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EEG Biomarkers for Identifying Depressive State in Healthy Individuals during Resting-state and Stimulus Processing

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Chapter 1 Introduction

1.1 Background

Depression is a major global health concern with significant individual and societal impacts. Characterized by persistent sadness and a lack of interest in life, depression affects over hundreds of millions worldwide. Early detection is crucial for effective treatment, yet current diagnostic methods, which rely heavily on subjective assessments, are insufficient. This underscores the need for objective biomarkers that can detect the disorder before clinical symptoms become apparent.

Electroencephalography (EEG) is a promising tool in psychiatric research, offering a non-invasive, cost-effective method for examining brain activity with high temporal resolution. Biomarkers, by definition, are measurable indicators of some biological state or condition, they include molecular, neuroimaging, and neurophysiological categories. EEG stands out for its ability to track brain function changes, which could provide insights into the neurobiological mechanism of depression.

Molecular biomarkers, such as genetic markers and protein levels, have been studied for their role in depression but offer limited specificity due to the heterogeneity of the disorder. Neuroimaging biomarkers, including changes in brain structure and function visible via MRI and PET scans, have also been explored. Compared to other neuroimaging techniques, EEG is portable, relatively affordable, and allows for large-scale data collection, making it a promising tool for developing clinically useful biomarkers. Despite its promise, EEG research in depression faces significant challenges. There is a need for standardization in EEG methodologies and a deeper understanding of EEG patterns in non-clinical populations.

The identification of EEG data during both resting-state (without emotion induction) and external emotional image processing is crucial in the field of neuroscience and psychology for several reasons. Resting-state EEG provides insights into the brain's baseline activity when it is not stimulated by any external task. This state is crucial for understanding the intrinsic organization of the brain, including its default mode network,

which is active during passive rest and involved in internal thought processes such as daydreaming, recalling memories, or planning. During external emotional image processing, the brain is actively engaged in interpreting and reacting to emotional stimuli. This active state allows researchers to study how emotions affect brain activity and to identify which areas of the brain are involved in emotional responses. The identification of EEG data during resting state and external information processing can reveal deeper insights into how individuals with different depressive states differ in their brain response patterns.

This study aims to identify EEG biomarkers that can predict depressive states in healthy individuals by examining specific EEG patterns during resting-state and stimulus processing. The successful identification of reliable EEG biomarkers could significantly advance psychiatry, particularly in early detection and prevention of depression. This research may lead to more personalized and effective treatment strategies, improving outcomes for those at risk. Additionally, integrating EEG biomarkers into regular health assessments could encourage a proactive approach to mental health care, potentially easing the global burden of depression.

1.2 The Definition of Depression

♦ ***The prevalence of depression***

Depression is a complex and serious mental health disorder that affects millions globally, impacting individuals' emotional and physical health. As illustrated by the Burden of Mental Illness (Figure 1.1), the impact of depressive disorders is substantial, with most significant social and economic consequences and has the highest lifetime prevalence among all the mental illnesses. As the shown in Prevalence of Major Depressive Disorder (Figure 1.2), the increasing trend with the year accelerated rapidly after the corona pandemic.

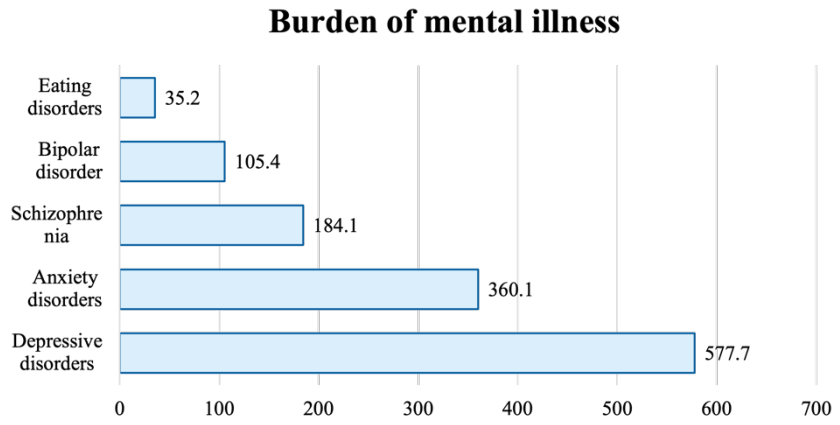

Figure 1.1 Burden of mental illness (IHME, Global Burden of Disease, 2024)

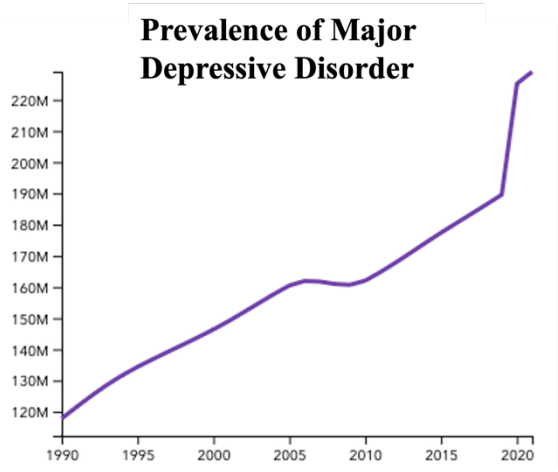

Figure 1.2 Prevalence of Major Depressive Disorder (GBD, 2021)

♦ ***The symptoms of depression***

Depression is normally understood as the paradox between the depressed patient's image and the objective truth, and it's puzzling that the patient's attitude is in contrast to some principles of human nature such as maximizing pleasure and minimizing pain (Beck, 1967). Characterized primarily by persistent sadness and a loss of interest in activities once enjoyed, depression extends far beyond these features. Patients often experience a wide range of emotional symptoms including feelings of worthlessness, pervasive guilt, and a marked decrease in motivation or pleasure in nearly all activities. These emotional disturbances are frequently accompanied by significant physical symptoms such as changes in appetite or weight, sleep disturbances (either insomnia or hypersomnia), psychomotor agitation or retardation, and chronic fatigue, which can further impair an individual's daily functioning (Kessler et al., 2003).

♦ ***Cognitive impact of depression***

Cognitively, depression is associated with a diminished ability to think, concentrate, or make decisions. This cognitive decline often exacerbates other symptoms and may impair personal and professional relationships (Beck, 1967). From a behavioral perspective, individuals with depression may exhibit withdrawal from social interactions, reduced productivity, and a lack of responsiveness, which can be misinterpreted by others as disinterest or personal dislike (Gotlib and Hammen, 2009).

1.3 Importance of Early Detection

Depression frequently begins to manifest around the age of 19, a critical period of emerging adulthood characterized by significant social, educational, and biological transitions (Figure 1.3). Effective early intervention strategies are crucial, as they not only support healthy development during these formative years but also mitigate the risk of

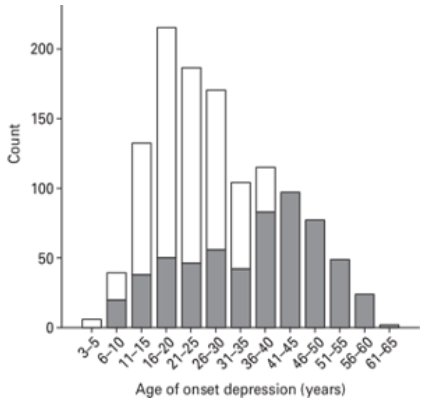

Figure 1.3 Distribution of age at onset of first depression
(Van Noorden, et al., 2010)

long-term psychological issues. Such interventions can significantly alter developmental pathways, potentially preventing the escalation of both social and academic difficulties often exacerbated by untreated depression (Kessler et al., 2005).

Without early detection and treatment, depression can become a recurrent or chronic condition (Figure 1.4). Studies have demonstrated that with each subsequent episode of

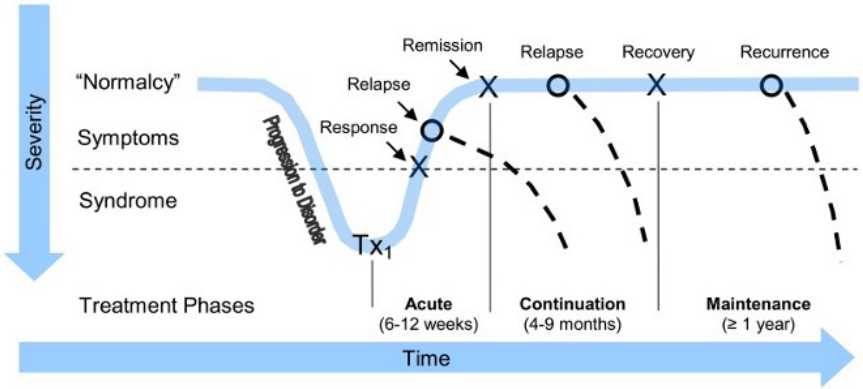

Figure 1.4 Phase of treatment of depression (Gartlehner, et al., 2015)

depression, the likelihood of recurrence increases. Therefore, early therapeutic interventions are crucial in altering the course of the disorder and improving long-term outcomes.

Early detection increases the efficacy of treatment options. Interventions such as psychotherapy, pharmacotherapy, or a combination of both be more effective when implemented early in the course of the disorder. This can prevent the progression to more severe depressive states, which are often more complex and harder to treat (Cuijpers et al., 2014). Meanwhile, depression frequently co-occurs with other mental and physical illnesses, which can complicate treatment and worsen the prognosis. Early detection and treatment of depression can prevent the development of comorbid conditions, such as anxiety disorders and substance abuse, which are more common in untreated or late-treated depression (Katon et al., 2002). However, current diagnostic methods, primarily based on clinical interviews and self-report questionnaires, are often subjective and may not capture subclinical levels of depression (Beck et al., 1996).

1.4 Current Biomarkers for Depression

Biomarkers are defined as objectively measurable indicators of some biological state or condition. In psychiatric disorders, biomarkers can be broadly classified into three categories: molecular, neuroimaging, and physiological. Molecular biomarkers include genetic markers or changes in gene expression, neuroimaging biomarkers involve alterations in brain structure or function detectable through techniques like MRI or PET, and physiological biomarkers refer to changes in body functions that can be measured, such as heart rate variability or EEG activities.

1.4.1 Molecular Biomarkers

Molecular biomarkers in depression primarily include genetic markers, proteins, and metabolites that can provide insights into the biological underpinnings of the disorder. Previous studies have identified several genetic polymorphisms associated with an increased risk of depression, such as those involving the serotonin transporter gene (5-HTT) and brain-derived neurotrophic factor (BDNF) gene (Caspi et al., 2003; Sen et al., 2003). These findings suggest that genetic predispositions can influence neurotransmitter systems critically involved in mood regulation and stress responses.

Proteomic and metabolomic profiling has also gained traction in identifying potential biomarkers for depression. Altered levels of specific proteins and metabolites in the blood, such as inflammatory cytokines and cortisol, have been linked to depression. Elevated cytokine levels, for instance, have been shown to correlate with the severity of depressive symptoms, suggesting an inflammatory component to the disorder (Dowlati et al., 2010).

- ***The disadvantage of molecular biomarker***

Despite these advances, molecular biomarkers for depression face several challenges. The heterogeneity of depression means that no single biomarker is likely to be definitive for all patients. Furthermore, the influence of environmental factors on gene expression and protein levels complicates the interpretation of these biomarkers (Uher, 2014). Additionally, molecular biomarkers often have a limited ability to predict the onset of depressive states due to their static nature—they typically provide a snapshot in time

rather than continuous feedback, which is essential for monitoring dynamic changes in mental state.

1.4.2 Neuroimaging Biomarkers

Neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) have provided significant insights into the structural and functional changes in the brains of individuals with depression. Structural MRI studies have consistently shown reductions in the size of the hippocampus in depressed patients, which is believed to reflect the effects of prolonged exposure to stress hormones (Malykhin et al., 2010). Functional MRI (fMRI) revealed increased connectivity within the dorsal nexus of the brain links cognitive control, default mode, and affective networks, suggesting a central role in depression's symptomatology and presenting a potential therapeutic target (Sheline et al., 2010). PET study revealed that individuals with major depression exhibit significantly increased resting-state functional connectivity in the subgenual cingulate and thalamus within the default-mode network (Greicius et al., 2007).

- ***The disadvantage of neuroimaging biomarker***

While these findings are compelling, neuroimaging biomarkers are not without limitations. High costs, limited availability, and the requirement for specialized equipment and trained personnel restrict their routine use in clinical settings. Moreover, similar brain changes may be present in other neurological and psychiatric conditions, which can affect the specificity of these biomarkers for depression (Arnone et al., 2012).

1.4.3 Physiological Biomarkers

Physiological biomarkers offer critical insights for diagnosing and understanding depression by providing objective measures of bodily functions. These include heart rate variability (HRV), EEG patterns, and Magnetoencephalography (MEG) signals, which reflect autonomic and neural activities associated with depressive states, serving as potent tools in the diagnosis and monitoring of neurological and psychiatric conditions.

- ***Heart rate variability (HRV)***

Previous research demonstrated that reduced HRV, indicating impaired parasympathetic nervous system activity, is associated with depression, highlighting its potential as a biomarker for emotional dysregulation (Carney et al., 2001). Similarly, the

study found a significant correlation between major depressive disorder and reduced HRV, further supporting its diagnostic utility (Licht et al., 2008).

- ***EEG***

EEG's effectiveness in revealing characteristic brain wave patterns in depression, such as asymmetrical alpha activities (Gordon et al., 2010). Previous studies also revealed that EEG could track changes in brain electrical activity related to emotional and cognitive processing in depression (Pizzagalli, 2007). EEG's portability facilitates its use in a variety of settings, from clinical environments to patient homes, thus broadening its application in longitudinal studies and everyday clinical practice.

- ***MEG***

MEG, while less portable and more costly than EEG, offers superior spatial resolution in detecting the brain's magnetic fields. This technique has been instrumental in mapping brain activity and understanding the cortical organization and timing involved in cognitive functions, which are often impaired in psychiatric conditions like depression (Hämäläinen et al., 1993).

- ***Advantages of neurophysiological biomarkers***

When compared to other neuroimaging techniques, such as MRI and PET scans, neurophysiological methods like EEG and MEG provide faster and more dynamic data on brain function. This is particularly useful for capturing the transient changes in brain activity that are associated with mental health conditions and assessing their progression or response to treatment (Uhlhaas and Singer, 2010). However, they require complex interpretation, are sensitive to external variables, and can be costly and inaccessible, particularly technologies like MEG.

1.4.4 EEG as a Promising Tool

EEG is a non-invasive technique used to record electrical activity in the brain. It was first used clinically by Hans Berger in the 1920s, who discovered that brain activity produces electrical signals that can be measured from the scalp (Berger, 1969). EEG has since become a fundamental tool in both research and clinical settings for studying brain function and diagnosing conditions (Yücel et al., 2004).

♦ ***Unique advantages and applications***

EEG occupies a distinct position among biomarkers for depression due to its non-invasive nature, affordability, and high temporal resolution. Unlike molecular biomarkers, which often require invasive sampling, or neuroimaging techniques such as MRI and PET that are costly and less accessible, EEG is particularly suited for longitudinal studies necessary for monitoring the progression of depression and evaluating patient responses to treatment.

It can detect subtle fluctuations in brain electrical activity associated with emotional and cognitive disturbances in depressed individuals. Additionally, the versatility of EEG to function effectively across various environments—from hospital settings to patient homes—greatly enhances its utility.

♦ ***Weaknesses compared to other biomarkers***

However, EEG also presents certain limitations. Its spatial resolution is inferior to that of advanced imaging techniques like fMRI or PET, which can more precisely localize changes within the brain. This lower spatial resolution means that while EEG offers excellent temporal insights, it is less capable of pinpointing the exact brain regions involved in depression (Nunez and Srinivasan, 2006).

♦ ***Critical role in depression research and treatment***

Despite these challenges, EEG remains an essential tool for studying brain function in response to cognitive tasks and emotional stimuli, areas where other biomarkers may not provide real-time data. The ability of EEG to measure how the brain's electrical activity changes in response to specific challenges enhances its utility, providing comprehensive insights into a patient's neurophysiological profile during both resting-state and task-evoked conditions. Abnormalities detected in resting-state EEG connectivity can be further explored in task-evoked studies to better understand their functional implications in everyday cognitive and emotional challenges, thereby offering richer diagnostic and therapeutic insights (Olbrich & Arns, 2013).

1.5 Research Gap

While the use of EEG as a biomarker for depression holds promise, it faces significant challenges and limitations. A primary gap in current research is the inadequate understanding of neuroactivity differences among individuals with subthreshold depressive states. The complexity of major depressive disorder (MDD) and its enormous impact highlight the urgent need for reliable methods of early diagnosis.

- ***The continuum between subthreshold depressive states and MDD***

Depressive states in healthy individuals and those with MDD differ quantitatively, but not qualitatively (Cox et al., 2001). The qualitative differences refer to different types of expression, such as psychological experiences and depressive symptoms. Meanwhile, quantitative differences refer to differences in the degree of depression or severity of symptoms rather than the type of symptoms (Flett et al., 1997). Previous studies have found a continuum of depressive symptoms through cluster analysis, where the depressive state is on a continuum or spectrum, and as the severity of a symptom increases, so too does the likelihood that it will be categorized as depressive in the cluster analysis (Figure 1.5).

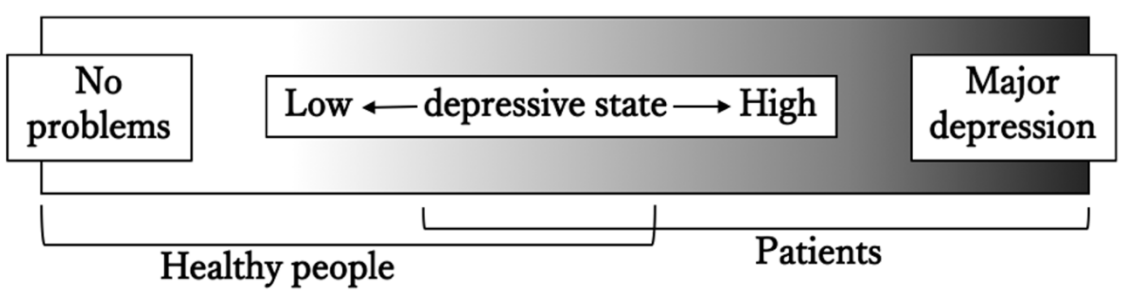

Figure 1.5 Continuum between subthreshold depressive states and MDD (Cox et al., 2001)

- ***Effects of depressive states on individuals***

Individuals with mild depression are more likely to develop moderate depression than those without depression, and psychotherapy has been proven to be effective in treating subclinical depression (Cuijpers et al., 2014). The prevalence of mild depression is on a gradual upward trend and has lifelong implications (An et al., 2022). Mild

depression is no less socially and clinically significant than moderate depression, and early intervention in subthreshold depression is more likely to yield a positive impact on adolescents (Cuijpers et al., 2021).

- ***The prevalence of subthreshold depression***

Individuals with subthreshold depression (sD) have a greater likelihood of developing MDD compared with individuals without sD (Cuijpers et al., 2014). sD is showing a progressively increasing prevalence and has a lifelong impact (An et al., 2022), and the social and clinical impacts of sD are no less than those of MDD, with the higher prevalence of sD increasing its impact in terms of excess economic costs and mortality (Cuijpers et al., 2021). During the COVID-19 pandemic, the prevalence of both sub-threshold depression and major depressive disorder among university students was alarmingly high, underscoring the importance of early diagnosis and targeted interventions for this population (Langer Á et al., 2022).

- ***Position of current research***

The critical limitation is the understanding and interpretation of EEG data in the context of healthy individuals. Most EEG studies focus on populations already diagnosed with depression, which provides less insight into the early detection and preventive potential of EEG biomarkers. Therefore, research into sD will contribute to a more detailed estimation of depressive states in healthy individuals, and thus to symptomatic treatment, and exploration of the neural mechanisms will help to explain the pathological mechanisms of depression.

1.6 Objective of the Current Study

1.6.1 Research Objective

The primary objective of this study is to investigate the potential of EEG biomarkers for the early detection of depressive states in healthy individuals. This investigation is guided by the hypothesis that specific EEG features, identifiable during both resting-state and stimulus processing, could serve as early indicators of depressive symptoms before they manifest clinically (Figure 1.6).

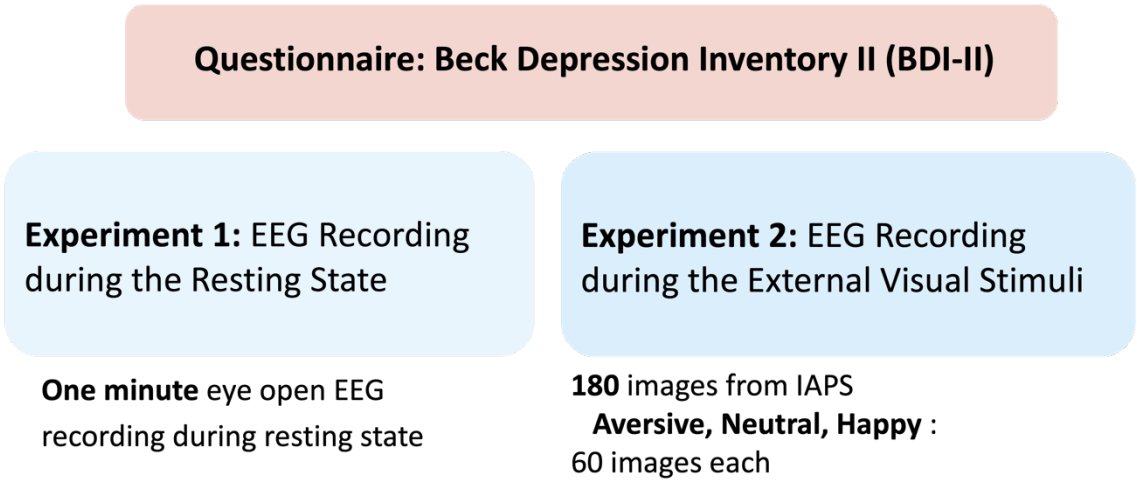

Figure 1.6 Research protocol of this study

♦ ***Research questions:***

Differentiation of Depressive States: Can distinct EEG patterns be identified that effectively differentiate between healthy individuals at various stages of depressive states?

Continuum Detection in Subthreshold Depression: Can EEG responses be used to detect the continuum in subthreshold depression, thereby providing insight into its progression?

Neural Mechanisms and Connectivity: Are there observable differences in neural mechanisms and connectivity during the resting state that correlate with varying levels of depressive risk?

Dynamic EEG Patterns: How do EEG patterns vary during cognitive and emotional processing tasks between individuals at high risk and those at low risk of developing depression?

1.6.2 Development of Depression

This research draws upon Beck's model of depression as its theoretical foundation. Before delving into this model, it is essential to clarify two fundamental concepts: schema and cognitive bias (Figure 1.7). Understanding the interplay between schemas and cognitive biases is crucial for grasping how individuals experience and interpret depressive symptoms.

- ***Schema***

The schema refers to the internal cognitive structure that organizes and stores representations of past experiences. Schemas help individuals make sense of the world by providing a framework for interpreting new information. They influence how we perceive, remember, and respond to various situations. Schemas can be adaptive, allowing for efficient processing of information, but they can also become maladaptive, particularly when they are negative or distorted.

Schema is formed through original character and personal experiences, and they evolve over time. Schemas guide attention and interpretation of new information. When faced with new experiences, individuals often filter information through their existing schemas, which can lead to biased cognition of that information.

- ***Cognitive bias***

Cognitive bias, which emerge from the schema, is pivotal in understanding how our minds interpret and react to information. Cognitive biases are manifested in three primary ways:

Biased Attention: Biased attention refers to the tendency to focus on specific types of information while neglecting others, often leading to an inadequate allocation of attention to positive cues. This bias can lead to increased anxiety, stress, and depressive symptoms, as individuals become fixated on negative aspects of their environment or experiences.

Biased Processing: This involves the interpretation and integration of information

in a way that aligns with existing schemas, leading to a distorted view of reality. Biased processing can lead to misunderstandings and conflicts in relationships, as individuals may misinterpret others' intentions based on their negative biases.

Biased Memory: Unlike schema, which is for more efficient processing of new information, biased memory refers to the selective recall of information that aligns with one's existing mood or beliefs. Regarding depression, this often manifests as a biased recall of negative or failure-related memories over positive outcomes. This bias can hinder emotional resilience, making it challenging for individuals to bounce back from setbacks or view their experiences in a balanced light.

- ***Beck's model of depression***

As shown in Figure 1.7, based on Beck's cognitive model, the depression is formed by original character and pervious experience, they influence schema, which is the way one feeling their experience internally. Schema influence cognitive bias, and for in depressed individuals, cognitive biases influence how they process external stimuli. Cognitive bias includes biased attention, processing, and memory, and it refers to deviations from rational judgment caused by the brain's inherent schemas in processing information. Incoming information is filtered by schemas, highlighting elements consistent with them, which then trigger cognitive biases. These biases distort thinking, leading individuals to selectively focus on the negative aspects of situations. These biases result in depressive symptoms, maintain a cycle with schema, and remain people in a state of depression. Based on this model, the present study aimed to investigate whether this cognitive bias can be detected by brain activity in the absence as well as in the presence of external stimuli, thus providing a potential biological indicator for recognizing depressive states.

1.6.3 The Necessity of Studying Resting-State EEG

The resting state serves as a dynamic substrate for brain activity, encompassing a range of operational modes from sensory processing to attention. Previous research indicated that 60% to 80% of the brain's energy budget was dedicated to supporting neuronal communication during the resting state, underscoring the predominance of this activity in brain function (Raichle, 2006). The DMN plays a crucial role in understanding resting-state activity and provides insights into the neural mechanisms of neurological

disorders (Mohan et al., 2016). Resting state EEG can help elucidate the underlying neural mechanisms of depression. For instance, studies have found differences in EEG amplitude and patterns between individuals with high and low vulnerability to depression (Kaushik et al., 2023). Besides, resting state EEG data can be used with advanced machine learning techniques to improve depression diagnosis and severity assessment.

1.6.4 The Necessity of Studying Stimulation Processing

According to Beck's cognitive model of depression (Disner et al., 2011), depression has an effect on schema, which leads to distorted perceptions of information about the external world. The schema of depression causes biased attention, biased processing, and biased memory, which therefore worsen the depressive situation (Disner et al., 2011). Studying emotional information processing helps identify and quantify these biases. Sub-threshold depression individuals exhibited difficulties of negative emotion inhibition (Zhang et al., 2023). Biased information processing may serve as a vulnerability factor for developing depression (Figure 1.7). Research in this area can elucidate the brain mechanisms underlying biased emotional processing in depression.

The significance of this study lies in its potential to fill critical gaps in our current understanding of depression. By identifying reliable EEG features that can detect depression early in asymptomatic individuals, this research could lead to the development of proactive intervention strategies. Early detection allows for the timely implementation of preventive measures, potentially reducing the severity of depression or even preventing its full development.

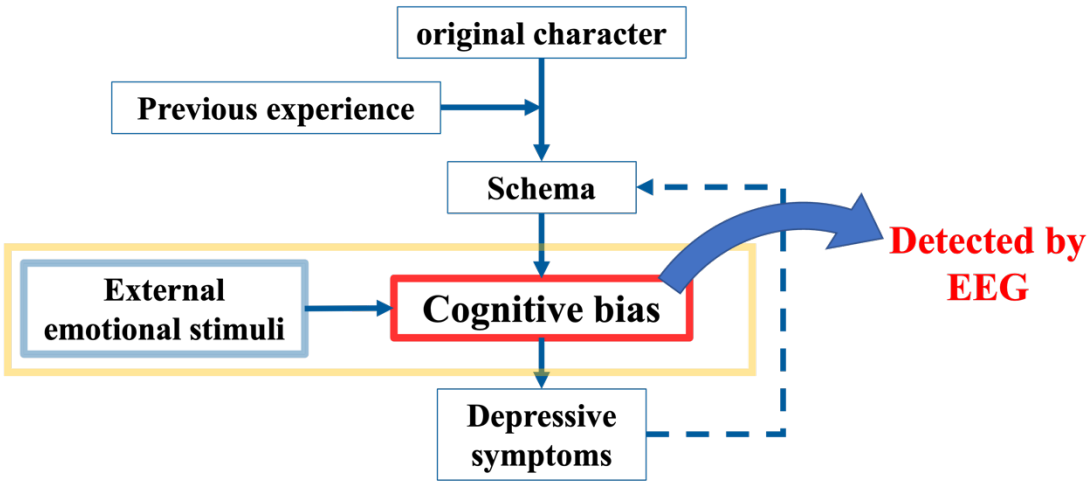

Figure 1.7 Beck's cognitive model of depression (Disner et al., 2011)

1.7 Structure of the Present Paper

This paper is organized as follows.

Chapter 1, "Introduction," delved into the definition and symptoms of MDD, explored the continuum of severity between MDD and sD, along with their social and economic consequences. The chapter also discussed the causes of depression within the framework of the cognitive model of depression and how cognitive biases influence the behavioral and neural responses of depressed individuals during information processing.

Chapter 2, "Experimental Methods," shifted the focus to the evaluation methods for depressive states and the use of external stimuli designed to evoke distinct emotions. Participants were categorized into high, middle, and low depressive state groups based on their responses to the Beck Depression Inventory-II (BDI-II). The International Affective Picture System (IAPS) was employed as the visual stimulus, with pictures categorized as negative, neutral, and positive based on their valence. The experimental conditions, setup, and procedures were comprehensively described, noting that measurements included the eye-open resting state and brain activity, alongside behavioral responses, in reaction to various emotional states triggered by external visual stimuli.

Chapter 3, "Analysis of Neural Activity during the Resting State," focused on identifying critical EEG biomarkers in the resting state, a dynamic substrate recognized for its broad spectrum of operational modes, from sensory processing to attention mechanisms. This chapter detailed an investigation into the power spectrum density (PSD) and the region-based phase-locking value (PLV) across individuals with various depressive states. Significant differences in theta and beta band power were observed, as well as correlations in the theta-beta ratio for the frontal lobe and phase-locking connections across the frontal, parietal, and temporal lobes. Notable differences in resting state neural networks, particularly in the frontal and temporal lobes among the three groups, were identified using standardized low-resolution brain electromagnetic tomography (sLORETA).

Chapter 4, "Analysis of Cognitive Biases during Visual Stimuli Processing," investigated whether attentional bias could be detected through reaction times during the perception of image stimuli and whether significant differences in neural activities existed

during emotional visual information processing. The analysis of event-related potentials (ERPs) and event-related spectrum perturbation (ERSP) changes in the delta, theta, and alpha bands was conducted. It was observed that as depressive states increased, the P300 amplitude tended to decrease, and latency increased for all emotional stimuli. For ERSPs, the high depressive group showed a more pronounced decrease in alpha amplitude. The identification of these neural patterns associated with depressive states could act as the parameters for evaluating depressive states in healthy individuals, potentially serving as early diagnosis methods for depression.

Chapter 5, “Conclusion,” summarized the key findings and highlighted new insights gained from this study. The chapter also outlined specific directions for future research, discussed how the results of this research could potentially contribute to the well-being of society, particularly in the area of mental health, by enhancing early diagnosis and interventions for depression.

Chapter 2 Experimental Method

2.1 Introduction

This chapter forms the methodologies employed to explore EEG biomarkers for detecting depressive states in healthy individuals. This study meticulously recruited 46 participants to undergo EEG measurement experiment while resting state and stimulation processing, aiming to investigate the neural activities, providing deeper insights into the neural differences and similarities associated with depressive states. This chapter details each step of the experimental process, from participant recruitment and data collection through data analysis methods, ensuring a comprehensive understanding of the methods used.

2.2 Participants

The experiment recruited 46 participants (16 women and 30 men; mean age, 22 years) who had not received a depression diagnosis and were not receiving medication. This study was approved by the Ethical Review of Human Subject Research of the Tokyo Institute of Technology (Approval Number: A20202) and Ethical Review of Human Research of Tokai University (Approval Number: 21134). All methods were performed in accordance with relevant guidelines and regulations, and informed consent was obtained from all subjects. Data from 3 participants were removed due to incomplete data or because they had significantly different responses from other participants in the experiment.

2.3 Depressive State Evaluation

The BDI-II was used to evaluate the participants' depressive states. The BDI-II contains 21 questions related to the respondents' life and psychological conditions in the last 2 weeks. Each question has four options, with points scored from 0 to 3 and a higher score corresponding to a stronger state of depression. Thus, the depression is rated from 0 to 63 (the lower the overall score, the lower the depressive state). Participants answered all of the questions on the Google Form before the EEG recording experiment, and their depressive state was scored and evaluated. Because the participants in this study were healthy individuals who had not been diagnosed with a psychiatric disorder, including depression, there were no participants with significantly high BDI-II scores and the score variation was considered to be small (mean, 6.413; standard deviation, 4.773).

2.3.1 Distribution of Depressive States

The present study enrolled 43 participants, and the distribution of their depressive states is shown in Figure 2.1. The participants' depressive states were evaluated with the BDI-II. Although the maximum score for the BDI-II was 63, the maximum score for this experiment was 20 because the participants were healthy. Based on previous research, a score of 9 is commonly utilized to delineate the threshold for none to minimal depression, whereas the specific cutoffs of BDI-II 9 and 21 are applied in examining the continuity of depression symptoms, with scores exceeding 21 aligning closely with the clinical

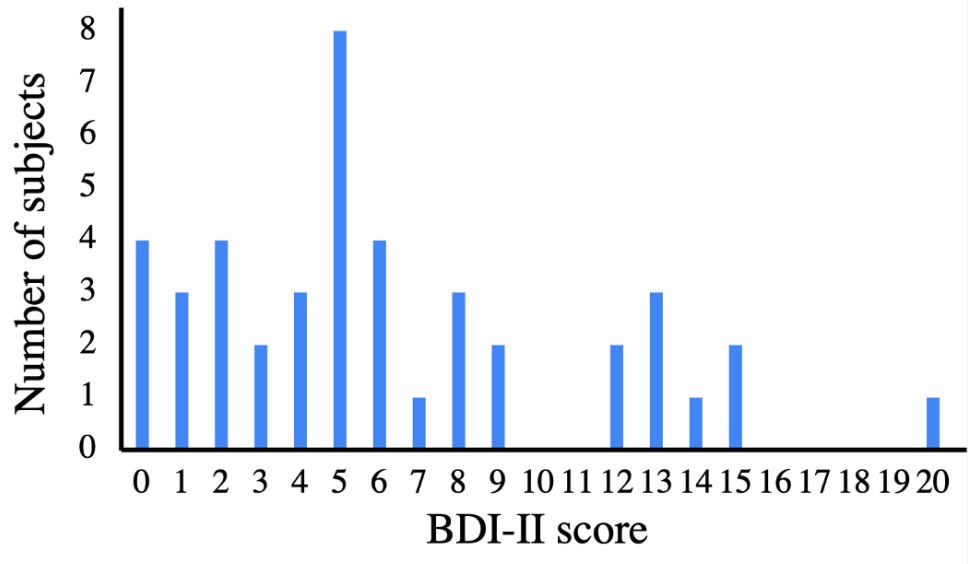

Figure 2.1 Number of subjects by BDI-II score

cluster (Edelstein et al., 2010). The mean average BDI-II score for individuals identified as devoid of depressive tendencies at 4, thereby current research set the low depressive state as a score less than 4 (from 0 to 3) (Xie et al., 2018). Therefore, we classified participants with scores between 0 and 3 into the low depressive state group (n=13), those with scores between 4 and 9 into the middle depressive state group (n=21), and those with scores between 10 and 20 into the high depressive state group (n=9).

2.4 Data Measurement and Preprocessing

The EEG data were recorded by an EEG amplifier (Polymate Pro MP6100, Miyuki Giken Co., Tokyo, Japan), and the signals were acquired based on the International 10-20 system from 21 electrodes as shown in Figure 2.2, including two electrodes measuring vertical electrooculograms (VEOGs) and horizontal electrooculograms (HEOGs), with a sampling rate of 500 Hz. The impedance of the electrodes was below 50 kΩ, as recommended.

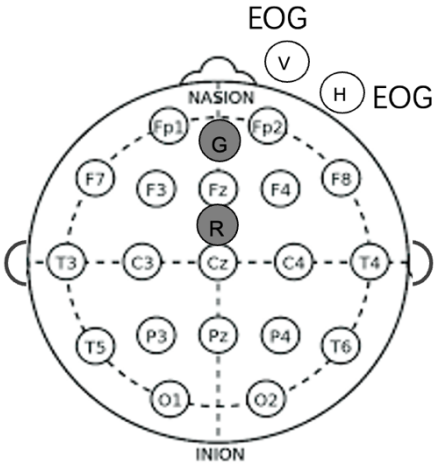

Figure 2.2 Electrodes placement using International 10-20

Data processing was conducted using a MATLAB-based script in conjunction with the EEGLAB toolbox. Raw signals were initially referenced to AFz during the collection phase and then re-referenced to the average of all EEG electrodes during pre-processing. A 0.5-50-Hz bandpass filter was implemented. The Infomax Independent Component Analysis algorithm was used to remove eye movement-, blink-, muscle-, and heart-related artifacts from EEG recordings.

2.5 Design of the Resting-state EEG Measurement

The overall experiment consisted of three sections: depression state assessment, resting-state EEG, and EEG during emotional visual stimuli. The first EEG measurement focus on exploring how depressive states are reflected in resting-state EEG.

The experiment design was shown in Figure 2.3. First, depression was assessed using the BDI-II questionnaire, which was followed by placement of the EEG electrodes, explanation of the experimental procedure, and the EEG measurement session. For the EEG measurement session, a "+" mark was displayed in the center of the screen monitor to guide the participants' gaze, during which time they were instructed to clear their minds as much as possible. To ensure the length of the data, we recorded EEG data for approximately 1.5 min. The experiments were conducted in a bright soundproof room, with the participant sitting comfortably on a chair and their head placed on a chin rest to prevent head movement.

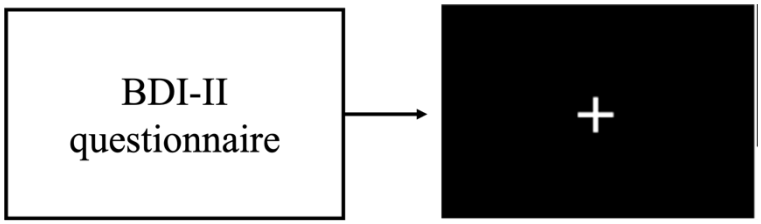

Figure 2.3 The experimental design of resting-state EEG measurement

2.6 Design of the Stimulation Processing EEG Measurement

2.6.1 Visual Stimulation

In this experiment, the IAPS was used as the external stimulus presented to the participants during the experiment (Lang and Bradley, 2007). The IAPS is a set of affective images comprising 956 different images of, for example, objects, scenes, plants and animals, and human faces. It is widely used in affective and cognitive experiments worldwide, mainly to induce emotions. The IAPS is accompanied by three kinds of emotional values that have been evaluated by the makers of IAPS in their emotional evaluation experiments for each image, and users can select the most suitable image for their experiments using these values as a reference (Lang et al., 2017). The three emotional parameters are valence, arousal, and dominance. In this experiment, the valence parameter, which represents pleasantness-unpleasantness, was used to select the image stimuli. The selected images were classified into three groups according to valence: negative (unpleasant images), neutral (image without strong emotional induction), and positive (pleasant images) (Hiromi, 2016). As shown in Figure 2.4, images with a low valence value (1.66–2.93) were considered negative images with unpleasant impressions[1], images with a medium valence value (4.50–5.01) were considered neutral

	Negative	Neutral	Positive
Value of Valence	1.66 - 2.93	4.50 - 5.01	7.09 - 8.34

Figure 2.4 IAPS dataset and the example of stimuli

[1] https://steemit.com/story/@rezawijaya/sad-stories-of-children-facing-war

images without particularly strong emotional induction[2], and images with a high valence value (7.09–8.34) were considered positive images with pleasant impressions[3]. In total, 60 images of each type were selected and used in the experiment.

2.6.2 Experimental Design

First, depression was assessed using the BDI-II questionnaire, followed by the resting-state EEG recording, and then a practice session for the emotional stimulation experiment. Then, the experiment involving the presentation of IAPS images was performed in two sessions with a break in between. In each session, 90 IAPS images were presented randomly, and the total time of the two sessions including breaks was about 30 min. As shown in Figure 2.5, the experimental process in each trial was divided into three stages. (1) First, a "+" mark was displayed in the center of the screen monitor for 1.5 s to guide the participants' gaze, during which time they waited without moving their bodies. (2) After that, an IAPS image was randomly displayed, and the participants recognized what the image was and switched to the next evaluation screen by pressing the Shift key on the keyboard if they could rate their impressions as pleasant or unpleasant. The Shift key was to be pressed as soon as possible within 3 s after the image was displayed and, after 3 s, the evaluation screen was automatically switched to the next stage. (3) In the evaluation stage, the participants rated the pleasant and unpleasant impressions obtained

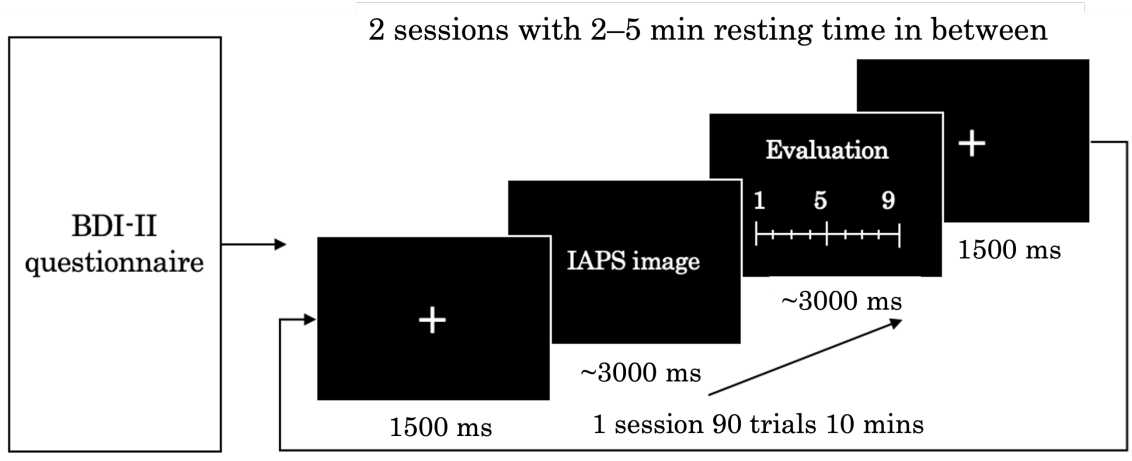

Figure 2.5 The protocol of the experiment

[2] https://axcis.jp/item/id-143453302

[3] https://parenting.firstcry.com/articles/how-to-raise-a-happy-child-10-effective-parenting-tips/

from the images on a scale of 1 to 9 by pressing the numeric keys from 1 to 9 on the keyboard, with 1 being pleasant and 9 being unpleasant. The number keys were to be pressed as soon as possible within 3 s after the evaluation screen was displayed and, after 3 s, the screen was automatically switched to the next trial. The experiments were conducted in a bright soundproof room, with the participants sitting comfortably in a chair and keeping their heads on a chin rest to prevent head movement.

2.7 Summary

Chapter 2 provides a detailed description of the methodologies employed to investigate EEG biomarkers for detecting depressive states in healthy individuals. The chapter begins with the participants recruitment who were selected based on specific criteria to ensure reliability. Depression levels among participants were assessed using the Beck Depression Inventory II (BDI-II), facilitating the classification into different depressive state groups for the analysis of EEG patterns. The EEG data collection involved a standard electrode setup and rigorous preprocessing protocols, including re-referencing, filtering, and artifact removal, to ensure the integrity of the data.

The experimental design was structured to capture neural activities during both the resting-state and emotional stimulus-response phases. This approach allowed for an in-depth exploration of how depressive states manifest in neural activity both at baseline and in response to external stimuli. The implementation of the experiment was meticulously managed to maintain consistency and reliability across all sessions.

Chapter 3 Analysis of Neural Activity during the Resting State

3.1 Introduction

Major depressive disorder (MDD) is a pervasive mental health challenge that affects over 322 million people globally, and its prevalence tends to increase with age (Disner et al., 2011). Characterized by profound alterations in mood, cognitive function, and overall well-being, MDD not only diminishes individual quality of life but also imposes a significant societal burden.

Several biomarkers reflect the significant effects of depression on brain activity and can be used in its diagnosis. However, most studies have focused on differences in EEG characteristics between MDD patients and healthy controls, and it remains unclear whether there are differences in the EEG characteristics of healthy individuals with different depressive states. Further investigation is essential to understand how the brain functions differently in the resting state among healthy individuals, which would potentially add new perspective on how depressive states affect neural activity. Additionally, resting-state EEG is less demanding for participants, which might make it more broadly applicable to the early detection of depression. Therefore, we investigated brain activity of healthy individuals in the resting state and hypothesized that this continuum might be present in the resting-state neural activity of healthy individuals.

In this study, we investigated whether there are significant differences in the neural activity of healthy individuals with different depressive states during the resting state. We assessed participants' depressive states using the Beck Depression Inventory Second Edition (BDI-II), and EEG activity was recorded during the experiment. We investigated whether participants with more severe depressive states had reduced theta-band power, increased delta-band power, and lower power ratios relative to participants with less severe depressive states. We also investigated whether there was frontal-parietal impairment of functional neural connectivity, based on a PLV analysis of participants with different depressive states.

3.2 Feature 1: Power Spectrum Density

3.2.1 Literature Review

Power Spectrum Density (PSD) is a critical feature in EEG analysis that quantifies the power of various frequency bands within the EEG signal. This analysis is essential for understanding the distribution of electrical activity across different brain states and is particularly useful in studies related to neurological disorders like depression.

EEG has been suggested to assist in differentiating patients with depression from those with other clinical disorders and from normal individuals (Jaseja, 2023). A previous study demonstrated the effectiveness of power spectrum density (PSD) in analyzing EEG signals for early-stage depression, offering a deeper understanding of brain activities under different physiological conditions (Grin-Yatsenko et al., 2009). Several studies have reported differences in EEG power between patients with MDD and healthy individuals. Increased delta-band phase lag and reduced resting-state gamma current density in the anterior cingulate cortex have been found in MDD patients (Simmatis et al., 2023). Another study found that MDD patients showed significantly elevated current density in delta, theta, alpha, beta1, and beta2 frequency bands relative to controls in the anterior cingulate and prefrontal cortices (Korb et al., 2008). Additionally, it has been reported that the frontal gamma power in individuals with depression is increased relative to healthy controls, and that delta power during sleep is lower in individuals with depression than in healthy controls (Meerwijk et al., 2015). Analysis of EEG power ratios has also shown significant differences in specific ratios between depressed patients and healthy controls, including the alpha–beta ratio (ABR) and the theta–beta ratio (TBR), suggesting that these ratios could be used as biomarkers of depression (Chang and Choi, 2023).

3.2.2 Analysis Method

In this study, the PSD of EEG signals was computed using the pwelch function in MATLAB. Welch's algorithm implements a periodogram-based spectral estimation method, using fast Fourier transform (FFT). This technique involves dividing the EEG time series into eight segments with 50% overlap. Each segment is then windowed with a Hamming window to minimize spectral leakage. The FFT is applied to each windowed

segment to obtain periodograms, which are then averaged to determine the estimated PSD (Welch, 1967). The PSD was calculated for the preprocessed EEG recordings, utilizing the 1-min-long EEG data from each participant. To assess temporal fluctuations in resting-state EEG, the 1-min recording was segmented into six 10-s intervals, allowing for a nuanced PSD analysis across distinct frequencies and timeframes. Calculations were confined to specific frequency ranges: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-50 Hz)[4]. Average frequency-specific power values were computed to characterize the power spectrum within each band. Subsequently, the relative power for each frequency band was ascertained by normalizing the absolute power to the total power spectrum for each individual participant. To discern the influence of depressive states, statistical analyses were undertaken across three distinct groups, with adjustment for multiple comparisons.

For power ratios, we calculated the alpha–theta ratio (ATR), ABR, and TBR for each participant, and then conducted correlation analyses of these three power ratios separately to determine their correlation with the BDI-II score.

3.2.3 Results

PSD analysis was conducted to evaluate the impact of depressive states on EEG spectral power across different frequencies. The PSD serves as an indicator of the distribution of signal power among frequency components. Subsequently, a one-way analysis of variance was applied to determine the influence of depressive states on resting-state EEG activity. The findings are presented in Figure 3.1. Significant differences were observed mainly in the theta and beta bands across various time intervals. From 0 to 10 s, notable differences were observed in central beta power at Cz and C4. From 10 to 20 s, notable differences were observed in central beta power at Cz. From 20 to 30 s, notable differences were observed in frontal theta power at Fp2. From 30 to 40 s, notable differences were observed in frontal theta at Fp1 and Fp2, and central beta powers at Cz. From 40 to 50 s, notable differences were observed in frontal theta at Fp2, F3, and Fz, and parietal beta powers at C4 and P4. From 50 to 60 s, notable differences were observed

[4] https://www.mathworks.com/help/signal/ref/pwelch.html

in central and parietal beta powers at F7, Cz, C3, C4 and P4. Results of the statistical analysis are given in Table 1.

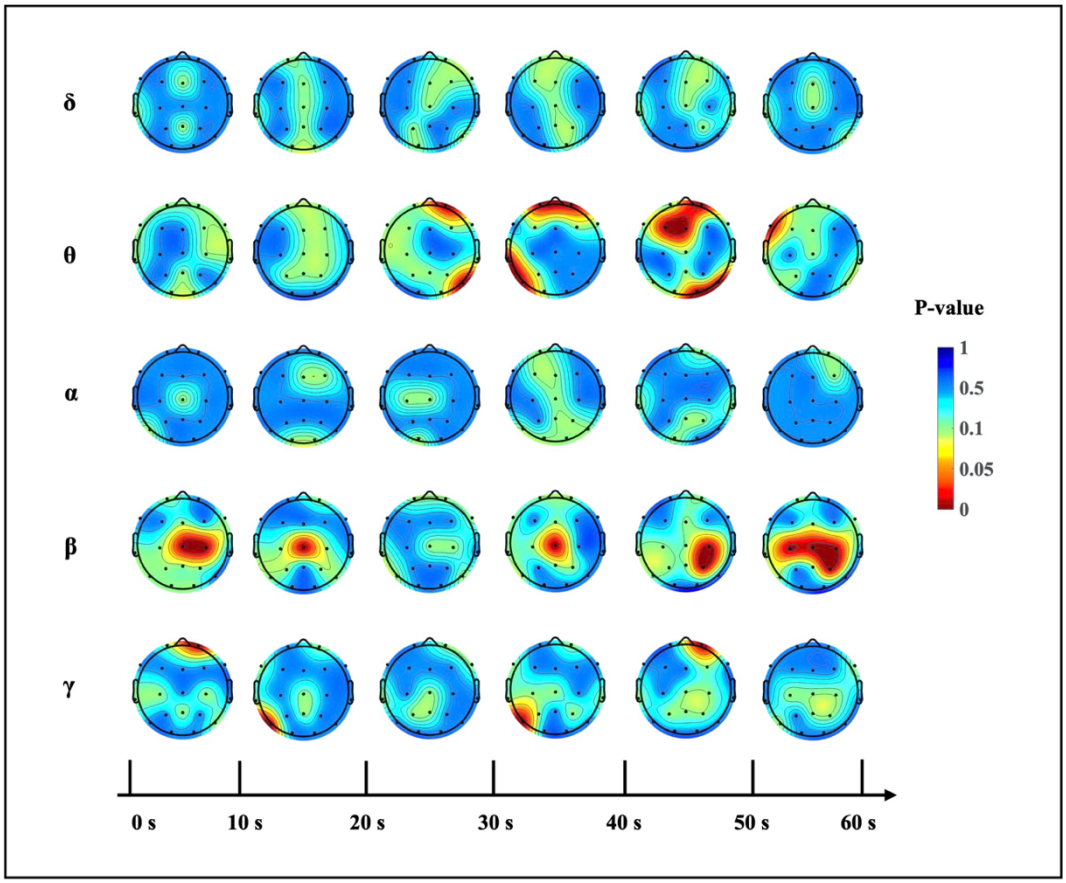

Figure 3.1 P-value topography across time intervals by frequency band. Topographic maps displaying the statistical significance of PSD differences among depressive states over one-minute EEG, segmented into six 10-second intervals. The color gradient, with red indicating lower p-values, shows one-way ANOVA results ($p < 0.05$).

Table 1. Statistical analysis of PSD by time interval, brain region, and frequency band

Time Interval (s)	Brain Region	Frequency Band	Statistic	F-Value	p-Value	Effect Size (η^2)
0-10	Cz	Beta	F (2, 40)	4.0	0.038	0.17
	C4	Beta	F (2, 40)	3.5	0.038	0.15
10-20	Cz	Beta	F (2, 40)	3.5	0.039	0.15
20-30	Fp2	Theta	F (2, 40)	9.2	0.001	0.31
30-40	Fp1	Theta	F (2, 40)	5.5	0.031	0.22
	Fp2	Theta	F (2, 40)	4.1	0.031	0.17
	Cz	Beta	F (2, 40)	4.2	0.023	0.17
40-50	Fp2	Theta	F (2, 40)	3.6	0.037	0.15
	F3	Theta	F (2, 40)	5.3	0.023	0.21
	Fz	Theta	F (2, 40)	4.4	0.023	0.18
	C4	Beta	F (2, 40)	4.3	0.036	0.18
	P4	Beta	F (2, 40)	3.6	0.036	0.15
50-60	F7	Beta	F (2, 40)	3.9	0.029	0.16
	Cz	Beta	F (2, 40)	6.1	0.012	0.23
	C3	Beta	F (2, 40)	4.4	0.019	0.18
	C4	Beta	F (2, 40)	5.4	0.012	0.21
	P4	Beta	F (2, 40)	5.3	0.012	0.21

Figure 3.2(a) shows the topographic mapping of correlation for ATR, ABR, and TBR. In this figure, red indicates a significant correlation between BDI-II score and power ratio. This correlation was found in the TBR in the left frontal area ($R = -0.31$, $p < 0.05$), as shown in Figure 3.2(b).

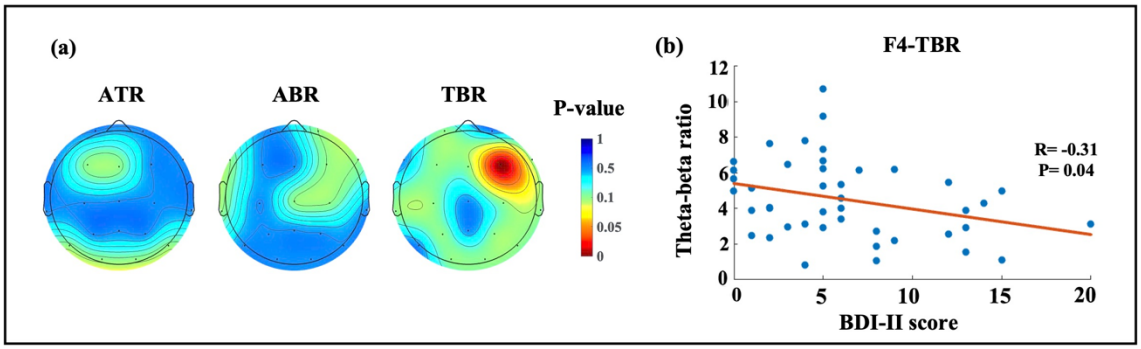

Figure 3.2 Topographic maps and scatter plot for correlation between BDI-II score and power ratio. (a) Topographic mapping of correlation for Alpha-theta ratio (ATR), Alpha-beta ratio (ABR) and Theta-beta ratio (TBR). The red color indicates a smaller p-value ($p < 0.05$), which represents the significant correlation between BDI-II score and the power ratio. (b) Relationship between the BDI score and TBR. Each dot represents the TBR of one participant.

3.2.4 Discussion

- ***Changes in delta band***

The PSD results indicated an increasing trend in the delta band in the prefrontal area in the resting state, but this difference was not statistically significant. This may suggest a more complex or different neural mechanism than hypothesized. In previous studies, resting-state EEG delta power was reported to be associated with psychological pain in adults with a history of depression (Meerwijk et al., 2015). Resting-state EEG delta power has been found to have predictive utility in predicting the response of individuals with depression to cognitive behavioral therapy (Schwartzmann et al., 2023). In addition, previous studies have shown that for patients with depression, higher delta bands in the left frontal region during resting states are associated with greater self-disgust (Amico et al., 2023) and with greater cognitive load associated with visual input during eye-open

resting (Kan et al., 2017). Higher delta power in the left temporal region is associated with different thought wandering processes (Spironelli et al., 2021). Therefore, delta power that shows an increasing tendency with increasing depressive states might be associated with unstable mental states.

- ***Changes in theta band***

The theta band of the resting state tends to increase with the severity of the depressive state in the frontal area, and a significant difference was found in the prefrontal cortex. Resting-state theta activity has been linked to information content-specific coding levels during response inhibition (Pscherer et al., 2022). A higher resting theta activity was found to be associated with a stronger N2 peak during successful response inhibition for no-go tasks, suggesting that the resting-state theta activity forms the foundation for a neural state that is helpful in enhancing inhibitory control mechanisms more effectively (Pscherer et al., 2022). In my previous research, the low depressive state group showed a stronger N2 peak during stimuli processing (Li et al., 2023), and the present study found stronger resting theta power in the low depressive state group. Therefore, the higher resting theta power of the low-depression state may indicate better control over external stimuli, and thus maintenance of a stable mental state. Another study demonstrated a negative correlation between theta power of the right central region and depressive states in patients with depression (Gao et al., 2023). Therefore, the PSD results of the present study may indicate that neural activity is modulated by depressive states and that it is derived from a state of psychological distress and a lack of inhibition of negative information.

- ***Changes in theta-beta ratio***

The TBR at the F4 electrode was found to be negatively related to depressive states. A decreased TBR has been proposed as a potential biological marker of depression, with significant differences observed across various electrode ranges, indicating alterations in EEG power ratios in the resting state of depression (Chang and Choi, 2023).

3.3 Feature 2: Phase Locking Value

3.3.1 Literature Review

In clinical neuroscience, the phase locking value (PLV) has been a valuable tool for identifying aberrant neural connectivity patterns in various neurological disorders, offering new perspectives on the pathophysiology of these disorders (Uhlhaas and Singer, 2006). Previous studies have explored the relationship between EEG patterns and changes in depressive mood and found that individuals' changes in depressive mood over certain consecutive time periods were associated with resting-state EEG features, particularly phase reset rates; these findings provide new insights into the detection of early depression (Morita et al., 2023). The potential of PLV to detect abnormal neural synchrony patterns in patients with MDD has been demonstrated. Moreover, resting-state EEG has been investigated for the detection of MDD, and the coherence feature has been identified as a reliable and effective solution for EEG-based detection of MDD (Wu et al., 2021). Previous studies have also demonstrated differences in EEG functional connectivity between MDD patients and healthy individuals. Alpha-band functional connectivity in the default mode network (DMN) can predict depression severity and is more prominent in MDD patients than in healthy individuals (Simmatis et al., 2023). A previous study found that depressed patients had significantly reduced resting PLV-based functional connectivity in the delta band compared with healthy controls (Huang S. S. et al., 2023). Another study identified specific EEG features in MDD patients (e.g., lower alpha and higher gamma phase lag index-based connectivity) compared with healthy individuals (Huang Y. et al., 2023).

3.3.2 Analysis Method

PLVs were calculated for each subject to quantify the synchronization strength between electrode pairs on the scalp in order to gain insight into the functional connectivity of the brain. PLVs range from 0 to 1, with values closer to 1 representing stronger synchronization. This analysis aimed to understand how the depressive state affects the functional connectivity between different areas.

For calculation of the PLV between two electrodes, the process begins with bandpass filtering of the data from each electrode within a specific frequency range. Subsequently,

the Hilbert transform is applied to these filtered signals. This transformation converts the real-valued EEG signals into complex-valued analytic signals, which reveal the instantaneous phase of the EEG signal at each time point. In the next step, the instantaneous phase is extracted for each signal, and the phase difference between the two signals at each time point is calculated. Finally, the computation of the PLV is carried out by taking the mean of the exponential values of the complex phase differences over time, which quantifies the degree of phase synchronization between the two signals (Aydore et al., 2013).

The equation for the PLV between two electrodes is as follows:

$$PLV_{pq}^{f} = \left| \frac{1}{N} \sum_{t=1}^{N} e^{i\left(\phi_p^f(t) - \phi_q^f(t)\right)} \right|.$$

Here,

- $\phi_p^f(t)$: instantaneous phases of signals from frequency band f and electrodes p at time point t.
- $\phi_q^f(t)$: instantaneous phases of signals from frequency band f and electrodes q at time point t.
- N: total number of time points in the signal.
- The computation involves summing the exponential of the phase differences at all time points, followed by calculating the absolute value of this average to yield the PLV.

We calculated PLVs for each frequency band and between each electrode pair for each subject and normalized them to ensure comparability across participants[5]. We employed Min-Max normalization to scale the values, which transformed the data into a standardized range of 0 to 1. This normalization was achieved by subtracting the minimum value from each data point and then dividing the result by the difference between the maximum and minimum values. We then divided the brain into different regions and quantified the synchronization strength by calculating the average of the

[5] https://www.mathworks.com/help/signal/ref/hilbert.html

connection strength of one electrode to all electrodes in a specific region. We divided 19 electrodes based on the 10-20 system as follows (Figure 3.3): the prefrontal cortex (PFC) region, containing Fp1 and Fp2; the dorsolateral prefrontal cortex (DLPFC) region, containing F3 and F4; the ventrolateral prefrontal cortex (VLPFC) region, containing F7 and F8; the midline frontal cortex (mFC) region, containing Fz and Cz; the temporal cortex (TC) region, containing T3, T4, T5, and T6; the parietal cortex (PC) region, containing C3, C4, P3, P4, and Pz; and the occipital cortex (OC) region, containing O1 and O2 (Chai et al., 2019). We then performed a correlation coefficient analysis to explore the relationship between depressive states and the strength of neural synchronization across different electrodes and regions.

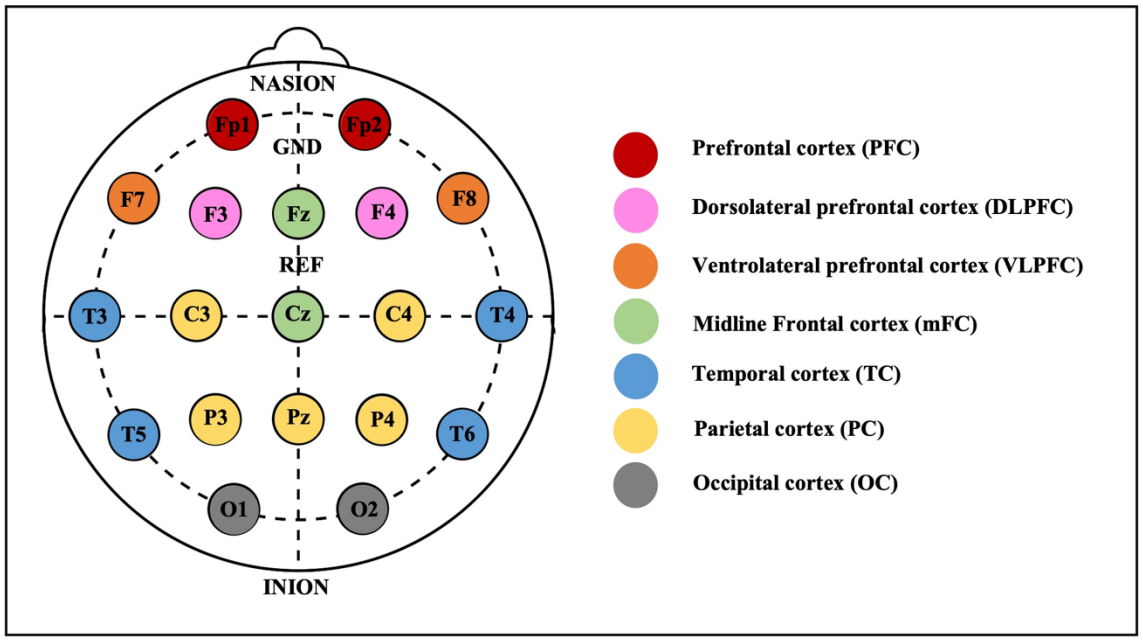

Figure 3.3 Electrodes placement using International 10-20 system and the electrodes corresponding to different areas. The 19 electrodes are categorized into 7 distinct brain regions, denoted by color-coded circles. Each region is integral to subsequent Phase Locking Value (PLV) analysis, which examines the neural connectivity across different areas of the brain.

3.3.3 Results

We performed a correlation coefficient analysis to explore the relationship between depressive state and neural synchronization strength. For example, as shown in Figure 3.4, when the connection region was VLPFC and the band was the beta band (13-30 Hz), a relationship between BDI-II score and the connection strength of F4, with respect to beta band in VLPFC region, was demonstrated ($p < 0.05$). This indicates that the strength of neural synchronization in the beta band of the F4 with respect to the VLPFC region was significantly negatively correlated with the depressive state. This analysis was performed for each electrode and each specific frequency and was transformed into topographic maps to show the distribution and strength of the correlation between depressive state and synchronization intensity across the scalp.

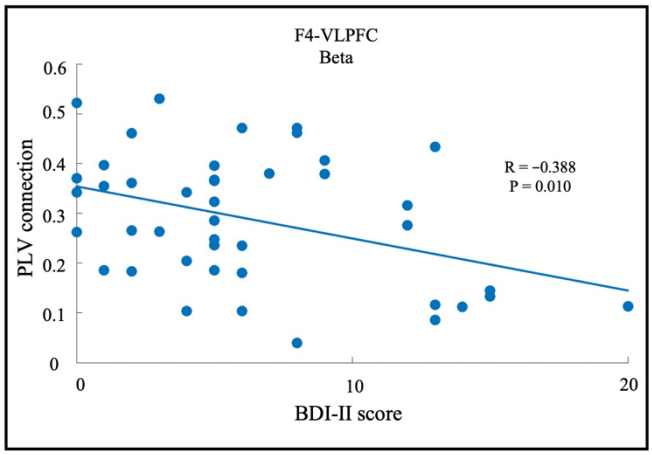

Figure 3.4 Relationship between the BDI score and PLV strength. The x-axis shows the BDI score, with a higher score associated with a higher depressive state. The y-axis shows the PLV strength between F4 and VLPFC, which was defined as the mean PLV strength between one electrode and electrodes of an area. Each dot represents the average PLV strength of one participant.

As shown in Figure 3.5, significant correlations were observed between the strength of brain connections in various regions and depressive states across different frequency bands. For the delta band, there were notable correlations involving the connection strength within the mFC region and between the C3 and PC regions in relation to depressive states. For the theta band, connections between the Pz and OC regions showed

a significant relationship with depressive states. For the alpha band, the connectivity strength between the C4 and PFC regions, between the C3 and TC regions, and within the PC region (specifically at locations C3, P3, and P4) were all significantly correlated with depressive states. For the beta band, connection strengths that showed significant correlations with depressive states included those between the F4 and PFC regions, the F4 and VLPFC regions, the C3 and TC regions, the C3 and PC regions, and the P4 and TC regions. For the gamma band, the connections between the PFC region and Fz, F4, and O1, as well as connections from the DLPFC region to Fp1 and T5, showed significant associations with depressive states. Additionally, connections from the mFC region to Fp1 and within the PC region to F4 and C4 also presented notable correlations with depressive states. Results of the statistical analysis are given in Table 2.

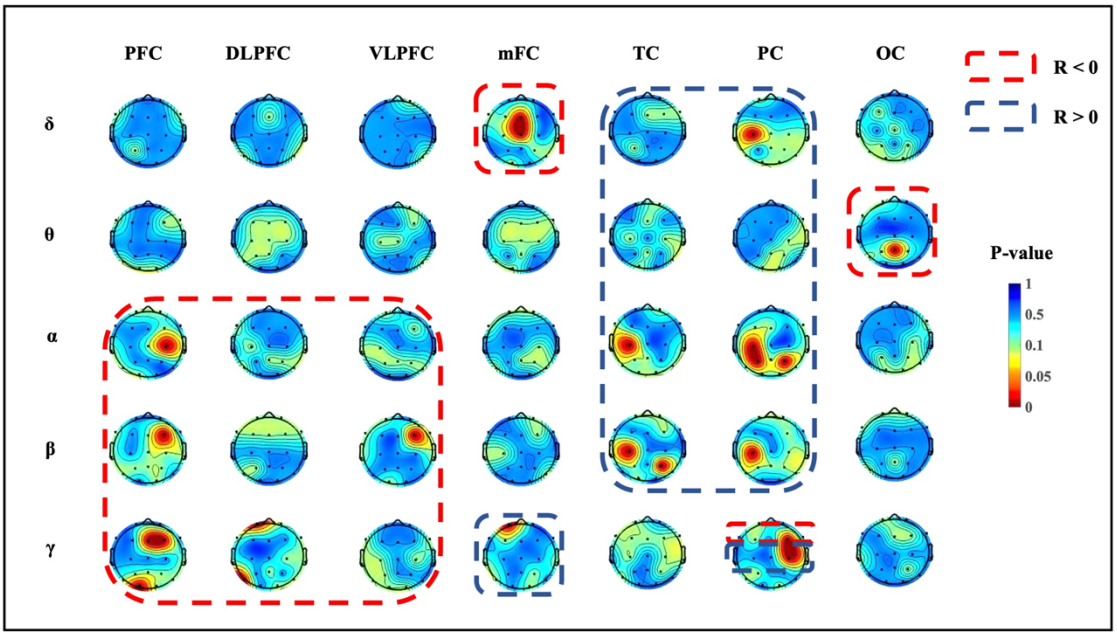

Figure 3.5 Topographic mapping of significant correlations in the PLV for different regions. The red color indicates a smaller p-value ($p < 0.05$), which represents the significant correlation between BDI-II score and the PLV strength of certain area and frequency.

Table 2. Correlation between EEG connectivity and depressive state across different frequency bands

Frequency Band	Connection Between Regions	Correlation Coefficient (R)	p-Value
Delta	mFC intra-region	−0.3	0.05
	C3 and PC	0.32	0.04
Theta	Pz and OC	0.36	0.02
Alpha	C4 and PFC	−0.35	0.02
	C3 and TC	0.33	0.03
	PC intra-region (C3)	0.32	0.04
	PC intra-region (P3)	0.33	0.03
	PC intra-region (P4)	0.3	0.05
Beta	F4 and PFC	−0.35	0.02
	F4 and VLPFC	−0.39	0.01
	C3 and TC	0.3	0.05
	C3 and PC	0.38	0.01
	P4 and TC	0.3	0.05
Gamma	Fz and PFC	−0.31	0.04
	F4 and PFC	−0.45	<0.01
	O1 and PFC	−0.31	0.04
	Fp1 and DLPFC	−0.36	0.02
	T5 and DLPFC	−0.35	0.02
	Fp1 and mFC	0.43	<0.01
	F4 and PC	−0.35	0.02
	C4 and PC	0.35	0.02

3.3.4 Discussion

The PLV results demonstrate the correlation between the strength of PLV connections and the depressive state. In the present study, a negative correlation within the frontal lobe was found in the delta, beta, and gamma bands. In patients with MDD, alterations in delta-band connectivity have been observed, with reduced resting brain connectivity in the delta band relative to healthy controls (Qiu et al., 2022). Compared

with healthy controls, decreased beta-band functional connectivity has been found in MDD patients during emotional stimuli processing (Zuchowicz et al., 2019). A negative correlation between the frontal and parietal lobes could be found in the alpha and gamma bands, and a negative correlation between the frontal and temporal lobes could be found in the gamma band. A previous study found that the average functional connectivity of the alpha band during the resting state showed a negative correlation with the severity of depression (Shim et al., 2018). Research has also shown that resting-state EEG activity, particularly in the beta band, is a marker of the strength of frontoparietal connections, which are associated with attentional performance (Rogala et al., 2020). Additionally, increased theta and alpha connectivity for resting EEG have been identified in dysphoria, which may represent the risk of depression (Dell'Acqua et al., 2021). Negative correlations of resting-state EEG functional connectivity in the frontal regions may indicate that synchronization or communication in frontal regions decreases with an increasing depressive state, and that the severity of the sub-threshold depressive state may be identified by the degree of reduction in functional connectivity in the frontal area.

Positive correlations within the parietal lobe were found in the delta, alpha, beta, and gamma bands, and between the parietal lobe and temporal lobe in the alpha and beta bands. Alterations in alpha-band connectivity have been observed in patients with MDD, with increased coherence primarily involving the prefrontal region (Leuchter et al., 2012). A previous study found that beta-band EEG functional connectivity in MDD patients was stronger than that in healthy controls in an eyes-closed resting state (Huang S. S. et al., 2023). Increased beta-band phase synchronization was found in the brain activity of MDD patients who did not respond to repetitive transcranial magnetic stimulation treatment (Zuchowicz et al., 2019). Increased resting gamma-band phase synchronization has been associated with the severity of depression, indicating a potential link between gamma-band connectivity and the characteristics of depressive symptoms (Yang et al., 2023). Additionally, deficits in gamma-band oscillations have been observed in other psychiatric conditions, including bipolar disorder, suggesting that gamma-band synchronization may be a relevant marker for understanding various mental health disorders (Tsai et al., 2023). The positive correlation in resting-state EEG functional connections in the parietal area indicates that the synchronization in the parietal region is strengthened with an increasing depressive state. Additionally, enhanced resting-state EEG connectivity in the posterior

region was observed in patients with moderate to severe late-life depression relative to patients with mild depression, and was associated with attention deficits (Zeng et al., 2024). Leuchter et al. (2012) reported that, in comparison to healthy controls, unmedicated individuals with MDD had significantly higher overall coherence in the delta, theta, alpha, and beta frequency bands, indicating a loss of selectivity in resting functional connectivity. These results suggest that brain functional abnormalities in subthreshold depression are associated with changes in the functional connectivity in the frontal and parietal lobes, which may be important for the early detection and diagnosis of depression in the future.

3.4 LORETA

Low-resolution brain electromagnetic tomography (LORETA) is capable of using EEG data to determine the characteristics of resting-state networks across intrinsic frequency bands (Aoki et al., 2015). A previous study using LORETA demonstrated increased resting-state current source density in the frontal regions across the delta, theta, and beta bands (Korb et al., 2008). Another study identified decreased spectral power activity in the right middle temporal gyrus compared with healthy controls (Lubar et al., 2003).

3.4.1 Analysis of Source Localization

Resting-state EEG data recorded from 19 scalp electrodes were analyzed via standardized low-resolution electromagnetic tomography (sLORETA) for source localization (Pascual-Marqui, 2002). For each participant, 60 s of resting-state EEG data was utilized for cross-spectral computations. Functional independent component analysis was employed to determine the spectral density of electric neuronal generators across 6239 cortical voxels within the seven classical EEG frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), and gamma (30-50 Hz). This analysis aimed to identify specific regions and frequency bands associated with the resting-state network (Herrmann et al., 1979). Statistical evaluations were performed on the coefficients of 15 components to determine how various depressive states influence network utilization. A pairwise *t*-test was conducted among the three groups, with multiple testing corrections applied through statistical nonparametric mapping (SnPM) using 5000 permutations.

3.4.2 Results

The neural substrates underlying the variations in resting neural networks among depressive states were examined using sLORETA, employing a one-tailed significance test. The exceedance proportion test from sLORETA determined significant component differences between conditions ($p < 0.05$). When comparing the low and high groups, the exceedance proportion test indicated a threshold of −2.100 corresponding to a p-value of 0.075; as shown in Figure 3.6(a), significant beta-band variations were localized to the right middle frontal gyrus ($t = 2.33$, MNI coordinates: $X = 35$, $Y = 60$, $Z = -5$). When comparing the middle and high groups, beta-band differences were localized to the left

middle temporal gyrus (t = 2.88, MNI coordinates: X = −65, Y = −50, Z = −10), with a threshold of −2.018 linked to a p-value of 0.015, as shown in Figure 3.6(b). Differences in the gamma band were localized to the left middle temporal gyrus (t = 2.12, MNI

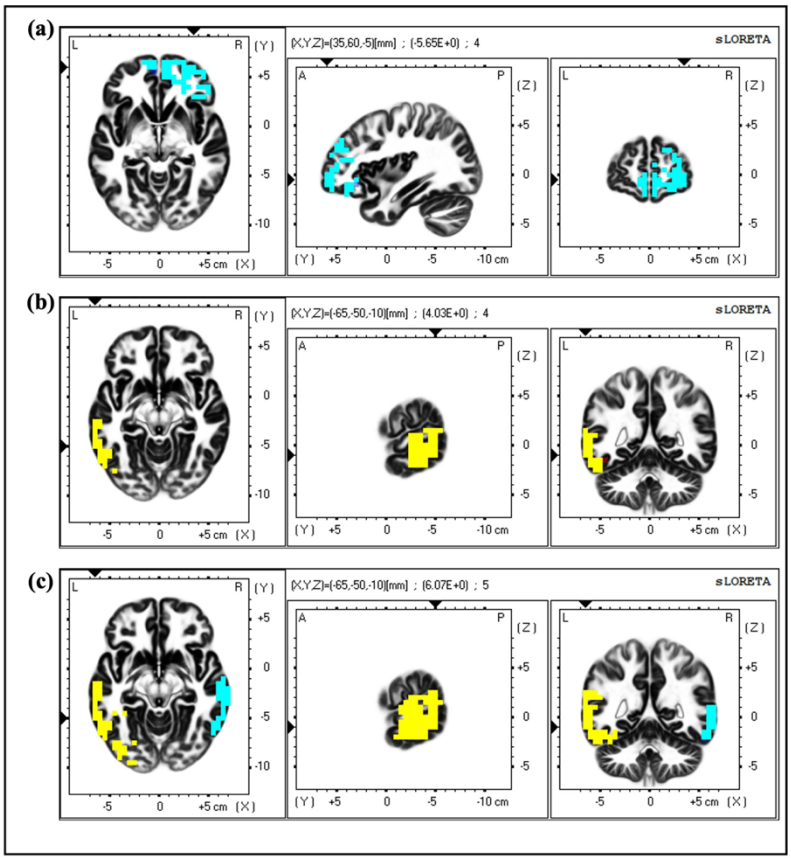

Figure 3.6 Resting state brain network analysis using standardized low resolution electromagnetic tomography method (sLORETA) source localization. (a) The beta band's spatial distribution is linked to the functional independent component displaying the highest significant difference across the three depressive state groups, with the maximum theta band location (positive, color-coded yellow) identified in the frontal areas. (b) The beta band's spatial distribution is linked to the functional independent component displaying the highest significant difference across the three depressive state groups, with the maximum beta band location (positive, color coded yellow) identified in the temporal areas. (c) The gamma band's spatial distribution is linked to the functional independent component displaying the highest significant difference across the three depressive state groups, with the maximum gamma band location (positive, color-coded yellow; negative, color-coded blue) identified in the temporal areas. Horizontal (left), sagittal (middle), and coronal (right) sections through the voxel with the maximal t-statistic are displayed.

coordinates: X = −65, Y = −50, Z = −10) and the right middle temporal gyrus (t = 2.12, MNI coordinates: X = 65, Y = −30, Z = −10) (Figure 3.6(c)).

3.4.3 Discussion

In addition to the results of scalp-recorded EEG activity, the results of the source localization analysis provided further support for a more localized difference in the beta band in the frontal lobe among the three depressive state groups, suggesting that different levels of depressive states affect the resting-state network in the frontal region, specifically the middle frontal gyrus. Results of the source localization analysis also confirmed a specific variation of the gamma band in the temporal lobe across three depressive state groups, suggesting that varying degrees of depressive states influence the resting-state network in the temporal region, particularly in the middle temporal gyrus.

3.5 Summary

This experiment investigated the effects of different depressive states on neural activity in healthy individuals by analyzing the changes in power spectrum density, power ratio, and region-based phase locking value with respect to the depressive state during the resting state. In terms of PSD, the theta band of the prefrontal cortex showed a tendency to decrease as the depressive state increased, and the delta band showed an upward trend as the depressive state increased. In terms of power ratio, the TBR of the right frontal region showed a decreasing trend with an increasing depressive state. In terms of functional connections, significant correlations were observed within the frontal and parietal region. In terms of source localization by sLORETA, frontal beta, temporal beta, and temporal gamma activities were identified.

This study also has some limitations. While prior research has established the validity of classifying participants using BDI-II scores (Cox et al., 2001), the adequacy of the sample sizes of each of our groups remains uncertain. Future studies should aim to expand the number of participants in order to more robustly discern significant correlations with other biomarkers. Secondly, given that depression is more commonly observed in women (Piccinelli and Wilkinson, 2000), the fact that male participants accounted for approximately two-thirds of the study population represents a limitation. The under-representation of women may make the findings less applicable to the female population. To enhance generalizability, future studies should aim to address this by ensuring a more balanced sex distribution. The requirement of EEG for source localization is another limitation of this study. The analysis was conducted with 19-channel EEG recordings, which could provide a broad overview of brain activity. In a previous study, sources of resting-state EEG activity were estimated using 19-channel EEG recordings with LORETA (Aoki et al., 2015). However, a recent study suggests that a minimum of 64 electrodes is recommended for a robust source localization analysis (Hatlestad-Hall et al., 2023). Consequently, the source localization results obtained in this study should be considered a preliminary estimate. A more detailed source localization analysis using high-density EEG data is currently planned to enhance the accuracy and reliability of the findings.

In this study, it is observed that the PSD in the theta band, the TBR, source localization tomography (sLORETA), and the PLV in the frontal and parietal lobes varied according to the depressive state in healthy individuals during a resting state. These findings suggest that depressive states may influence neural activity during resting states, potentially affecting cognitive functions. The PSD, power ratio, and connectivity within the neural circuits, particularly between the frontal and parietal lobes, could serve as an effective indicator and contribute to improving the understanding of neural activity during the resting state in healthy individuals. The identification of these neural patterns associated with depressive states could act as parameters for evaluating depressive states in healthy individuals, potentially serving as early markers for MDD.

Chapter 4 Analysis of Cognitive Biases during Visual Stimuli Processing

4.1 Introduction

Major depressive disorder (MDD) is a mental illness accompanied by many depressive symptoms, including feelings of worthlessness, low mood, easy fatigue, and inability to concentrate, which can gravely affect people's daily lives and their functioning in society (Disner et al., 2011). Subthreshold depression (sD) and major depression are considered to occur on a continuum, and there are only quantitative and not qualitative differences between depressive states in healthy people and patients with MDD (Cox et al., 2001). Qualitative differences refer to the different types of phenomena, such as psychological experience and depressive symptom. Quantitative differences, on the other hand, means that they differ in terms of how much depression is present, or how severe the symptoms are, but not in the type of symptoms that are present (Flett et al., 1997). The depressive states lie on a single continuum or spectrum, where the main difference between mild, moderate, and severe depression is how severe or how many symptoms are, not the specific type or nature of the symptoms.

The significant effect of depression on cognitive processes is reflected in the bias toward negative information. Previous research found that participants with MDD gaze longer at faces with negative expressions (Keller et al., 2020) and focus more on negative self-evaluation words (Yang et al., 2011). In terms of unconscious situations, participants with MDD lack an attentional bias toward negative emotions when unconscious compared with healthy participants, which would influence negative stimulus processing during consciousness (Yang et al., 2011). Patients who are more depressed have a greater attentional bias toward emotional stimuli (Ajilchi and Nejati, 2013), and this is reflected in the longer reaction time required to shift attention from emotional stimuli (Beiting et al, 2020; Wang and Dai, 2020). Such biased processing is also reflected in neural responses, including event-related potentials (ERPs) and event-related spectrum perturbation (ERSP), which present EEG oscillations at certain frequencies.

The above studies demonstrate the presence of biased cognition and differential neural activity in patients with MDD. Three competing theories—positive attenuation, negative potentiation, and emotion context insensitivity—are used to explain the distorted perception (Zhang et al., 2023). Individuals with depression often exhibit poor inhibition of negative stimuli and struggle to disengage from negative and neutral stimuli, demonstrating a bias in attention (Mennen and Norman, 2019). When exposed to happy, neutral, and sad stimuli, depressive individuals showed a lower reaction to affective stimulation compared with healthy individuals (Rottenberg et al., 2005; Edelstein et al., 2010). However, it remains unclear how different depressive states in healthy individuals affect neural activities in emotional information processing. Therefore, in the present study, we used negative, neutral, and positive images to investigate the different influences of various emotional stimuli. We thus investigated the different responses of healthy individuals to visual stimuli and, based on previous theories concerning the continuum between sD states and MDD, we hypothesized that this continuity might be present in the neural activities of healthy individuals.

In this study, we investigated whether the attentional bias could be detected by reaction time during the perception of image stimuli and whether there were significant differences in neural activities among healthy individuals with different depressive states during this procedure. We used the Beck Depression Inventory-Second Edition (BDI-II) to evaluate participants' depressive states and the International Affective Picture System (IAPS) as the external visual stimulus. We grouped the IAPS images into negative, neutral, and positive categories and randomly presented one image per trial, with participants required to provide an evaluation score as soon as possible during the presentation. The image reaction time and EEG activity were recorded during the experiment. We investigated whether participants with different depressive states have attentional systems with various degrees of impairment and whether participants with higher depressive states have slower reaction times, smaller P300 amplitudes, stronger alpha oscillations, and weaker delta and theta oscillations compared with participants with lower depressive states.

4.2 Behavior Data Analysis

4.2.1 Behavior Data Analysis Method

We used Python scripts to write the whole experiment, using an Arduino to connect the EEG amplifier (Polymate Pro MP6100) to the PC displaying the experimental procedure so that we could record the exact time at which each experimental stage started. The reaction time, which was defined as the time from the appearance of the IAPS image until the individual pressed the Shift key, and the evaluation score for the image were recorded in a text file. Trials with a reaction time equaling 3000 ms were eliminated, and the remaining data were used for behavioral result analysis. Polynomial curve fitting[6] and polynomial evaluation[7] were applied to fit a simple linear regression model to the sets of BDI-RT data and BDI evaluation data.

4.2.2 Results

In each experimental trial, participants were asked to evaluate the pleasant and unpleasant impressions obtained from the images by pressing the numeric keys on the keyboard; the images were rated on a scale of 1 to 9, with 1 being pleasant and 9 being unpleasant. The distribution of the evaluation scores of the images by the participants for each type of image (negative, neutral, and positive) is shown in Figure 4.1. The negative images were distributed in a low score range (minimum, 1 point; maximum, 4 points), indicating unpleasantness, while the positive images were distributed in a high score range (minimum, 3 points; maximum, 9 points), indicating pleasantness. In addition, the neutral images had more evaluations with a median score of 5 points. Thus, it can be concluded that specific emotions were correctly elicited when the IAPS images were presented as visual stimuli. Therefore, the three types of images in the current experiment showed the validity of specific evoked emotions.

[6] https://jp.mathworks.com/help/matlab/ref/polyfit.html?lang=en/
[7] https://jp.mathworks.com/help/matlab/ref/polyval.html?s_tid=doc_ta/

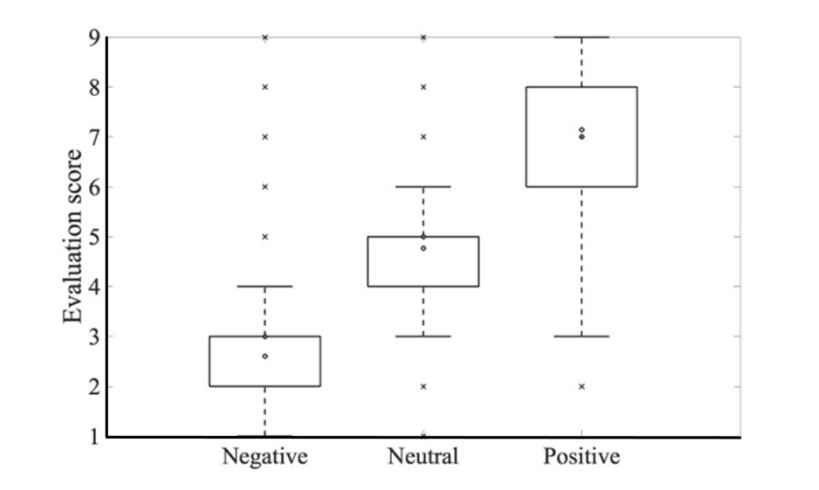

Figure 4.1. Evaluation score by image valence

Furthermore, to determine the influence of different depressive states on reaction time, the correlation between the reaction time for each BDI-II score, rather than the three depressive state groups (high, middle, and low), is shown in Figure 4.2. For all valence types of images, there were no correlations between the reaction time and BDI-II score (negative images, r=0.191 [p=0.220]; neutral images, r=0.182 [p=0.244]; positive images, r=0.198 [p=0.203]). The averaged reaction time of three groups is shown in Figure 4.3. Statistical analysis revealed no significant influence of the groupings on reaction times (F=0.44, p=0.65).

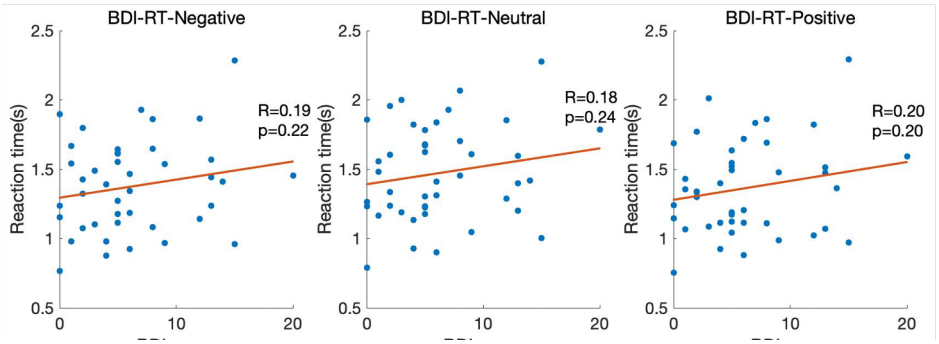

Figure 4.2 Relationship between the BDI score and reaction time. The x-axis shows the BDI score, with a higher score associated with a higher depressive state. The y-axis shows the reaction time, which was defined as the time from the appearance of the IAPS image until the subject pressed the Shift key. Each dot represents the average reaction time of one participant.

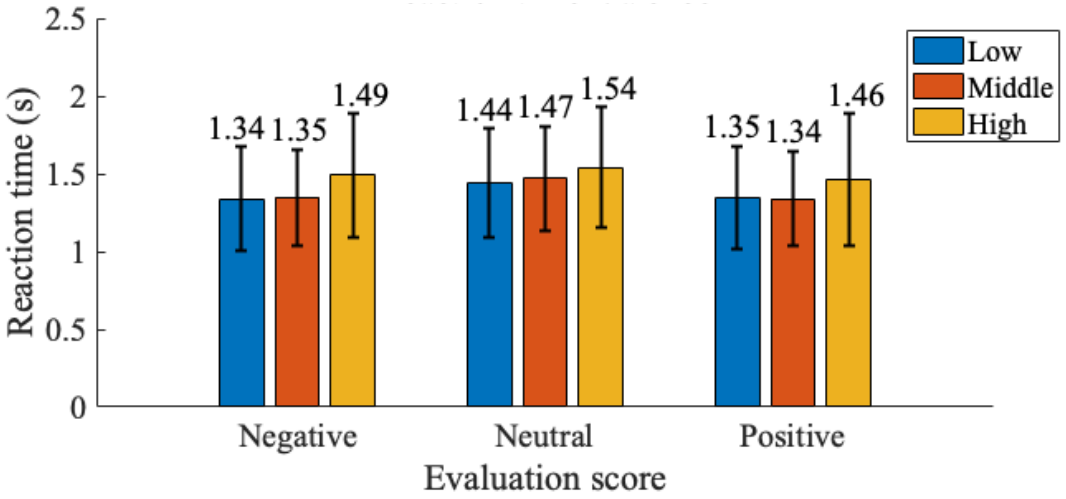

Figure 4.3 The averaged reaction time (RT) for three groups

4.2.3 Discussion

For behavioral results, the correlations between the reaction time and BDI score were not significant for any of the emotional stimuli, which might be because the effect of depressive state is small for healthy participants. However, the effect of depressive states impacts EEG activity with significant differences, which suggests that EEG analysis, rather than behavioral analysis, is necessary to assess depressive states in healthy participants.

4.3 Feature 1: Event-related Potential (ERP)

4.3.1 Introduction

ERP is an EEG feature with high temporal resolution obtained by averaging the neural activity of the cerebrum after a certain stimulus is presented (Ding et al., 2017). Participants with MDD have ERPs that are significantly sensitive to negative pictures compared with healthy controls (Kaiser et al., 2015), and they have a weaker frontal-parietal network, which is thought to be associated with impaired attentional selection, emotion regulation, and cognitive attentional control (Keller et al., 2020; Wang et al., 2021). Sub-threshold subjects showed sharper ERP response and slower reaction time for emotional stimuli (Jiang et al., 2022). Depressed patients have significantly lower explicit self-esteem than healthy controls and that their central parietal P300 amplitude is attenuated in implicit self-esteem versus positive contexts[8].

4.3.2 Analysis Method for ERP

The raw data were referenced online to AFz and re-referenced to the average of all electrodes in pre-processing. Eye movement components that were similar to two EOG recordings were removed by the Infomax ICA algorithm. The EEG analysis was based on a MATLAB script and EEGLAB toolbox, as well as its plugin ERPLAB. Regarding the pre-processing of EEG data, a bandpass filter was applied from 0.5 to 30 Hz.

The ERP analysis was applied from −200 to 1000 ms with respect to the time when the IAPS image appeared. The ERP amplitude of each epoch was extracted by image type (negative, neutral, and positive) and then divided into three depressive state groups (high, middle, and low depressive) based on BDI-II score. One-way ANOVA was applied to each 100-ms time period from 0 to 500 ms and each image type to investigate if there were significant differences among the three depressive state groups. For statistical analysis, we assessed 19 channels, applying a correction for multiple comparisons to examine the primary effect of the depressive state. Due to the significant differences and a representative pattern in the waveform, our focus was narrowed to the Pz channel (Figure 4.4). The calculation of mean amplitudes was conducted within time windows

[8] https://eeglab.org/tutorials/08_Plot_data/Time-Frequency_decomposition.html/

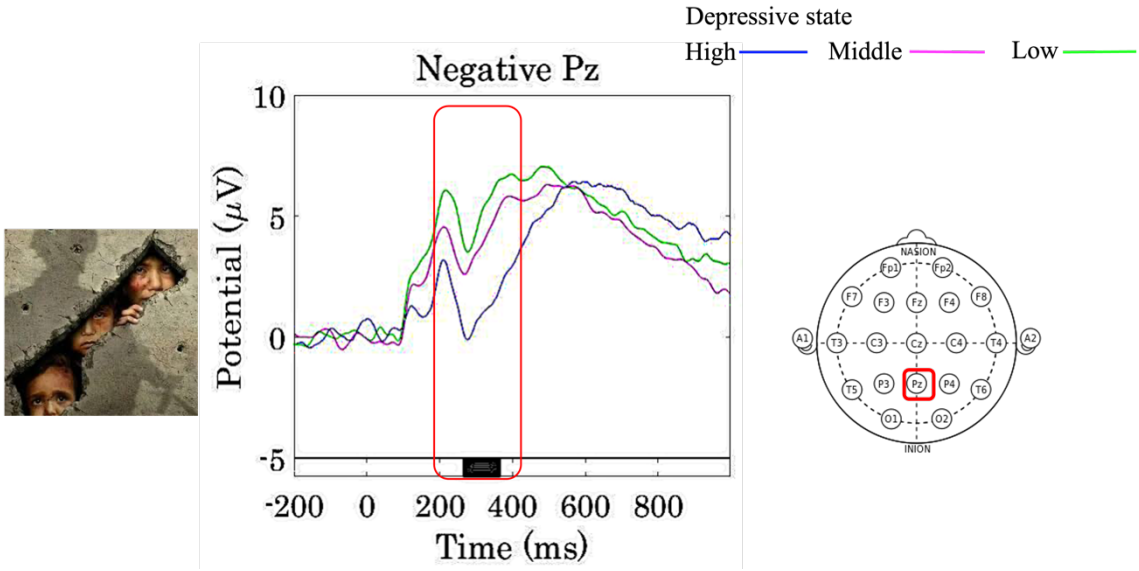

Figure 4.4 Example of ERP results during negative stimulus processing from Pz electrode

centered at the peak latencies of ERP components in the grand-mean waveforms, utilizing shorter window lengths for early components and longer lengths for late components. Our analysis encompassed the average amplitudes of the parietal P100, P200, and P300. Specifically, the P100 amplitude was calculated as the average amplitude at Pz between 150 to 180 ms following the onset of words. The P200 amplitude was determined in the timeframe of 180 to 220 ms post-stimulus at Pz, and the P300 amplitude was ascertained as the average amplitude at Pz between 250 to 400 ms post-stimulus. The LPP latency was calculated as the time at which the relative-to-baseline peak value at Pz between 300 to 800 ms post stimulus.

4.3.3 Results

P100, which appears approximately 100 ms after visual stimulation, is considered to represent general visual information processing and is an EEG response that occurs mainly in the occipital region. The ERP results obtained at the Pz electrode, where the response is particularly evident, are shown in Figure 4.5. The ERP results for high, middle, and low depressive states are remarkable at P100, P200 and P300, followed by the late positive potential (LPP), with an increase up to peak and a subsequent return to a stable state. The latencies of P100 and P200 were similar and without significant differences. For the LPP, the waveform peaked at around 500 ms in the middle and low depressive state groups, whereas the high depressive state group showed a slower response with a peak at around 600 ms. The LPPs of the middle and low depressive state groups showed larger responses to the negative and positive images but a relatively small response to the neutral images.

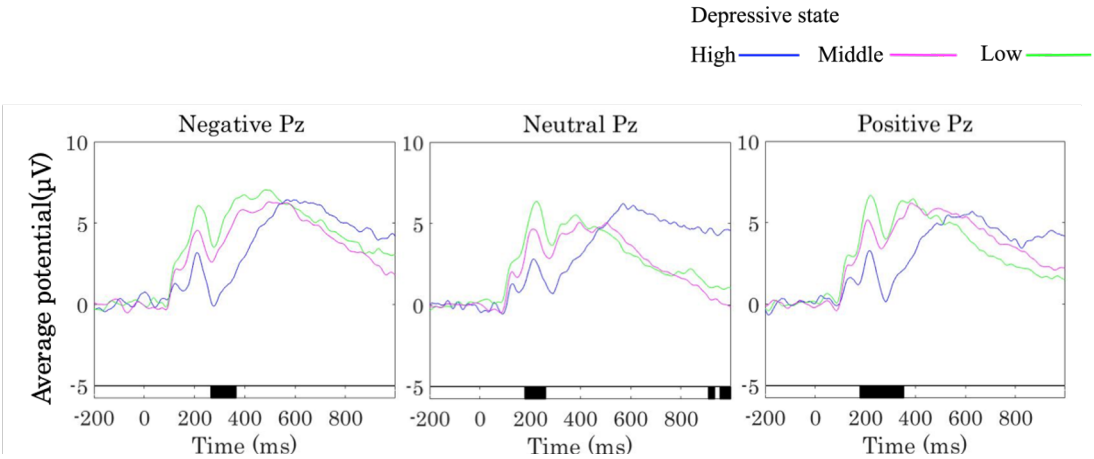

Figure 4.5 Grand averages of the event-related potential (ERP) for the three groups of IAPS images presented at Pz. On the left is the ERP figure of negative images, in the middle is the ERP figure of neutral images, and on the right is the ERP figure of positive images. The blue line represents EEG data from the high depressive state group, the pink line represents the middle depressive state group, and the green line represents the low depressive state group. The black line below the ERP figure represents the time window in which the ANOVA showed a significant difference in EEG potential according to the various depressive states.

Analysis of variance (ANOVA) was conducted for each image type to examine whether the ERPs were affected by different depressive states (Figure 4.5). The black bar attached to the time axis indicates the time range at which significant differences (FDR-$p<0.05$, one-way ANOVA with repeated measures) were found. Thus, significant differences in ERPs due to depression are shown at around 250 ms to 380 ms for negative images, at around 180 ms to 300 ms for neutral images, and at around 160 ms to 380 ms for positive images.

The topographic maps of the p-values obtained by ANOVA (Figure 4.6) were examined to determine whether the effects of different depressive states on the ERPs for each image type depended on the cerebral cortex position. Each 100-ms time interval from 0 ms to 500 ms after stimulus onset is shown. From 0 ms to 100 ms, no significant differences were observed immediately after stimulus onset. From 100 ms to 200 ms, significant differences were observed in the frontal region (FDR-$p<0.01$, one-way ANOVA with repeated measures) in the negative image group only and in the central and parietal regions for the negative (FDR-$p<0.05$, one-way ANOVA with repeated measures) and positive (FDR-$p<0.05$, one-way ANOVA with repeated measures) image groups. From 200 ms to 400 ms after stimulus onset, in all three image groups, the p-values were small in the parietal region (FDR-$p<0.01$, one-way ANOVA with repeated measures) centered on Pz and with a lateral deviation to the right hemisphere in the negative and positive image groups. In the negative image group only, there was a decrease in the degree of the significant difference in the frontal region from 100 ms to 400 ms. The correlation between BDI score and ERP amplitude are shown in Figure 4.7(a), and the correlation between BDI score and LPP latency are shown in Figure 4.7(b). The two-way ANOVA was applied to investigate the effect of group (low, middle, and high) and stimuli (negative, neutral, and positive) and their interaction effect on P100, P200 and P300. The statistical differences are shown in Table 3.

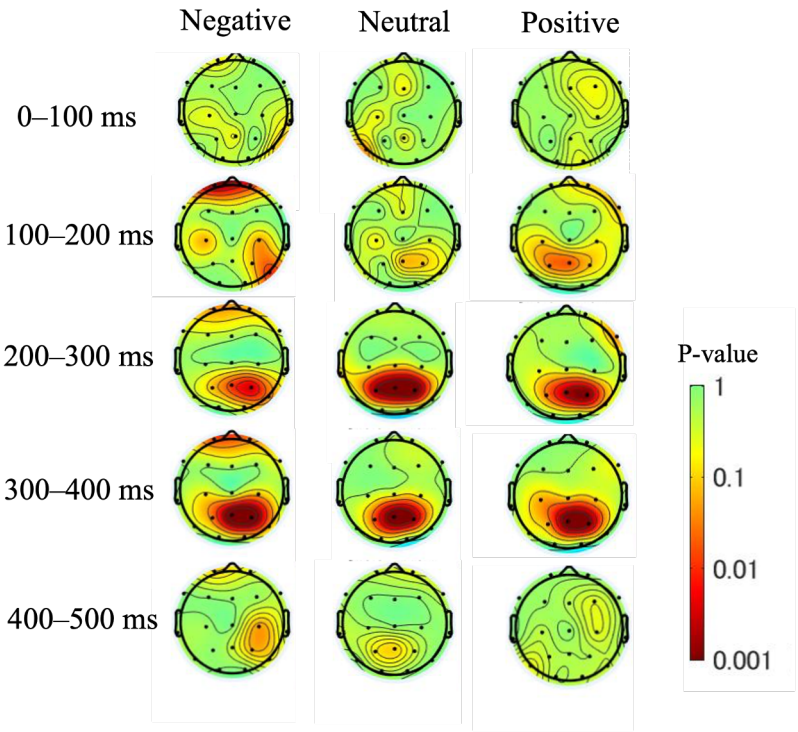

Figure 4.6 Topographic mapping of statistical differences in the ERP amplitude among the three different depressive states every 100 ms from 0 ms to 500 ms. The red color indicates a smaller p-value (FDR-$p<0.05$, one-way ANOVA with repeated measures).

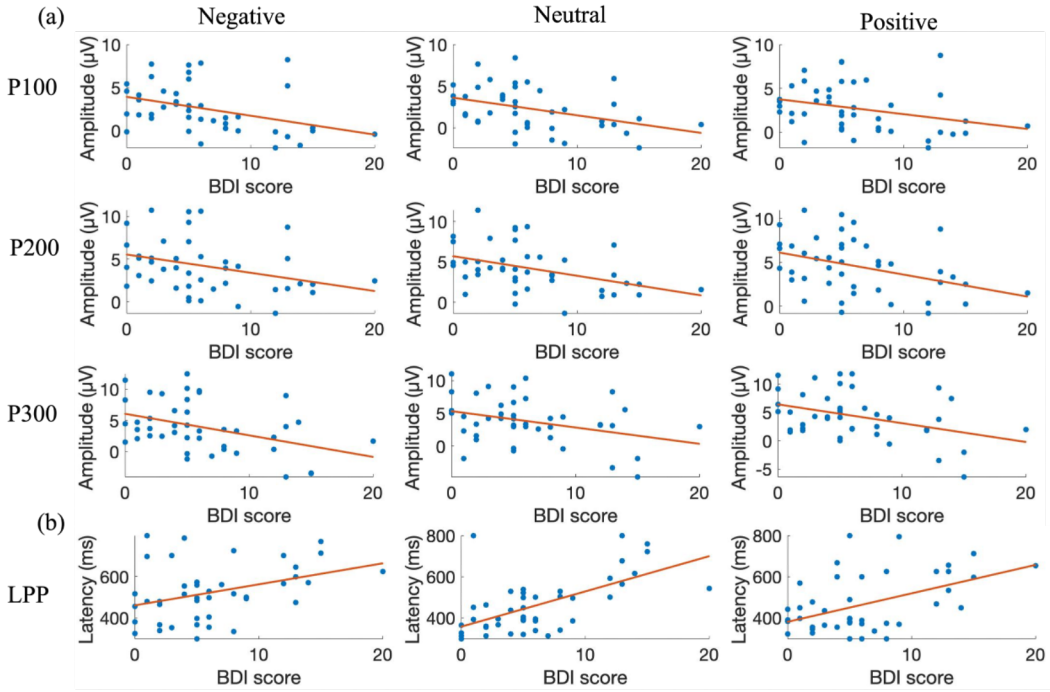

Figure 4.7 (a) Relationship between the BDI score and ERP amplitude. For all three groups of images (negative, neutral, and positive), the ERP amplitude were extracted and averaged and then plotted by BDI-II score. The x-axis shows the BDI score, with a higher score associated with a higher depressive state. The y-axis shows the average amplitude. The correlation of P100, P200, and P300 components are shown from up to down. (b) Relationship between the BDI score and ERP latency. The x-axis shows the BDI score, and the y-axis shows the peak latency.

Table 3. Statistical differences for ERP components

ERP components	F	P
P100-group	6.36	0.002
P100-group*stimulus	0.09	0.98
P200-group	8.53	0.0003
P200-group*stimulus	0.03	0.99
P300-group	7.85	0.0006
P300-group*stimulus	0.1	0.98

4.3.4 Discussion

The ERP results showed that ERPs from around 100 ms to 400 ms after the presentation of the visual stimulus, mainly in P300 for the negative, neutral, and positive image groups, differed among the high, middle, and low depressive states. The ERP amplitude, which is related to attention level, tended to decrease as the depressive state increased, a finding that is consistent with our hypothesis that healthy people with a higher depressive state are impaired in their attention. Studies have shown that many ERP components are related to attention and emotional processing, such as N1, P1, P3, and LPP, and are related mainly to ERP amplitude and have little of a relationship with latency (Xie et al., 2018). For example, the early component is associated with physical feature extraction of emotional stimuli and is found mainly in the occipital lobe, the middle latency component is related to selective processing and stimulation discrimination, and the LPP is related to memory evocation, emotional processing, and top-down processing (Olofsson et al., 2008). Regarding the early ERP component, previous research has found that highly demanding visual processing tasks can be completed in less than 150 ms (Thorpe et al., 1996). The positive peak P300 that appears afterward is considered to be

involved in comparison, evaluation, judgment, selective attention, and updating of the cognitive context in response to stimuli (Tarkka et al., 1996; Singh et al., 2000). The amplitude of P300 is negatively related to the degree of depression and a delay in the latency is positively related to it (Yang et al., 2011). It has also been found that patients with MDD have a bias toward negative stimuli in both early and late ERP components, indicating the bias ranges for emotion recognition and evaluation (Gan et al., 2019). Therefore, it is considered that the ERP responses to depression can be measured, and the ERPs elicited by external stimuli are lower in people with a high depressive state compared with the low group. This is equivalent to one of the hypotheses that the depressive state impairs the attentional system and that greater depressive state people need more time to respond to external stimuli. In addition, because the depressive state in healthy people is not qualitatively different from that of patients with MDD, but occurs on a continuum in terms of severity, this slowing of the ERP latency is also considered to occur on a continuum from people with a low depressive state to those with a high depressive state for healthy people not diagnosed with MDD.

A previous study showed that the role of P300 in regulating different emotions is more pronounced in healthy people and that the regulatory effect of LPP is impaired in individuals with high depression (Cuthbert et al., 2000). The P300 reflects the allocation of attention to significantly emotionally disposed stimuli, whereas the LPP is more connected with the cognitive process of distinction among emotions (Hu et al., 2017). Compared with neutral pictures, pictures with emotional tendencies can elicit a greater LPP, which appears at around 400 ms, showing the selective processing of emotional stimuli in the brain (Dainer-Best et al., 2017). The LPP also reflects a biased processing of self-referential stimuli (Yang et al., 2011). Patients with generalized anxiety disorder show less attentional adjustment in response to negative stimuli, as found through the LPP (MacNamara and Proudfit, 2014). In this study, the P300 amplitude decreased in the high depressive state group in response to emotional stimuli, and the LPP latency increased significantly with the increasing level of the depressive state, which might reflect the biased processing and impaired processing procedure. In addition, the topographic images showed a significant difference among depressive state groups in the frontal potentials only in the negative image group, which might suggest that the information processing is particularly affected by depressive state in the frontal lobe. ERP

responses originating from external stimuli are believed to occur from about 30 ms after the presentation of visual stimuli, and comprehensive rough cognition appears to take place in the frontal cortex (Foxe and Simpson, 2002). Regarding the early ERP component, previous research has found that highly demanding visual processing tasks can be completed in less than 150 ms (Thorpe et al., 1996). This might suggest that only the negative image group with negative impressions consistent with the schema, influenced by different schema depending on the degree of the depression, will show a significant difference by depressive state.

4.4 Feature 2: Event-related Spectral Perturbation (ERSP)

4.4.1 Introduction

ERSP shows oscillations in the power spectrum, including event-related desynchronization (ERD) and synchronization (ERS) (Lee et al., 2017). ERD is a decrease in the neural rhythmic activity of a particular frequency when an event occurs (Schoenberg and Speckens, 2014), whereas ERS is increased rhythmic activity, which represents the synchronization in the cortical response. In terms of EEG oscillation, participants with MDD show a stronger frontocentral theta synchronization after treatment with cognitive therapy (Mennella et al., 2015), individuals with depression have strong alpha activity, especially in the right hemisphere (Meerwijk et al., 2015), and people with a history of depression show less activated frontal delta oscillation (Wu et al., 2022). Alpha oscillation shows significant difference between sub-threshold depression and healthy subjects during emotional facial expression (Reichenberger et al., 2017).

4.4.2 Analysis Method for ERSP

For the time-frequency domain feature, the ERSP analysis was applied. To compute it, the signal of each trial was submitted to a Morlet wavelet transform, and the baseline power from −200 ms to 0 ms was subtracted from the spectral power after stimulus onset. Then, the results were averaged based on the three types of images of different valences (negative, neutral, and positive) and different depressive states. One-way ANOVA was conducted for each electrode and every 100 ms. The time interval was set to 100 ms from 0 ms to 700 ms after stimulus onset, and the average ERSP strength of the alpha band (8–12 Hz) was extracted to investigate if there were significant differences among the three depressive state groups. The statistical analysis was against 19 channels with correction of multiple comparisons to test the effect of depressive state. Because of the significant difference could be mainly found in frontal area, we focused on Fz channel for ERSP analysis. The selection of electrodes was a post-hoc decision based on our data.

4.4.3 Results

The ERSP, which expresses the event-related changes in the power spectrum, was applied to understand if depressive states affect the power changes at certain time and

frequency bands during visual stimuli. As in ERP analysis, three types of images (negative, neutral, and positive) and three types of depressive state groups (high, middle, and low) were used to group and average the EEG data. The epoch length was 1800 ms (from −400 ms before the stimulus onset to 1400 ms after it), with 400 ms before the onset used as baseline. The time-frequency result from 1 Hz to 30 Hz obtained from Fz is shown in Figure 4.8. For the ERSP result, the power increase in the delta (0–4 Hz) and theta (5–8 Hz) bands and power decrease in the alpha band (8–12 Hz) were quite pronounced from around 200 ms after stimulation onset.

As shown in Figure 4.8, in terms of a decrease in amplitude, the latency of the different depressive states was similar, but activities appeared to vary in strength. The high depressive group showed a stronger decrease in the alpha band from 8 Hz to 12 Hz, starting at around 250 ms, whereas the low and middle depressive state groups showed less of a decrease from 10 Hz to 15 Hz. Regarding the amplitude decrease within groups for different valence pictures, the high depressive state group tended to show a greater decrease for negative and neutral images, whereas the low depressive state group showed a higher activity of the amplitude decrease for negative images. Figure 4.9 shows the statistical analysis result of the p-value topographic map to understand the effect of depressive states on the alpha band (8–12 Hz) ERSP. From 200 ms to 300 ms after stimulus onset, in all three image groups, the p-values were small in the frontal region (FDR-$p<0.01$, one-way ANOVA with repeated measures) and with a lateral deviation to the left hemisphere in the frontal and temporal regions for the negative and positive image groups. From 300 ms to 400 ms after stimulus onset, the p-value was small in the centro-frontal region (FDR-$p<0.05$ for the positive image, one-way ANOVA with repeated measures) for all three image groups. From 400 ms to 600 ms, there was a decrease in the degree of the significant difference in the frontal region (FDR-$p<0.05$ for positive image, one-way ANOVA with repeated measures). Besides the frontal region, significant differences were also found in the occipital lobe (FDR-$p<0.01$, one-way ANOVA with repeated measures) from 200 ms to 700 ms for the negative and positive image groups and from 300 ms to 700 ms for the neutral image group.

However, the result of the increase in Figure 4.8 showed that the lower the amplitude increase, the more severe the depressive state. The high depressive group demonstrated a weaker amplitude increase for the delta and theta bands and shorter durations, with almost

no increase produced after 600 ms, whereas individuals of low and middle depressive states showed a larger consistently sustained increase. In terms of the within-group amplitude increase for different valence pictures, the high depressive group showed a more pronounced increase for negative and neutral images, the middle depressive group showed a stronger increase for negative images, and the low depressive group showed a stronger increase for positive images.

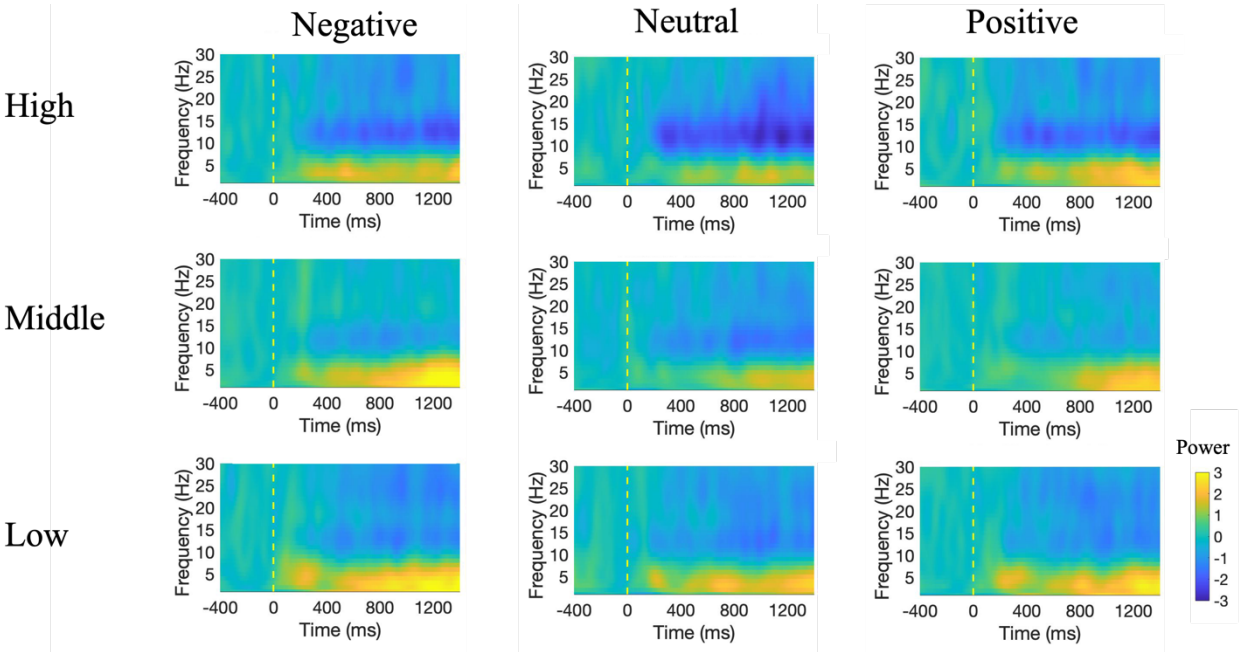

Figure 4.8. ERSP results for the three groups and three types of stimuli at Fz. The x-axis shows the time from −400 ms to 1400 ms, where 0 ms represents the time at which the IAPS image was first displayed. The y-axis shows the frequency range from 0.5 Hz to 30 Hz. In each figure, the yellow area is associated with synchronization and the blue area is associated with desynchronization. The three columns represent the different picture types (negative, neutral, and positive) and the three rows represent the different depressive states (high, middle, and low group).

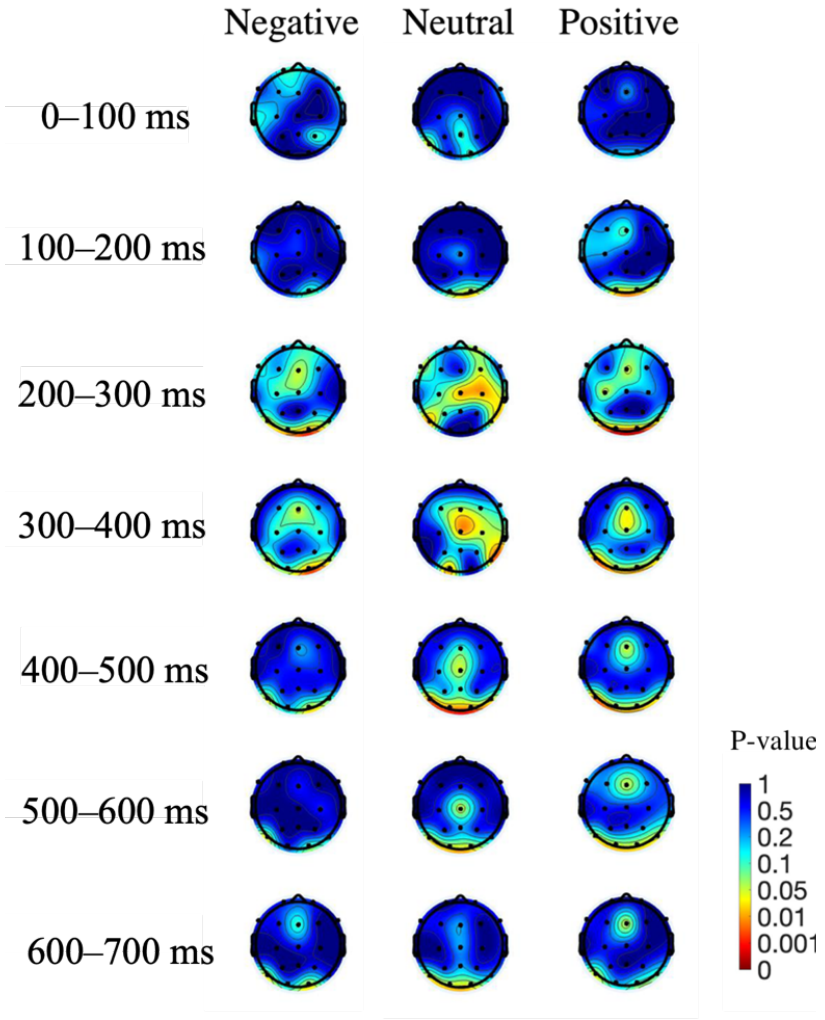

Figure 4.9 Topographic mapping of statistical differences in the ERSP amplitude of the alpha band (8–12 Hz) among the three depressive states every 100 ms from 0 ms to 700 ms. The red color indicates a smaller p-value (FDR-$p<0.05$, one-way ANOVA with repeated measures).

4.4.4 Discussion

This research explored the EEG oscillation based on high, middle, and low depressive states during emotional stimulation by time-frequency features. Previous research found that participants with high emotional intelligence exhibited less upper alpha desynchronization in emotion recognition testing (Jaušovec, N and Jaušovec, K, 2005). People with low emotional granularity[9], who are unable to express their emotions with discrete words, show greater alpha ERD, which is thought to be associated with greater effort to recognize affective stimuli (Lee et al., 2017). Later-stage alpha oscillation is associated with higher cognitive functions, such as the discrimination of emotional stimuli (Aftanas et al., 2004). Alpha desynchronization is associated with special tasks and increased information transmission (Benedek et al., 2011), whereas frontal alpha synchronization is related to top-down processing and creative tasks and theta synchronization is related to the evaluation of emotional stimuli (Sun et al., 2012). In this study, it is found that the higher depressive group showed a higher alpha ERD, suggesting that depressive states may be related to the degree of awareness of emotions, with high depressive state people having a more stunted perception and recognition of emotions.

Furthermore, topographic analysis revealed significant differences from 100 ms to 300 ms in the posterior region and left prefrontal region among the depressive state groups, with the difference found in turn at the frontal area and central area. Previous research identified increased alpha power in the frontal-parietal lobe in patients with MDD (Jaworska et al., 2012). A neural mechanism for top-down visual stimulus recognition proposes that visual stimuli are first projected to the prefrontal cortex for initial recognition and then to the temporal cortex in combination with bottom-up processes, allowing for more rapid recognition (Bar, 2003). The dorsolateral prefrontal cortex in the left hemisphere has also been associated with attention regulation (Grimm et al., 2008). Therefore, the results might indicate that the neural mechanisms of top-down emotion regulation in response to emotional stimuli differ among depressive state groups, and there may be a significant relationship between how they respond to negative stimuli and their cognitive schema (Figure 4.10).

[9] https://en.wikipedia.org/wiki/Emotional_granularity/

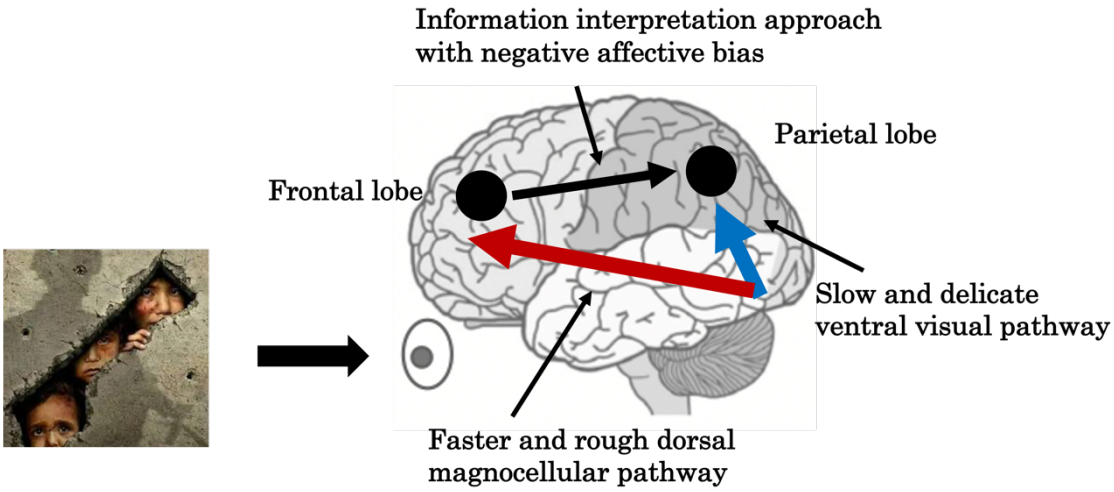

Figure 4.10 Visual information processing mechanism (Bar, 2003)

In terms of delta and theta bands, it is found the opposite tendency, that is, the higher the depressive state, the lower the ERS. Delta synchronization was determined to occur at an earlier time and to be involved in detecting emotional significance. Previous research found that the enhancement of theta synchronization in posterior and anterior regions is related to the degree of concentration and to the mechanisms for emotion processing (Emotional granularity. Wikipedia, 2022). In terms of emotional tendency, high emotional salience stimuli induce larger delta and theta band synchronization (Dainer-Best et al., 2017). Theta synchronization in the posterior region has been correlated with evaluations of emotional salience, with scary stimuli eliciting more intense synchronization (Benedek et al., 2011). Thus, the lower delta and theta ERS may reflect a lack of attentional resources and a deficit in the detection of emotional salience in individuals with a higher depressive state compared with those with a lower depressive state.

4.5 Summary

This study examined neural activity differences among healthy individuals with various depressive states through analysis of ERP and time-frequency amplitude changes in the delta, theta, and alpha bands during emotional visual information processing. Regarding ERPs, a tendency emerged for the P300 amplitude to decline with an increasing depressive state for all emotional stimuli. For ERSPs, the high depressive group showed a stronger decrease in the alpha amplitude, while the low depressive group showed a stronger increase in the delta and theta amplitudes. Moreover, the three depressive state groups showed significant differences in the frontal and parietal lobes at different time periods.

The current experiment also has some limitations. First, depression is more prevalent in the female population (Piccinelli and Wilkinson, 2000), but about two-thirds of the participants in this experiment were men. This gender imbalance may not allow for replication across the female population, and future research will have to improve the generalizability. Furthermore, although the previous study validated the effectiveness of using the BDI-II score to group participants (Cox et al., 2001), it was difficult to conclude that there was a sufficient sample for each group, and future studies will need to increase the sample to identify significant relationships in the behavioral data.

In this study, we found that the amplitude and latency of ERP components and the strength of alpha desynchronization and theta synchronization in response to emotional visual stimuli were modulated by depressive state in healthy participants. Thus, we suggest that depressive states in healthy individuals may also modulate early cognitive and later attentional control, as well as emotion discrimination processes. This neural circuit based on the response between frontal and parietal regions may contribute to the understanding of emotion-cognition regulation in healthy individuals. This circuit contains both top-down and bottom-up bidirectional neural circuits, reflecting the formation of depressive states accompanied by schema reinforcement and diminished attentional control. The finding of these neural responses associated with depressive states is informative and can be used as one of the parameters to assess the evaluation of depressive states in healthy individuals and might serve as an early indicator of the possibility of MDD.

Chapter 5 Conclusion

5.1 Outcomes of This Research

Depression is a prevalent and debilitating mental health condition that affects millions globally. Early detection and intervention are crucial for improving outcomes and preventing the escalation of symptoms. This research encompasses a comprehensive exploration of the use of electroencephalography (EEG) as a biomarker tool for detecting early signs of depression in healthy individuals. This research bridges the gap in traditional depression studies by focusing not only on distinguishing depressed patients from healthy controls but also on identifying subclinical depressive states that may not be otherwise observable through conventional clinical assessments.

EEG offers a promising method to probe the neurophysiological substrates associated with depressive states. By analyzing EEG signals, researchers can capture dynamic changes in brain activity that correlate with emotional and cognitive functions. The application of machine learning algorithms to these signals enables the prediction and classification of depressive states beyond traditional diagnostic methods.

The research methodology involved two main experimental studies, each utilizing EEG data from healthy subjects who exhibited a range of depressive symptoms as measured by established psychological scales. The EEG data included one-minute resting-state recordings and responses during visual stimulation tasks that collected from 43 subjects.

Chapter 3 explored the impact of varying depressive states on neural activities in healthy individuals by examining changes in power spectrum density (PSD), power ratio, and region-based phase locking value (PLV) during rest. Key findings included a decrease in theta band PSD and an increase in delta band PSD in the prefrontal cortex as depressive states intensified. Additionally, a decreasing trend in the theta/beta ratio (TBR) in the right frontal region and significant correlations within frontal and parietal regions were noted. Source localization indicated activities in frontal and temporal regions, particularly in beta and gamma bands. Overall, the results suggest that depressive states can influence

resting-state neural activity, with potential implications for using these measures as early indicators of major depressive disorder (MDD).

Chapter 4 investigated the neural activity differences among healthy individuals with varying depressive states by analyzing ERP and time-frequency amplitude changes in the delta, theta, and alpha bands during emotional visual information processing. Key findings include a decrease in P300 amplitude with increasing depressive states across all emotional stimuli, and distinctive patterns in ERSP. Significant differences were noted in the frontal and parietal lobes among the three depressive state groups during various time periods. The research concludes that depressive states in healthy individuals can modulate neural responses related to early cognitive and later attentional control processes during emotional discrimination tasks. This modulation is evident in the interaction between frontal and parietal regions, involving both top-down and bottom-up neural circuits, suggesting that these patterns could serve as early markers for major depressive disorder (MDD) by reflecting underlying changes in emotion-cognition regulation.

This study has successfully identified distinct EEG patterns that differentiate between healthy individuals across various stages of depressive states, which demonstrate the capability of EEG in distinguishing different levels of subclinical depression. The EEG responses analyzed in this study provide significant evidence for detecting the continuum in subthreshold depression. Notably, the gradual changes in P300 amplitudes and latencies across different depressive states offer insights into the progression of these subclinical conditions. The research also revealed observable differences in neural mechanisms and connectivity, particularly in the frontal and parietal lobes, highlighting the role of specific brain regions in the modulation of depressive states.

In summary, this study provides compelling evidence that EEG is a valuable tool for not only differentiating and detecting the continuum of depressive states in healthy individuals but also for understanding the underlying neural mechanisms and offering predictive insights into the onset of depression, thereby contributing significantly to both clinical and preventive psychiatry.

5.2 Research Positioning and Future Directions

In this section, I will delve into the positioning of our research within the broader context of neuroscience and outline prospective avenues for future studies. Our investigation bridges vital gaps in understanding the neural underpinnings of depressive states through EEG biomarkers, setting a foundation for expanding knowledge in both theoretical and applied domains. The findings herein not only reinforce existing theories but also open new paths for innovative therapeutic strategies and diagnostic tools. Moving forward, future research aims to address the identified limitations and explore the nuanced interactions between neural activity patterns and depressive symptoms, potentially revolutionizing the approach to mental health diagnostics and intervention.

5.2.1 Research Positioning

- ***Comparison with neuroimaging studies***

Findings of neuroimaging studies: The sD state detection using MRI has also been an area of active research. Regarding the capabilities of MRI techniques to detect sub-threshold depression and how these findings compare with current EEG data, previous MRI study has found that individuals with sD show structural brain changes similar to those seen in major depressive disorder in both gray and white matter microstructure (Allan et al., 2016). Compared our study, while EEG provides dynamic features into brain function, MRI offers structural details, which deepen our understanding of depressive states from sub-threshold to clinical depression.

In discussing functional connectivity disruptions, previous resting-state fMRI study has highlighted abnormal connectivity patterns in sD. It observed correlations within the frontal region negatively related to BDI-II scores, and positive correlations within the parietal region, findings that align with those of our study. Additionally, pervious study has identified disrupted connectivity between the right and left pallidum, associated with symptoms such as dysphoria and hyposensitivity to rewards, prevalent in depressive conditions (Sato et al., 2023). However, my current research did not examine the hemispheric connections, a gap that future studies should address. Investigating these interhemispheric links could provide deeper insights into the neural underpinnings of depressive states, enhancing our comprehension and the development of targeted

therapeutic strategies.

Unique contributions of current research: While MRI can indeed detect subthreshold depressive states, EEG studies still provide unique and valuable insights in researching sD.

From an academic research perspective, firstly, EEG has excellent temporal resolution (milliseconds), allowing researchers to study rapid changes in brain activity associated with sD. This is particularly useful for examining cognitive processes and emotional responses in real-time, which MRI cannot capture with the same precision. Secondly, EEG directly measures electrical activity of neurons, providing a more immediate representation of neural functioning compared to the indirect measures of brain activity obtained through fMRI. Thirdly, EEG allows for the examination of specific frequency bands (e.g., alpha, beta, theta) which can provide insights into different cognitive and emotional processes relevant to sD. Lastly, while fMRI is often used for functional connectivity analysis, EEG can provide unique insights into functional connectivity patterns, particularly in terms of phase synchronization between different brain regions.

From a practical application point of view, EEG is generally more accessible and cost-effective than MRI, making it suitable for larger-scale studies, longitudinal research, and repeated measurements over time. Besides, EEG equipment can be more easily used in various settings, including more naturalistic environments, allowing for the study of brain activity in contexts that more closely resemble real-life situations. EEG data can also be used for neurofeedback interventions, potentially offering therapeutic applications for individuals with sD.

In summary, while MRI is valuable for detecting subthreshold depressive states, EEG studies offer unique advantages in temporal precision, direct neural measurement, and flexibility of application. These characteristics make EEG an essential tool in the comprehensive study of subthreshold depression, providing insights that complement and extend beyond those obtainable through MRI alone.

- ***Contribution of an objective biomarker on sD detection***

Our study highlights significant neural activity changes within the frontal and parietal lobes, marking these regions as potential biomarkers for the early detection and

remote monitoring of depressive states. The accessibility and cost-effectiveness of EEG technology make it especially valuable for widespread application, offering substantial benefits for early intervention and continuous management of depression across various settings.

It is not uncommon for individuals to present a facade of happiness, influenced by social desirability biases or a lack of self-awareness regarding their depressive symptoms. This difference can mask underlying issues, complicating accurate diagnosis and effective treatment. Our study utilizes objective markers of depression derived from EEG and other neurophysiological assessments to provide an insight into brain activity that may not be apparent from subjective reports alone. These objective markers uncover patterns and potential issues that individuals might not fully recognize or may actively minimize.

Our methodology integrates subjective assessments via the Beck Depression Inventory-II (BDI-II), which captures self-reported symptoms and the personal experience of depression, with objective measurements derived from EEG signals. This dual approach significantly enhances the reliability and comprehensiveness of our findings, providing a robust framework for understanding the multifaceted nature of depression.

The subjective component allows us to access the patient's personal perspective and self-perceived symptoms, enriching the clinical context. Conversely, the objective EEG data provide quantitative insights into underlying brain activity, revealing aspects of depression that may not be consciously perceived by individuals. This method not only confirms the presence of depressive states but also deepens our understanding of the neural mechanisms involved, supporting more targeted and effective treatment strategies.

- ***Validation of Beck's model of depression***

Our study validates the Beck's model of depression and demonstrates that cognitive biases can be detected in the absence as well as in the presence of stimuli. The effects of biased processing, biased memory, and biased attention on resting state and stimulus processing can be understood through their differential effects on brain activity and functional connectivity. How each aspect affects these two states is described separately below:

Biased Processing: Biased processing can lead to alterations in resting-state functional connectivity. Individuals with biased processing exhibit different patterns of connectivity in brain networks associated with emotion regulation and information perception, thereby affecting the way these networks communicate in the resting state and enhancing the processing of relevant information while impairing the processing of neutral or incongruent stimuli.

Biased Memory: Biased memory can affect the neural activity associated with memory retrieval during resting state. For example, individuals with a bias towards negative memories may show altered activity in regions like the prefrontal cortex and hippocampus, which are involved in memory processing and emotional regulation (Peng et al., 2020). During stimuli processing, biased memory can influence how individuals recall past experiences related to the stimuli, leading to inaccuracies in perception and judgment.

Biased Attention: The presence of attentional biases may influence baseline activation levels in brain regions associated with attention and vigilance, potentially leading to a heightened state of alertness even at rest. Biased attention directly influences how stimuli are processed, leading individuals to focus on certain aspects of the environment while ignoring others. It can also increase cognitive load during stimuli processing, as individuals may expend more mental resources on processing biased stimuli, potentially affecting overall cognitive performance and emotional responses.

- ***Broad applicability of findings***

Detection of different levels of depression : Our research supports the hypothesis that subthreshold depression (sD) and major depressive disorder (MDD) form a continuum, rather than distinct categories. This continuum is evident in the features extracted from EEG data, which demonstrate changes in brain activity correlating with varying degrees of depressive severity. By employing EEG biomarkers, we can effectively detect these shifts, providing a valuable tool for assessing depression. This insight is crucial as it underlines the potential of EEG in monitoring and possibly predicting the progression of depression from its milder subthreshold stages to more severe forms. This approach not only enriches our understanding of the neurophysiological underpinnings of depression but also enhances the potential for early

intervention and tailored treatment strategies.

Monitoring of treatment effects: EEG biomarkers are proving to be a valuable tool in the field of psychiatry, particularly for predicting treatment outcomes in major depressive disorder (MDD). This capability enables clinicians to make more informed decisions about therapeutic strategies tailored to individual patient needs at various stages of depression. By utilizing EEG biomarkers, clinicians can identify early signs of relapse or inadequate response to treatment. This early detection is vital as it allows for prompt adjustments in therapeutic approaches, potentially before the patient is even aware of symptom changes. For instance, shifts in EEG patterns might signal the onset of depressive symptoms anew, providing a preemptive alert that can guide clinical interventions. Additionally, the capacity for continuous EEG monitoring offers a significant advantage over traditional methods that rely heavily on patient self-reporting. This method reduces the impact of subjective biases and enhances the objectivity in managing depression, especially in severe cases where patients might underreport symptoms or experience cognitive impairments. This objective approach could revolutionize how we manage depression, leading to more dynamic and responsive treatment plans.

5.2.2 Future Directions

- ***Higher spatial resolution measurement***

Given the higher prevalence of depression among women, the gender imbalance may restrict the generalizability of the findings across genders. Additionally, the research utilized a 19-channel EEG for source localization, which, while effective for preliminary analysis, is not ideal for detailed spatial mapping of brain activity. This configuration may lead to less precise localizations compared to what could be achieved with high-density EEG systems, potentially affecting the accuracy of the results.

Future research should prioritize the use of high-density EEG systems that provide greater spatial resolution, enhancing the accuracy and reliability of source localization. Such advancements would allow for a more detailed understanding of the neural mechanism of depressive states, facilitating finer distinctions between different levels of depressive severity.

- ***Analysis of the correlation between the two experiments***

The current study did not explicitly investigate the relationships between resting state and stimuli processing EEG activities across different experimental settings, which represents a limitation in the understanding of how these neural activities interconnect across varying cognitive conditions.

For future research, a more integrated approach that examines the correlations and potential causative relationships between resting state EEG and ERP during stimuli processing could be pivotal. This approach could provide valuable insights into whether resting state and stimuli processing EEG responses share a direct relationship independent of depression. Understanding these mechanisms could help refine existing models of depression and stimulate further inquiry, ultimately leading to a more comprehensive understanding of the neural basis of depressive states.

- ***Investigation of the neurophysiologic complexity of depression's causes***

In terms of the correlation between BDI-II scores and the underlying brain mechanisms of depression, our research points to the necessity of delving deeper into the complex neurophysiology of depression. Although the BDI provides a unidimensional score for depression severity, it does not reflect the neurobiological diversity that exists among individuals who share similar BDI scores.

The data reveal that identical BDI scores can coincide with significantly varied brain activity patterns among different individuals. This variability suggests the presence of diverse neurobiological pathways that could lead to similar depressive symptoms but originate from different underlying mechanisms. Such findings underscore the limitation of relying solely on BDI scores for a comprehensive understanding of depression's etiology.

Moving forward, future research aims to transcend the traditional reliance on BDI scores for classifying depressive states. By categorizing subjects based on distinct neural mechanisms rather than uniform symptomatology scores, we hope to uncover more precise biological markers of depression.

♦ ***Integration of multi technologies***

Unlike neuroimaging techniques such as fMRI or PET scans, EEG lacks the spatial resolution necessary for precise localization of neural activity. This restricts our ability to pinpoint the exact origins of observed neural discrepancies within the brain, which can be critical for understanding complex psychiatric conditions. Molecular biomarkers, another crucial category in depression research, provide insights into the biochemical changes associated with depressive disorders, predominantly aiding in medication development. These biomarkers allow researchers to identify and target specific biochemical pathways, paving the way for personalized treatment options.

Given these considerations, our future research aims to integrate EEG findings with those from other biomarker categories, such as molecular and neuroimaging markers. This integrated approach would not only enhance the accuracy of detecting and monitoring depression but also deepen our understanding of its underlying biological mechanisms. Combining these diverse methods promises a more holistic and nuanced framework for treating and studying depressive states, potentially revolutionizing current diagnostic, and therapeutic protocols.

♦ ***Classification based on multi-channel feature selection***

Our study explored the significant EEG features for estimating BDI-II scores, highlighting several challenges and directions for future research. In terms of the variability in EEG feature from single electrode and its use in estimating BDI-II scores underscores a significant aspect of our research—improving the accuracy and reliability of mental health assessments through neurophysiological data. To enhance the stability of estimating BDI scores from EEG, Future studies could explore the extraction of features from multiple EEG channels to provide a comprehensive picture of brain activity across various regions. This method could facilitate the creation of an extensive feature map, capturing diverse neural dynamics essential for accurate depression classification.

Future research could utilize machine learning techniques to delve deeper into these multichannel EEG features and construct robust predictive models that link EEG data to multifaceted depressive symptoms as measured by the BDI-II. This approach not only improves the accuracy of the model, but also allows us to explore the subtle relationships between specific EEG patterns and different dimensions of depression.

In preliminary validation tests, this strategy was applied, including the construction of feature maps based on electrode positions and the selection of power spectral densities (PSDs) at different frequencies. Preliminary experimental categorization results showed a high accuracy of 92.33% during resting state and 87.43% during stimulation processing, providing strong evidence of the validity of our method. These findings are critical as they highlight the potential for developing reliable, non-invasive biomarkers of depression using advanced EEG analysis techniques. This is consistent with our overall goal of advancing mental health diagnostics through innovative neurotechnological approaches that provide insights that can significantly improve the monitoring and treatment of depressive disorders.

5.3 Achievements and Prospects

The research presented in this study offers significant insights and advancements in the fields of cognitive neuroscience, bioengineering, and clinical psychology, with a focus on understanding depressive states (Figure 5.1).

- ***Cognitive neuroscience***

The study significantly advanced our understanding of neural patterns associated with depressive states, providing insights into how different levels of depression affect cognitive processing. By developing models that describe neural mechanisms, this research contributes to a deeper knowledge of the brain's functioning under various emotional and cognitive states. One key achievement is the identification of systematic differences in cognitive processing across depressive states, which has paved the way for developing neural mechanism models. These models are critical for future research aiming to understand and predict behavioral outcomes based on neural responses.

- ***Bioengineering***

From a bioengineering perspective, the study has refined EEG feature extraction methodologies, which enhance the precision and reliability of detecting and interpreting neural signals associated with depression. The insights gained into the mechanisms of depressive states facilitate the development of predictive models that could be used for early identification of depression, significantly impacting preventive healthcare strategies. Additionally, the integration of these refined methodologies into BCI systems opens new avenues for applying EEG technologies in robotic and AI applications, enhancing user interaction and responsiveness in therapeutic settings.

- ***Clinical psychology***

In clinical psychology, the study has enhanced the understanding of the continuum of depression, offering new possibilities for clinical assessments. The identification of EEG biomarkers for depressive states allows for more nuanced diagnostics and tailored treatment approaches, improving patient outcomes. Furthermore, the potential for these biomarkers to be incorporated into EEG-based assessments in clinical therapy offers a non-invasive tool for ongoing patient evaluation. This could greatly benefit mental health care, especially in settings like elderly care facilities. Additionally, the integration of

EEG-based depressive state detection in telemedicine could enhance remote healthcare services, allowing psychiatrists to monitor and adjust treatments remotely, improving outcomes and optimizing therapeutic strategies.

♦ ***Future prospects***

The study's implications extend into developing advanced tools for clinical practice, such as the integration of EEG assessments in telemedicine and personalized medicine. By leveraging the strengths of bioengineering and cognitive neuroscience, future research can create more sophisticated models that predict individual risk profiles and treatment responses. Moreover, the potential applications in robotics and AI highlight the interdisciplinary nature of this research, suggesting that future technological innovations could include autonomous systems capable of adapting to users' emotional states, thereby offering novel solutions in mental health interventions.

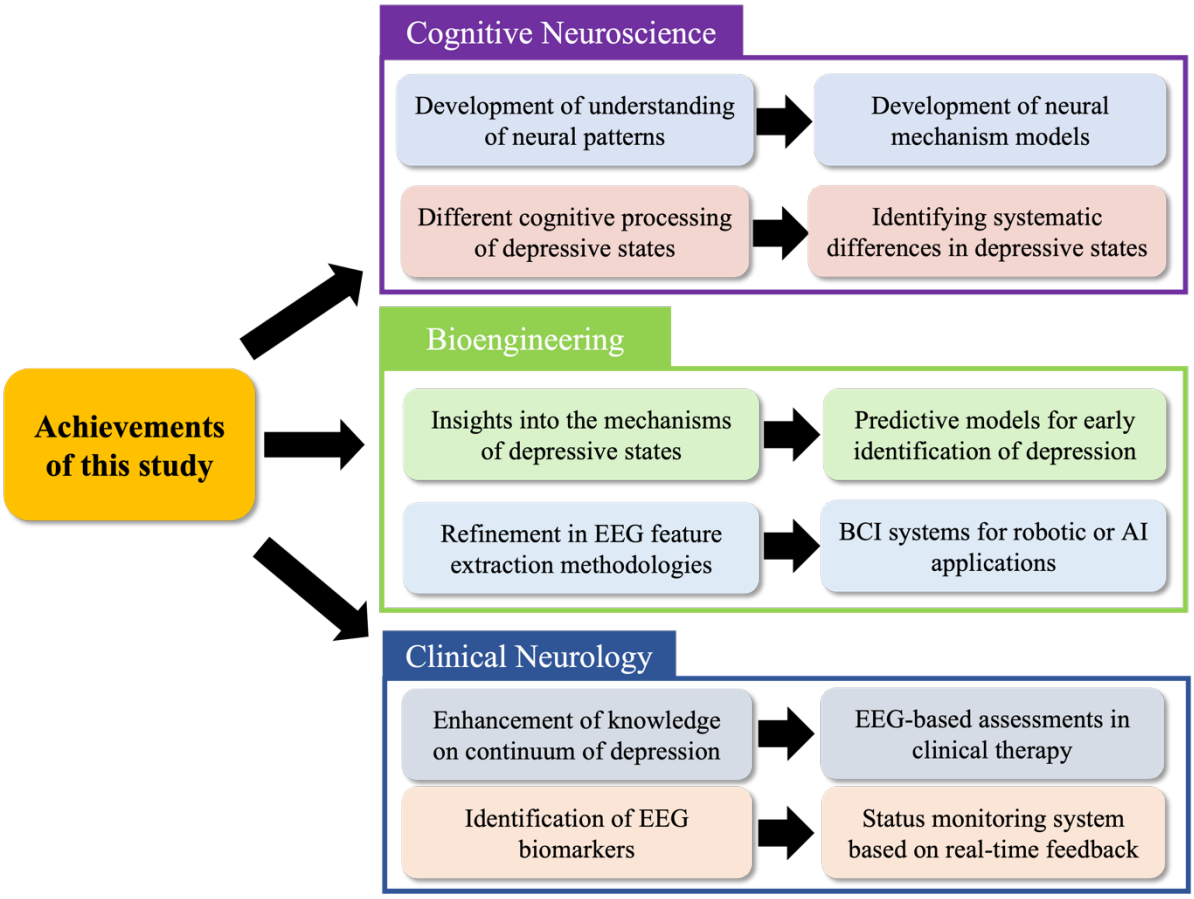

Figure 5.1 Achievements of this study and future prospects

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Appendix A Beck's Depression Inventory II

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully. And then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

Sadness

0. I do not feel sad.
1. I feel sad much of the time.
2. I am sad all the time.
3. I am so sad or unhappy that I can't stand it.

Pessimism

0. I am not discouraged about my future.
1. I feel more discouraged about my future than I used to.
2. I do not expect things to work out for me.
3. I feel my future is hopeless and will only get worse.

Past Failure

0. I do not feel like a failure.
1. I have failed more than I should have.
2. As I look back, I see a lot of failures.
3. I feel I am a total failure as a person.

Loss of Pleasure

0. I get as much pleasure as I ever did from the things I enjoy.
1. I don't enjoy things as much as I used to.
2. I get very little pleasure from the things I used to enjoy.

3. I can't get any pleasure from the things I used to enjoy.

Guilty Feelings

0. I don't feel particularly guilty.
1. I feel guilty over many things I have done or should have done.
2. I feel quite guilty most of the time.
3. I feel guilty all of the time.

Punishment Feelings

0. I don't feel I am being punished.
1. I feel I may be punished.
2. I expect to be punished.
3. I feel I am being punished.

Self-Dislike

0. I feel the same about myself as ever.
1. I have lost confidence in myself.
2. I am disappointed in myself.
3. I dislike myself.

Self-Criticalness

0. I don't criticize or blame myself more than usual.
1. I am more critical of myself than I used to be.
2. I criticize myself for all of my faults.
3. I blame myself for everything bad that happens.

Suicidal Thoughts or Wishes

0. I don't have any thoughts of killing myself.
1. I have thoughts of killing myself, but I would not carry them out.
2. I would like to kill myself.
3. I would kill myself if I had the chance.

Crying

0. I don't cry more than I used to.
1. I cry more than I used to.

2. I cry over every little thing.
3. I feel like crying, but I can't.

Agitation

0. I am no more restless or wound up than usual.
1. I feel more restless or wound up than usual.
2. I am so restless or agitated it's hard to stay still.
3. I am so restless or agitated that I have to keep moving or doing something.

Loss of Interest

0. I have not lost interest in other people or activities.
1. I am less interested in other people or things than before.
2. I have lost most of my interest in other people or things.
3. It's hard to get interested in anything.

Indecisiveness

0. I make decisions about as well as ever.
1. I find it more difficult to make decisions than usual.
2. I have much greater difficulty in making decisions than I used to.
3. I have trouble making any decisions.

Worthlessness

0. I do not feel I am worthless.
1. I don't consider myself as worthwhile and useful as I used to.
2. I feel more worthless compared to others.
3. I feel utterly worthless.

Loss of Energy

0. I have as much energy as ever.
1. I have less energy than I used to have.
2. I don't have enough energy to do very much.
3. I don't have enough energy to do anything.

Changes in Sleeping Pattern

0. I have not experienced any change in my sleeping.

1a. I sleep somewhat more than usual.

1b. I sleep somewhat less than usual.

2a. I sleep a lot more than usual.

2b. I sleep a lot less than usual.

3a. I sleep most of the day.

3b. I wake up 1-2 hours early and can't get back to sleep.

Irritability

0. I am not more irritable than usual.

1. I am more irritable than usual.

2. I am much more irritable than usual.

3. I am irritable all the time.

Changes in Appetite

0. I have not experienced any change in my appetite.

1a. My appetite is somewhat less than usual.

1b. My appetite is somewhat greater than usual.

2a. My appetite is much less than before.

2b. My appetite is much greater than usual.

3a. I have no appetite at all.

3b. I crave food all the time.

Concentration Difficulty

0. I can concentrate as well as ever.

1. I can't concentrate as well as usual.

2. It's hard to keep my mind on anything for very long.

3. I find I can't concentrate on anything.

Tiredness or Fatigue

0. I am no more tired or fatigued than usual.

1. I get tired or fatigued more easily than usual.

2. I am too tired or fatigued to do a lot of the things I used to do.

3. I am too tired or fatigued to do most of the things I used to do.

Loss of Interest in Sex

0. I have not noticed any recent change in my interest in sex.
1. I am less interested in sex than I used to be.
2. I am much less interested in sex now.
3. I have lost interest in sex completely.

List of Achievements

［学術雑誌発表論文］（〇印は学位論文に関連するもの）

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3. Connelly, A., **Li, P.,** Rangpong, P., Wilaiprasitporn, T., Yagi, T. “Effects of Trial-Adjusted Neurofeedback Training on Motor-Imagery Based Brain-Computer Interface Performance”, 2023 IEEE International Symposium on Medical Measurements and Applications (MeMeA), 2023, June.
4. Liu, Z., **Li, P.,** Connelly, A., Rangpong, P., Wilaiprasitporn, T., Yagi, T. “EEG Based Detection of Three Hand Motor Imagery Task”, 15th Biomedical Engineering International Conference (BMEiCON), 2023, October.
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6. Thi, M. T. V., Tsuta, I., **Li, P.,** Watanabe, Y., Shibata, T., Yagi, T. “Effects of Multisession Transcranial Direct Current Stimulation on Arithmetic Performance”, 15th Biomedical Engineering International Conference (BMEiCON), 2023, October.

［国内学会における発表］

① 筆頭または登壇者

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［プレスリリース］

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