.694	0.946	0.942	0.740
$\frac{RP(\gamma)}{RP(\theta)}$	0.155	0.582	0.717	0.712	0.562	0.904
$\frac{RP(\gamma)}{RP(\alpha)}$	0.286	0.303	0.895	0.932	0.885	0.614

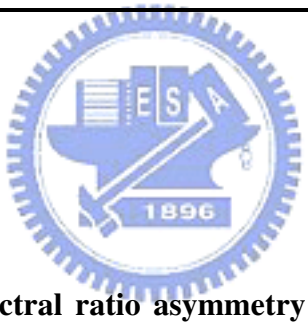
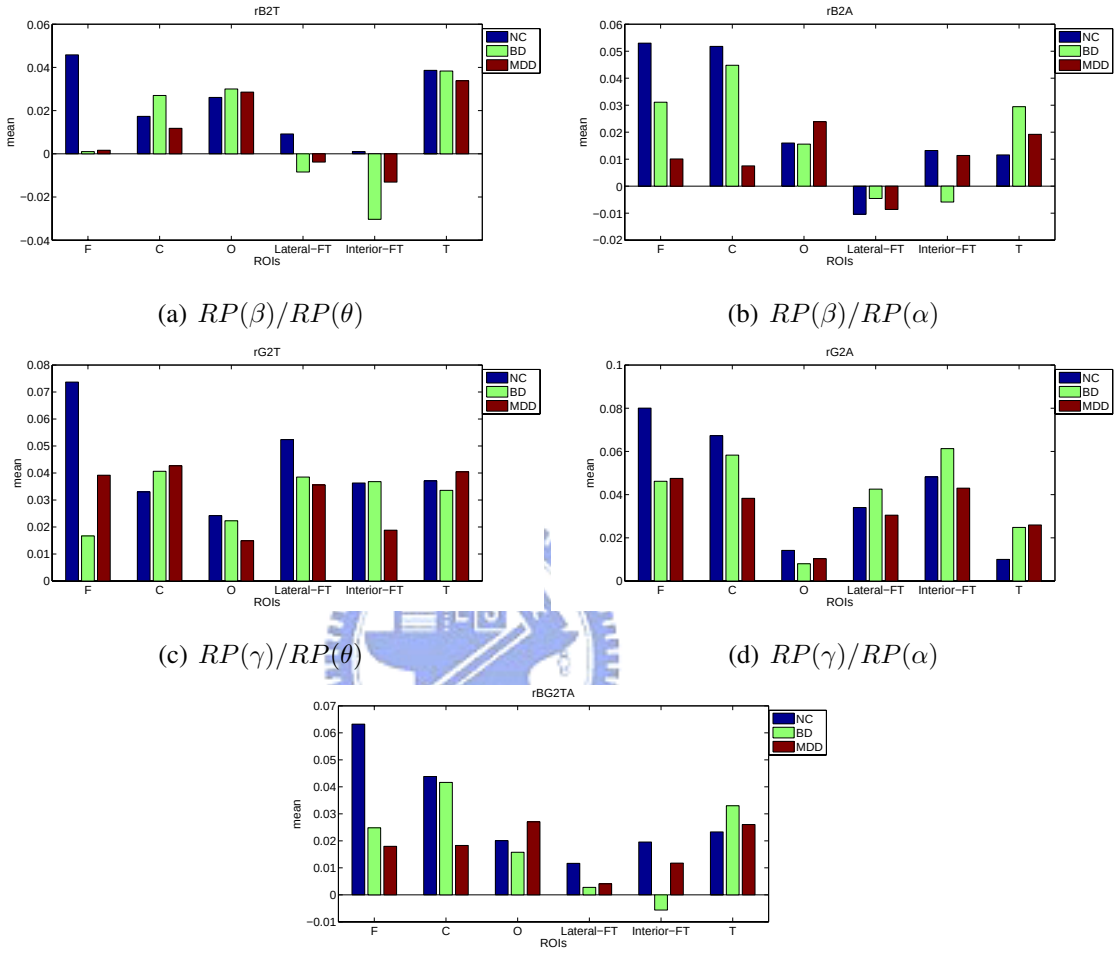


Table 4.25: **The p-values of spectral ratio asymmetry between BD and MDD.** The asymmetry of the spectral ratio $RP(\beta)/RP(\alpha)$ between BD and MDD patients are significant different in the central.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
$\frac{RP(\beta)+RP(\gamma)}{RP(\theta)+RP(\alpha)}$	0.686	0.085	0.493	0.963	0.262	0.710
$\frac{RP(\beta)}{RP(\theta)}$	0.971	0.330	0.930	0.887	0.386	0.815
$\frac{RP(\beta)}{RP(\alpha)}$	0.372	**0.028**	0.635	0.868	0.369	0.623
$\frac{RP(\gamma)}{RP(\theta)}$	0.243	0.913	0.782	0.949	0.541	0.819
$\frac{RP(\gamma)}{RP(\alpha)}$	0.964	0.411	0.936	0.780	0.524	0.973



(a) $RP(\beta)/RP(\theta)$

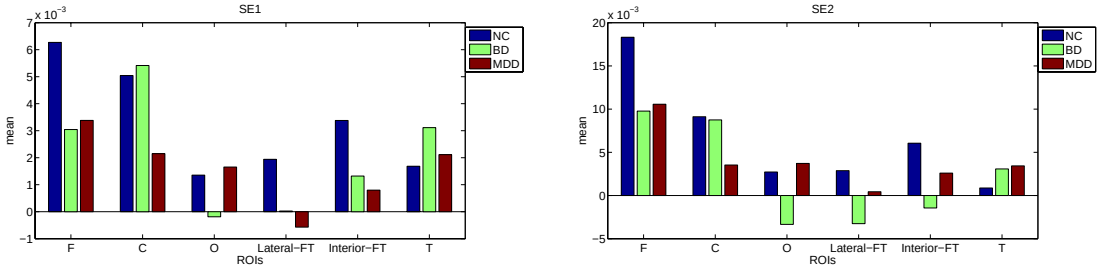
(b) $RP(\beta)/RP(\alpha)$

(c) $RP(\gamma)/RP(\theta)$

(d) $RP(\gamma)/RP(\alpha)$

(e) $(RP(\beta)+RP(\gamma))/(RP(\theta)+RP(\alpha))$

Figure 4.11: **Hemispheric asymmetry of spectral ratios.** The bar charts show the hemispheric asymmetry of five kinds of spectral ratios. In the NC case, the ratio asymmetry of $RP(\beta)/RP(\theta)$, $RP(\gamma)/RP(\theta)$, and $(RP(\beta)+RP(\gamma))/(RP(\theta)+RP(\alpha))$ are larger than those of BD and MD pateints. In the MDD case, the ratio asymmetry of $RP(\beta)/RP(\alpha)$ and $(RP(\beta)+RP(\gamma))/(RP(\theta)+RP(\alpha))$ are obviously smaller than NC and BD patients.



(a) Spectral Entropy 1.

(b) Spectral Entropy 2.

Figure 4.12: **Hemispheric asymmetry of spectral entropies.** F:Frontal, C:Central, O:Occipital, FT:Frontotemporal, T:Temporal.

Table 4.26: **The p-values of spectral entropy 1 (SE1) asymmetry.** Compared with NC, BD and MDD patients have differences in frontal, but only BD reach the significant level.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
NC vs. BD	**0.029**	0.865	0.501	0.544	0.313	0.544
NC vs. MDD	0.059	0.172	0.887	0.389	0.241	0.837
BD vs. MDD	0.762	0.095	0.434	0.815	0.746	0.651

Table 4.27: **The p-values of spectral entropy 2 (SE2) asymmetry.** The difference between NC and BD patients reach a significant level in the frontal.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
NC vs. BD	**0.043**	0.928	0.194	0.271	0.066	0.591
NC vs. MDD	0.083	0.159	0.825	0.629	0.410	0.449
BD vs. MDD	0.710	0.127	0.116	0.380	0.233	0.930

4.5.4 Spectral Entropy

Fig. 4.12 shows the mean of spectral entropy asymmetries of the three groups. In the frontal, NC has obvious larger asymmetric values of both type of spectral entropies than BD and MDD patients. On the contrary, patients with MDD have smaller asymmetric values of both spectral entropies in the central.

Table 4.5.3 and Table 4.5.3 show the p-values of t-test between any tow of the three groups. Only the comparison between NC and BD patients reach the significant level.

4.5.5 Lempel-Ziv Complexity

Table 4.5.5, Table 4.5.5 and Table 4.5.5 show the p-values of t-test of LZC asymmetries between NC and BD, NC and MDD, BD and MDD respectively. In the NC and BD case, the features of asymmetric LZC in frontal reach the significant level in most scales, and some of them reach the level of $p < 0.01$. In the NC and MDD case, the LZC asymmetries in frontal also have significant differences between the two groups. Besides, in the BD and MDD case, the differences of LZC asymmetries are in central with larger scales and in interior-frontotemporal with smaller scales.

Table 4.28: **The p-values of LZC asymmetry between NC and BD in multiple scales.** The p-values of frontal show a significant difference in hemispheric asymmetry of LZC.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
1	**0.030**	0.747	0.742	0.868	0.426	0.727
2	**0.031**	0.763	0.691	0.848	0.354	0.632
3	**0.014**	0.687	0.881	0.877	0.404	0.641
4	**0.026**	0.554	0.828	0.687	0.477	0.677
5	**0.041**	0.944	0.790	0.806	0.448	0.465
6	**0.035**	0.964	0.663	0.818	0.380	0.619
7	**0.007**	0.491	0.658	0.690	0.454	0.722
8	**0.005**	0.754	0.614	0.744	0.648	0.346
9	0.053	0.750	0.791	0.590	0.741	0.473
10	**0.015**	0.591	0.754	0.573	0.608	0.358
11	**0.037**	0.590	0.734	0.497	0.880	0.716
12	**0.011**	0.357	0.830	0.465	0.725	0.453
13	0.071	0.941	0.773	0.569	0.795	0.455
14	**0.009**	0.395	0.679	0.391	0.544	0.305
15	0.083	0.872	0.822	0.379	0.835	0.226
16	**0.005**	0.555	0.791	0.435	0.536	0.187
17	0.140	0.634	0.922	0.475	0.205	0.501
18	**0.011**	0.373	0.896	0.361	0.156	0.236
19	**0.031**	0.460	0.582	0.402	0.195	0.577
20	**0.012**	0.583	0.783	0.303	0.397	0.329

Table 4.29: **The p-values of LZC asymmetry between NC and MDD in multiple scales.** The differences of LZC asymmetries are obvious in frontal, but only the features with larger scales reach the significant level.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
1	0.069	0.520	0.445	0.460	0.328	0.826
2	0.075	0.475	0.444	0.380	0.375	0.823
3	0.068	0.499	0.574	0.363	0.375	0.815
4	0.069	0.583	0.526	0.286	0.405	0.813
5	0.099	0.456	0.495	0.351	0.325	0.761
6	0.071	0.294	0.607	0.333	0.255	0.886
7	**0.033**	0.633	0.493	0.308	0.208	0.856
8	**0.044**	0.407	0.478	0.304	0.248	0.829
9	**0.040**	0.398	0.525	0.273	0.193	0.614
10	0.080	0.392	0.746	0.285	0.220	0.767
11	0.066	0.558	0.366	0.201	0.308	0.792
12	**0.016**	0.426	0.463	0.268	0.356	0.600
13	**0.014**	0.161	0.267	0.296	0.109	0.759
14	**0.002**	0.271	0.301	0.255	0.209	0.575
15	**0.048**	0.327	0.282	0.228	0.533	0.707
16	**0.034**	0.362	0.243	0.205	0.201	0.445
17	0.053	0.117	0.228	0.259	0.230	0.626
18	**0.025**	0.386	0.285	0.329	0.229	0.594
19	**0.048**	0.409	0.269	0.364	0.233	0.947
20	**0.036**	0.072	0.168	0.291	0.259	0.733

Table 4.30: **The p-values of LZC asymmetry between BD and MDD in multiple scales.** There are some features of LZC asymmetries with larger scales reach the significant level in central, and some with smaller scales in interior-frontotemporal.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
1	0.800	0.291	0.676	0.498	0.077	0.952
2	0.771	0.265	0.717	0.417	0.075	0.870
3	0.544	0.245	0.708	0.362	0.086	0.883
4	0.722	0.209	0.699	0.400	0.126	0.913
5	0.768	0.353	0.700	0.386	0.071	0.761
6	0.842	0.241	0.938	0.352	**0.044**	0.781
7	0.691	0.203	0.833	0.408	**0.033**	0.903
8	0.566	0.203	0.872	0.365	0.086	0.523
9	0.887	0.174	0.753	0.441	0.093	0.888
10	0.587	0.099	0.995	0.471	**0.050**	0.568
11	0.799	0.192	0.661	0.416	0.195	0.941
12	0.885	0.067	0.665	0.599	0.154	0.816
13	0.504	0.142	0.504	0.528	0.135	0.690
14	0.695	**0.044**	0.633	0.663	0.451	0.640
15	0.878	0.184	0.468	0.646	0.573	0.403
16	0.314	0.179	0.234	0.438	0.351	0.558
17	0.540	**0.019**	0.297	0.476	0.995	0.827
18	0.854	0.089	0.495	0.946	0.934	0.525
19	0.739	0.091	0.182	0.851	0.951	0.620
20	0.686	**0.019**	0.165	0.928	0.616	0.511

4.5.6 Sample Entropy

Table 4.5.6, Table 4.5.6 and Table 4.33 show the p-values of t-test of sample entropy asymmetries between NC and BD, NC and MDD, BD and MDD respectively. Compare NC with BD patients, the sample entropy asymmetries are significant different with smaller scales in frontal, and with larger scales in interior-frontotemporal. Compare BD with MDD, there are also significant differences in occipital and interior-frontotemporal with larger scales. However, in the NC and MDD case, there are no obvious differences found.

Table 4.31: **The p-values of SampEn asymmetry between NC and BD in multiple scales.**

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
1	**0.034**	0.890	0.480	0.977	0.615	0.463
2	**0.032**	0.848	0.434	0.983	0.485	0.427
3	**0.030**	0.829	0.403	0.974	0.406	0.425
4	**0.030**	0.808	0.354	0.946	0.329	0.397
5	**0.030**	0.680	0.311	0.964	0.264	0.401
6	**0.028**	0.664	0.289	0.899	0.234	0.340
7	**0.032**	0.608	0.279	0.923	0.216	0.353
8	**0.039**	0.637	0.278	0.944	0.195	0.339
9	0.061	0.652	0.185	0.959	0.146	0.291
10	**0.028**	0.805	0.209	0.995	0.101	0.321
11	0.060	0.680	0.188	0.959	0.062	0.366
12	**0.034**	0.698	0.215	0.891	**0.044**	0.255
13	0.052	0.853	0.154	0.986	0.069	0.284
14	0.087	0.617	0.232	0.935	**0.043**	0.289
15	**0.046**	0.677	0.199	0.964	**0.032**	0.316
16	0.080	0.678	0.179	0.837	**0.016**	0.272
17	0.172	0.561	0.281	0.949	0.052	0.345
18	0.071	0.792	0.356	0.944	**0.018**	0.212
19	0.177	0.765	0.339	0.964	**0.012**	0.250
20	0.056	0.978	0.297	0.922	**0.007**	0.223

Table 4.32: **The p-values of SampEn asymmetry between NC and MDD in multiple scales.**

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
1	0.103	0.868	0.781	0.466	0.382	0.745
2	0.114	0.756	0.800	0.383	0.371	0.698
3	0.122	0.685	0.846	0.339	0.389	0.637
4	0.132	0.645	0.860	0.324	0.375	0.569
5	0.130	0.708	0.912	0.291	0.384	0.565
6	0.150	0.715	0.885	0.288	0.371	0.504
7	0.134	0.766	0.950	0.281	0.417	0.477
8	0.184	0.688	0.976	0.296	0.435	0.422
9	0.317	0.667	0.955	0.287	0.458	0.328
10	0.240	0.592	0.953	0.340	0.384	0.451
11	0.282	0.641	0.964	0.295	0.302	0.381
12	0.240	0.830	0.813	0.372	0.384	0.292
13	0.312	0.774	0.832	0.380	0.537	0.309
14	0.321	0.802	0.524	0.343	0.401	0.298
15	0.173	0.876	0.651	0.368	0.441	0.390
16	0.390	0.907	0.402	0.380	0.301	0.271
17	0.605	0.856	0.402	0.375	0.623	0.394
18	0.697	0.911	0.223	0.468	0.603	0.252
19	0.741	0.413	0.363	0.337	0.519	0.202
20	0.473	0.867	0.333	0.699	0.333	0.195

Table 4.33: **The p-values of SampEn asymmetry between BD and MDD in multiple scales.** p-value of Sample Entropy of BD vs. MDD.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal
				Lateral	Interior	
1	0.643	0.741	0.742	0.420	0.659	0.779
2	0.576	0.581	0.668	0.312	0.795	0.783
3	0.525	0.492	0.588	0.263	0.939	0.839
4	0.498	0.443	0.516	0.259	0.951	0.874
5	0.493	0.399	0.419	0.209	0.813	0.874
6	0.427	0.394	0.406	0.239	0.760	0.859
7	0.481	0.383	0.335	0.205	0.647	0.898
8	0.425	0.350	0.278	0.203	0.570	0.942
9	0.334	0.349	0.208	0.170	0.412	0.999
10	0.250	0.414	0.173	0.192	0.371	0.841
11	0.346	0.356	0.140	0.130	0.316	0.996
12	0.278	0.537	0.111	0.149	0.170	0.942
13	0.291	0.616	0.062	0.211	0.158	0.953
14	0.378	0.425	**0.038**	0.226	0.137	0.982
15	0.487	0.544	**0.044**	0.259	0.098	0.815
16	0.227	0.738	**0.009**	0.378	0.092	0.969
17	0.312	0.424	**0.034**	0.281	0.105	0.871
18	0.060	0.860	**0.012**	0.382	**0.035**	0.823
19	0.176	0.645	**0.033**	0.241	**0.041**	0.904
20	0.105	0.848	**0.028**	0.728	**0.041**	0.973

4.6 Classification Results

After the procedure of feature extraction, we have totally 756 features. We select useful features and classify them according to the procedures depicted in Fig. 3.1. First, the features with p-value smaller than 0.03 were reserved. Second, the features were ordered by the weighting of projection matrix in LDA, and then the features with larger weighting were selected for classification. Support vector machine (SVM) was then used for classificaion where we used the LIBSVM tools [11] with radial kernal and a leave-one-out validation to evaluate accuracy.

What follows is the result of these procedures for classification. Section 4.6.1 to section 4.6.2 are concerning about the two-groups classifications, and section 4.6.4 is about the three-groups classification.

4.6.1 Normal Control vs. Bipolar Disorder

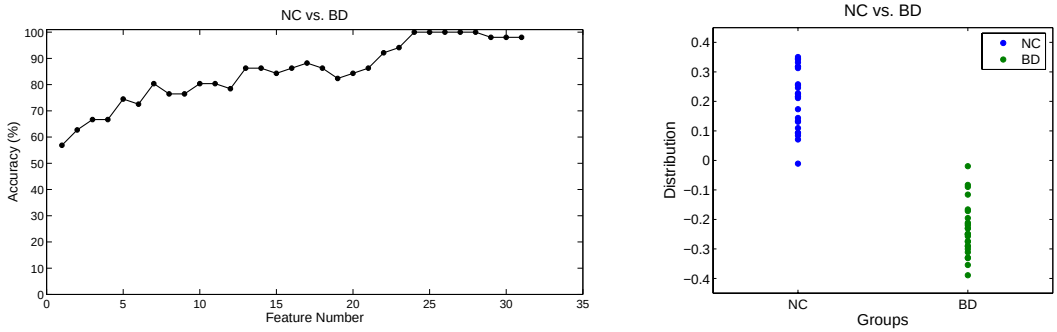
In the beginning of the NC and BD classification, there were totally 756 features, including PSD features, features of temporal complexity, and the brain asymmetric features of them. The first step, we set a p-value threshold as $p < 0.03$ to select the features, and then 31 of 756 features were preserved.

Then LDA was applied to the 31 features which reached the significant of $p < 0.03$. From LDA, a projection matrix was gotten. We chosen features by the weighting of the projection matrix in a decreasing order. And then LDA was applied again to the new features selected by the weighting, and then project the features to one dimension and classified by svm with a leave-one-out validation. Fig. 4.13(a) is the map of accuracy and the number of selected features. We can see that with LDA projection, the combination of 24 features with larger weighting is sufficient to get 100% accuracy.

Finally, we choosed the features with the largest weighting in LDA projection matrix as the final features. Table 4.6.1 shows these features and Fig. 4.13(b) shows the distribution of the one dimensional feature which was projected by the LDA projection matrix from 24 features. The one dimensional feature is linearly separate, and got a classification accuracy of 100%.

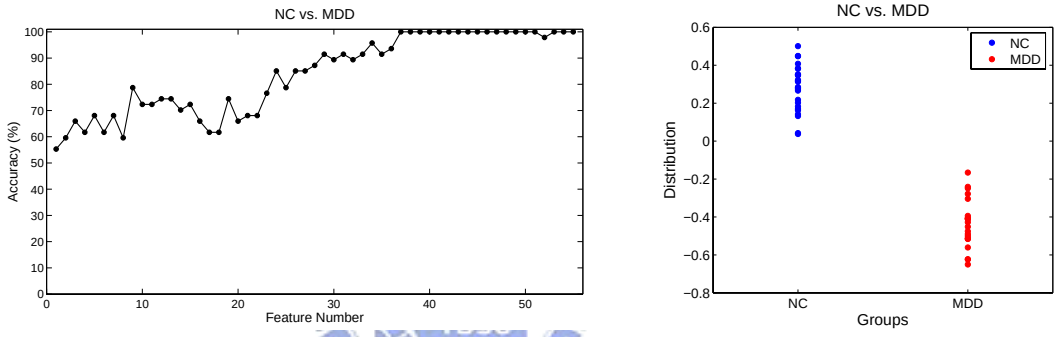
Table 4.34: **The features used in NC and BD classification.** The 24 features are finially used to classify NC and BD patients, and are sorted by the weighting in decreasing order. The feature of rB2T represents the spectral ratio of beta band power to theta band power ($RP(\beta)/RP(\theta)$).

	Weighting	Feature name			ROIs
1	1.98457262	Asymmetry	SampEn	scale=03	frontal
2	-1.78261301	Asymmetry	SampEn	scale=05	frontal
3	-1.54122528	SampEn		scale=13	Frontal
4	0.99134190	SampEn		scale=12	Frontal
5	0.77102447	Asymmetry	LZC	scale=03	frontal
6	0.73446601	Asymmetry	SampEn	scale=19	interior-frontotemporal
7	-0.62631195	Asymmetry	LZC	scale=04	frontal
8	0.50526149	Asymmetry	LZC	scale=08	frontal
9	-0.42286715	Asymmetry	SampEn	scale=16	interior-frontotemporal
10	-0.41936631	Asymmetry	SampEn	scale=06	frontal
11	0.41031930	SampEn		scale=15	Frontal
12	-0.37058944	Asymmetry	SampEn	scale=20	interior-frontotemporal
13	0.36019586	Asymmetry	rB2T		frontal
14	0.24925431	SampEn		scale=17	Frontal
15	-0.24766209	Asymmetry	rG2T		frontal
16	0.23275340	Asymmetry	SampEn	scale=18	interior-frontotemporal
17	-0.23177122	Asymmetry	MF		frontal
18	-0.21870709	Asymmetry	theta		frontal
19	-0.21305363	Asymmetry	LZC	scale=14	frontal
20	0.19206423	Asymmetry	SampEn	scale=10	frontal
21	-0.15493302	Asymmetry	LZC	scale=10	frontal
22	0.15283248	Asymmetry	LZC	scale=18	frontal
23	-0.12515979	Asymmetry	LZC	scale=07	frontal
24	0.09990728	Asymmetry	theta		central



(a) Selection of feature number. (b) Distrubution after MDA projection.

Figure 4.13: **Results of the NC and BD classification.**



(a) Selection of feature number. (b) Distrubution after MDA projection.

Figure 4.14: **Results of the NC and MDD classification.**

4.6.2 Normal Control vs. Major Depressive Disorder

First, we sifted 55 features from totally 756 features by a threshold of $p < 0.03$. Then LDA was applied to the 55 selected features which reached the significant level. From LDA, a projection matrix was gotten. We chosen features by the weighting of the projection matrix in a decreasing order. And then LDA was applied again to only the new features selected by the largest weighting, and then project the features to a one dimension space and classified by svm with a leave-one-out validation. Fig. 4.14(a) is the map of accuracy and the number of selected features. We can see that with LDA projection, the combination of 37 features with larger weighting is sufficient to get 100% accuracy.

Table 4.35: **The features used in NC and MDD classification.** The 37 features are finially used to classify NC and MDD patients, and are sorted by the weighting in decreasing order.

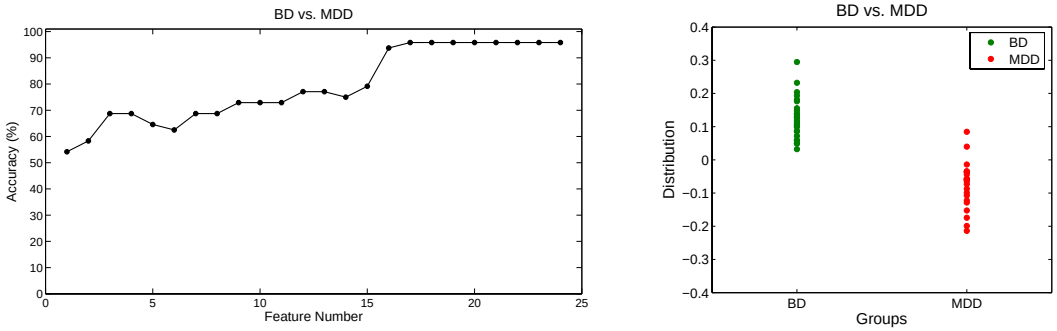
	Weighting	Feature name		ROIs
1	-14.01774542	SampEn	scale=08	Right-Frontotemporal
2	-13.63825602	SampEn	scale=10	Right-Frontotemporal
3	12.77152235	SampEn	scale=12	Right-Frontotemporal
4	11.23568247	SampEn	scale=07	Left-Frontotemporal
5	-10.93894964	SampEn	scale=08	Left-Frontotemporal
6	8.12984708	SampEn	scale=15	Right-Frontotemporal
7	-7.76276291	SampEn	scale=16	Right-Frontotemporal
8	-7.40142785	SampEn	scale=07	Right-Frontotemporal
9	-6.95764122	SampEn	scale=01	Left-Frontotemporal
10	6.45049846	SampEn	scale=01	Right-Frontotemporal
11	6.12959971	SampEn	scale=09	Right-Frontotemporal
12	4.46160166	SampEn	scale=03	Right-Frontotemporal
13	3.94147113	MF		Right-Frontotemporal
14	3.92347404	SampEn	scale=09	Left-Frontotemporal
15	3.78727188	SampEn	scale=04	Right-Frontotemporal
16	3.51463991	ratio	Gamma/Theta	Left-Frontotemporal
17	-3.15803665	gamma		Right-Frontotemporal

Then, we used thease 37 features with the largest weighting in LDA projection matrix as the final features. Table 4.6.2 and Table 4.6.2 show the 37 features used for classification. Fig. 4.14(b) shows the distribution of the one dimensional feature which was projected by the LDA projection matrix from the selected 37 features. The one dimensional feature are linearly separate, and got a classification accuracy of 100%.

Table 4.36: **The features used in NC and MDD classification.** The 37 features are finially used to classify NC and MDD patients, and are sorted by the weighting in decreasing order. The feature of ratio BG2TA represents the spectral ratio of the sum of beta and gamma band powers to the sum of theta and alpha band powers ($(RP(\beta)+RP(\gamma))/(RP(\theta)+RP(\alpha))$).

	Weighting	Feature name			ROIs
18	2.94641587	SampEn		scale=02	Right-Frontotemporal
19	-2.71046140	ratio	Gamma/Theta		Central
20	-2.56638010	MF			Left-Frontotemporal
21	2.39732852	SampEn		scale=02	Left-Frontotemporal
22	2.35965965	ratio	BG2TA		Central
23	-2.35158901	ratio	BG2TA		Right-Frontotemporal
24	2.14702434	LZC		scale=15	Frontal
25	2.01076164	SampEn		scale=05	Right-Frontotemporal
26	-1.99082568	LZC		scale=01	Right-Frontotemporal
27	1.99019020	SampEn		scale=14	Right-Frontotemporal
28	1.92155568	ratio	BG2TA		Left-Temporal
29	-1.86764138	SampEn		scale=06	Right-Frontotemporal
30	-1.72296591	MF			Left-Temporal
31	1.58483320	SampEn		scale=11	Right-Frontotemporal
32	-1.58336487	LZC		scale=20	Frontal
33	1.52990182	gamma			Central
34	-1.42253021	SampEn		scale=13	Right-Frontotemporal
35	-1.38197055	ratio	BG2TA		Frontal
36	-1.14072261	gamma			Left-Frontotemporal
37	1.05130077	SampEn		scale=01	Central

4.6.3 Bipolar Disorder vs. Major Depressive Disorder



(a) Selection of feature number.

(b) Distrubution after MDA projection.

Figure 4.15: **Results of the BD and MDD classification.**

In the two-group classification of BD and MDD patients, we first selected the features reaching the significant level of $p < 0.03$ and 24 features were selected. And then LDA was applied to the 24 features and then got a projection matrix. We selected the features with higher weighting in the projection matrix, and then LDA was applied again to the new selected features. Fig. 4.15(a) is the map of accuracy and the number of selected features. Then we found that the combination of 17 features got the hightest accuracy of 95.83%.

Then, we used these 17 features with the largest weighting in LDA projection matrix as the final features. Table 4.6.3 shows the 17 selected features and Fig. 4.15(b) shows the distribution of the one dimensional feature which was projected by the LDA projection matrix from the selected 17 features. The one dimensional feature is linearly separate, and got a classification accuracy of 95.83%. And the confusion matrix is

Table 4.37: **The confusion matrix of the BD and MDD classification.** 2 patients with MDD were classified to the BD group.

	BD	MDD
BD	26	0
MDD	2	20

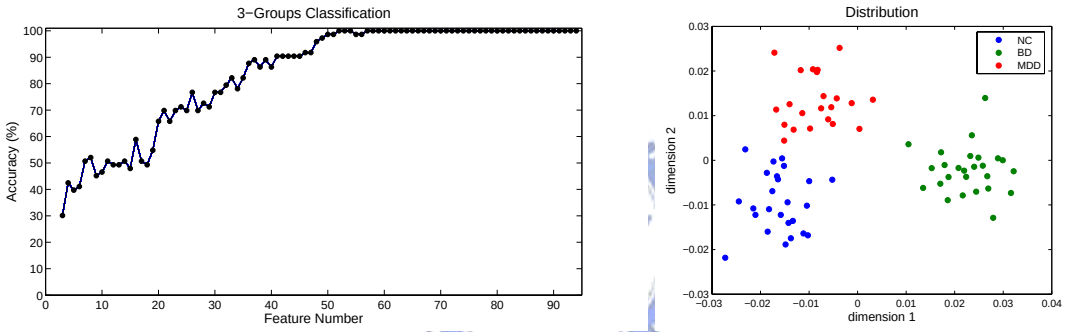
Table 4.38: **The features used in BD and MDD classification.** The 17 features are finially used to classify BD and MDD patients, and are sorted by the weighting in decreasing order.

	Weighting	Feature name			ROIs
1	-2.83793749	SampEn		scale=02	Right-Frontotemporal
2	-2.79725404	LZC		scale=03	Right-Frontotemporal
3	2.61441807	LZC		scale=04	Right-Frontotemporal
4	2.59517446	SampEn		scale=04	Right-Frontotemporal
5	-1.41301179	SampEn		scale=07	Right-Frontotemporal
6	-1.22504464	LZC		scale=02	Right-Frontotemporal
7	1.15325490	SampEn		scale=03	Right-Frontotemporal
8	0.90333558	LZC		scale=01	Right-Frontotemporal
9	0.71481472	SampEn		scale=01	Right-Frontotemporal
10	0.56142456	SampEn		scale=06	Right-Frontotemporal
11	-0.38640497	SampEn		scale=05	Right-Frontotemporal
12	0.21251990	Asymmetry	SampEn	scale=16	occipital
13	-0.16385012	Asymmetry	SampEn	scale=18	occipital
14	0.13790595	LZC		scale=13	Right-Frontotemporal
15	0.09340350	Asymmetry	LZC	scale=17	central
16	-0.08185154	Asymmetry	gamma		central
17	0.07862150	Asymmetry	alpha		central

4.6.4 The three groups classificaiton

94 features were chosen by the p-values of $p < 0.03$. The 94 features are the union set of the features of $p < 0.03$ from the t-test between NC and BD, NC and MDD, and BD and MDD.

Fig. 4.16(a) is the map of accuracy and the number of selected features. We can see that with LDA projection, the combination of 52 features with larger weighting is sufficient to get 100% accuracy. The weighting here are the square sum of the two dimensions. And then these 52 features with the largest square sum of weighting are projected by the LDA to a 2 dimensional space showed in Fig. 4.16(b). And we got the 100% classification accuracy. Table 4.6.4 and Table 4.6.4 show the 52 selected features used to 3-groups classification.



(a) Selection of feature number. (b) Distrubution after MDA projection.

Figure 4.16: **Results of the 3-groups classification.**

Table 4.39: **The features used in 3-groups classification.** The 52 features are finially used to classify NC, BD and MDD patients, and are sorted by the square sum of the two weightings in decreasing order. The feature of ratio BG2TA represents the spectral ratio of the sum of beta and gamma band powers to the sum of theta and alpha band powers ($(RP(\beta) + RP(\gamma))/(RP(\theta) + RP(\alpha))$).

	Weighting 1 - 2		Feature name			ROIs
1	0.3089	-0.3975	SampEn		scale=12	Right-Frontotemporal
2	0.2368	-0.2749	Asymmetry	SampEn	scale=03	frontal
3	-0.2476	0.2646	SampEn		scale=05	Right-Frontotemporal
4	0.2582	-0.2215	LZC		scale=01	Right-Frontotemporal
5	-0.2569	0.1780	gamma			Left-Frontotemporal
6	-0.2093	0.1990	SampEn		scale=15	Right-Frontotemporal
7	-0.2405	0.1392	ratio	BG2TA		Left-Frontotemporal
8	-0.1804	0.1890	SampEn		scale=07	Right-Frontotemporal
9	0.2363	-0.1054	MF			Left-Frontotemporal
10	-0.1570	0.2025	SampEn		scale=04	Right-Frontotemporal
11	-0.1082	0.2162	SampEn		scale=06	Right-Frontotemporal
12	-0.2284	0.0351	Asymmetry	SampEn	scale=05	frontal
13	0.1917	-0.1118	SampEn		scale=09	Left-Frontotemporal
14	-0.1846	0.0791	SampEn		scale=09	Right-Frontotemporal
15	0.1815	-0.0834	SampEn		scale=01	Right-Frontotemporal
16	0.1470	-0.1313	SampEn		scale=11	Right-Frontotemporal
17	0.0200	0.1839	ratio	BG2TA		All
18	0.1516	-0.0923	ratio	BG2TA		Frontal
19	-0.0602	0.1559	Asymmetry	SampEn	scale=18	interior-frontotemporal
20	0.1311	-0.0811	SampEn		scale=02	Right-Frontotemporal
21	-0.0248	-0.1508	ratio	BG2TA		Central
22	0.0619	-0.1392	SampEn		scale=01	Central
23	-0.1357	-0.0599	LZC		scale=15	Frontal
24	0.0891	-0.1181	SampEn		scale=01	Left-Frontotemporal
25	0.1093	-0.0943	gamma			Right-Frontotemporal
26	-0.0440	-0.1372	LZC		scale=04	Right-Frontotemporal

Table 4.40: **The features used in 3-groups classification.** 52 features are finially used to classify NC, BD and MDD patients, and are sorted by the square sum of the two weightings in decreasing order. The feature of ratio BG2TA represents the spectral ratio of the beta and gamma band power to the theta and alpha band power ($(RP(\beta) + RP(\gamma))/(RP(\theta) + RP(\alpha))$).

	Weighting 1 - 2		Feature name			ROIs
27	-0.1046	0.0971	MF			Right-Frontotemporal
28	0.0202	0.1411	Asymmetry	SampEn	scale=06	frontal
29	0.0293	0.1285	MF			Central
30	-0.0734	-0.1058	SampEn		scale=18	Frontal
31	0.0956	-0.0841	SampEn		scale=14	Frontal
32	0.0961	-0.0830	Asymmetry	LZC	scale=07	frontal
33	-0.0539	0.1124	Asymmetry	SampEn	scale=18	occipital
34	-0.1225	-0.0030	SampEn		scale=02	Central
35	-0.0956	0.0651	SampEn		scale=15	Frontal
36	0.0827	-0.0780	SE2			Left-Frontotemporal
37	-0.0020	-0.1131	ratio	BG2TA		Left-Temporal
38	0.0833	-0.0745	SampEn		scale=13	Right-Frontotemporal
39	-0.0077	0.1032	gamma			Central
40	-0.0492	0.0859	LZC		scale=18	Frontal
41	-0.0918	0.0201	LZC		scale=03	Right-Frontotemporal
42	0.0540	0.0723	SampEn		scale=13	Frontal
43	0.0192	-0.0879	Asymmetry	SampEn	scale=16	occipital
44	-0.0060	-0.0882	SampEn		scale=14	Right-Frontotemporal
45	0.0310	0.0824	SampEn		scale=08	Left-Frontotemporal
46	0.0871	0.0091	LZC		scale=15	Right-Temporal
47	-0.0851	0.0037	MF			Right-Temporal
48	-0.0537	0.0648	SampEn		scale=10	Left-Frontotemporal
49	0.0512	0.0596	SampEn		scale=16	Right-Frontotemporal
50	-0.0247	0.0730	LZC		scale=13	Right-Frontotemporal
51	-0.0150	0.0747	Asymmetry	LZC	scale=04	frontal
52	0.0513	-0.0556	ratio	BG2TA		Right-Frontotemporal

4.7 Correlation Between Rating and Features

To verify the relationship between the features for classification and the diseases, we calculated the significance of correlation between them. Table 4.41 shows the subject demographic data used to calculate correlation where 4 MDD were excluded due to missing data.

19 ratings are included: duration of illness (duraill), Montgomery-sberg Depression Rating Scale (MADRS), Hamilton Depression Scale (HAMD-17), Hospital Anxiety Rating Scale(HARS), Young Mania Rating Scale (YMRS), number of depressive episode (depepiso), number of manic episode (manicepi), number of total episode (totepiso), manic-depression ratio (mdratio), major depressive episode (minimdd), dysthymia (mindysth), suicidality (minisuic), (Hypo) manic episode (inimani), Panic disorder or agoraphobia (minipani), agoraphobia (miniagor), social anxiety disorder (minisp), Obsessive compulsive disorder (miniocd), Posttraumatic stress disorder (miniptsd), and generalized anxiety disorder (minigad).

Fig. 4.7 and Fig. 4.7 show the significance of correlation between ratings of BD patients and the 24 selected features for classification which are listed in Table 4.6.1. The correlations of agoraphobia and obsessive compulsive disorder are discarded in this table due to all subjects have the same rating value. Fig. 4.7 to Fig. 4.7 show the significance of correlation between ratings of MDD patients and the 37 selected features for classification which are listed in Table 4.6.2 and Table 4.6.2. In MDD case, rating value of (hypo) manic episode are all the same for all MDD subject, thus we discard the result from the table.

Table 4.41: **Demographic data of subjects.** The table shows the demographic data of BD group and MDD group used for calculating correlation between features and ratings.

Variable	BD	MDD
n	26	18
Gender, n(%), male	10 (38.46)	5 (27.78)
Age, mean (SD), years	34.62 (10.40)	35.44 (8.99)
Duration of illness, mean (SD), years	7.96 (6.13)	8 (5.82)

Table 4.42: **The significance of correlation between ratings and features in the BD case.** The boldface of the word means the correlation reach a significant level of $p < 0.05$.

Features	duraill	madrs	hamd17	hars	ymrs	depepiso	manicepi	totepiso	mdratio
Asymmetry SampEn scale=03 frontal	0.6077	0.9693	0.9490	0.9429	0.8799	0.0721	0.3114	0.7072	**0.0491**
Asymmetry SampEn scale=05 frontal	0.5696	0.7954	0.7692	0.7309	0.6678	0.0862	0.2941	0.7540	**0.0432**
SampEn scale=13 Frontal	0.3703	0.6296	0.8290	0.9690	**0.0359**	0.8560	**0.0145**	0.1423	0.0581
SampEn scale=12 Frontal	0.3493	0.5683	0.9036	0.9458	**0.0229**	0.7332	**0.0081**	0.0960	0.0615
Asymmetry LZC scale=03 frontal	0.3916	0.2568	0.4256	0.3823	0.2956	0.3502	0.1884	0.8095	0.1464
Asymmetry SampEn scale=19 interior-frontotemporal	0.7827	0.4658	0.7507	0.4597	0.6933	0.6943	0.3998	0.7874	0.6899
Asymmetry LZC scale=04 frontal	0.4663	0.4804	0.6743	0.5321	0.1901	0.2515	0.1790	0.8858	0.1160
Asymmetry LZC scale=08 frontal	0.5788	0.5060	0.7021	0.7893	0.2540	0.2237	0.1017	0.7907	**0.0137**
Asymmetry SampEn scale=16 interior-frontotemporal	0.7570	0.4991	0.7212	0.5510	0.9548	0.9716	0.2553	0.5255	0.6355
Asymmetry SampEn scale=06 frontal	0.5289	0.7473	0.7203	0.7387	0.6330	0.0997	0.2992	0.7760	**0.0450**
SampEn scale=15 Frontal	0.4794	0.7251	0.7904	0.9401	**0.0370**	0.5964	**0.0123**	0.0882	0.0675
Asymmetry SampEn scale=20 interior-frontotemporal	0.6915	0.5137	0.7549	0.5808	0.6636	0.8064	0.4731	0.7795	0.8705
Asymmetry rB2T frontal	0.7307	0.9661	0.9753	0.5475	0.3030	0.1796	0.2177	0.1438	0.5146
SampEn scale=17 Frontal	0.4304	0.7325	0.8436	0.9313	**0.0182**	0.5837	**0.0148**	0.0927	0.0649
Asymmetry rG2T frontal	0.6058	0.3817	0.6633	0.3846	0.2513	0.9176	0.1065	0.3887	0.1741
Asymmetry SampEn scale=18 interior-frontotemporal	0.6793	0.3560	0.5169	0.3806	0.6624	0.9116	0.3464	0.6298	0.6987
Asymmetry MF frontal	0.9117	0.4418	0.6235	0.4536	0.0933	0.8098	0.0501	0.3318	**0.0105**
Asymmetry theta frontal	0.8328	0.8016	0.5944	0.9154	0.5641	0.5164	0.3528	0.8577	0.0892
Asymmetry LZC scale=14 frontal	0.9291	0.6628	0.6818	0.9622	0.5777	0.2083	0.4389	0.8148	0.0523
Asymmetry SampEn scale=10 frontal	0.4942	0.3969	0.3720	0.4471	0.3593	0.1630	0.3826	0.8032	**0.0338**
Asymmetry LZC scale=10 frontal	0.6847	0.7655	0.9038	0.9850	0.6829	0.1933	0.2190	0.9996	**0.0316**
Asymmetry LZC scale=18 frontal	0.8164	0.6090	0.7661	0.8596	0.5941	0.9606	0.1479	0.3920	0.1883
Asymmetry LZC scale=07 frontal	0.4886	0.2571	0.3856	0.4460	0.2574	0.2575	0.1311	0.8092	0.0693
Asymmetry theta central	0.4520	0.8805	0.8502	0.6532	0.6324	0.5783	0.6895	0.5904	0.9677

Table 4.43: **The significance of correlation between ratings and features in the BD case.** The boldface of the word means the correlation reach a significant level of $p < 0.05$.

Features	minimdd	mindysth	minisuic	inimani	minipani	minisp	miniptsd	minigad
Asymmetry SampEn scale=03 frontal	0.7214	0.9542	0.8393	0.5750	0.8503	0.4709	0.4512	0.3846
Asymmetry SampEn scale=05 frontal	0.7555	0.6891	0.7186	0.5468	0.8164	0.5747	0.4067	0.3692
SampEn scale=13 Frontal	0.6692	0.9834	0.2266	0.7329	0.3592	0.8000	0.6539	0.3235
SampEn scale=12 Frontal	0.6888	0.9304	0.1918	0.7951	0.3256	0.8728	0.7510	0.2320
Asymmetry LZC scale=03 frontal	0.6389	0.6331	0.6349	0.9549	0.8936	0.1921	0.3449	0.5098
Asymmetry SampEn scale=19 interior-frontotemporal	0.9083	**0.0012**	0.7726	0.3614	0.8324	0.7539	**0.0260**	0.5136
Asymmetry LZC scale=04 frontal	0.9209	0.5887	0.8007	0.8526	0.5091	0.4885	0.6495	0.2071
Asymmetry LZC scale=08 frontal	0.5842	0.8001	0.6498	0.7060	0.5095	0.4564	0.3327	0.2396
Asymmetry SampEn scale=16 interior-frontotemporal	0.6534	**0.0014**	0.7375	0.3712	0.6930	0.8461	0.0519	0.5884
Asymmetry SampEn scale=06 frontal	0.6955	0.7001	0.6941	0.5886	0.9835	0.6702	0.4339	0.4059
SampEn scale=15 Frontal	0.6210	0.8836	0.1848	0.8133	0.7335	0.6217	0.7248	0.4524
Asymmetry SampEn scale=20 interior-frontotemporal	0.8614	**0.0018**	0.7406	0.3079	0.5752	0.8758	**0.0439**	0.7418
Asymmetry rB2T frontal	0.9666	0.1357	0.3944	**0.0380**	0.2771	0.4762	0.7189	0.3329
SampEn scale=17 Frontal	0.4933	0.6572	0.1759	0.8381	0.6052	0.6144	0.7096	0.4026
Asymmetry rG2T frontal	0.8355	0.3152	0.6721	0.0832	0.9156	0.5825	0.3262	0.3176
Asymmetry SampEn scale=18 interior-frontotemporal	0.7537	**0.0010**	0.9650	0.2825	0.5709	0.7796	**0.0366**	0.6115
Asymmetry MF frontal	0.5386	0.0628	0.2488	0.4030	0.9629	0.3153	0.3432	0.2141
Asymmetry theta frontal	0.3910	0.4704	0.7317	**0.0120**	0.7727	0.4994	0.7472	0.2564
Asymmetry LZC scale=14 frontal	0.2457	0.6077	0.7571	0.7182	0.7088	0.2020	0.8779	0.2104
Asymmetry SampEn scale=10 frontal	0.6332	0.6278	0.5721	0.7070	0.9745	0.7316	0.5095	0.4610
Asymmetry LZC scale=10 frontal	0.4248	0.8414	0.9770	0.9656	0.6220	0.6388	0.5766	0.3065
Asymmetry LZC scale=18 frontal	0.7898	0.9422	0.6946	0.9900	0.9526	0.4686	0.3683	0.1499
Asymmetry LZC scale=07 frontal	0.4778	0.6200	0.5914	0.9306	0.7855	0.2905	0.7736	0.3399
Asymmetry theta central	0.4252	0.4720	0.0983	0.9764	0.9188	0.8988	0.6258	0.4880

Table 4.44: **The significance of correlation between ratings and features in the MDD case.** The boldface of the word means the correlation reach a significant level of $p < 0.05$. MDD patients do not have manic episodes and manic-depression ratio, thus the significance of correlation is presented as NaN.

Features	duraill	madrs	hamd17	hars	ymrs	depepiso	manicepi	totepiso	mdratio
SampEn scale=08 Right-Frontotemporal	0.3096	0.2360	0.3185	0.1512	0.2746	0.1491	NaN	0.1491	NaN
SampEn scale=10 Right-Frontotemporal	0.3795	0.1538	0.2105	0.0855	0.2759	0.1830	NaN	0.1830	NaN
SampEn scale=12 Right-Frontotemporal	0.4796	0.0935	0.1324	0.0507	0.3496	0.1790	NaN	0.1790	NaN
SampEn scale=07 Left-Frontotemporal	0.3631	0.2306	0.2622	0.1142	0.6478	0.5103	NaN	0.5103	NaN
SampEn scale=08 Left-Frontotemporal	0.4015	0.1937	0.2312	0.0955	0.6519	0.5281	NaN	0.5281	NaN
SampEn scale=15 Right-Frontotemporal	0.6745	**0.0476**	0.0616	**0.0252**	0.5927	0.1577	NaN	0.1577	NaN
SampEn scale=16 Right-Frontotemporal	0.8356	**0.0457**	0.0507	**0.0258**	0.7552	0.1176	NaN	0.1176	NaN
SampEn scale=07 Right-Frontotemporal	0.2810	0.2899	0.3804	0.1933	0.2812	0.1468	NaN	0.1468	NaN
SampEn scale=01 Left-Frontotemporal	0.2378	0.4639	0.4718	0.2590	0.6483	0.4420	NaN	0.4420	NaN
SampEn scale=01 Right-Frontotemporal	0.2124	0.6116	0.7603	0.4977	0.3678	0.1203	NaN	0.1203	NaN
SampEn scale=09 Right-Frontotemporal	0.3256	0.2105	0.2832	0.1242	0.2793	0.1669	NaN	0.1669	NaN
SampEn scale=03 Right-Frontotemporal	0.2249	0.5318	0.6518	0.4117	0.3293	0.1256	NaN	0.1256	NaN
MF Right-Frontotemporal	0.3609	0.0604	0.1210	**0.0284**	0.5755	0.1432	NaN	0.1432	NaN
SampEn scale=09 Left-Frontotemporal	0.4314	0.1517	0.1907	0.0736	0.6732	0.5231	NaN	0.5231	NaN
SampEn scale=04 Right-Frontotemporal	0.2332	0.4786	0.5899	0.3603	0.3130	0.1264	NaN	0.1264	NaN
ratio Gamma/Theta Left-Frontotemporal	0.3547	0.4586	0.5077	0.2262	0.5377	0.6235	NaN	0.6235	NaN
gamma Right-Frontotemporal	0.2698	0.9085	0.7896	0.9916	0.8340	0.0723	NaN	0.0723	NaN
SampEn scale=02 Right-Frontotemporal	0.2211	0.5753	0.7065	0.4569	0.3479	0.1249	NaN	0.1249	NaN
ratio Gamma/Theta Central	0.5193	0.1078	0.2193	0.0972	0.6178	0.4786	NaN	0.4786	NaN

Table 4.45: **The significance of correlation between ratings and features in the MDD case.** The boldface of the word means the correlation reach a significant level of $p < 0.05$. MDD patients do not have manic episodes and manic-depression ratio, thus the significance of correlation is presented as NaN.

Features	duraill	madrs	hamd17	hars	ymrs	depepiso	manicepi	totepiso	mdratio
MF Left-Frontotemporal	0.3505	0.0728	0.1260	**0.0373**	0.9082	0.2052	NaN	0.2052	NaN
SampEn scale=02 Left-Frontotemporal	0.2510	0.4350	0.4401	0.2389	0.6333	0.4688	NaN	0.4688	NaN
ratio BG2TA Central	0.4790	**0.0191**	**0.0416**	**0.0094**	0.5020	0.2194	NaN	0.2194	NaN
ratio BG2TA Right-Frontotemporal	0.4101	0.0848	0.1458	**0.0326**	0.2410	0.4292	NaN	0.4292	NaN
LZC scale=15 Frontal	0.5317	**0.0337**	0.0508	**0.0223**	0.5897	0.1168	NaN	0.1168	NaN
SampEn scale=05 Right-Frontotemporal	0.2366	0.4159	0.5191	0.3030	0.2979	0.1256	NaN	0.1256	NaN
LZC scale=01 Right-Frontotemporal	0.1690	0.7781	0.9160	0.6861	0.5056	0.0895	NaN	0.0895	NaN
SampEn scale=14 Right-Frontotemporal	0.6033	0.0523	0.0700	**0.0271**	0.4650	0.1639	NaN	0.1639	NaN
ratio BG2TA Left-Temporal	0.4943	**0.0395**	0.0877	**0.0242**	0.7193	0.3327	NaN	0.3327	NaN
SampEn scale=06 Right-Frontotemporal	0.2626	0.3534	0.4528	0.2486	0.2864	0.1370	NaN	0.1370	NaN
MF Left-Temporal	0.5279	**0.0391**	0.0906	**0.0266**	0.7831	0.4868	NaN	0.4868	NaN
SampEn scale=11 Right-Frontotemporal	0.4087	0.1166	0.1681	0.0631	0.2917	0.1974	NaN	0.1974	NaN
LZC scale=20 Frontal	0.9035	**0.0485**	0.0549	**0.0468**	0.4392	0.2042	NaN	0.2042	NaN
gamma Central	0.3505	0.2401	0.3879	0.2942	0.8137	0.1051	NaN	0.1051	NaN
SampEn scale=13 Right-Frontotemporal	0.5222	0.0717	0.0993	**0.0360**	0.3756	0.1837	NaN	0.1837	NaN
ratio BG2TA Frontal	0.4923	**0.0177**	0.0574	**0.0126**	0.6489	0.2623	NaN	0.2623	NaN
gamma Left-Frontotemporal	0.2393	0.7333	0.7591	0.5253	0.8951	0.2196	NaN	0.21958	NaN
SampEn scale=01 Central	0.3827	0.1399	0.2205	0.1565	0.8982	0.1827	NaN	0.1827	NaN

Table 4.46: **The significance of correlation between ratings and features in the MDD case.** The boldface of the word means the correlation reach a significant level of $p < 0.05$. The rating of (Hypo) manic episode is presented as NaN due to the same value.

Features	minimdd	mindysth	minisuic	minipani	miniagor	minisp	miniocd	miniptsd	minigad
SampEn scale=08 Right-Frontotemporal	0.8497	0.0583	0.1211	0.8125	0.6512	0.1664	0.4876	0.2083	0.7802
SampEn scale=10 Right-Frontotemporal	0.9009	0.0644	0.1285	0.7547	0.4231	0.1684	0.4290	0.1370	0.7445
SampEn scale=12 Right-Frontotemporal	0.8987	0.0760	0.1132	0.7724	0.3162	0.1284	0.3425	0.0878	0.7141
SampEn scale=07 Left-Frontotemporal	0.7957	0.2091	0.2525	0.5118	0.2874	0.1715	0.5137	0.3813	0.5673
SampEn scale=08 Left-Frontotemporal	0.8131	0.2117	0.2582	0.5306	0.2340	0.1692	0.5157	0.3594	0.5694
SampEn scale=15 Right-Frontotemporal	0.7978	0.1017	0.1061	0.9689	0.3337	0.0610	0.2081	0.0525	0.6946
SampEn scale=16 Right-Frontotemporal	0.7675	0.1564	0.0638	0.9744	0.3287	**0.0485**	0.1337	**0.0354**	0.6682
SampEn scale=07 Right-Frontotemporal	0.8090	0.0622	0.1189	0.8418	0.7496	0.1741	0.5074	0.2406	0.8112
SampEn scale=01 Left-Frontotemporal	0.7504	0.2046	0.2650	0.4695	0.6215	0.1741	0.5630	0.4909	0.6070
SampEn scale=01 Right-Frontotemporal	0.8303	0.0838	0.1644	0.9392	0.7675	0.2035	0.7507	0.6247	0.8683
SampEn scale=09 Right-Frontotemporal	0.8839	0.0630	0.1358	0.7912	0.5226	0.1704	0.4607	0.1727	0.7659
SampEn scale=03 Right-Frontotemporal	0.7508	0.0779	0.1301	0.9364	0.8436	0.2009	0.6347	0.4661	0.8892
MF Right-Frontotemporal	0.2789	0.0633	0.4918	0.4522	0.0823	0.1214	0.8035	0.3750	0.7956
SampEn scale=09 Left-Frontotemporal	0.7715	0.2110	0.2631	0.5223	0.1771	0.1656	0.5259	0.3578	0.5638
SampEn scale=04 Right-Frontotemporal	0.7476	0.0726	0.1215	0.9230	0.9121	0.1924	0.5894	0.3992	0.8755
ratio Gamma/Theta Left-Frontotemporal	0.3289	0.2553	0.5191	0.1709	0.2950	0.2016	0.8662	0.5585	0.3635
gamma Right-Frontotemporal	0.8974	0.1836	0.3733	0.6073	0.1476	0.1387	0.9618	0.7256	0.7227
SampEn scale=02 Right-Frontotemporal	0.7721	0.0833	0.1417	0.9390	0.7963	0.2063	0.6864	0.5398	0.8901
ratio Gamma/Theta Central	0.8940	0.1941	0.1895	0.3792	0.3290	0.1155	0.7679	0.3739	0.6734

Table 4.47: **The significance of correlation between ratings and features in the MDD case.** The boldface of the word means the correlation reach a significant level of $p < 0.05$. The rating of (Hypo) manic episode is presented as NaN due to the same value.

Features	minimdd	mindysth	minisuic	minipani	miniagor	minisp	miniocd	miniptsd	minigad
MF Left-Frontotemporal	0.2666	0.1253	0.4932	0.3699	0.0727	0.1088	0.7650	0.4012	0.9558
SampEn scale=02 Left-Frontotemporal	0.7933	0.2091	0.2448	0.4855	0.5836	0.1824	0.5394	0.4662	0.6010
ratio BG2TA Central	0.4153	0.0793	0.4710	0.4421	**0.0478**	0.2343	0.6407	0.1812	0.9791
ratio BG2TA Right-Frontotemporal	0.3955	0.0887	0.6373	0.3514	**0.0476**	0.4359	0.9122	0.2620	0.7858
LZC scale=15 Frontal	0.2858	0.2676	0.2376	0.4934	0.0972	**0.0299**	0.4818	0.3961	0.6435
SampEn scale=05 Right-Frontotemporal	0.7734	0.0643	0.1167	0.9051	0.9974	0.1844	0.5572	0.3408	0.8559
LZC scale=01 Right-Frontotemporal	0.9967	0.1087	0.1656	0.8838	0.6263	0.1813	0.7730	0.8553	0.8745
SampEn scale=14 Right-Frontotemporal	0.8263	0.0896	0.0968	0.8474	0.3073	0.0866	0.2245	**0.0474**	0.7031
ratio BG2TA Left-Temporal	0.3526	0.1315	0.5193	0.4594	**0.0313**	0.2622	0.7589	0.3286	0.9617
SampEn scale=06 Right-Frontotemporal	0.7811	0.0636	0.1162	0.8734	0.8883	0.1782	0.5386	0.2935	0.8313
MF Left-Temporal	0.2126	0.1456	0.6558	0.3654	**0.0170**	0.2852	0.9121	0.4264	0.9021
SampEn scale=11 Right-Frontotemporal	0.9128	0.0641	0.1393	0.7311	0.3649	0.1430	0.4060	0.1145	0.7208
LZC scale=20 Frontal	0.6834	0.5718	0.1340	0.6367	0.1191	**0.0450**	0.2576	0.1536	0.9014
gamma Central	0.7006	0.1361	0.1693	0.7280	0.5519	**0.0374**	0.6444	0.5735	0.8423
SampEn scale=13 Right-Frontotemporal	0.9238	0.0809	0.1161	0.7712	0.2681	0.1241	0.3076	0.0704	0.6765
ratio BG2TA Frontal	0.3825	0.0863	0.6326	0.6027	**0.0401**	0.1943	0.9279	0.3887	0.7759
gamma Left-Frontotemporal	0.6918	0.2475	0.4259	0.7232	0.7115	0.0721	0.6804	0.8522	0.6893
SampEn scale=01 Central	0.5118	0.0967	0.1189	0.6809	0.9413	0.0709	0.4284	0.2434	0.7033

Chapter 5

Discussion

5.1 Suitable Spectral Ratios for Mood Disorders

The concept of spectral ratios originated from the studies of Alzheimer's disease (AD). It is based on the particular phenomenon of this disease, slowing. The powers of the high frequencies are increasing apparently, and the powers of the low frequency band are decreasing. That is, the activities of the brain slow down. According to this, the researchers using the ratio of high to low frequency band power to enhance the difference of the slowing phenomenon.

However, mood disorders do not have the same characteristic of slowing, and that is different from Alzheimer's disease. Thus the spectral ratios designed for Alzheimer's disease may not work so well in the cases of mood disorders just like in AD case. To consider the characteristics of mood disorders, five new spectral ratios described in section 2.2.3 were designed to enhance the difference between different groups. These spectral ratios are mainly based on the discrepancies between NC and the patients with major depressive disorder. Because all of the beta and gamma band powers of MDD patients are larger than NC, and the theta and alpha band powers are almost smaller as shown in Fig. 4.3. Therefore, we use the ratio of beta and gamma bands to theta and alpha bands to reveal the differences between high frequencies to slow frequencies in mood disorders.

Table 5.1 shows the comparison of different spectral ratios between NC and MDD patients. The first three rows of the table are the spectral ratios brought up by the studies about Alzheimer's disease, and the last five rows are the ratios we used in this work. Obviously, most of the ratios we used have clearer differences between the two group than those used for Alzheimer's disease.

5.2 Spectral Entropies

In this work, we adopted two spectral entropies. The first type of spectral entropy ($SE1$) is defined in Eq. 2.12 where all frequency bins in PSD are directly used to calculate spectral entropy. However, we often focus on the frequency bands rather than each frequency bins while researching on brain activities. Moreover, the resolutions in frequency are different in low frequencies and high frequencies. For example, theta band is generally defined

Table 5.1: **Comparison of different spectral ratios.** Comparison of different spectral ratios.

Variable	Frontal	Central	Occipital	Frontotemporal		Temporal		All
				Left	Right	Left	Right	
$\frac{RP(\alpha)}{RP(\theta)}$	0.229	0.620	0.363	0.553	0.816	0.420	0.612	0.494
$\frac{RP(\alpha)+RP(\beta)+RP(\gamma)}{RP(\delta)+RP(\theta)}$	0.912	0.968	0.559	0.666	0.725	0.795	0.929	0.949
$\frac{RP(\beta)}{RP(\delta)}$	0.146	0.135	0.187	0.144	0.146	0.211	0.117	0.127
$\frac{RP(\beta)+RP(\gamma)}{RP(\theta)+RP(\alpha)}$	**0.018**	**0.020**	0.101	**0.028**	**0.024**	**0.030**	**0.037**	**0.027**
$\frac{RP(\beta)}{RP(\theta)}$	0.071	0.060	0.250	0.077	0.072	0.105	0.106	0.096
$\frac{RP(\beta)}{RP(\alpha)}$	**0.031**	**0.040**	0.111	0.056	0.061	**0.044**	0.066	**0.046**
$\frac{RP(\gamma)}{RP(\theta)}$	0.077	**0.005**	0.856	**0.012**	**0.009**	0.129	0.162	0.057
$\frac{RP(\gamma)}{RP(\alpha)}$	0.070	**0.043**	0.705	0.063	0.099	0.181	0.389	0.135

as 4-8 HZ, alpha band is 8-13 Hz, and beta band is 13-30 Hz. Each band has different bandwidth: theta band is 4 Hz, alpha band is 5 Hz, and beta band is 17 Hz. Therefore, different frequency bands have different weighting and contribution in the first type of spectral entropy ($SE1$).

On the contrary, $SE2$ which is defined in Eq. 2.14 uses average power of individual frequency bands, and the value won't be influenced by the width of the frequency band.

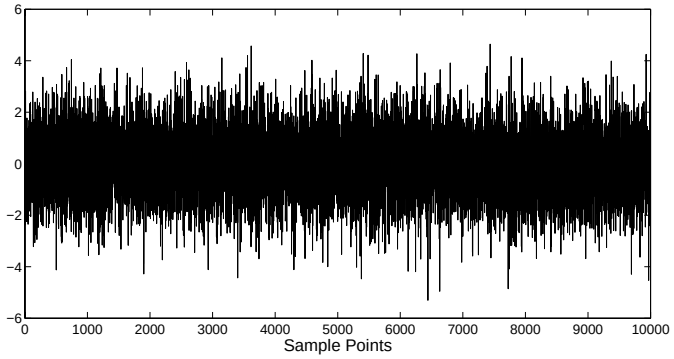
Although the two spectral entropies are quite similar, they have their meaning. In this work, both of them were adopted and they show different results. The hemispheric asymmetries of SE1 show the differences between NC and BD patients, and NC and MDD patients in frontal. On the contrary, SE2 shows the differences between NC and MDD in the frontal and frontotemporal, and between BD and MDD in the frontotemporal and temporal.

5.3 The Parameters in Multi-scale Sample Entropy

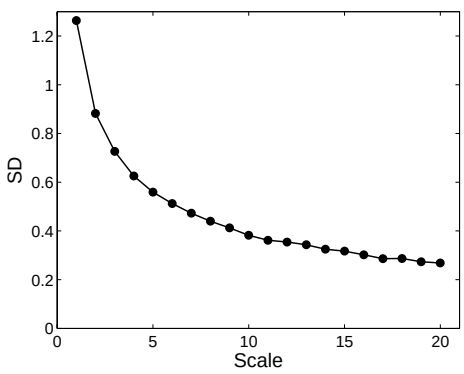
The objective of MSE method described in section 2.3.3 is to measuring entropy at different scales. When MSE method was applied to sample entropy, there is an issue about the parameters r and m in sample entropy.

r is the tolerant range of match. If the distance between two subsequences is larger than r, then the two subsequences are different, otherwise they are considered as equal subsequences. The output of sample entropy provides a likelihood measure that two sequences within tolerance range r remain close at the next point. The smaller the sampEn is, the more regular the sequence is. As the r decrease, the sampEn increases because the criterion for the similarity becomes strict. Typically, r is suggested to be 10% to 25% of standerd deviation (SD) of the sequence.

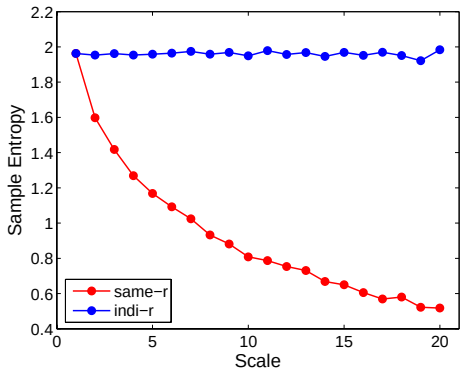
The MSE algorithm brings up the idea of using sample entropy for different scale τ and then creating several coarse-grained sequences with different scales. Some studies set r at a certain percentage of the original time series SD, and remains constant for all scales [12,18]. However, the coarse-grained sequences are reconstructed by means of every τ sample points in original time series. That is similar to smoothing of the data, and cause



(a) White noise



(b) Standard deviation



(c) Sample entropy

Figure 5.1: **The influence of different r in multi-scale sample entropy.** (a) Original white noise signal. (b) The change of standard deviation with different scales. (c) The change of sample entropies with different scales where the red stands for the situation that r is fixed and the blue stands for individual r varing with different scales.

the decreasing of SD. Therefore, when the scale τ increases, the corresponding standard deviation of the time series will decrease. If we set r at a certain percentage of the original time series SD, the r will be relatively larger in the coarse-grained sequences with $\tau > 1$. It means the looser criterion of similarity and lead to a smaller value of sample entropy.

Fig. 5.1 shows a simple experiment of MSE in white noise. After scaling the original signal, the standard deviation decreases showed in Fig. 5.1(b). Fig. 5.1(c) shows a MSE result by using the fixed r for all scales and using the individual r as 0.25 times of SD in every scale.

m is a window size (subsequence length) used for compare. To deside the parameter of m in multi-scale analysis, we consider an experiment showed in Fig. 5.2 and which was brought up by Costa [13]. In the experiment, Costa tried the parameter m between $m = 1$ and $m = 8$, and found that the mean values of sample entropies vary less than 2% and the coefficient of variation (the ratio of standard deviation to mean) is less than 3% for two types of noise between $m = 1$ and $m = 5$. Besides, the sample entropies and coefficient of variation increase with larger m due to the finite number of data points since it need a longer time series for statistical accuracy. It means that the value of parameter m doesn't influence the sample entropy significantly. Therefore, we use $m = 1$ in this work for well efficiency.

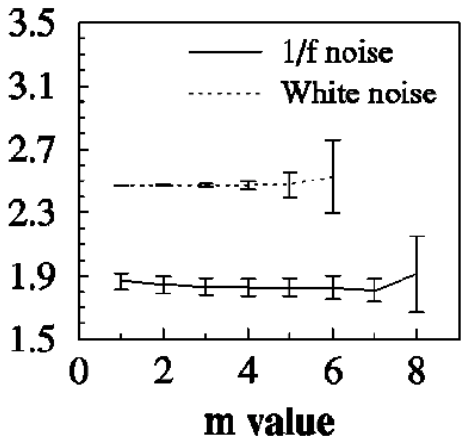


Figure 5.2: **The influence of different m in multi-scale sample entropy [13].**

5.4 Features for Classification

In the two-groups classification of NC and BD patients, the features about hemispheric asymmetry seems very important, and this characteristic is obvious especially in the frontal and the interior-frontotemporal. The most important features, with largest weightings, are almost about temporal complexity including LZ complexity and sample entropy. The next are the asymmetry of spectral ratios in frontal, and then MF and theta band. Besides asymmetric features, only the feature of sample entropies play a part in classification.

To verify the relationship between these features and bipolar disorder, we calculated the significance of correlation between them. YMRS and the number of manic episode have a consistent result, and they are correlated with sample entropy in frontal with scales of 12 to 17. Manic-depression ratio correlates with asymmetric indices of sample entropy, LZC and mean frequency (MF) in frontal. Dysthymia has the strongest correlation ($p \approx 0.001$) with asymmetric sample entropy in interior-frontotemporal where the scales are large. Posttraumatic stress disorder has a similar result to dysthymia, but the correlation is not as strong as dysthymia. Besides, about (hypo) manic episode, the correlations with asymmetric relative theta band power and spectral ratio of beta to theta ratio are significant in frontal.

In the classification of NC and MDD patients, the features with the largest weighting are almost locate in the frontotemporal, especially in right frontotemporal. The next are in the central and frontal, and a liitle locate in the left temporal. The features with the largest 15 weightings are all sample entropies, besides MF. Gamma band powers and the spectral ratios about gamma band also contribute to classification. Contrast to the classification between NC and BD patients, there are no hemispheric asymmetric features used for classification.

The features selected for classification between NC and MDD are correlated with dysthymia, agoraphobia, social anxiety disorder, posttraumatic stress disorder, and the indices about depression: MADRS, HAMD-17, and HARS. Among them, MADRS and HARS are closely related with major depressive disorder, but the correlation with dysthymia does not reach significant level. MADRS and HARS are correlated with sample entropy in frontotemporal of the scales around 15, and others are LZC in frontal, spectral ratio of beta

and gamma power to theta and alpha power in frontal, central, temporal, and then MF in frontotemporal and left temporal. Agoraphobia is realated to the spectral ratio of beta and gamma band power to theta and alpha band power in frontal, central, right frontotemporal and left temporal. In the case of social anxiety disorder, significant correlations occur in sample entropy in right frontotemporal, LZC in frontal, and relative gamma band power in central. Besides, posttraumatic stress disorder only correlate with sample entropy in right frontotemporal.

In the classification of BD patients and MDD patients, the features about temporal complexity play an important role. Twelve of seventeen selected featurs are LZC and sample entropy in the right frontotemporal, and the others are the features about hemispheric asymmetry in the occipital and central. They are sample entropies in the occipital and the LZC, gamma and alpha band power in the central.

Chapter 6

Conclusions

In this work, we tried to differentiate BD patients, MDD patients and healthy controls by the resting MEG signals.

We began from the feature extraction. Eight ROIs and three kinds of features are included in this work. The ROIs include frontal, central, occipital, left frontotemporal, right frontotemporal, left temporal, right temporal, and an union of the seven area. The features are about power spectral density (PSD), temporal complexity, and hemispheric asymmetry. About the PSD features, we first analyzed the relative band power. To enhance the difference of band powers, we designed the spectral ratios which are beneficial to classification of mood disorders. MF and SEF90 were used to summarize the trend of band power distribution. And then two types of spectral entropies were used to quantify the flatness of the power spectral density. About the features of temporal complexity, LZC and sample entropy (SampEn) were applied to measure the complexity of time series. To overcome the problems caused by different sampling rate, multi-scale entropy (MSE) is applied to not only sample entropy but also LZC. About the features of hemispheric asymmetry, we normalized the difference, of the features mentioned above, between left and right hemisphere.

For all ROIs and all kinds of features, there are totally 756 features extracted. To select a reasonable number of features for classification, t-test and Linear Discriminant Analysis (LDA) were applied. The p-values of t-test assist in select the features with a significant difference. LDA was then used to determine which feature is beneficial to classification. Not only for selecting features, LDA also used to reduce the feature set. We used the projection matrix of LDA to project features set into a low dimension space where there is a better distinction between group and group. Finally, the classification was brought out by support vector machine (SVM). By this procedure, we project the 756 dimensional feature space into a one or two dimensional subspace, and then used for classification. The result of classification showed that we got almost 100% accuracy through this procedure.

The weighting of the projection matrix showed the importance of a feature for classification. From the weightings, we got a conclusion about the most different features between group and group as follows:

- **NC vs. BD** Asymmetry of LZC and sample entropy in frontal, and interior-frontotemporal.

- **NC vs. MDD** Sample entorpies in frontotemporal.

- **BD vs. MDD** LZC and Sample entropies in right frontotemporal.

Bibliography

[1] J. Ziv A. Lempel. Compression of two-dimensional data. *IEEE Trans. Inf. Theory*, 32(IT-1):2–8, 1986.

[2] M. Aboy, R. Hornero, D. Abasolo, and D. Alvarez. Interpretation of the lempel-ziv complexity measure in the context of biomedical signal analysis. *IEEE Trans Biomed Eng*, 53(11):2282–8, 2006. 0018-9294 (Print) Journal Article Research Support, Non-U.S. Gov't.

[3] Jacob Ziv Abraham Lempel. On the complexity of finite sequences. *IEEE TRANSACTIONS ON INFORMATION THEORY*, IT-22, 1976.

[4] J. J. Allen, W. G. Iacono, R. A. Depue, and P. Arbisi. Regional electroencephalographic asymmetries in bipolar seasonal affective disorder before and after exposure to bright light. *Biol Psychiatry*, 33(8-9):642–6, 1993. 0006-3223 (Print) Journal Article Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.

[5] Jacob Ziv Amos Lapidoth. On the universality of the lz-based decoding algorithm. *IEEE Trans. Inf. Theory*, 44(5):1746–1755, 1998.

[6] Robert P.W. Duin Anil K. Jain and Jianchang Mao. Statistical pattern recognition: A review. *IEEE Transactions on pattern analysis and machine intelligence*, 22(1):4–37, 2000.

[7] Berthold Bein. Entropy. 20(1):101–109, 2006.

[8] K. Bennys, G. Rondouin, C. Vergnes, and J. Touchon. Diagnostic value of quantitative

eeg in alzheimer's disease. *Neurophysiol Clin*, 31(3):153–60, 2001. 0987-7053 (Print) Clinical Trial Journal Article.

[9] G. E. Bruder, R. Fong, C. E. Tenke, P. Leite, J. P. Towey, J. E. Stewart, P. J. McGrath, and F. M. Quitkin. Regional brain asymmetries in major depression with or without an anxiety disorder: a quantitative electroencephalographic study. *Biol Psychiatry*, 41(9):939–48, 1997. 0006-3223 (Print) Journal Article Research Support, U.S. Gov't, P.H.S.

[10] Shannon CE. A mathematical theory of communication. *Bell System Technical Journal*, 27:623–656, 1948.

[11] C.C. Chang and C.J. Lin. Libsvm : a library for support vector machines, 2001. software available at http://www.csie.ntu.edu.tw/ cjlin/libsvm.

[12] M. Costa, A. L. Goldberger, and C. K. Peng. Multiscale entropy analysis of complex physiologic time series. *Phys Rev Lett*, 89(6):068102, 2002. 0031-9007 (Print) Journal Article Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.

[13] M. Costa, A. L. Goldberger, and C. K. Peng. Multiscale entropy analysis of biological signals. *Phys Rev E Stat Nonlin Soft Matter Phys*, 71(2 Pt 1):021906, 2005. 1539-3755 (Print) Clinical Trial Controlled Clinical Trial Journal Article Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.

[14] J. Escudero, R. Hornero, D. Abasolo, A. Fernandez, and J. Poza. Magnetoencephalogram blind source separation and component selection procedure to improve the diagnosis of alzheimer's disease patients. *Conf Proc IEEE Eng Med Biol Soc*, 2007:5437–40, 2007. 1557-170X (Print) Evaluation Studies Journal Article Research Support, Non-U.S. Gov't.

[15] J. Escudero, R. Hornero, J. Poza, D. Abasolo, and A. Fernandez. Assessment of classification improvement in patients with alzheimer's disease based on magnetoencephalogram blind source separation. *Artif Intell Med*, 43(1):75–85, 2008. 0933-3657 (Print) Journal Article Research Support, Non-U.S. Gov't.

[16] A. A. Fingelkurts, A. A. Fingelkurts, H. Rytsala, K. Suominen, E. Isometsa, and S. Kahkonen. Composition of brain oscillations in ongoing eeg during major depression disorder. *Neurosci Res*, 56(2):133–44, 2006. 0168-0102 (Print) Comparative Study Journal Article Research Support, Non-U.S. Gov't.

[17] Ronald A. Fisher. The use of multiple measurements in taxonomic problems. *Annals of Eugenics*, 7:179–188, 1936.

[18] C. Gomez, R. Hornero, D. Abasolo, A. Fernandez, and J. Escudero. Analysis of meg recordings from alzheimer's disease patients with sample and multiscale entropies. *Conf Proc IEEE Eng Med Biol Soc*, 2007:6184–7, 2007. 1557-170X (Print) Journal Article Research Support, Non-U.S. Gov't.

[19] C. Gomez, R. Hornero, D. Abasolo, A. Fernandez, and M. Lopez. Complexity analysis of the magnetoencephalogram background activity in alzheimer's disease patients. *Med Eng Phys*, 28(9):851–9, 2006. 1350-4533 (Print) Journal Article Research Support, Non-U.S. Gov't.

[20] F. Graae, C. Tenke, G. Bruder, M. J. Rotheram, J. Piacentini, D. Castro-Blanco, P. Leite, and J. Towey. Abnormality of eeg alpha asymmetry in female adolescent suicide attempters. *Biol Psychiatry*, 40(8):706–13, 1996. 0006-3223 (Print) Journal Article.

[21] V. D. Gusev, L. A. Nemytikova, and N. A. Chuzhanova. On the complexity measures of genetic sequences. *Bioinformatics*, 15(12):994–9, 1999. 1367-4803 (Print) Journal Article Research Support, Non-U.S. Gov't.

[22] E. Harmon-Jones and J. J. Allen. Behavioral activation sensitivity and resting frontal eeg asymmetry: covariation of putative indicators related to risk for mood disorders. *J Abnorm Psychol*, 106(1):159–63, 1997. 0021-843X (Print) Journal Article Research Support, Non-U.S. Gov't.

[23] A. Lempel J. Ziv. Compression of individual sequences via variable-rate coding. *IEEE Trans. Inf. Theory*, IT-24(5):530–536, 1978.

[24] V. Jelic, M. Blomberg, T. Dierks, H. Basun, M. Shigeta, P. Julin, M. Jensen, L. Lannfelt, B. Winblad, and L. O. Wahlund. Eeg slowing and cerebrospinal fluid tau levels in patients with cognitive decline. *Neuroreport*, 9(1):157–60, 1998. 0959-4965 (Print) Journal Article Research Support, Non-U.S. Gov't.

[25] N. Kannathal, M. L. Choo, U. R. Acharya, and P. K. Sadasivan. Entropies for detection of epilepsy in eeg. *Comput Methods Programs Biomed*, 80(3):187–94, 2005. 0169-2607 (Print) Evaluation Studies Journal Article.

[26] V. Knott, C. Mahoney, S. Kennedy, and K. Evans. Eeg power, frequency, asymmetry and coherence in male depression. *Psychiatry Res*, 106(2):123–40, 2001. 0165-1781 (Print) Journal Article Research Support, Non-U.S. Gov't.

[27] A. F. Leuchter, I. A. Cook, T. F. Newton, J. Dunkin, D. O. Walter, S. Rosenberg-Thompson, P. A. Lachenbruch, and H. Weiner. Regional differences in brain electrical activity in dementia: use of spectral power and spectral ratio measures. *Electroencephalogr Clin Neurophysiol*, 87(6):385–93, 1993. 0013-4694 (Print) Journal Article Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.

[28] K. Linkenkaer-Hansen, S. Monto, H. Rytsala, K. Suominen, E. Isometsa, and S. Kahkonen. Breakdown of long-range temporal correlations in theta oscillations in patients with major depressive disorder. *J Neurosci*, 25(44):10131–7, 2005. 1529-2401 (Electronic) Comparative Study Journal Article Research Support, Non-U.S. Gov't.

[29] R. Nagarajan. Quantifying physiological data with lempel-ziv complexity–certain issues. *IEEE Trans Biomed Eng*, 49(11):1371–3, 2002. 0018-9294 (Print) Comparative Study Journal Article.

[30] J. Poza, R. Hornero, D. Abasolo, A. Fernandez, and J. Escudero. Analysis of spontaneous meg activity in patients with alzheimer's disease using spectral entropies. *Conf Proc IEEE Eng Med Biol Soc*, 2007:6180–3, 2007. 1557-170X (Print) Journal Article Research Support, Non-U.S. Gov't.

[31] J. Poza, R. Hornero, D. Abasolo, A. Fernandez, and M. Garcia. Extraction of spectral based measures from meg background oscillations in alzheimer's disease. *Med Eng Phys*, 29(10):1073–83, 2007. 1350-4533 (Print) Journal Article Research Support, Non-U.S. Gov't.

[32] J. Poza, R. Hornero, D. Abasolo, A. Fernandez, and A. Mayo. Evaluation of spectral ratio measures from spontaneous meg recordings in patients with alzheimer's disease. *Comput Methods Programs Biomed*, 90(2):137–47, 2008. 0169-2607 (Print) Evaluation Studies Journal Article.

[33] N. Radhakrishnan and B. N. Gangadhar. Estimating regularity in epileptic seizure time-series data. a complexity-measure approach. *IEEE Eng Med Biol Mag*, 17(3):89–94, 1998. 0739-5175 (Print) Journal Article Review.

[34] R. A. Roemer, C. Shagass, W. Dubin, R. Jaffe, and L. Siegal. Quantitative eeg in elderly depressives. *Brain Topogr*, 4(4):285–90, 1992. 0896-0267 (Print) Comparative Study Journal Article Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.

[35] KONSTANTINOS KOUTROUMBAS SERGIOS THEODORIDIS. *Pattern recognition*. Academic Press, U.S.A, second edition edition, 2003.

[36] Y. I. Sheline. Neuroimaging studies of mood disorder effects on the brain. *Biol Psychiatry*, 54(3):338–52, 2003. 0006-3223 (Print) Journal Article Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review.

[37] J. C. Soares and J. J. Mann. The anatomy of mood disorders–review of structural neuroimaging studies. *Biol Psychiatry*, 41(1):86–106, 1997. 0006-3223 (Print) Journal Article Research Support, U.S. Gov't, P.H.S. Review.

[38] H. Soininen, J. Partanen, V. Laulumaa, E. L. Helkala, M. Laakso, and P. J. Riekkinen. Longitudinal eeg spectral analysis in early stage of alzheimer's disease. *Electroencephalogr Clin Neurophysiol*, 72(4):290–7, 1989. 0013-4694 (Print) Journal Article Research Support, Non-U.S. Gov't.

[39] S. M. Strakowski, C. M. Adler, and M. P. DelBello. Volumetric mri studies of mood disorders: do they distinguish unipolar and bipolar disorder? *Bipolar Disord*, 4(2):80–8, 2002. 1398-5647 (Print) Journal Article Review.

[40] S. M. Strakowski, M. P. Delbello, and C. M. Adler. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Mol Psychiatry*, 10(1):105–16, 2005. 1359-4184 (Print) Journal Article Research Support, Non-U.S. Gov't Review.

[41] J. Szczepanski, J. M. Amigo, E. Wajnryb, and M. V. Sanchez-Vives. Application of lempel-ziv complexity to the analysis of neural discharges. *Network*, 14(2):335–50, 2003. 0954-898X (Print) Journal Article Research Support, Non-U.S. Gov't.

[42] Guy Louchard Szpankowski and Wojciech. On the average redundancy rate of the lempel-ziv code. *IEEE Trans. Inf. Theory*, 43(1):2–8, 1997.

[43] A.J. Tomarken and A.D. Keener. Frontal brain asymmetry and depression: a self-regulatory perspective. *Cognition and Emotion*, 12:387–420, 1998.

[44] P. H. Tonner and B. Bein. Classic electroencephalographic parameters: median frequency, spectral edge frequency etc. *Best Pract Res Clin Anaesthesiol*, 20(1):147–59, 2006. 1753-3740 (Print) Journal Article Review.

[45] M. Vuga, N. A. Fox, J. F. Cohn, C. J. George, R. M. Levenstein, and M. Kovacs. Long-term stability of frontal electroencephalographic asymmetry in adults with a history of depression and controls. *Int J Psychophysiol*, 59(2):107–15, 2006. 0167-8760 (Print) Controlled Clinical Trial Journal Article Research Support, N.I.H., Extramural.

[46] Erik Weber Jensen Xu-Sheng Zhang, Rob J. Roy. Eeg complexity as a measure of depth of anesthesia for patients. *IEEE Trans Biomed Eng*, 48(12):1424–1433, 2001.