CLASSIFYING SEVERITY OF DEPRESSION AND ANXIETY BY ANALYZING ELECTROENCEPHALOGRAPHY (EEG) SIGNALS FOR NEUROPHYSIOLOGICAL BIOMARKERS

By

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Classifying Severity of Depression and Anxiety By Analyzing Electroencephalography (EEG) Signals for Neurophysiological Biomarkers

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Abstract

Biomarkers detected in neurophysiological signals can be analyzed to determine indicators of disorders. Electroencephalography (EEG) detects neural activity in the brain and the signals can be analyzed to diagnose stress and mood disorders. The objective is to analyze EEG signals to identify and delineate the severity of depression and/or anxiety validated by the results of psychological test scores. Signals were analyzed from a public database of 119 participants aged 18 to 24 with 45 individuals having moderate to severe anxiety and/or depression and the remaining 74 people having minimal or none. Using extracted signal features, individual variations were compared during a testing protocol for both groups, affected and unaffected. Similarities, and asymmetry, were numerically and visually examined between the left and right brain hemispheres as well as the specific channels. In addition, machine learning classification was performed to predict the class based on the input data. The results demonstrate indications of physiological differences between participants, indicating a likely presence or absence of a mood disorder. Understanding the complexities of how mood and anxiety disorders, including its comorbidities, are physiologically manifested is critical for accurate and objective diagnosis.

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Dedication

This thesis is dedicated to anyone who has ever been affected by a mood disorder. Together, we can find answers and solutions for everyone.

Contribution

The research analysis performed for input to this thesis was performed entirely by the author. The work was conceptualized, developed, analyzed, and written with assistance from Dr. Kristiina Valter Mai and Dr. Dharmendra Gurve. These findings were partially shared in a poster presentation at the Ryerson Stress Research Summit virtual conference May 6th – 8th, 2021. A conference paper was accepted to the Engineering in Medicine and Biology (EMBC) 2021 conference set to occur between October 31, 2021 – November 4, 2021, titled "Feature Extraction to Identify Depression and Anxiety Based on EEG". Finally, as a teaching assistant for Ryerson's Human Computer Interaction (HCI) course, taught by Dr. Kristiina Mai, the HCI component of my thesis became clear. The course labs that I assisted in updating and modifying for virtual delivery were described at Ryerson's Teaching and Learning Conference May 19-20th, 2021 along with the other course contributors.

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List of Abbreviations

5-HT	5-Hydroxytryptamine
ACC	Anterior Cingulate Cortex
ACH	Acetylcholine
ACTH	Adrenocorticotropic Hormone
AD	Anxiety Disorders
ANS	Autonomic Nervous System
AppEN	Approximate Entropy
ASL	Arterial Spin Labeled
BCI	Brain Computer Interface
BDI	Beck's Depression Inventory
CAD	Canadian Dollar
CD	Correlation Dimension
CRF	Corticotropin-Releasing Factor
CSP	Common Spatial Pattern
DCT	Discrete Cosine Transform
DFA	Detrended Fluctuation Analysis
DLPFC	Dorsolateral Prefrontal Cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
DT	Decision Trees
ECoG	Electrocorticography
EEG	Electroencephalography
EMBC	IEEE Engineering in Medicine and Biology Society
EMD	Empirical Mode Decomposition
EN	Ensembles
EOG	Electrooculogram
ERP	Event Related Potential
FFT	Fast Fourier Transform
FMRI	Functional Magnetic Resonance Imaging
FRN	Feedback-Related Negativity
GABA	Gamma-Aminobutyric Acid
GAD	Generalized Anxiety Disorder
HAM	Hamilton Depression Rating Scale
HCI	Human-Computer Interface
HFD	Higuchi Fractal Dimension
HPA	Hypothalamic–Pituitary–Adrenal
IID	Independent and Identically Distributed Analysis
ID	Identification
KNN	K-Nearest Neighbor
LC	Locus Coeruleus

LE	Lyapunov Exponent
LOO	Leave One Out
LR	Logistic Regression
MDD	Major Depression Disorder
MEG,	Magnetoencephalography
MRI	Magnetic Resonance Imaging
NAcc	Nucleus Accumbens
NB	Naive Bayes
NCA	Neighborhood Classification Analysis
NMDA	N-Methyl-D-Aspartate Receptor
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PSD	Power Spectral Density
PTSD	Post-Traumatic Stress Disorder
QEEG	Quantitative EEG
REM	Rapid Eye Movement Sleep
SampEn	Sample Entropy
SASI	Spectral Asymmetry Index
SSRI	Selective Serotonin Reuptake Inhibitor
SVM	Support Vector Machine
WHO	World Health Organization
WT	Wavelet Transform

1. Introduction

Several indications of stress, depression and anxiety are reflected in Electroencephalography (EEG) signals. Being able to quantifiably identify mental illness will aid in understanding its complexities as well as enhance diagnosis and treatment. This research provides evidence for neurophysiological differences that exist in the presence of a mood or anxiety disorder. In this study, a new analysis method was proposed for differentiating people with depression and anxiety from healthy controls. Signal processing techniques will be more effective in identifying and classifying mood disorders compared to psychological evaluations which are subjective measures offering limited specificity. The EEG modality is more cost effective than other brain data acquisitions systems such as functional magnetic resonance imaging (fMRI). Based on previosuly published studies, features were chosen for the EEG analysis, however there are many features that can be extracted from signals.

The objective is to analyze EEG signals to detect and delineate the presence of depression and/or anxiety validated by the results of psychological tests. Using EEG, features were extracted and changes in individuals were compared during a testing protocol for both groups with and without mental illness. The data collected will give insight into how people affected with a mood disorder internalize external stressors and the associated neurophysiological manifestations. Hemispheric, anterior and posterior asymmetry patterns can be used as biomarkers for underlying psychopathology of depression, anxiety, or a comorbid condition.

The contribution of this thesis is three-fold. It presents three methods for analysing EEG signals for discriminatory identifiers to differentiate people with depression and/or anxiety from healthy controls. The methods are:

1) Feature Asymmetry

2) Visualization of Topographic Heat Maps

3) Severity Classification

The emphasis and main contribution of this thesis is on the asymmetry and contrast between affected and unaffected persons.

These findings will contribute to further research in classifying features as biomarkers for disease with the end goal of developing clinical grade hardware with signal processing capabilities for mental health diagnoses. Future applications upon accurately diagnosing an illness would include signal processing algorithms to help identify features to be used to determine effectiveness of antidepressant or antianxiety medications and/or therapies. Analytical biomarkers are yet to be used clinically as a method of diagnosis for mood disorders, however they can be used in research settings to provide information on the person. More research is required to confirm these findings as the tests may be sensitive to acquisition methods, signal durations and techniques, as well as sample population characteristics such as age and gender. Standardized methodologies are required to consistently measure and analyze the signals.

1.1 Problem Definition

Recognition of mood disorders such as depression is critical to being able to provide treatment because in Canada, it is estimated that 1 in 4 individuals will be depressed at one point in their life (Government of Ontario Ministry of Health, n.d.). By the age of 40, 50% of Canadians will have experienced a mental illness (CAMH, n.d.). 70% of mental health problems occur during childhood or adolescence. 15% of people who are depressed commit suicide (Government of Ontario Ministry of Health, n.d.) and this has become a leading cause of premature death (Hasin et al., 2017).

Understanding the complexities of depression including its comorbidities and impact on lifestyle and functional ability, is critical for the development of reliable, successful personalized treatment options. Depression has been associated with an increased risk for coronary artery disease, stroke, cancer, diabetes and reduced physical activity. A meta-analysis by Jia and colleagues (2015) concluded depression increases the risk of mortality and adds to the burden on the healthcare system. Overall, identifying and treating mood and anxiety disorders is critical to an individuals' overall wellbeing and can contribute to alleviating the load on the healthcare system when approached in a preventative manner.

Currently, psychiatrists and physicians diagnose mood disorders through a patient's subjective lifestyle account, their social and medical history along with standard psychological tests. Developing and introducing additional diagnostic tools into the equation will help to better equip clinical professionals to meet patient needs.

1.2 Mood Disorders

1.2.1 Depression

Major depressive disorder (MDD) is characterized by persistent sadness, emptiness, irritability, and anhedonia while also influencing cognitive changes and the ability to function. MDD is a serious mental disorder characterized by at least one depressive episode lasting for two or more weeks as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 2013). Depression symptoms can manifest themselves differently and vary. They can include trouble concentrating, fatigue, feelings of worthlessness and hopelessness, pessimism, insomnia or oversleeping, irritability, restlessness, loss of interest in things once pleasurable, changes in eating patterns, persistent sadness or emptiness and suicidal thoughts.

The main brain structures thought to be associated with depression are the dorsolateral prefrontal cortex (DLPFC), hippocampus, subgenual anterior cingulate cortex (ACC) and other limbic structures. Depressed individuals secrete higher levels of the hormone cortisol. The hypothalamic-pituitary-adrenal axis plays a major role in the regulation of cortisol. Corticotropin-releasing factor (CRF) is released from the hypothalamus and stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary into the blood. ACTH elicits glucocorticoid release (cortisol secretion) from the adrenal cortex. Due to hypersecretion, the pituitary and adrenal glands are enlarged, however the problem is initiated in the brain with the release of neurotransmitters. Regulatory neurotransmitters for CRF release are norepinephrine (NE), acetylcholine (ACH) and gamma-aminobutyric acid (GABA). Higher levels of CRF are found in the cerebrospinal fluid of depressed patients and as well as increased numbers of CRF producing cells in the hypothalamus in brain tissue. Increased cortisol can promote cell death in the hippocampus leading to cognitive dysfunction (Southwick et al., 2005). Glucocorticoids can lead to cell atrophy and

neurotoxic events; therefore, chronic stress and depression can lead to physiological deterioration (Sapolsky 2000). Dexamethasone, a corticosteroid, suppresses blood plasma cortisol and has been shown to be ineffective in individuals with depression (Thase et al., 2014). Individuals with depression have fewer numbers of metabolites of NE in their urine and fewer metabolites of 5-HT in their CSF (Thase et al., 2014).

Changes in neurological structures as shown through imaging modalities such as EEG and Functional Magnetic Resonance Imaging (fMRI). They provide insight into how the brain is performing and can highlight areas of increased or decreased activation. EEG measures brain activity through electrical outputs often decomposed into frequency bands which are specific to the regions surrounding electrodes on the scalp. fMRI measures brain activity by measuring changes in blood flow and structural changes. Imaging has shown increased connectivity for mood disorders. The increased connectivity suggests an abnormality, specifically,depression, as it leads to dysregulation of other functions (Sheline et al., 2010; Wang et al., 2012; Anand et al., 2005). Decreases in hippocampal volume are seen in people with prolonged depression but can also be seen as a causal factor for the mood disorder (Koolschijn, 2009; Chen et al., 2010). Anxiety and depressive disorders have been associated with hyperactivation of the amygdala, a brain structure associated with emotions. McClure and colleagues (2005) demonstrated with the use of fMRI, that patients who had high amygdala activity prior to taking a treatment of selective serotonin reuptake inhibitor (SSRI) responded well to the medication. Imaging has shown increased connectivity for mood disorders. This suggests there are biomarkers that can predict the effectiveness of antidepressant medication. These findings are indicative of neurobiological correlates of depression thereby validating the potential of detecting biomarkers in EEG signals.

1.2.2 Anxiety

Anxiety disorders, as described in DSM-5, are characterized by unrealistic, irrational fears or anxieties that cause significant distress or impairments in functioning. It is often coupled with bodily responses such as a worried facial expression, increased muscle tension, restlessness, impaired concentration, sleep disturbances and irritability. There are several different classifications of anxiety

disorders (AD) with the most common being generalized anxiety disorder (GAD). GAD is qualified by excessive anxiety and worry occurring more days than not for at least 6 months with respect to a variety of causes (school, work, family). The overlap of symptomology of GAD disorder and other mood disorders is common and many people with one type of anxiety disorder will often experience at least one more disorder, such as depression, concurrently or at a different period in their life. However, the phenotypical overlap of disorders may be due to diagnostic unreliability.

Anxiety evolved from an adaptive reaction to a threat. Stress elicits the autonomous nervous system (ANS) which activates the fight or flight response. This involves increased heart rate, blood pressure and elevated blood glucose. When this occurs, other body systems are deprioritized including the digestive system. Chronic stimulation of the ANS in this respect can lead to poor digestion, sleep disturbances, muscle fatigue and psychosomatic illnesses. Acute anxiety in response to significant life stresses can occur, particularly in response to the death of a loved one or a major life event.

Hippocampal atrophy can increase vulnerability to the development of a mental health disorder. In a study by Hettema and colleagues (2012), twins were studied with one having GAD. People with GAD were found to have decreased hippocampal volume. Van Praag and colleagues (2004) postulated that stress and anxiety can be a precursor to certain kinds of induced depression characterized by more aggressive behavior by causing a decrease in the 5-HT or serotonin, metabolism. Preventative measures can be established to take care of mental health by identifying a stress threshold as well as accurately identifying signs of depression and anxiety in various population groups.

Fear is an emotional response to a defined source of danger and should not be confused with anxiety or stress but may have similar manifestations. Structures involved in the fear response are the amygdala, hippocampus, hypothalamus, medial prefrontal cortex (mPFC) and brain-stem nuclei. The amygdala plays a central role in in emotion processing, which is part of the limbic system. When there is an imbalance

between the amygdala and associated control structures and the prefrontal cortex, anxiety disorders can occur.

Anxious individuals secrete higher levels of the hormone cortisol. This is due to dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. With constant high quantities of cortisol, rats have shown sensitivity to CRF (corticotropin-releasing factor). Therefore, this could explain why previous exposure to stress can result in a hypersensitivity of this system and small events can elicit the actions of the HPA axis. In accordance with sensitization of a person's response to increase CRF, several studies have noted differences of response linked to the basal cortisol levels. Individuals with high basal levels of cortisol were most resilient to stress as their circuitry was prepared to respond to the event. In contrast, those with lower basal cortisol levels demonstrate an overactive amygdala during a stressful time to cope with the event making these individuals more stress sensitive. This indicates that abnormal regulation of cortisol and lack of secretion results in abnormal behaviour (Het et al., 2012).

Early life stressors and traumatic events can cause vulnerability to a mood or anxiety disorder later in life. The prefrontal cortex is not fully developed until late adolescence to early twenties, and therefore subject to plastic changes. Neurotransmitters have a key role in regulating anxiety. GABA is an inhibitory amino acid. Noradrenergic cells in the locus coeruleus (LC) are inhibited by GABA and serotonin (5-HT). Benzodiazepines enhance GABA (inhibition) as it tones down the effects of the adrenergic system (Meyer, 2019). GABA regulates the activity of the central nucleus of the amygdala. There are many benzodiazepine receptor sites that are primarily located on the structures that form the limbic system (including the amygdala) which regulates emotional control, among other functions. Serotonin, another neurotransmitter, also has an impact on anxiety, but it is not well understood.

Anxiety is a sensation induced by the stress response itself and therefore poses a challenge to research and analysis. Stress can be chronic but also has distinct, acute impacts. The temporal sensitivity of stress and anxiety could make its quantification misleading. The dissipation of cortisol in the blood and saliva may be sensitive to time and intensity. A person may be anxious, however the mental state at the time of

data acquisition for research has significant implications for the results. Participating in a study itself is novel and elicits stress for many reasons including preoccupation with directions, the task to perform and meeting new people. The time of day in which testing is performed can impact results as levels of alertness vary with cortisol levels. Stress and anxiety are dynamic and there are many factors that influence its response and a researcher's ability to quantify the reaction. Despite its transient characteristics, the physiological indicators are suggestive of the capability to detect distinctive EEG activity for use in diagnosis.

1.2.3 Comorbidity

Comorbidity of mood disorders is the presence of two or more illnesses in the same person. Approximately half of the people diagnosed with a mood disorder also have more than one concurrent mental illness (Newman et al., 1998). The results of the National Comorbidity Survey indicated that 58% of patients with MDD also showed signs of an anxiety disorder (Ninan, 1999). For the purposes of this analysis, comorbidities among the following mental illnesses were included: anxiety disorders, mood disorders, schizophrenia, childhood and adolescent disorders, dementia, and substance use disorders. People with comorbid mental illnesses not only show more severe symptoms and longer lasting illness, but they also have higher rates of healthcare service use. The most prevalent comorbidity is anxiety present with a mood disorder, found more commonly in women. In an epidemiology study in the United States examining adults with depression, it was found that in their lifetime, there is a comorbidity prevalence of anxiety disorder of 37.3% and personality disorder of 31.9% with MDD (Wang et al., 2012). Many studies have shown that a substantial proportion of individuals who report symptoms consistent with a given DSM-IV mental disorder also have symptoms consistent with one or more other disorders. For example, according to the National Comorbidity Survey Replication conducted in the United States, approximately 45% of people aged 18 years or older that are diagnosed with a DSM-IV mental disorder have more than one mental disorder (Kessler et al., 2005; Smetanin et al.,2011).

Since subtypes of anxiety may exhibit different brain wave activity (Heller, W., & Nitschke, J. B.,1998), the co-occurrence of disorders will impact the diagnosis and

therefore, the treatment protocol (Regier et al., 1998). Comorbidity is not well studied, and the breadth of comorbidity studies should be explored. Anxiety disorder comorbidity with depression is the most common. A major risk factor for many comorbid mental illnesses is childhood trauma. Another risk factor for these two mood disorders is the trait of neuroticism defined as chronic distress and emotional sensitivity. They can be distinguished by their level of positive and negative affect. People with anxiety can be characterized by high levels of anxious hyperarousal and symptoms such as increased heart rate, trembling, dizziness, and shortness of breath (Hooley, Butcher, 2019). For instance, the prevalence of a mood disorder with an eating disorder ranges between 50% to 90% (Godart, 2007). The question arises whether comorbid presentation of depression may have a different treatment protocol compared to a single diagnosis. People with comorbidities could require psychotherapy to determine the underlying cause to be able to select the appropriate treatment. Identifying the most appropriate disorder as a diagnosis is critical to the treatment protocol. Early adulthood is when illness emerges, however onset can present differently. As an example, bipolar and depression may initially present similarly. Treating bipolar with antidepressants can induce mania vs. treating with mood stabilizers. The differences in activation between two mood disorders suggest that comorbid disorders will have unique presentations.

1.2.4 Significance

Today, death due to suicide is a devastating outcome for someone suffering with a mood disorder. In 2019, 4012 people died from suicide which is more than the number of assaults in Canada. 90% of people who committed suicide had a mental or addictive disorder, with 60% having depression (Statistics Canada, 2019). This statistic highlights the growing need to develop tools in healthcare to be able to better manage this increasingly prevalent and detrimental illness. Growing research in mental health in terms of recognition and diagnosis is needed and the public, not only clinicians, must be educated on all presentation types. In tandem, technology, once research is fully developed, will be a crucial element in aiding in diagnosing and classifying the illness to be able to predict courses of treatment. This is significant as suicide has become a leading cause of premature death (Ministry of Health, n.d.).

The World Health Organization (WHO) also considers MDD a major contributor to the global burden of disease and has significant financial burdens when untreated. As seen in the increase in literature being published relating to psychological computation, the brain is complex and various features can be selected to identify responses typically associated with a particular mood disorder. These findings will contribute to further research in classifying features as biomarkers for disease with the end goal of developing clinical grade hardware with signal processing capabilities for mood disorder diagnoses. Future applications upon accurately diagnosing an illness would include signal processing algorithms to help identify features to be used to determine effectiveness of antidepressant or antianxiety medications and/or therapies. Current clinical practice is to use psychological tests and subjective behavioural manifestations as described by the patient to diagnose an individual as having depression or other mood disorders.

1.2.5 Financial implications

Depression and anxiety contribute to the overall burden of disease. Specifically, in Canada, when a person is under psychological distress or experiencing depression, it is treated as any other illness in terms of emergency department visits with physician consults and diagnoses. Chiu and colleagues (2017) published a paper to evaluate the direct healthcare costs associated with psychological distress and major depression in Ontario, Canada, based on a 2002 Canadian Community Health Survey on Mental Health and Wellbeing. The age adjusted per capita costs were higher for both MDD ($3,210) and psychological distress ($3,364) compared to the control group ($2,629). In addition, the population wide costs for psychological distress ($441 million) were more than double the cost for MDD ($210 million). Therefore, the healthcare system should increase its expenditures in researching effective treatments or preventions to avoid burdens on the healthcare system in the future and to promote a healthy population.

1.2.6 Etiology of Depression & Anxiety

The prevalence of mental illness is increasing, and the etiology is inconclusive, yet broad. There are numerous hypothesized causes of depression and vulnerabilities

to development of a mood disorder. Genetics, gender, lifestyle, and life experiences can cause predispositions. The amplified HPA axis action resulting in higher blood levels of cortisol may initiate with stress or trauma early in life causing an overly responsive reaction and, therefore, permanent new body set point. Loneliness is also a risk factor which can lead to a vulnerability to depression (Heinrich & Gullone, 2006). Patients complain of loneliness likely stemming from a lack of connection from not being fully engaged in their life. Differentiating normal sadness and loneliness from depression is often difficult to discern. Dysthymia is mild persistent depression where patients feel like they cannot achieve happiness or a euphoric state. They feel a barrier in achieving this. It is critical that a clinician evaluate the patient's lifestyle to the best of their abilities to ensure they do indeed are depressed or otherwise afflicted. Modern day lifestyles potentially attribute to excessive dopamine levels due to social media and evolving diets (Canada Public Health, n.d.). The constant need for validation involving a surge of neurotransmitters exhausts the system and results in stark highs and lows throughout the day. Modern populations are increasingly overfed, malnourished, sedentary, sunlight-deficient, sleep-deprived, and socially isolated (Hidaka, 2012). If a person is staying up late watching TV, not very active, making poor diet choices, and not feeling well, then perhaps they should consider making lifestyle changes. Determining when symptoms began, severity and duration is important. Furthermore, cultural prevalence and presentations of depressive symptoms differ leading to misdiagnosis.

A genetic vulnerability may predispose an individual to developing a mood disorder. Epidemiological studies report family aggregation likelihood between 30-50% (Shimada-Sugimoto, et al., 2015). Specifically, if a person is characterized as having a trait termed neuroticism, which is tendency of having negative thoughts and having low emotional stability, it can predispose them to experience affected mood states. Looking at clusters of the types of anxiety disorders can help to identify susceptibility to an AD as there are many commonalities between the various subtypes making them challenging to distinguish. Lonsdorf and colleagues (2009) found that individuals who are carriers of one of the two variants of the serotonin-transporter gene, which is associated with highly neurotic characteristics, tend to

respond more effectively to conditioning. Cavanagh and colleagues (2019) investigated comorbid depression and anxiety with respect to responsiveness to reward and punishment. People who had anxiety demonstrated better avoidance learning. It was found that comorbidity with anxiety displayed the impacts of rewards and punishment whereas depression on its own did not have a significant impact or predict learning accuracies. Moral injury is when there is cognitive dissonance inaction transgressing our moral/ethical beliefs, expectations, and standards. Rumination stemming from moral injury has a profound impact on mental health and is a symptom of depression and mood disorders.

Varying presentations of symptomatology can lead to overdiagnosis or underdiagnosis. By not offering a patient a treatment for their symptoms, it could be construed as negligence, therefore, overdiagnosis is common more recently. In addition, there is a significant amount of stigma associated with the diagnosis of mental illness despite more widespread awareness and discussion of the topic worldwide. The illness itself can make a person feel shame, undesirability and lack of motivation which can inhibit an individual from seeking treatment. 70% of mental health problems have their onset during childhood or adolescence (Government of Canada, 2006). This period is already a vulnerable time and lack of a support network and understanding parents can make seeking treatment challenging.

Gender can affect the type of treatment and care sought (Canada Public Health, n.d.). Women are more likely than men to experience depression and those aged 15 to 24 in Canada had the highest prevalence of depression (Steensma et al., 2015). Stress and anxiety are sexually dimorphic. Childhood trauma can predispose someone to depression later in life and women are more often prone to gendered experiences that evoke injury. For example, there is increased risk of sexual assault (Vicary et al., 1995), sexual harassment (Skoog and Ozdemir, 2016), peer victimization (Hamlat et al., 2915), sexual rumor (Reynold and Juvonen, 2011) racial and general discrimination (Seaton and Carter, 2019) and a decrease in body esteem (Hamlat et al, 2015). Notably, high estradiol and cortisol predict depression symptoms only in early maturing girls (Chafkin et al., 2020) and stress exposure during pubertal development reversed anti-depressive effects of estradiol in adults (Ismail et al.,

2013). The ratio of men to women who experience an anxiety disorder is 1:1.7. It is not equal. In a study by Goldstein and colleagues (2010), the response difference between males and females was studied in response to presented images. In the group of women (in different phases of their menstrual cycle), there were greater changed observed in the brain circuitry studied. This suggests that female response to stress is regulated by natural hormone fluctuations. Recognizing and understanding the existence of gender differences will help healthcare providers to better support individuals presenting with symptoms.

1.3 EEG Modality

Brain-computer interfaces (BCI) quantify physiological parameters and convert them to interpretable signals. Electroencephalography (EEG) is a modality that detects neural activity which is non-invasive or surgical. It offers high temporal resolution allowing for the evaluation of the signal in response to the presented stimuli. Two imaging modalities can be used to identify biomarkers in the brain for mood disorders: EEG and fMRI. EEG demonstrates high temporal specificity and fMRI demonstrates high spatial resolution. Independent studies have been performed using each of the modalities to detect biomarkers for incidence of illness and for therapeutic drug impact. EEG is a more cost-effective imaging technique (ranging around several thousand dollars CAD, depending on the quality) compared to an MRI machine (in the range of a few million dollars CAD). EEG has many applications in neuroscience for detection of signal abnormalities. As well, with increasing availability of public datasets and algorithm development for signal processing, many advancements have been made in machine learning and deep learning to help understand the brain. Historically and most notably, the common use of EEG output allows for seizure detection and sleep analysis. In the last two decades, EEG signals have begun to be used to classify depression for diagnostic purposes, pharmacologic treatment prediction as well as for the evaluation of antidepressant treatment efficacy. Commercial EEG devices are currently available and implemented as neurofeedback devices for training and assessment of meditative state (Muse™, Emotiv™, Neurosky™).

1.4 EEG Signal Preprocessing

Typical EEG processing includes preprocessing and filtering to remove artefacts, feature extraction and classification (Craik & Contreras-Vidal, 2019). For preprocessing, various filters may be applied such as Butterworth filter (intended to 'flatten' or smooth signal) and a bandpass frequency range is selected (often between 0.5 Hz and 50 Hz). EEG signals can be analyzed and delineated by common frequency bands as described in

Table 1 (Nayak & Anilkumar, 2021).

Table 1: Frequency Bands

Band	Frequency (Hz)	Notable Characteristics and Associations
Alpha	8 - 12	• Resting state and dominant during period before sleep • Related to thalamocortical activity • Usually higher in amplitude on the dominant side
Beta	12 - 30	• Present during complex thinking, action, cognitive processing (fast activity) • Represents a state of alertness • Typically symmetrical distribution • Present when eyes are open
Theta	4 - 8	• Prominent during early sleep • Highly emotional states can elicit activity
Delta	0.5 - 4	• Prominent during deep sleep
Gamma	30 +	• Cognitive function • Epilepsy

The activity and mental state of the person during the EEG recording affects the signal greatly. Signals can be recorded during the resting state condition while the

person is sitting calmly and quietly with either eyes open or eyes closed. The outputs of the individual in this state are frequently researched as consistency can be achieved. Alternatively, tasks can be performed by the person to elicit various features for comparison such as event related potentials (ERPs) which are temporally denoted thereby easily relating a particular stimulus to a specified time response. Tasks can include emotion recognition, motor imagery, mental/cognitive task, seizure detection, sleep analysis or ERP detection post stimulus (P300) (Craik & Contreras-Vidal,2019).

Typically, we are most familiar with viewing real time data and signals on a time scale, however frequency scales may provide power spectrum data and a different angle of analysis. EEG signals can be decomposed using various methods into components for further analysis. Examples include fast Fourier transform (FFT), wavelet transform (WT), discrete cosine transform (DCT), empirical mode decomposition (EMD) and power spectral density (PSD), to name a few. These methods decompose the raw EEG signal into an array of signals that, together, illustrate the entire complexity, but separately, may provide elucidated insight and feature clarity. For the analysis, the focus is on temporal scale EEG analysis.

Generally, EEG signals are acquired for processing in ideal conditions with medical grade equipment. Typical medical grade EEG setup includes an array of between 64 to 128 electrodes adhered to the scalp with conductive gel. Electrodes are attached to leads bringing the signal to the processor. These electrodes detect electrical activity on a microvolt scale. Impedances should be low which indicates good contact with the skin. This value may vary depending on the system and set up. The charges picked up by electrodes are amplified and displayed on a computer on a temporal (live) scale. The EEG output is entirely dependent on the quality of setup achieved.

Electrodes are arranged on the head according to the 10-20 system. 10 and 20 refer to the spacing of electrodes indicating a percentage of the distance positioned of the total front to back or right to left distance of the skull. Often, a cap is placed over the individual’s head with the spacing already marked for each electrode position. Different cap sizes are available for use. The electrodes follow a standard naming

convention which refer to their topographical location: prefrontal cortex (Fp), frontal (F), temporal (T), parietal (P), occipital (O) and finally 'C' referring to the centerline position from each side. The 'Z' label refers to the midline sagittal plane. Electrodes on the mastoid or ear (tragus or auricle) can be used as reference. Figure 1 shows the electrode location and names while Figure 2 is an example of an electrode cap (Rojas et al., 2018; Waveguard™ EEG Cap Product Lines, website).

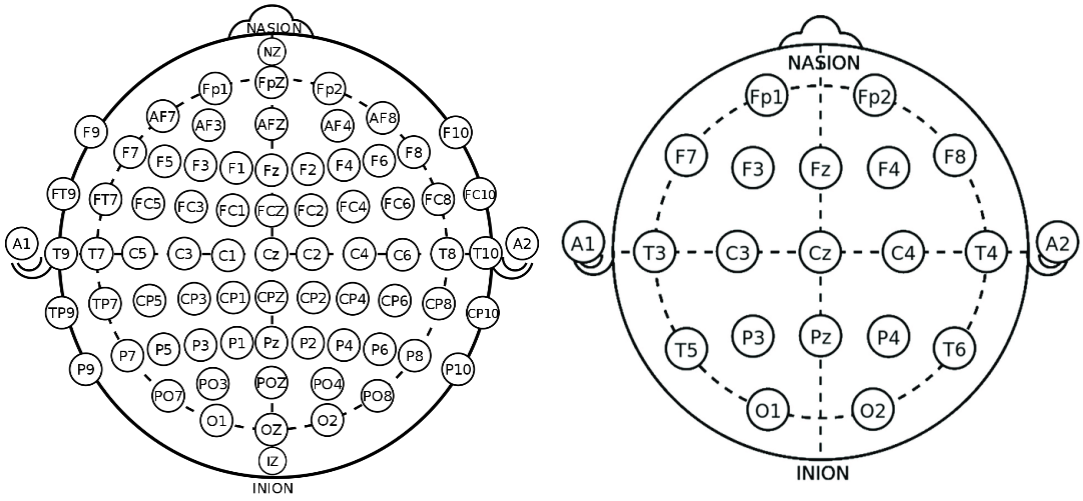

Figure 1: EEG Set up and Channels

Figure 2: Electrode Cap

Signal acquisition errors may be high if setup is done improperly. This could include poor signal due to hair, poor conduction, or noise from outside sources. The electrode detects signal mainly from the cerebral cortex due to depth limitations of only a few centimeters. However, the signals could be correlated to deep brain structures by comparing performed tasks to resting state and the underlying structures involved.

1.5 Neurofeedback

Neurofeedback is a therapeutic technique which allows a person to monitor, visualize, and become mindful of their own biometrics (i.e., EEG signals). It is effectively used to train the brain to alter physiological responses and represents the possibility for the technology to provide both diagnosis and potential treatment. This can be performed with the supervision of a medical professional or at home with commercial devices. The increasing availability of devices, data and human-computer interaction has a significant impact on mental health. Training the mind to focus and work as intended is a skill that can be effectively mastered through neurofeedback. The development of built-in software programs to hardware devices can allow consumers the ability to interpret their own EEG signals at home.

1.6 EEG Biomarkers

In literature, several techniques have been proposed for MDD recognition from EEG signals (Yang & Tsai, 2013; Baskaran et al., 2012; Thibodeau et al., 2006; Allen & Reznik, 2015). Several studies have investigated biomarkers in the brain, which are characteristics extracted/observed from the EEG signals that indicate an illness, particularly with MDD. These indicators include but are not limited to, elevated alpha wave activity, alpha wave asymmetry, EEG coherence and event related potential (ERP) latency (Baskaran et al., 2012). In addition, the person is generally sitting down quietly with either their eyes closed or open. Signals can also be acquired when the person is performing a task and then the signals can be temporally marked to analyze the individual's response.

Apart from the signal acquisition conditions, other factors may influence the output including hand dominance, any underlying neurological condition as well as various substances such as caffeine, alcohol, nicotine, psychotropics and prescribed medication such as antidepressants or antipsychotics. One study reported a decrease in the delta and theta bands in alcoholics which was then associated with poor inhibitory control (Kamarajan, 2003). In a review summarizing EEG indicators of mental illness as well as possible baseline and post treatment signals to predict responders and non-responders, several patterns were identified. Differences in prefrontal theta cordance values after 1 week of treatment of depressive symptoms might be a tool in early detection of response to antidepressant medication (Bares et al., 2012). In a study by Bruder and colleagues (2008), the pre-treatment EEG signals prior to taking prescribed selective serotonin reuptake inhibitors (SSRI's), a common antidepressant, were examined. It was found that there was a difference in alpha power seen in the occipital lobe between responders and non-responders to the drug. This information can help to predict the treatment response in individuals prior to following a medication protocol.

With increasing incidences of individuals struggling with mental health, there is a need to understand the brain better in response to therapeutic drugs to ensure their effectiveness. The results of this research could lead to personalized mental healthcare. It can prevent months of adverse side effects endured with no benefits. It will ensure effective treatment, earlier. The trial-and-error approach can result in a delay in therapy, be demotivating for people and cause them to stop taking any medication at all which has the potential to improve their quality of life

1.6.1 Alpha Asymmetry

Alpha asymmetry is calculated as the difference in the alpha spectral power or frequency between the left and right frontal channels (primarily F3 and F4). Mumtaz and colleagues (2015) summarize that alpha wave asymmetry in the prefrontal cortex has been indicative of depression, however some studies failed to reproduce the results in post-menopausal women. Alpha waves appear on both sides of the brain but are slightly higher in amplitude on the non-dominant side, generally observed in people who are right-handed. Elevated alpha wave activity has also shown potential

to be an indicator of depression (Mumtaz et al., 2010). Kemp and colleagues (2010) examined the specificity of brain laterality and found reduced left frontal activity in patients with MDD and overall increased alpha power through EEG acquisition under resting state, eyes closed conditions. In addition, there was greater activity seen in patients with PTSD in the right-parietotemporal region compared to MDD patients (Kemp et al., 2010). In a study conducted on 49 undergraduate students during the examination period using EEG, it was found that during low stress periods, there was greater left frontal activity and during high stress periods, there was relatively greater right frontal activity asymmetry (Lewis, Weekes, & Wang, 2007). The EEG recording protocol consisted of a memory task and a baseline EEG asymmetry task consisting of recording with periods of eyes open and eyes closed. A review by Coan and Allen (2004) shows that positive moods are associated with relatively greater left prefrontal activity and negative moods are associated with relatively greater right prefrontal activity. A meta-analysis reviewed numerous studies that examined alpha wave asymmetry in the frontal cortex and concluded that it is an indicator of anxiety and depression. Inconsistencies on this subject in the past was attributed to research practices such as short recording periods (Allen & Reznik, 2015). More work is required to determine biomarkers of comorbidity of anxiety and depression (Thibodeau, Jorgensen, & Kim, 2006).

1.6.2 General Asymmetry

Several studies have examined whether greater left or right anterior EEG activity can predict psychopathology of depression or anxiety. Greater relative left frontal EEG activity is associated with positive emotion whereas greater relative right frontal EEG activity is associated with negative emotions. Previously depressed individuals exhibited greater relative right anterior EEG activity. Consequently, there was greater right anterior EEG activity (depression indicator) and relatively less right posterior activity (Blackhart, Minnix & Kline, 2006). In a study designed to assess whether EEG signal asymmetry was predictive of mental health, EEG activity was recorded twice for participants spaced three weeks apart. One year later, participants completed the Beck's Depression Inventory (BDI) psychological test as well as a trait anxiety test. The EEG data alpha wave asymmetry was used to determine whether it was

predictive of future mental health status. It was found that parietotemporal alpha wave asymmetry was predictive of the depression psychological score outcome one year post acquisition (Blackhart, Minnix & Kline, 2006).

Similar to depressed persons, greater right relative anterior as well as posterior EEG activity has been associated to anxiety. Similarly, people with comorbid anxiety and depression exhibit higher right anterior and posterior activity. These neurophysiological patterns are not conclusive and consistent across all studies on this matter, however asymmetry indicates underlying psychopathology and requires further investigation. It has been suggested that asymmetry fits into the diathesis-stress model serving as a risk factor for developing a mood or anxiety disorder (Coan & Allen, 2004).

1.6.3 Coherence

EEG coherence is a statistical similarity between two brain signals indicating normal or abnormal activity (Bowyer, 2016). It indicates whether two brain regions have similar oscillating patterns with each other. Increased neurophysiological connectivity was found to be associated with MDD patients (Mumtaz et al., 2010). Coherence as a measure of abnormality, is subject to electrode reference and volume conduction for consistent representation (Mumtaz et al., 2015). Increased connectivity between prefrontal cortex and limbic areas is associated with successful treatment of depression (Dichter et al., 2015).

In a study by V. Knott et al. (2001), EEG signals were acquired during resting state eyes closed condition of 70 males with unipolar depression compared to 23 male healthy controls. It was found that in the delta, theta, alpha and beta frequency band coherence was reduced compared to the controls. Fingelkurts et al. (2007) examined 12 people with major depression during resting state (all scoring over 18 on the Hamilton Depression Rating Scale (HAM) and 10 controls. It was concluded that structural synchronous EEG pairs were localized on the right anterior and left posterior brain areas. In healthy controls, the synchronous pairs were symmetric in the anterior region. This indicated stronger functional connectivity within these brain regions for persons with depression and therefore higher coherence. Sun et al. (2008) evaluated partial directed coherence (DC) which measures the degree of linear

interdependence of EEG channel activity based on the frequency bands. In this study, 12 people with depression performed a mental arithmetic task during EEG signal acquisition which was then compared to resting state and the control group. The depressed group demonstrated lower frontal cortical interdependence in both the resting and mental arithmetic task states. In the resting state, there was reduced left hemispheric interdependencies seen as well as decreased interhemispheric connectivity.

In contrast, there are some studies that reported the opposite in that increased coherence demonstrates depression. Leuchter and colleagues (2012) compared a depressed group, who had been medicated with or were currently taking antidepressants, with the HAM scores greater than 16 compared to healthy controls. Coherence was calculated between all pairs of channels. In the alpha frequency band, connections were between the frontal or DLPFC regions and the temporal or parieto-occipital regions, whereas in the beta band, the connections were mostly within the prefrontal, temporal, and parietooccipital regions.

Inconsistences can be attributed to methodological differences (reference channel chosen such as mastoid, Cz or the average of channels) and diagnostic issues (singular mood disorder and/or comorbidities) (Knott et al., 2001). Choosing the reference channel for comparison or self similarity impacts the results and alters the outcome. This affects the interpretation of results, particularly if the electrode has a noisy signal or is compromised due to measurement. Other limitations include lack of consistency between studies, algorithms employed (no standard), different set up and activity performed). In addition, in the studies mentioned where it was found that with depression, there is reduced coherence, all persons were unmedicated. Therefore, this feature on its own may be a valid tool for diagnosis, but only when consistent or clear methods are applied.

1.6.4 Event Related Potential in Response to Presented Stimuli

Event related potential (ERP) is a signal variability that occurs in response to a stimulus. The P300 wave is a classic ERP associated with decision making. It is elicited typically 300 milliseconds after a random stimulus that is seen as a positive wave deflection. Longer latencies were observed with depressed patients. Hetzel and

colleagues (2004) discovered that after depressed participants took antidepressants for 4 weeks, the auditory ERP P300 response was normalized and the latency period decreased, however this has not been a consistent result after therapeutic drug treatment. The reward positivity (Rew-P) is an ERP elicited by rewards and is augmented by a better-than-expected outcome (Cavanaugh et al., 2019). The Rew-P feature is predominantly seen in the delta band frequency (Cavanaugh et al., 2019). Variability observed between persons can be attributed to medication use and other mood disorder comorbidity. The feedback-related negativity (FRN) is a feature detected in the theta frequency band that is triggered through punishment and augmented through worse than expected outcomes (Cavanaugh et al., 2019).

1.6.5 Reward-Related Response

Neurophysiological systems underlying the reward and pleasure response have been studied through neuroimaging and are associated with the medial prefrontal cortex (Berridge & Kringelbach, 2008). The ventromedial prefrontal cortex (vmPFC) and rostral anterior cingulate cortex (rACC) regions have elevated dopamine neurotransmitters. This projects onto the striatum, especially the nucleus accumbens (NAcc). This activity often leads to a bias and preference towards reward-based decisions, which can be detected by EEG electrodes. Wacker et al. found a positive correlation between anhedonia and the vmPFC (consequently, the rACC) in response to positive stimuli. In addition, anhedonia is associated with weaker responses to positive stimuli in the vmPFC and rACC, reduced NAcc volume and increased EEG delta activity (reduced overall resting brain activity) (Wacker, 2009). Figure 3 and Figure 4 show the pertinent brain structures associated with reward.

Anhedonia is a primary symptom of depression which involves a reduced sense of pleasure, motivation, and experience of rewards. Studies have shown that anhedonia leads to an inhibition of learning regardless of associated reward (Huys, 2020). Primary reward sensitivity is not affected. Etiology of the impact of reward learning could be derived from mood or the learning process. Mood can affect a person's perception of a reward outcome. Behaviour is motivated by an analysis of cost vs. benefit compared to cognitive or physical effort. Baseline striatal dopamine synthesis, measured by PET can predict an individual's desire to engage in cognitive effort

(Westbrook et al., 2020). Moreover, medications that alter the low baseline levels could impact a person's motivation to take on a previously, perceived onerous engagement (Mayniel et al., 2016) This may be a reason as to why antidepressants work to alleviate anhedonia symptoms. Studies involving groups of people taking antidepressants for 4 - 8 weeks show more willingness to exert effort. Effort based decision making has a major impact on desire to respond to stimuli. Increasing reward and incentive could also encourage a person to be willing to increase effort. Someone who is depressed feels helpless and hopeless and may not believe their actions can influence a positive outcome.

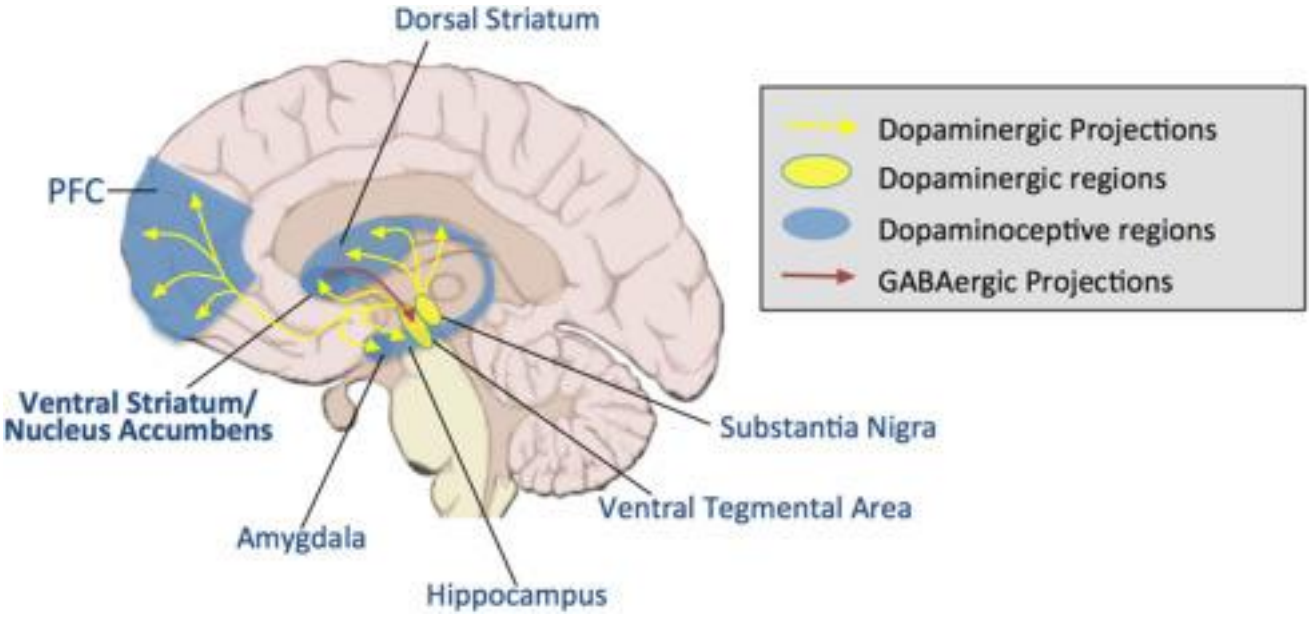

Figure 3: Neuroanatomy highlighting the reward circuit, specifically the location of the PFC and the striatum (Telzer, 2016)

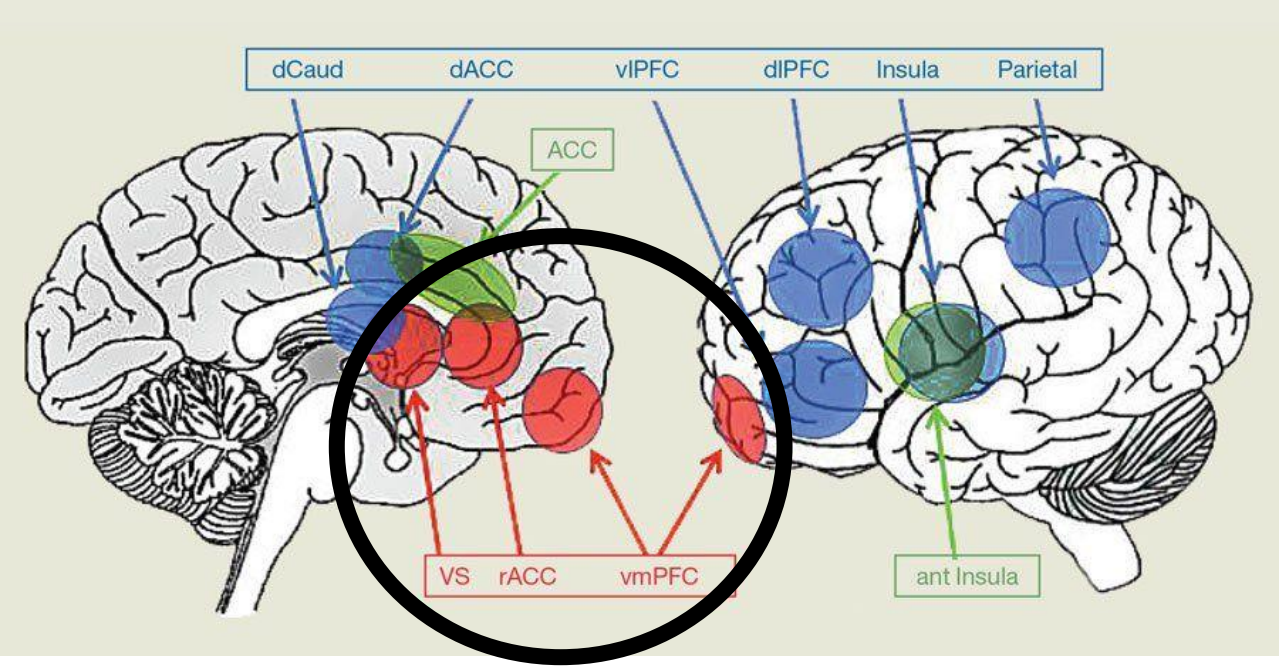

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Figure 4: VS: ventral striatum, rACC: rostral anterior cingulate cortex and vmPFC: ventromedial prefrontal cortex. These structures, coloured in red are the critical structures for the reward pathway for anhedonia (Neurobiology of Eating Disorders: Clinical Implications, website)

As seen in Figure 3 and Figure 4, the rACC and vmPFC, indicative of the anhedonia reward pathway, are are considered deep brain structures. EEG detects cortical activity and is not often associated with deep source localization techniques, so the relation to these structures would require future investigation to determine how the deep brain structures influence the signals detected in the cortical brain regions. Studying the reward pathway in people with mood disorders provides novel biomarkers for detection and understanding. Table 2 summarizes the function of notable brain regions important for the reward related response.

Table 2: Summary of Key Brain Regions Involved in the Reward Related Response

Brain Region	Function
Dorsal Striatum	Mediates cognition, reward, and coordinated movements

Ventromedial Prefrontal Cortex	Emotional processing, decision-making, memory, self-perception, and social cognition in general
Rostral Anterior Cingulate Cortex	Integrates emotion and cognition and is thereby primed to influence amygdala-dependent learning
Nucleus Accumbens	Cognitive processing of motor function related to reward and reinforcement and the regulation of slow wave sleep, specifically, it facilitates the acquisition of reward
Amygdala	Fear and emotional processing

1.7 Prior Dataset Publications

The dataset used was originally published in a paper by Cavanagh and colleagues in 2019 called "Multiple Dissociations Between Comorbid Depression and Anxiety on Reward and Punishment Processing: Evidence from Computationally Informed EEG". They were investigating the impact of reward and punishment on patients with variable severities and comorbidities of depression and anxiety, described in 0. It was concluded that the control group and the depressive group did not differ significantly in terms of performance, however anxiety predicted learning bias in favor of No Go learning (punishment). The symptoms of the people also could not be correlated with accuracy of response. This indicates that depression did not impair the ability to complete tasks. The results from this paper show an investigation of learning and how it relates to mood and anxiety disorders, however it did not involve psychological score validation or feature analysis to confirm a diagnosis.

A second paper was later published at a conference on the same public dataset in 2020 by Trambaiolli and Biazoli titled, "Resting-state global EEG connectivity predicts depression and anxiety severity". The focus of this paper was to determine whether resting state EEG can predict depression and anxiety severity. The group analyzed the resting state EEG signal where people were not performing the probabilistic learning task. The global connectivity (spectral coherence) was calculated for EEG frequency bands and classifiers were implemented (support vector

regressor) to train the dataset on the psychological test scores to predict symptoms. It was found that the most discriminating feature was the global connectivity of the alpha band.

1.8 Psychological Test Indicators

Beck's Depression Inventory (BDI) is a psychological test evaluation used clinically for diagnosis. BDI-II is a questionnaire consisting of 21 questions to which the respondent selects the statement that best describes the way they have felt in the previous two weeks (Beck et al., 1996). Test scores can be used to classify minimal depression (BDI less than 13), mild depression (BDI between 14 and 19), moderate depression (BDI between 20 and 28) and severe depression (BDI greater than 29) (Beck, 2019b). The Spielberger Trait Anxiety Inventory (TAI) is a psychological questionnaire developed to differentiate anxiety from depression (Spielberger, 2010). There are 20 questions each with a 4-point scale of response. Higher scores indicate higher levels of anxiety. A TAI score less than 37 can be classified as minimal anxiety, 38 to 44 is considered moderate anxiety and greater than 44 is severe anxiety.

Psychological tests are subjective scales of measurement of a mood disorder. It is not a structured interview conducted by a clinician. Consistency of results of the BDI test range between 0.73 to 0.92 (mean of 0.86) (Beck, Steer, & Garbin, 1988). The reliability score (alpha coefficient) is 0.86. These tests are consistently used in clinical practice and research settings, however there are limitations. People may misinterpret the question or not respond accurately based on their own experiences. There is a lack of personalization with the tests and comorbid mood disorders may have different manifestations in diverse cultural groups at varying times.

1.9 Objectives

To better understand the complexities of depression and anxiety, the EEG signal can be further quantified and compared to control signal parameters. The goal of this research is to develop a novel analysis that may validate psychological test scores to diagnose depression, as well as validate prior findings performed in the field of EEG analytics related to the quantification of mood disorders. The proposed analysis techniques can contribute to an additional diagnostic tool for clinical professionals for

their patients and/or in commercial products as their processing power increases. The objectives of the research include:

1) Perform a hemispheric asymmetry statistical analysis to examine feature topographic differences across the range of severities of depression and anxiety.

   It is hypothesized that persons with depression will have hemispheric asymmetry, particularly in features that characterize complexity.

2) Produce topographic heat maps to determine the influence of specific channels on the presentation of depression and anxiety.

   It is hypothesized that channels in the prefrontal cortex will show variation with increasing depression and anxiety.

3) Perform classification using machine learning on the dataset using extracted features as predictors.

   It is hypothesized that persons with high depression and high anxiety will exhibit a range of different feature values compared to a baseline individual with none to minimal depression or anxiety. The different feature values can be categorized to delineate the severity of the mood disorder.

2. Methodology

2.1 Data Sourcing

Due to covid, data acquisition and experimental parameters for this thesis was not possible. Therefore, existing EEG signals for the detection and identification of mood disorders were investigated.

OpenNeuro (https://openneuro.org/) is an online free and open platform for sharing MRI, MEG, EEG, iEEG, ECoG, ASL, and PET data. It contains over 550 public datasets comprising of more than 19,000 subjects. The dataset used for this thesis was selected due to the large sample size (122) relative to others available with people who had depression and anxiety (between 20 to 60). The demographic data was available as well as the psychological test scores. In addition, the original paper was recently published in 2019.

PRED+CT (http://predict.cs.unm.edu/) is another patient repository of EEG data and computational tools with free open access. It is a project led by Dr. James F. Cavanagh; the originator of the database used for this research. The EEG dataset used is also available on this website.

Another database found is called Brain-CODE (https://www.braincode.ca/) which is an informatics platform on which open data sets of participants with a variety of brain disorders can be accessed with over 22,000 human records and over 1,500 animal records. It is managed by the Ontario Brain Institute which is funded by the provincial government in order to allow researchers and clinicians to provide and deliver services to those living with brain disorders.

Advancement in using EEG signals as a clinical tool can only be made with more robust and reliable identification of biomarkers which can only be done with available datasets for data mining. In general, EEG analysis and processing follows a general procedure. Figure 5 summarizes the high-level signal analysis steps for EEG signal analysis.

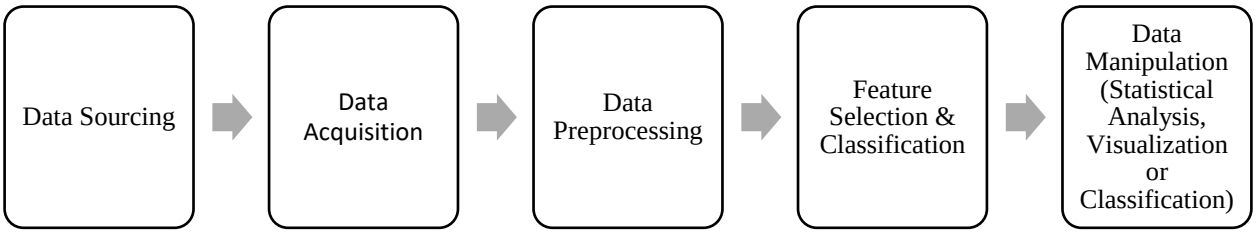

Figure 5: Signal Processing Methodology

2.2 Data Acquisition

The dataset used in this study was acquired from a public database from PRED+CT originally published by Cavanaugh et al. in 2019. Electroencephalography (EEG) signals were acquired from 119 people between the ages 18 to 24 who were asked to perform a probabilistic learning task requiring people to pair Japanese characters correctly. EEG signals were measured using a Synamps2 system (Neuroscan) using 64 electrodes in total referenced to FCz. The first 6 minutes of the recordings were also available publicly and during this time, people were sitting with their eyes opened and closed in a resting state condition. This dataset of resting state condition was uploaded to openneuro.org on January 18, 2021. 45 individuals had moderate to severe anxiety and/or depression and the remaining 74 individuals had minimal, or none as defined by the BDI and TAI psychological test scores. Demographic data on participants included gender, age, symptomology and administered psychological test scores. The database included a total of 122 subjects, however this work presented includes only 119 subjects. Participant ID544 in the dataset had incomplete data and it was noted that they were an 'invalid participant'. It was also noted that they had an unstable/unreliable BDI score when comparing the lab assessment to the mass assessment and therefore would be an unreliable metric. People with ID's 599 and 600 were removed due to missing/incomplete data which did not allow for a complete analysis. It is important to note that the accuracy of the psychological test scores directly impact the research results. During data acquisition for quantifying mood and anxiety disorders, it would be critical to ensure the validity of the score per participant by assessing their medical history and/or administering an additional psychological test.

Table 3 shows the demographics and psychological test scores of the participant data.

Table 3: Database Demographics and Test Scores

	Age	**Sex**	**No. of Participants**	**Average BDI Score >13**	**Average TAI Score>=38**
Depressed	19	Females	33	22.15	55.79
		Males	12	23.17	55.58
		All	45	22.42	55.73
Anxiety	19	Females	40	19.08	53.63
		Males	11	18.36	49.45
		All	51	18.92	52.73
Control	19	Females	34	1.21	29.09
		Males	30	1.87	30.27
		All	64	1.52	29.64

* Note all people who met the depression criteria also met the anxiety criteria. These participants (meeting both criteria) were used as the affected group for analysis.

EEG signals were measured using a Synamps system (Neuroscan) using 64 electrodes in total referenced to Cz and CPz. Positioning followed the 10-20 international system. Two electrodes were placed on the mastoid and two were Electrooculography (EOG), electrodes near the eyes to detect ocular muscle movements. The sampling frequency was 500 Hz and impedance was less than 10 kΩ. For more information, please refer to the original paper (Cavanagh et al., 2019. The channels include:

Table 4: Channel Labels

Brain Region				
Frontal	**Temporal**	**Occipital**	**Parietal**	**Central**
AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8	T7, T8, TP7	O1, Oz, O2.	P7, P5, P3, P1, Pz, P2, P4, P6, P8,	C5, C3, C1, Cz, C2, C4, C6
FT7, FT8			CP5, CP3, CP1, CPz, CP2, CP4, CP6,	
FP1, FPz, FP2				
		PO7, PO5, PO3, POz PO4, PO6, PO8		
TP8				
FC5, FC3, FC1, FCz, FC2, FC4, FC6				

2.3 Data Preprocessing

The original codes for signal processing of the database from the original study were publicly available. For the EEG data for the GO/NO GO Learning task, the initial code titled "STEP1_PREPROC" preprocessed the data such that the critical trials of 4 seconds of data were extracted. This code was used as it accurately denoted the events in the signal which can only be done by being present during the data acquisition and marking specific time points.

EEG can be decomposed in various ways for analysis. For my analysis, I decomposed the EEG signal into four frequency bands on a time scale. Using the passband function in Matlab, specifying the specific frequency bands, it allowed for filtering of undesired high and low frequency noises in the data. Generally, higher frequency bands have been most effective in demonstrating trends in data. Typically, the beta and alpha bands are more descriptive and dominant in a person during an active condition (Go or NO GO learning or resting state, respectively). The theta and delta bands could have been disregarded, however eliminating data without reason would reduce accuracies and potential findings.

In general, signal processing includes data segmentation, preprocessing to remove noise and high/low frequencies, feature selection and extraction and then interpretation (Leis, 2011). The interpretation can include a statistical analysis and/or machine learning with classification. Data segmentation includes selecting which window of time will be analyzed within the entire signal. Typically for EEG, it is only a few seconds. For this thesis, two state conditions were evaluated in similar ways: resting state and an active state when a person was performing a learning task.

For selecting the resting state signal, a few segments were randomly selected of 4 seconds in duration as there were no indications of any significant time period in the signal. For the GO/NO GO task, significant trials were extracted from the signal using a code written by the original author of a duration of 4 seconds. Next, the data was preprocessed and filtered by frequency to remove noise. The frequency filter applied was based on the four desired passbands: alpha, beta, theta and delta. Figure 6 shows 2 seconds of the EEG signal from participant 1 in the resting condition. Note, the y-axis range varies.

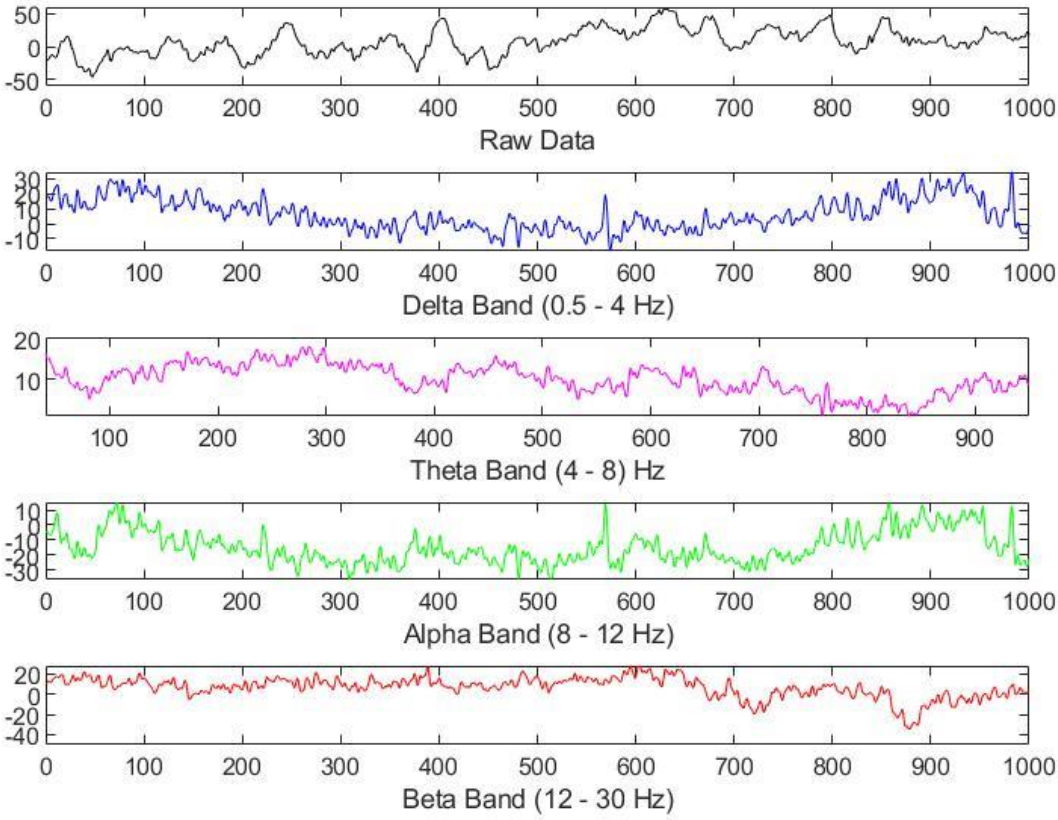

Figure 6: EEG Frequency Bands

2.4 Non-Linear Features

The EEG measures activity that is complex, dynamic and a non-linear signal. Its complexity cannot be entirely captured by implementing linear analysis. In the last several years, more non-linear analysis has been published in the literature. The various frequency bands have been associated with varying states of alertness. Specifically, alpha, beta and theta bands have been rigorously studied for neurophysiological biomarkers of depression and anxiety with non-linear features. The frequency bands are alpha (8 - 12 Hz), beta (12 - 30 Hz), delta (0.5 - 4 Hz), theta (4 - 8 Hz) and gamma (30 - 50 Hz).

2.4.1 Approximate Entropy (AppEn)

Entropy is a measure of disorder or complexity of a signal. It allows for dynamic analysis of a non-linear signal. Most entropy algorithms diverge when the signal is

noisy, hence the development of the approximate entropy (AppEn) algorithm (Pincus, 1991). It estimates signal complexity by statistical computation through the conditional probability that two signals are similar within a tolerance (Richman & Moorman, 2000). Approximate entropy is an algorithm applied to time series data to quantify its regularity or irregularity, which is generally difficult to predict on a temporal scale. For a shorter data length, the algorithm detects episodic behavior not obviously identifiable in amplitudes and events (Faust et al., 2014).
The algorithm assigns a positive number to a data segment with higher values corresponding to more complexity. In other words, small values of AppEN indicates predictable data whereas higher values indicate unpredictable data. Therefore, reduced complexity (lower AppEn) can be a symptom of or a result of depression. Healthy controls are found to have higher AppEN than those persons with depression (Faust, Puthankattil & Joseph, 2014).

$$App_{EN} = \log \frac{correlation(a)}{correlation(b)}$$

Equation 1

In a study by Chen & Shen (2020), EEG signals were analyzed, and the resting state condition signal results were compared with signals acquired during the Test of Variables of Attention which is when participants are instructed to press a button when non-target figures appear on the screen. It was found that patients with MDD had a higher AppEn than the control group when performing a cognitive task. The severity of depression was positively correlated with AppEn.

2.4.2 Higuchi's Fractal Dimension (HFD)

Higuchi's Fractal Dimension (HFD) quantifies the complexity and self-similarity of a signal. HFD calculates the fractal dimension of time series data, which is a ratio of complexity. The higher the similarity and complexity means higher HFD. It works in the time domain, with short segments and is computationally fast. A disadvantage is the lack of specificity as HFD values can represent multiple signals and therefore they cannot be easily distinguished (Bachmann. et al., 2013).

$$L_m(k) = \frac{1}{k} \frac{\sum_{i=1}^{\frac{N-m}{k}} x(m+ik) - x(m+(i-1)k(N-1)}{\frac{N-m}{k}}$$

Equation 2

Where k is a constant and m=1,2,...k. $L_m(k)$ denotes the length of the data. To find the HFD, the mean of equation 3 is computed as:

$$HFD = \frac{1}{K} \sum_{M=1}^{K} L_m(k)$$

Equation 3

Studies have found higher beta and gamma band complexity (higher HFD) in patients with MDD compared to controls. This was found in the parietal and frontal regions of the brain (Akar et al., 2015, Bachmann et al., 2013). Čukić et. al (2020) showed that sample entropy (SampEn) and Higuchi's Fractal Dimension (HFD) can classify persons with depression from controls with 90.24% to 97.56% classification accuracy. SampEn was found to be more accurate for lower frequency bands and HFD in higher frequency bands. Another study found that using HFD and other non-linear features produced a high accuracy, particularly with correlation dimension (CD).

2.4.3 Correlation Dimension (CD)

Correlation dimension (CD) is a feature which estimates the correlation of a uniformly sampled time-domain signal in matrix. It is a method to determine the dimension of a nonlinear signal. Two arbitrary points very close together are compared to quantity their degree of separation.

$$C(r) = \frac{2}{N(N-1)} \sum_{(i \neq j)} \theta(r - |X(i) - X(j)|$$

Equation 4

Higher CD values have been associated with more complex thinking and reduced correlation dimension values have been associated with symptoms of depression (Nandrino et al., 1994). The degree of dimension increases with cognitive activity.

2.4.4 Lyapunov Exponent (LE)

Lyapunov exponent (LE) quantifies the exponential divergence or convergence of nearby trajectories in phase space (Hosseinifard et al., 2013). LE can characterize instability or predictability of a system, also termed as the chaoticity. It characterizes the separation of infinitesimally close trajectories of a signal. If the largest value of Lyapunov exponents is positive, it means that the system is chaotic/irregular. In general, during resting state (eyes open or eyes closed), dimensions of complexity are reduced compared to an active performance state. A negative exponent indicates commonality or the convergence of a signal to a fixed point. A zero exponent indicates stability and a consistent signal.

$$LE = LE(0)e^{(\lambda \times i \times \delta t)}$$

Equation 5

In a 1994 study examining EEG dynamics during sleep in depressive and schizophrenic participants, a significant increase of the principal LE during rapid eye movement (REM) sleep was detected ($p < 0.05$) (Röschke & Mann,1994). Similar to other complexity measures, lower LE values have been associated with depression as higher activity is required for emotional processing.

2.4.5 Detrended fluctuation analysis (DFA)

A higher detrended fluctuation analysis (DFA) value is demonstrated within depression groups (Lee et al., 2007). DFA is used in time series analysis to determine the statistical self-similarity of a signal. It is useful for non-stationary signals such as for EEG. The fluctuation is repeated over different windows of which the log-log graph indicates self-similarity (Hosseinifard et al., 2013).

$$F(n) = \sqrt{\frac{1}{N}\sum_{k=1}^{N}(X_t - Y_t)^2}$$

Equation 6

Where X_T of length N is:

$$X_t = \sum_{(i=1)}^{t} (x_i - x)$$

Equation 7

Higher DFA values have been associated with depression (higher signal correlations). Lee et al. (2007) discovered that depressed patients demonstrate higher values of the scaling exponents of DFA at all channels compared to healthy controls. Significant differences were notes at channels F3, C3, T3, T4 and O1.

2.5 Feature Asymmetry Methodology

This analysis was performed on the EEG signals acquired from the GO/NO GO conditions. Using selected feature algorithms, a numerical output unique to each participant for the specified channels was extracted. The 6 selected features used for analysis included Higuchi Fractal Dimension, approximate entropy, correlation dimension, detrended fractal dimension and Lyapunov's Exponent (2 different algorithms labelled as 'LE' and 'Lorenz'). These were each extracted from the 4 frequency bands (alpha, beta, theta, and delta). The final matrix output dimension was 24 x 119 as there were 24 features (6 features x 4 frequency bands) and 119 subjects. People were separated into two groups for the comparisons: affected (having moderate to severe depression and anxiety) and unaffected (those with minimal anxiety and/or depression). Note that affected participant scores were BDI $\geq$ 13 and TAI $\geq$ 38. Channel values in each group were averaged over the left and right hemispheres, as well as the left and right prefrontal cortices. The ANOVA II analysis was performed to compare the 24 features between the left and right sides (in the two iterations of different brain topographies) to determine whether there was asymmetry. If statistical analysis p value outputs indicate a significant difference, it would demonstrate hemispheric asymmetry. The occurrence of this was compared between the two conditions of affected and unaffected. If neither or both conditions showed a significant difference, then the feature would not be discriminatory. However, if the two conditions were different, it would indicate a discriminatory feature to help differentiate a person who was affected vs. unaffected. Note, depression and anxiety

were not analyzed separately as there was a high incidence of comorbidity in the dataset and therefore there were not enough people classified as only having depression and/or only having anxiety to be sufficient for classification. Figure 7 is a visual representation of what topographic regions of the brain were compared for the asymmetry analysis for all conditions.

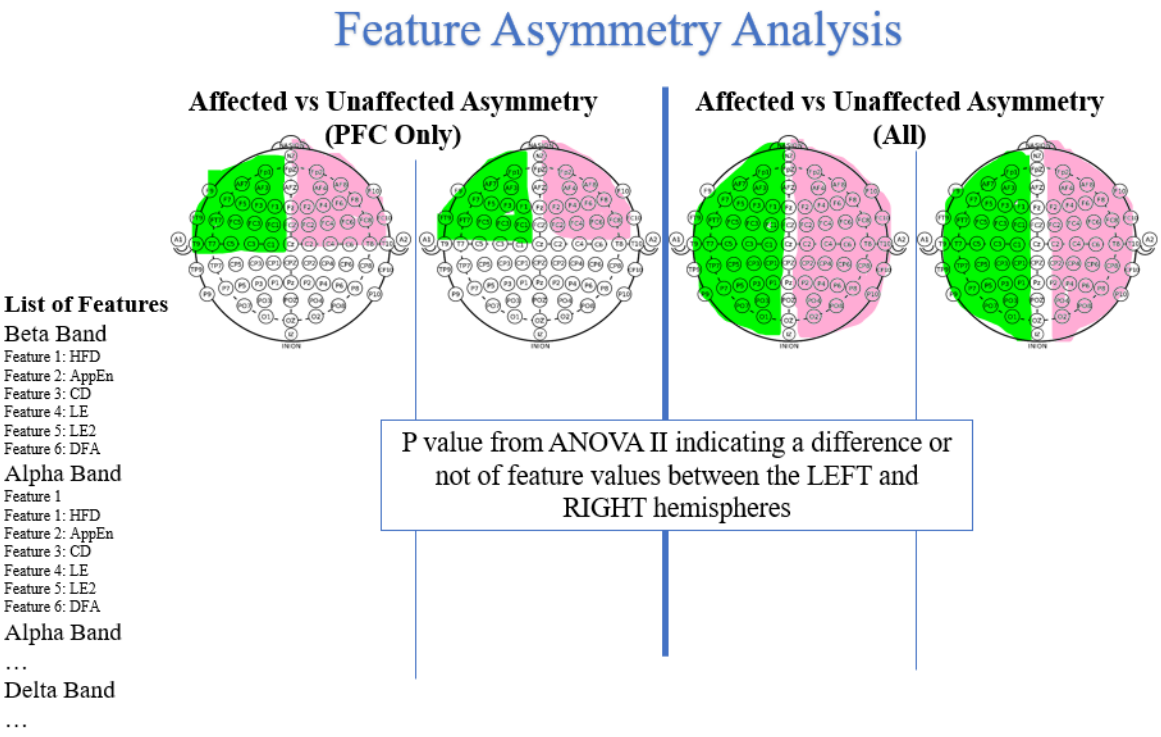

Figure 7: Feature Asymmetry Analysis

Figure 8 shows the names of the specific channels selected for the asymmetry analysis.

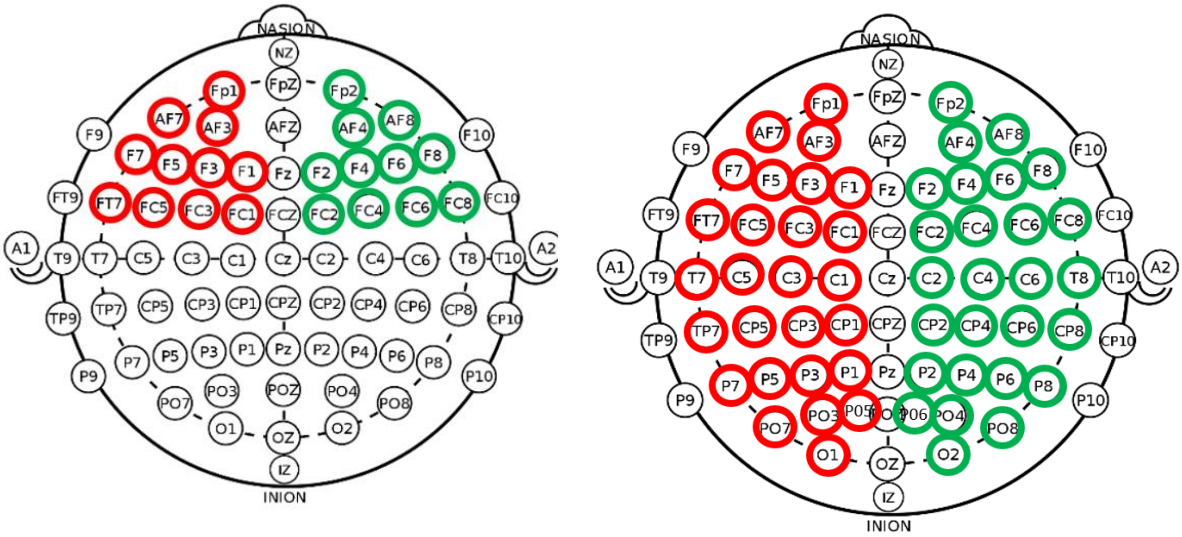

Figure 8: Selected channels averaged across two groups of people (affected and unaffected) for the left and right prefrontal cortices (left) and left and right hemispheres (right)

2.6 Visualization of Topographic Heat Maps

Visualization of topographic plots (heat maps) of the EEG signals can offer novel insight as opposed to solely evaluating numerical outputs. In addition to a statistical analysis performed on extracted features looking at hemispheric asymmetry, heat maps were plotted to evaluate discriminatory channels. The purpose is to be able to visually differentiate the heat map output from a person with anxiety and/or depression from a healthy control. The heat maps plotted were based on features that showed significant asymmetry disparities based on the ANOVA II statistical analysis described in Feature Asymmetry. Otherwise, thousands of heat maps could be generated, and any meaningful contribution gleaned from them would likely be overlooked due to the quantity.

The heat maps were generated using Matlab. As input to the function, the channel locations delineated by the angle (theta), radius and x, y and z coordinates were needed for input. This information was available within the database of signals and is unique to the EEG setup. Figure 9 illustrates at a high level the methodology of producing the plots.

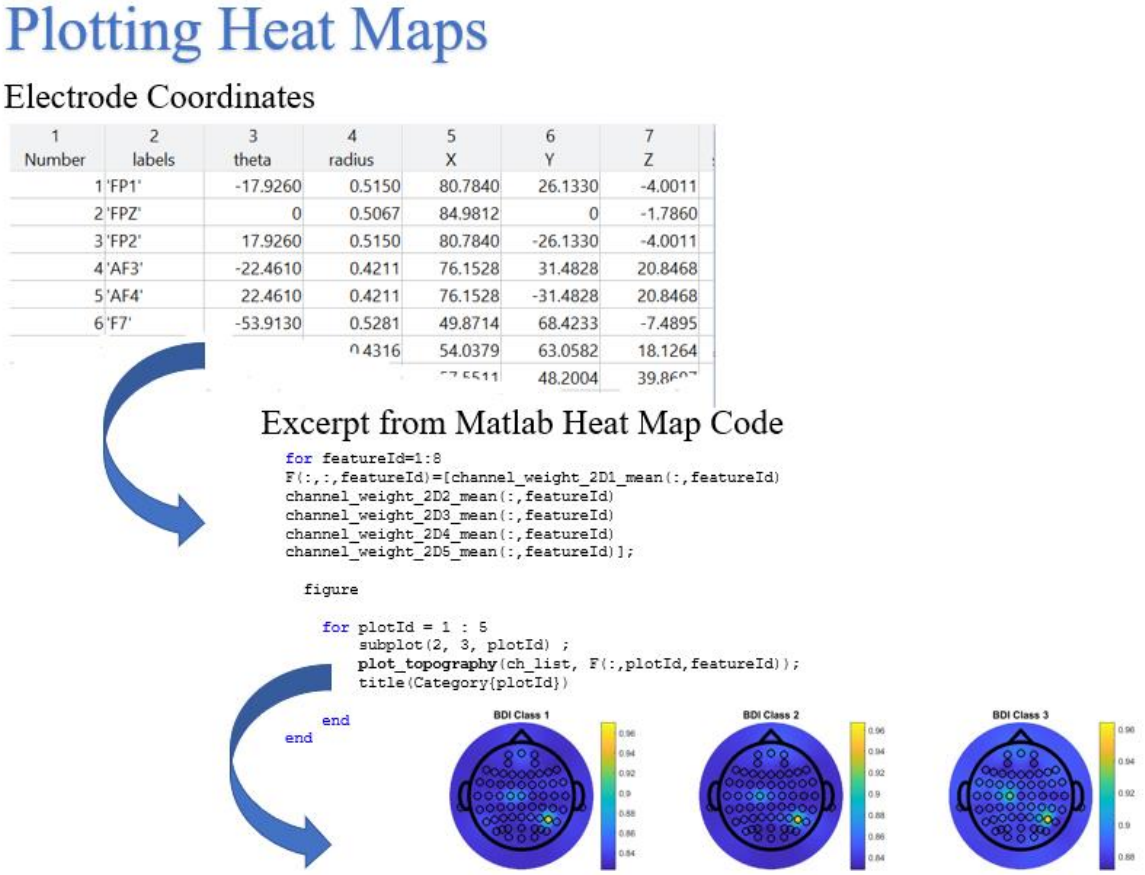

Figure 9: Plotting Heat Maps

2.7 Severity Classification Methodology

Classification is a type of machine learning in which an algorithm is used to categorize data based on already known and specified labels. Labelled data is used to train the algorithm and then its accuracy is tested and validated on the remaining data. The classifier attempts to characterize each different class by particular features. Common classification methods include decision trees (DT), discriminant analysis (linear, quadratic, etc.), support vector machines (SVM), logistic regression (LR), K-nearest neighbors (KNN), naive Bayes (NB), ensembles (EN), and neural networks (NN). These classifiers predict the possibility of occurrence of the distinct datasets. The objective is to have high classification accuracy to distinguish persons with

depression by their BDI score and persons with anxiety by their TAI score. In classifying depression, the support vector machine (SVM) classifier has provided the high accuracy in comparison to other methods including DT, KNN and NB (Čukić et al., 2020, Trambaiolli, L.R. & Biazoli, C.E., 2020).

The classification learner application was used in Matlab to train models on a specified matrix of extracted features per person based on labels. Labels were created in Matlab to categorize the individuals as having none to moderate depression (BDI < 13) and moderate to severe depression (BDI > 13), giving two labels or categories for classification. Likewise, anxiety was also divided into two categories for classification (TAI < 38 & TAI > 38). The dataset was originally trained on 70% of the data and then the result was tested on the remaining 30% to test the accuracy of prediction. This was selected using a permutation function so it would be randomized every iteration to ensure reliability of the classification method. Matlab updated this application and automatically classifies the input based on specified classifiers and provides the validated classification accuracy. More than two label categories decreased the classification accuracy as there were fewer participants for training in each specified class. Figure 10 shows the Matlab classification learner application interface. The list of classifiers the application runs through are displayed with the classification accuracy on the left of the figure. The plot shows the matrix of features with different colours representing the labelled categories. High classification accuracy would be demonstrated by a more distinct separation between the data points in the classes.

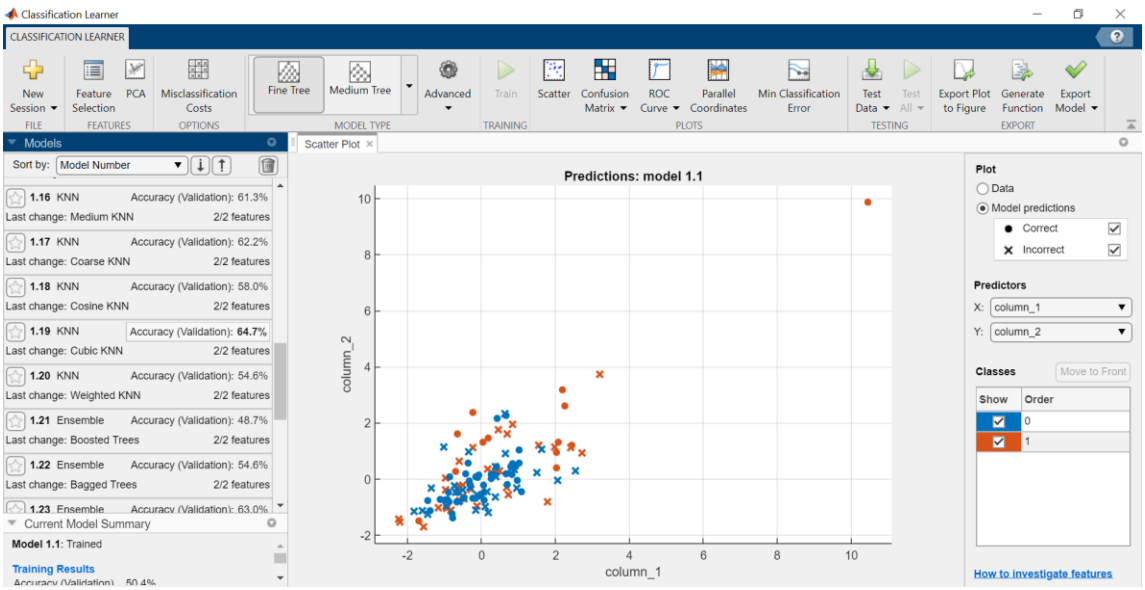

Figure 10: Matlab Classification Learner Application

In an effort to perform EEG signal classification to predict severity of depression and anxiety based on the standardized test score, several different analyses were performed. For classification, initially the participants were indexed into 5 classes of severity of depression (BDI) and anxiety (TAI). However, not many people fell into the categories (limiting the usefulness of machine learning), therefore, 2 classes of severity were used for training and categorizing the dataset. In order to extract different trials from the dataset of the GO/NO GO (probabilistic learning task), different segments were extracted, and the processing code was run. Hand accuracy results were recorded while performing the task and data was extracted based on the hand used. ERP's provide information on the dataset immediately after introducing a stimulus. Unfortunately, in the dataset, there were no markers of when stimuli were introduced and the author's code to extract ERPs was not clear as to which variables represent the ERP in response to a stimuli so this analysis could not be performed as the origins of the recordings were not available. Numerous iterations and data manipulations were attempted to achieve a high classification accuracy.

Classification analysis was performed on both the EEG acquired while the participants completed a probabilistic learning task and on the resting state signal. Two feature selection methods were used: Riemannian geometry and selected non-linear features described in the section Non-Linear Features. Feature weights for

classification were determined using neighborhood component analysis (NCA) for classification using assigned labels. In addition, common spatial pattern (CSP) was also implemented to enhance the difference between the two categories.

2.7.1 Covariance Matrix

A covariance matrix numerically defines the variance between each pair of elements. The output is a symmetric, square matrix with the diagonal being the covariance with itself with avalue of 1.

$$\mathrm{Cov} = \begin{bmatrix} \mathrm{Var(x1)} & \dots & \mathrm{Cov(xn, x1)} \\ \cdots & \dots & \cdots \\ \mathrm{Cov(x1, xn)} & \dots & \mathrm{Var(xn)} \end{bmatrix}$$

Equation 8

Where the covariance is calculated as:

$$\mathrm{Cov}(x_i) = \frac{\sum_{i=1}^{n}(X_1 - \bar{x}1)(X_n - \overline{xn})}{n - 1}$$

Equation 9

Where n is the number of values in the vector, Var(xn) is always equal to one, and x1…xn are the vector values (or the EEG time series data recorded at the electrodes). The covariance is calculated with other channel values. This allows for channel selection and weighted analysis. Covariance mapping can show a 2-dimensional representation of the relationship between the two vectors. This pictorial representation of independent regions aids in visually understanding the correlation between channels. It is a useful analytical tool when comparing two datasets or categories such as evaluating persons with mood disorders vs. healthy controls. The magnitude of the spread of the covariance matrix is indicative of the degree of difference between the parameters.

2.7.2 Neighborhood Component Analysis

Neighborhood component analysis (NCA) is a learning algorithm that classifies multivariate data pursuant to a distance metric. It is a feature selection and weighting technique to maximize the leave-one-out (LOO) classification accuracy for

the data. A reference point, x, is selected based on a kernel function and compared to the rest of the sample points, y_i. The distance metric is defined based on feature weight (Malan & Sharma, 2019). The algorithm makes no assumptions about the distribution of the data (non-parametric) lending itself useful for multivariate, non-linear datasets (Yang, Wang & Zuo, 2012). NCA is s a supervised learning metric and associates an input with an output based on an already known input-output which enhances the action of classifiers (Russell & Norvig, 2010).

2.7.3 Common Spatial Pattern

Common spatial pattern (CSP) is a method of classification that can be used for multi-channel EEG to maximize the difference between classes. It uses linear transform and eigenvectors to maximize the variance of the signals using the covariance matrices of each class. The projection matrix can be represented by:

$$Z = WX$$

Equation 10

Where Z is the resulting matrix, W is the projection matrix created using the covariance matrix of the classes and X is the original EEG multichannel array.

2.7.4 Riemannian Geometry

Brain-computer interface is the convergence of mathematics and the brain. It requires a user and a computer. A unique aspect of EEG is the topography. The spherical placement of electrodes on the scalp creates a unique analytical problem. Riemannian geometry can be used in brain-computer interface (BCI). It is differential geometry comprising of vectors, that takes into account Riemannian manifolds. Manifolds are n-dimensional topological spaces that account for each point. It would most closely account for the contours of a head/brain. The space at the base of a manifold is called the tangent space.

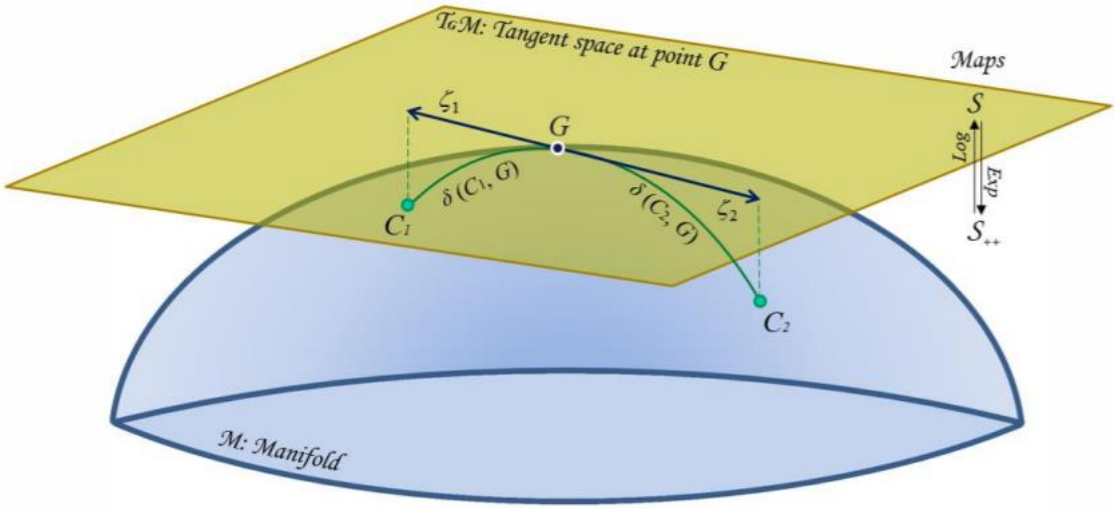

Figure 11: Riemannian Manifold

Where G is the geometric mean of two points and the tangent space at G. C1 and C2 are the covariance matrices. Riemannian geometry has been used for radar data processing, image processing, computer vision, shape analysis, medical imaging (especially diffusion magnetic resonance imaging), sensor networks, elasticity, mechanics, optimization, and machine learning. It has been implemented for detection of EEG artifacts, epileptic seizures and mental fatigue (Congedo, Barachant & Bhatia, 2017). Implementation of the Riemannian geometry is more precise than using Euclidian space geometry and has been effective for EEG artifact recognition (Blum et a., 2019). It is computationally efficient relative to other feature extraction methods. The extracted features can be used for classification. The tolerance is specified so that the significant features are selected for classification.

The Riemannian algorithms were obtained through GitHub (https://github.com/alexandrebarachant). The geometric mean is determined iteratively by projecting the covariance matrices in the tangent space, including estimating the arithmetic mean in the tangent space and onto the Riemannian manifold (Barachant, Bonnet, Congedo & Jutten, 2013). Algorithms are executed on a training set and a testing set where C_{train} is comprised of the training EEG data and C_{test} is the testing EEG data.

$$\mathrm{C}_{\mathrm{train}} = \mathrm{covariance(x)}$$

Equation 11

$$\mathrm{C}_{\mathrm{test}} = \mathrm{covariance(x)}$$

Equation 12

Where X is the preprocessed and filtered EEG signal. $\mathrm{C}_{\mathrm{ref}}$ is the mean of the covariance matrices and represents the point where the tangent plane is determined.

$$\mathrm{C}_{\mathrm{subj}} = \frac{1}{\mathrm{n}-1}\mathrm{X}_{subj_i}\mathrm{X}_{\mathrm{subj}}$$

Equation 13

$$\mathrm{C}_{\mathrm{ref}} = \frac{1}{\mathrm{subj}}\sum_{i=1}^{subj} C_{subj}$$

Equation 14

$$\mathrm{C}_{\mathrm{tangent}} = \mathrm{tangentspace}(\mathrm{C}_{\mathrm{train,}}\mathrm{C}_{\mathrm{ref}})$$

Equation 15

$$\mathrm{C}_{\mathrm{test}} = \mathrm{tangentspace}(\mathrm{C}_{\mathrm{test}}, \mathrm{C}_{\mathrm{ref}})$$

Equation 16

Riemannian distance between Cref and Csubj with the geometric mean can be calculated by:

$$\delta(\mathrm{C}_{\mathrm{ref}}\,, \mathrm{C}_{\mathrm{subj}}) = \left[\sum_{\mathrm{i}=1}^{\mathrm{E}} \log^2\ \lambda_{\mathrm{i}}\right]^{1/2}$$

Equation 17

Where λ_{i} is the eigenvalues calculated by:

$$\lambda_{\mathrm{i}}=\mathrm{C}_{\mathrm{ref}}^{-1}\mathrm{C}_{\mathrm{subj}}$$

Equation 18

NCA was implemented on the Riemannian feature selection prior to classification to evaluate feature weights and optimize the results. The complete Riemannian algorithm is detailed by Barachant, Bonnet, Congedo and Jutten (2013).

2.7.5 Classifier: Ensemble Subspace Discriminant

Ensemble learning classifiers combine individual classifiers to improve accuracy. The discriminant analysis method trains the data using its fitting function to estimate the parameters based on a Gaussian distribution. Discriminant analysis is a method to classify multivariate data into two distinct groups simplifying it to a univariate problem (Huberty, 1975).

2.7.6 Classifier: Support Vector Machine

Support vector machine (SVM) is a classifier that distinguishes patterns, typically for binary linear problems. SVM calculates a hyperplane in the feature space. If the data is separable, two parallel hyperplanes will divide the two classes such that the distance between them is maximized (Li et al, 2013). The region bound by the two hyperplanes is the margin. Figure 12 shows the delineation of the hyperplane with C1 and C2 being distinct data classes.

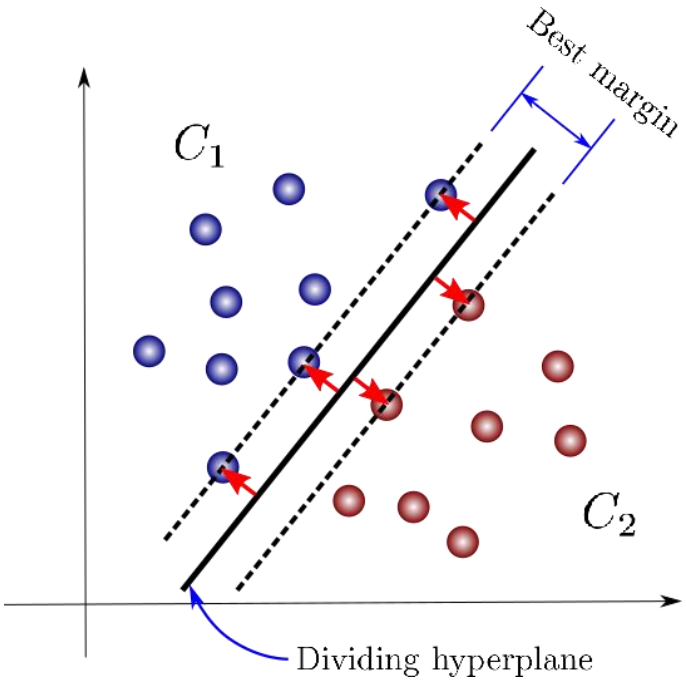

Figure 12: SVM Data Margin (Carrasaco, 2019)

2.7.7 Classifier: K-Nearest Neighbor

K-Nearest Neighbor (KNN) classifier is a learning algorithm that assigns weights to feature points surrounding a reference. Data points nearer to or the neighbors of the

point of reference contribute more to the average than more distance points. The weighting is proportional to 1/d where d is the distance to the neighboring point (Altman, 1992).

3. Results

The results of the research include three components. Each of these contributions provides insight into different analytical tools that could be applied in the future for the diagnosis of mood and/or anxiety disorders. They can be used individually or collectively for a more comprehensive understanding of the patient.

3.1 Feature Asymmetry

Table 6 shows the results of a feature asymmetry analysis. An ANOVA II analysis was performed on the extracted features to determine significant asymmetry. A p value less than 0.05 in any column indicates asymmetry between the left and right hemispheres or prefrontal cortex. If both affected and unaffected show asymmetry, it can be concluded that the feature does not discriminate between a mood disorder and a healthy control. Eight features showed asymmetry (bolded in the table) when comparing the affected to the unaffected group indicating a neurophysiological difference (highlighted in green when the p value is less than 0.05).

Table 5: Feature Asymmetry Statistical Analysis Results

		Prefrontal Cortex (PFC) Asymmetry		Left Hemisphere vs. Right Hemisphere	
		Unaffected	**Affected**	**Unaffected**	**Affected**
Features	**Frequency Band**	**P Value**			
HFD	Delta	0.000	0.000	0.000	0.000
AppEN		0.085	0.078	0.923	0.205
CorrDim		0.691	0.930	0.002	0.268
LyuopavExp		0.073	0.684	0.174	0.456
Lorenz		0.773	0.452	0.408	0.136
DFA		0.070	0.869	0.950	0.616
HFD	Theta	0.004	0.002	0.000	0.000
AppEN		0.167	0.135	0.466	0.756
CorrDim		0.174	0.029	0.000	0.000
LyuopavExp		0.478	0.629	0.021	0.656
Lorenz		0.966	0.356	0.404	0.054
DFA		0.133	0.436	0.349	0.034
HFD	Alpha	0.000	0.000	0.000	0.000
AppEN		0.042	0.053	0.084	0.102
CorrDim		0.884	0.159	0.749	0.750
LyuopavExp		0.222	0.006	0.557	0.006
Lorenz		0.506	0.261	0.976	0.495
DFA		0.092	0.691	0.009	0.000
HFD	Beta	0.000	0.000	0.000	0.000
Approx_Entropy		0.001	0.006	0.006	0.024
CorrDim		0.455	0.641	0.062	0.297
LyuopavExp		0.005	0.000	0.011	0.924
Lorenz		0.098	0.692	0.021	0.077
DFA		0.041	0.863	0.559	0.236

Normally, there is asymmetry in the hemispheres for affected and unaffected individuals. A power spectral analysis showing the dominant frequency band typically shows left hypoactivity of the alpha band in depression and hyperactivity of the alpha band in a healthy control. Interestingly, the HFD feature for each of the four

frequency bands showed a significant difference for all events, however due to this consistency, it is not a discriminatory feature. This is likely because the channel values were averaged for the topographic area and HFD values represent multiple signals, which taken together, lack specificity.

Table 6: Summary of Statistically Significant Features

		Prefrontal Cortex		Hemisphere	
		Affected	**Unaffected**	**Affected**	**Unaffected**
CD	Delta	0.930	0.691	0.268	0.002*
CD	Theta	0.029*	0.174	0.000	0.000
LE	Theta	0.629	0.478	0.656	0.021*
DFA	Theta	0.436	0.133	0.033*	0.349
AppEN	Alpha	0.053	0.042*	0.102	0.084
LE	Alpha	0.006*	0.222	0.006*	0.557
LE	Beta	0.000*	0.005*	0.924	0.011*
DFA	Beta	0.863	0.041*	0.236	0.559

*** Indicates significant statistical difference ($p < 0.05$)**

The results of the ANOVA II analysis given in Table 6 highlight the significant differences. Please note these results pertain to persons with comorbid depression and anxiety and do not demonstrate disorder-specific identifiers.

The key conclusions drawn from this statistical analysis include:

- AppEN in the alpha band differs between the right and left prefrontal cortex.
- LE in the alpha band differs between the right and left prefrontal cortex.
- CD in the delta band differs in the right and left hemisphere indicating a differential in the posterior brain region.
- LE in the theta band differs in the right and left hemisphere indicating a differential in the posterior brain region.
- CD in the theta band differs in the prefrontal cortex indicating that this region could be the origin of the asymmetry.

- DFA differs in the theta band in the right and left hemisphere between affected (depression/anxiety) and unaffected people..
- No differential noted for HFD between affected and unaffected people, however there was a hemispheric differential for all participants and all four frequency bands.

The delta band is linked to cognitive function and increases in the frontal cortex during arithmetic and semantic tasks. Harmony (2013) evaluated the significance of delta oscillations on cognitive function. It was concluded that the elevated delta frequencies during mental and arithmetic tasks are associated with functional cortical deafferentation which is the inhibition of the sensory afferent neurons that interfere with internal concentration.

The theta band is associated with activation of memory and retrieval. Frontal theta power is associated with key traits of anxiety. The underlying physiology causing this manifestation can be attributed to the midcingulate cortex, part of the limbic system, which is involved in regulating behaviour in response to stress (Cavanagh & Shackman, 2015).

3.2 Visualization of Topographic Heat Maps

Creating topographic heat plots of the extracted features shows channel specific values and provides more comprehensive, regional responses. In addition, visualizing the changes in feature values across different severity levels compared to the baseline condition of unaffected participants illustrates another level of detail. With the amount of data extracted, thousands of heat maps could have been produced since each map represents one feature in one frequency band. Therefore, based on the feature asymmetry results, the heat maps were created. Heat maps were created for the two disorders separately: depression and anxiety. Therefore, people were indexed and categorized into five groups by their BDI score based on interpretation of this test with an additional category if the individual had a zero-score indicating no depression (unaffected control). For anxiety, the heat maps were represented in three groups based on the TAI score (minimal, moderate and severe anxiety). In this case, none of the participants in the dataset had null or no anxiety whatsoever, therefore, a base category of no anxiety was not presented. The minimal anxiety condition can be

considered a control type situation for comparison. The mean of all 62 channels were displayed for each severity class to develop a heat map representative of a depression or anxiety rating score. This allowed for conclusions to be drawn based on mood disorder severity as participants were visually combined to be able to differentiate between groups based on a feature extracted from a frequency band.

Table 7: Class Labels Used for Visualizing Heat Maps

Class Label	Depression Score (BDI)	Number of Participants	Anxiety Score (TAI)	Number of Participants
Class 1	BDI = 0	19	TAI ≤ 37	64
Class 2	1 < BDI < 13	55	38 < TA Iv< 44	12
Class 3	14 < BDI < 19	15	TAI > 44	43
Class 4	20 < BDI < 28	25	-	-
Class 5	BDI > 28	5	-	-

Figure 13 shows the distribution of participants across the psychological test score categories of severity.

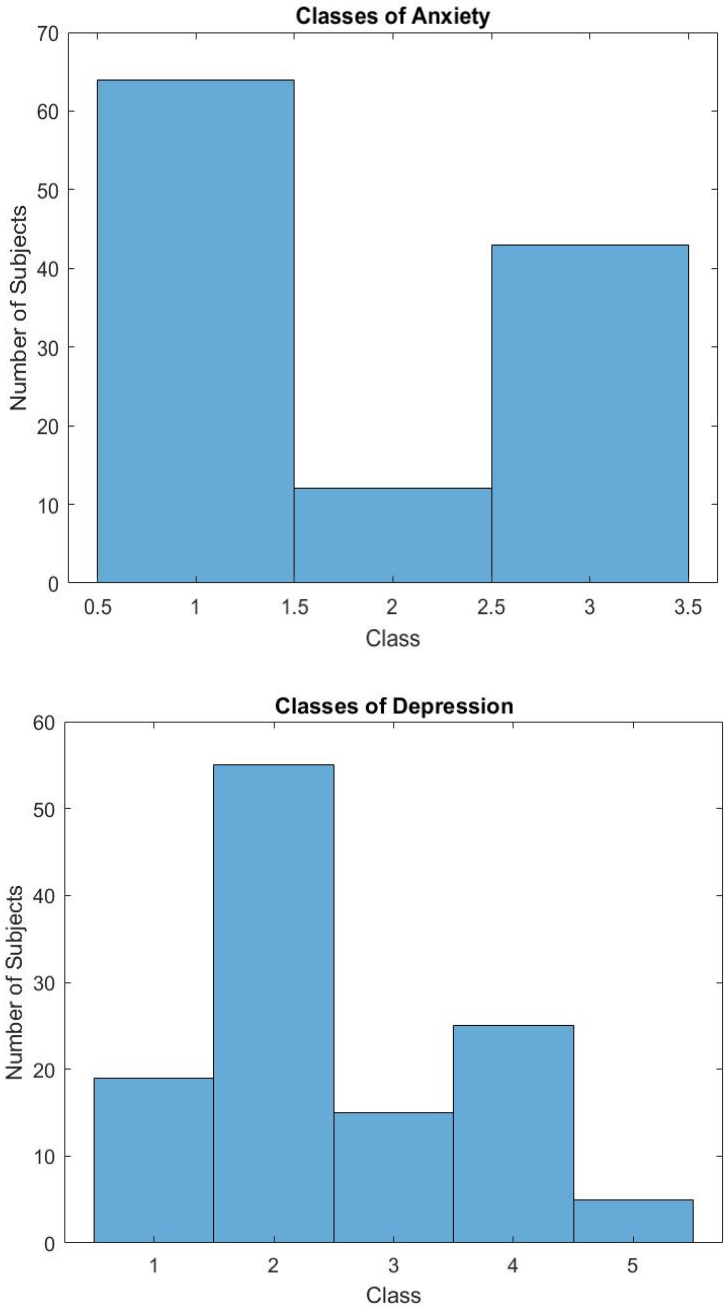

Figure 13: Histograms Showing Class Distribution of participants with Depression and Anxiety

Each heat map has its own legend. All of these parameters are normalized by the maximum feature value extracted from the particular frequency band. The normalized values allow for data redundancy and to be able to draw relational conclusions. The heat maps are generated by EEG signals for a period of 4 seconds. Within the 4 seconds of data analysed (2000 samples with a sampling frequency of

500 Hz), there were varying numbers of trials (marked time points at which an event occurred). Several iterations were produced including displaying the mean of all trials and as well, displaying only a singular trial result for visual discrimination. Averaging data eliminates features but can allow for generalizability.

Visually distinct variations between affected and unaffected individuals were observed and details were identified that the analytical analysis did not reveal. Table 8 summarizes the conclusions drawn from the topographic plots while participants performed the probabilistic learning task.

Table 8: Heat Maps of Extracted Features During the Learning Task

Feature	BDI Heat Map Characteristics	TAI Heat Map Characteristics
CD – delta	• *No conclusive visually discernible trends*	• Overall, less correlated with increasing TAI class
CD – theta	• *No conclusive visually discernible trends*	• *No conclusive visually discernible trends*
LE – theta	• Inversed channel values between class 4 and class 5	• Overall decrease in LE with increasing TAI class
DFA – theta	• Obvious difference between classes 1 - 4 and class 5 (P2 value)	• *No conclusive visually discernible trends*
AppEn – alpha	• Obvious difference between classes 1 - 4 and class 5 in the alpha band • Decrease in AppEn at P6 with higher BDI class	• At channel P8, a decrease in AppEn was observed in class 3 compared to classes 1 & 2
LE – alpha	• Overall *increase* in LE with increasing BDI	• Overall *decrease* in LE with increasing TAI class in alpha band

	class, notably in alpha and theta bands	
LE – beta	• *No conclusive visually discernible trends*	• In the left temporal region, LE beta band decreases in magnitude of LE (consistent with theory of more active right hem vs left/imbalance)
DFA - beta	• Higher DFA value at F8 with increasing BDI class	• Overall, less correlated with increasing TAI class

3.2.1 Key Depression Heat Maps

In the theta band for DFA, the value of channel P2 is consistently high for all severity classes of depression (see Figure 14). This occurred in the heat maps averaged for all trials so it may not be indicative of any trend, due potential loss of discriminatory events. It may represent consistent, high cognitive processing which occurs in the parietal region elicited by the learning task which is not impacted by the mood disorder.

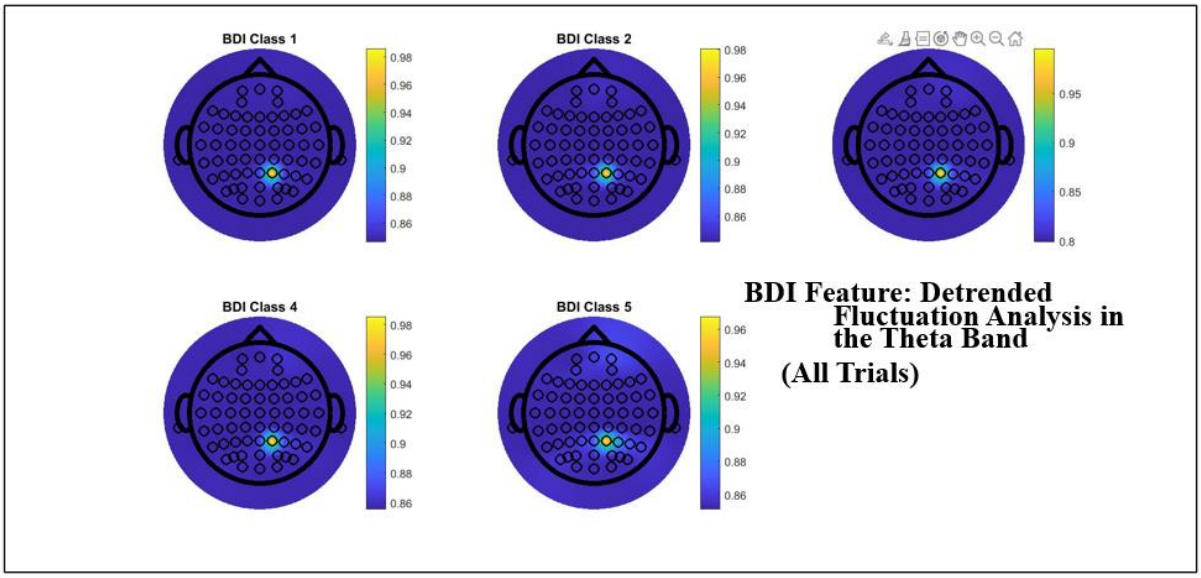

Figure 14:BDI Heat Map Approximate Entropy in the Alpha Band (All Trials)

In the beta band for DFA, the values at F8 increase with increasing BDI class (see Figure 15). This is consistent with prior studies described in 2.4.5. A higher DFA value is positively correlated with depression. Decreased activity is demonstrated by a higher correlation between regions as there are fewer connections being utilized.

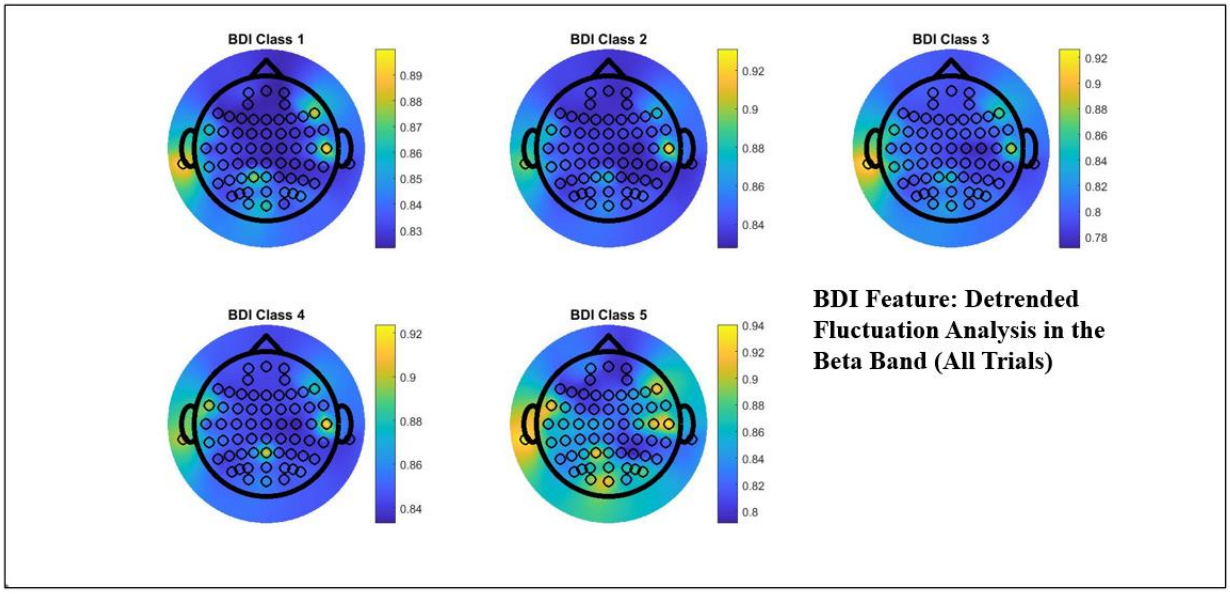

Figure 15: BDI Heat Map Detrended Fluctuation Analysis in the Beta Band (All Trials)

Overall, there was a higher AppEn in persons with severe depression in the alpha band with increasing severity (see Figure 16). However, at channel P6, the entropy values are consistently high.

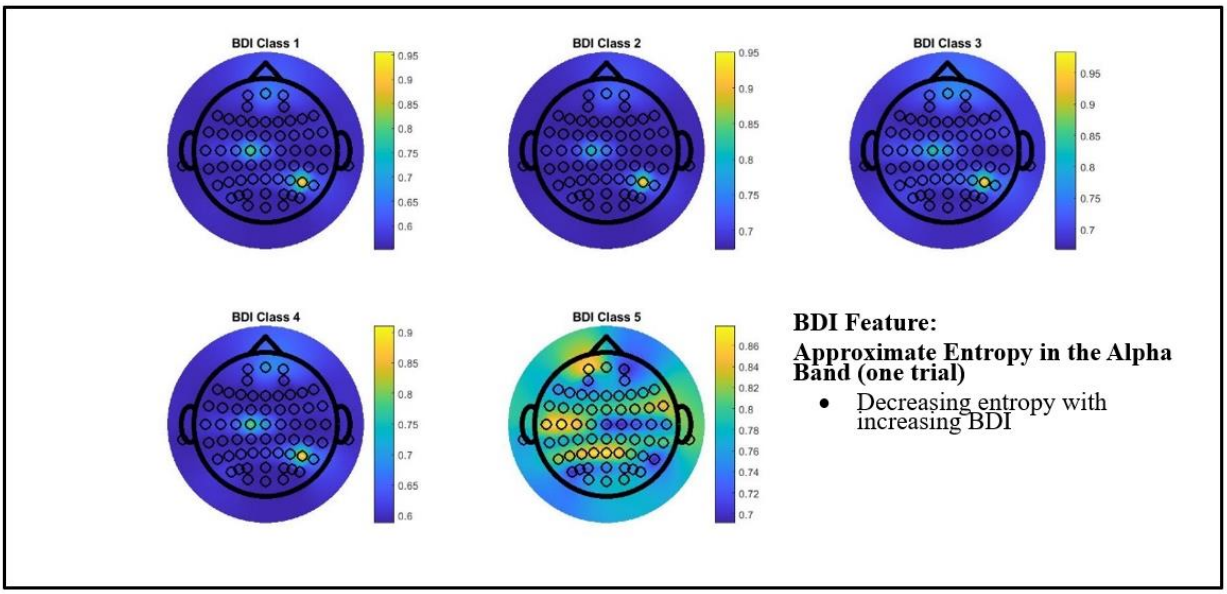

Figure 16: BDI Heat Map Approximate Entropy in the Alpha Band (One Trial)

For the averaged trials for approximate entropy in the alpha band for persons with depression, the averaged trials heat maps were not discriminatory (see Figure 17)

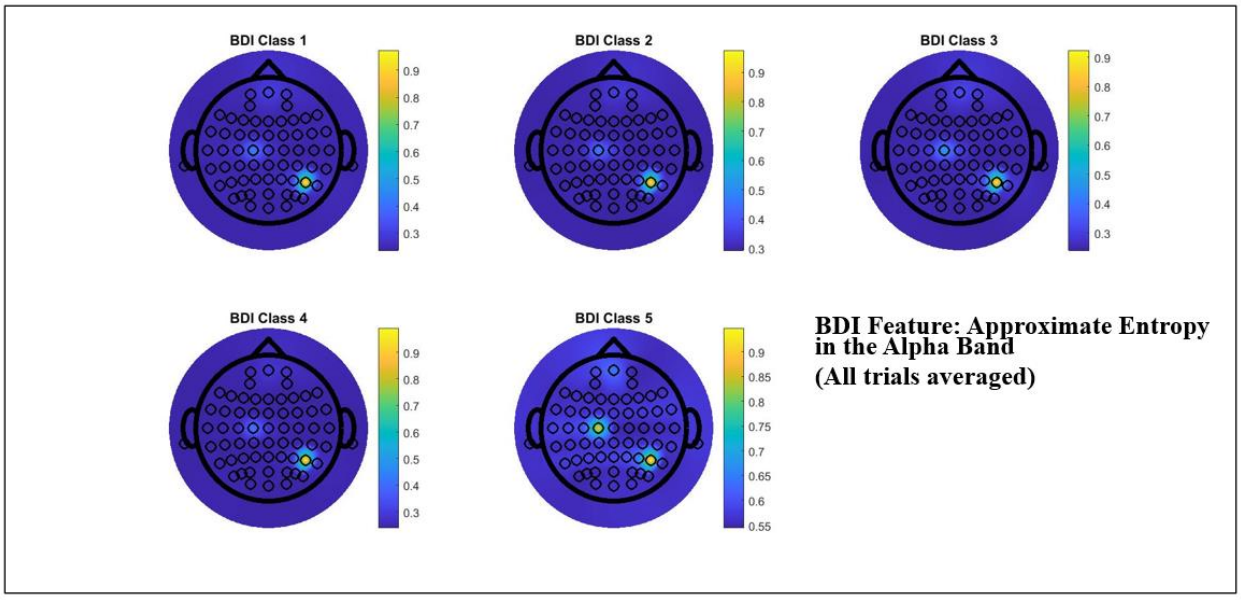

Figure 17: BDI Heat Map Approximate Entropy in the Alpha Band (All Trials)

Lyapunov's exponent was discriminatory for persons with depression, particularly in the alpha and theta bands (see Figure 18 and Figure 19). LE increased overall in the alpha and theta bands with increasing depression severity (note the different scale bars for each heat map).

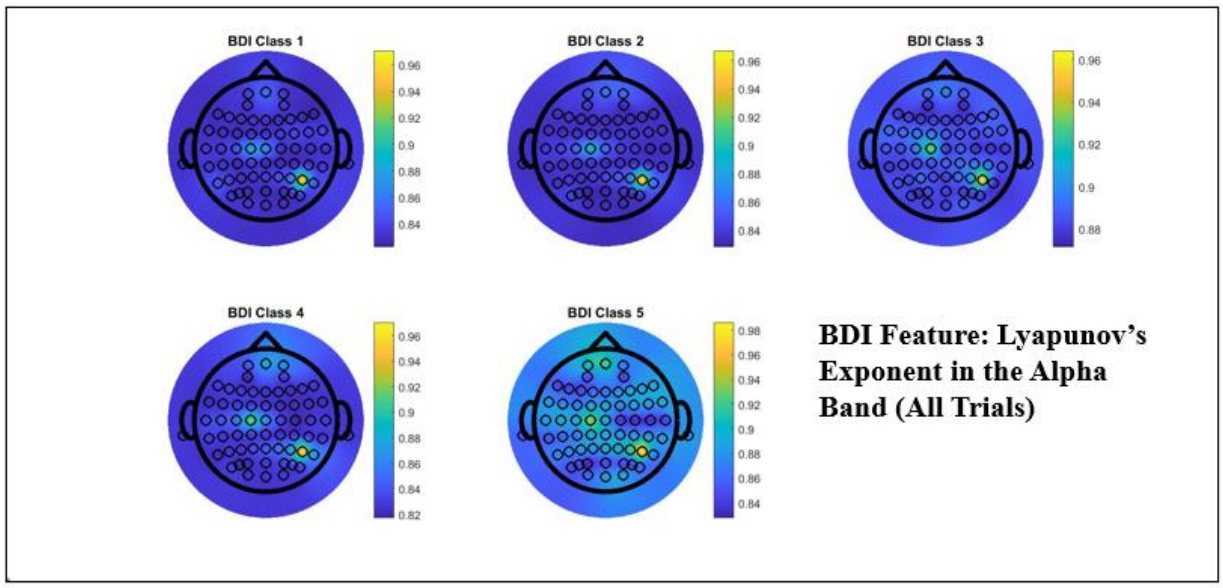

Figure 18: BDI Heat Map Lyapunov's Exponent in the Alpha Band (All Trials)

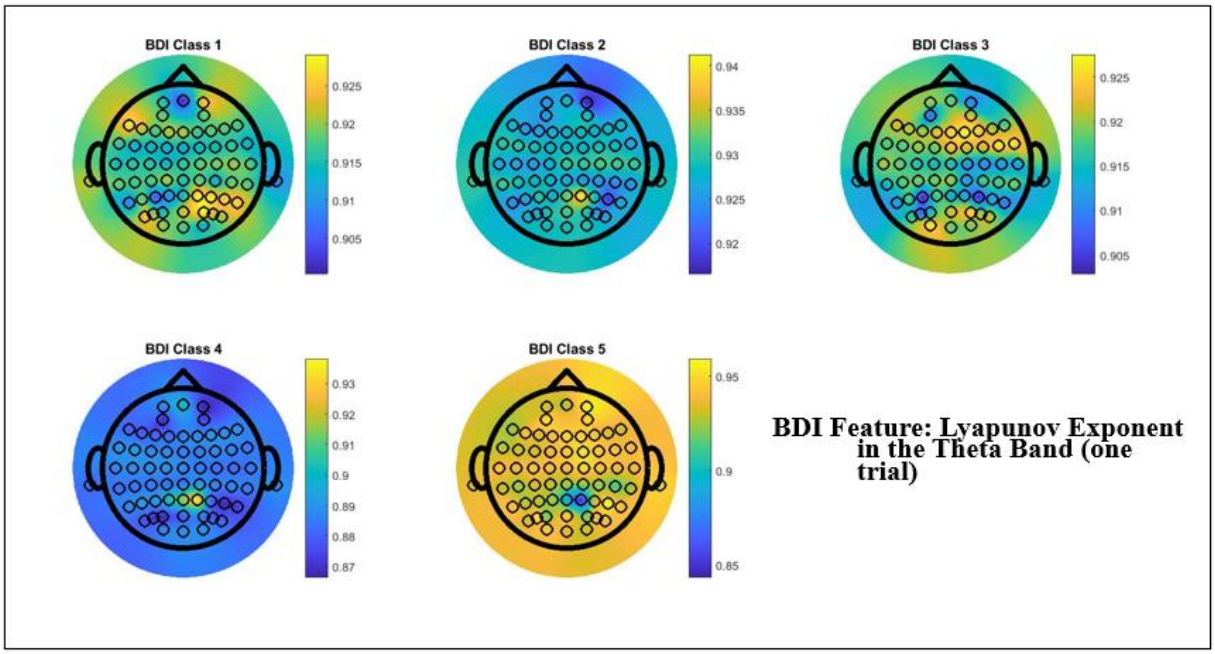

Figure 19: BDI Heat Map Lyapunov's Exponent in the Theta Band (One Trial)

3.2.2 Key Anxiety Heat Maps

Figure 20 shows that at channel P8, a very minor decrease in AppEn alpha band for individuals which occurred in class 3 compared to classes 1 & 2 (0.95 for classes 1& 2 vs. 0.9 for class 3).

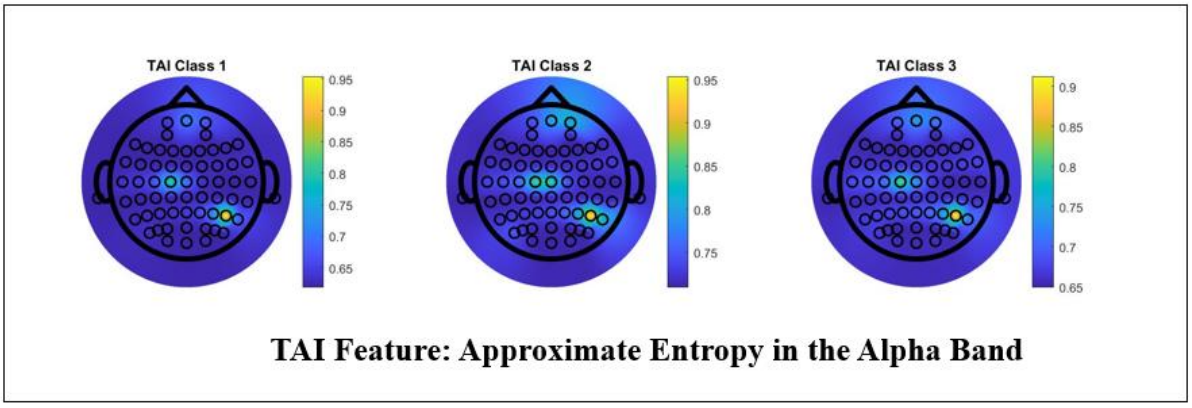

Figure 20: TAI Heat Map Approximate Entropy in the Alpha Band (OneTrial)

For persons with anxiety, LE decreases overall in magnitude in the alpha band (see Figure 21). Similarly, for the same feature but in the beta band, LE decreases but primarily in the left temporal and occipital regions (see Figure 22).

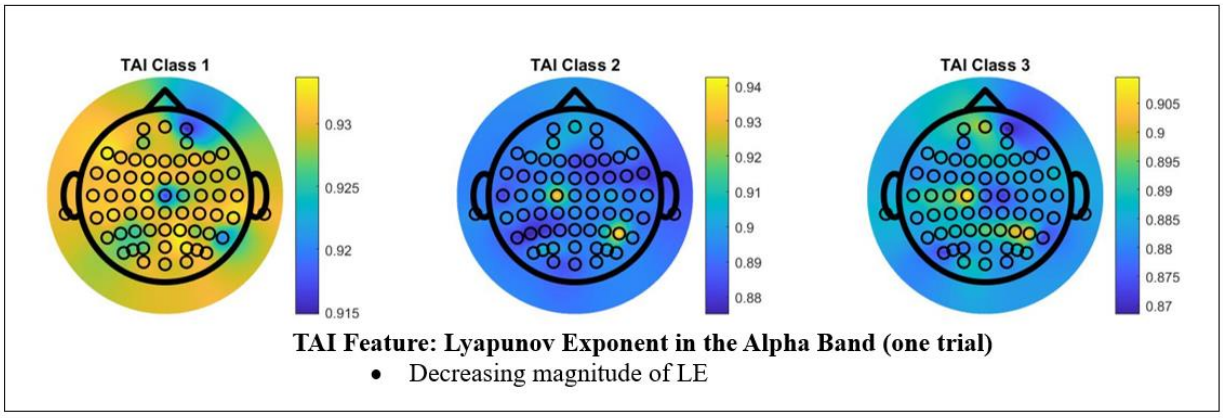

Figure 21: TAI Heat Map Lyapunov's Exponent in the Alpha Band (One Trial)

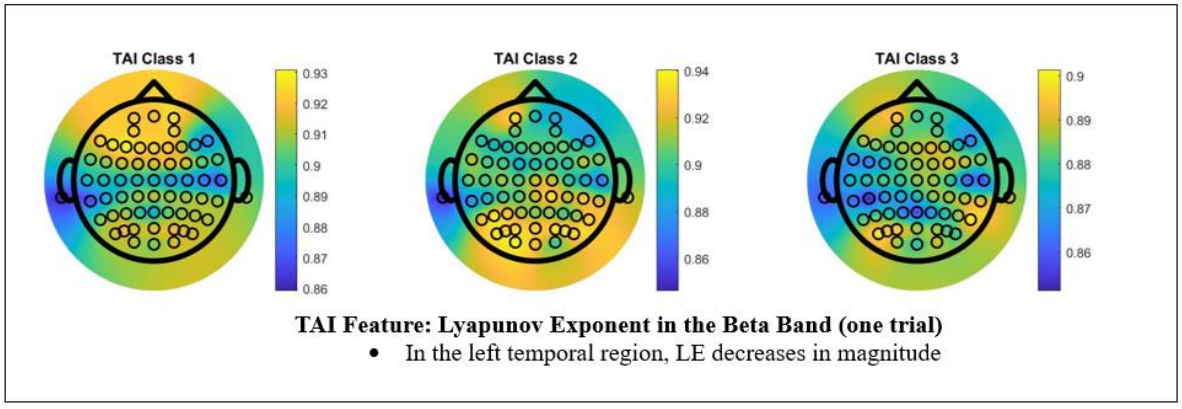

Figure 22: TAI Heat Map Lyapunov's Exponent in the Beta Band (One Trial)

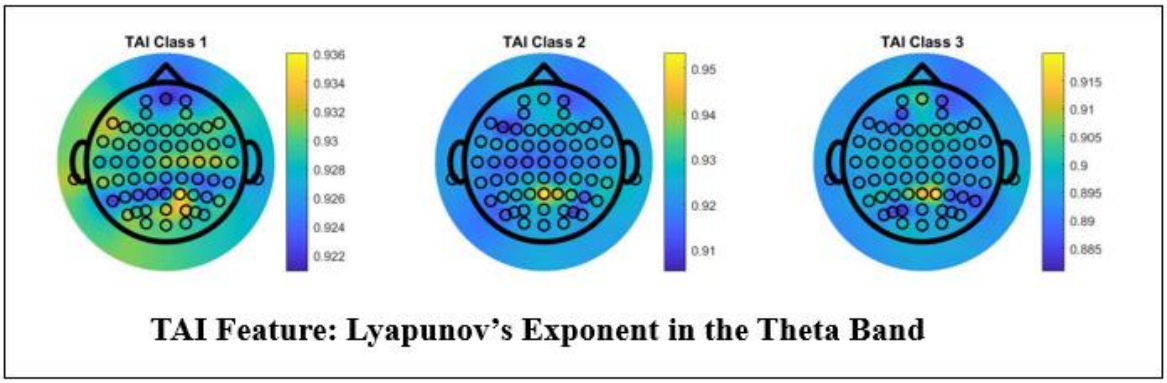

Figure 23: TAI Heat Map Lyapunov's Exponent in the Theta Band (One Trial)

3.3 Classification

For multiple iterations of classifying the EEG signals varying by the selected features, classifiers, and different data segments, the classification accuracies ranged between 60% to 70% for training and validation. The highest classification accuracies were achieved on the resting EEG signal. Figure 24, Figure 25, Figure 26 and Figure 27 display the notable classification outputs for the two feature extraction codes, each iterated on both the BDI and TAI labels. Table 9 summarizes these results.

Resting State BDI Classification

Feature Selection for each of the 4 frequency bands (CD, LE, DFA, AppEn, HFD)
67.2% Classification for Ensemble Subspace Discriminant

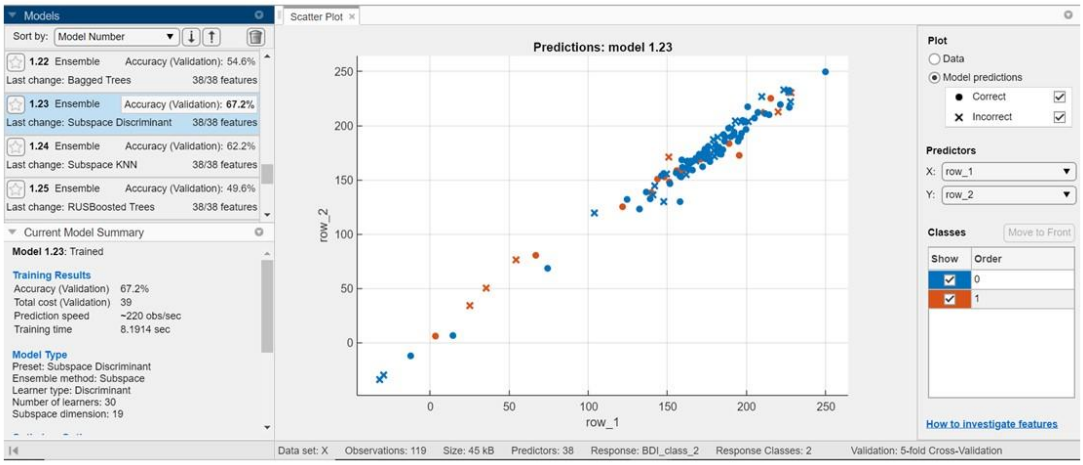

Figure 24: Resting State BDI Classification Based on Specified Features

Resting State TAI Classification

Feature Selection for each of the 4 frequency bands (CD, LE, DFA, AppEn, HFD)
64.7% Support Vector Machine (SVM Cubic)

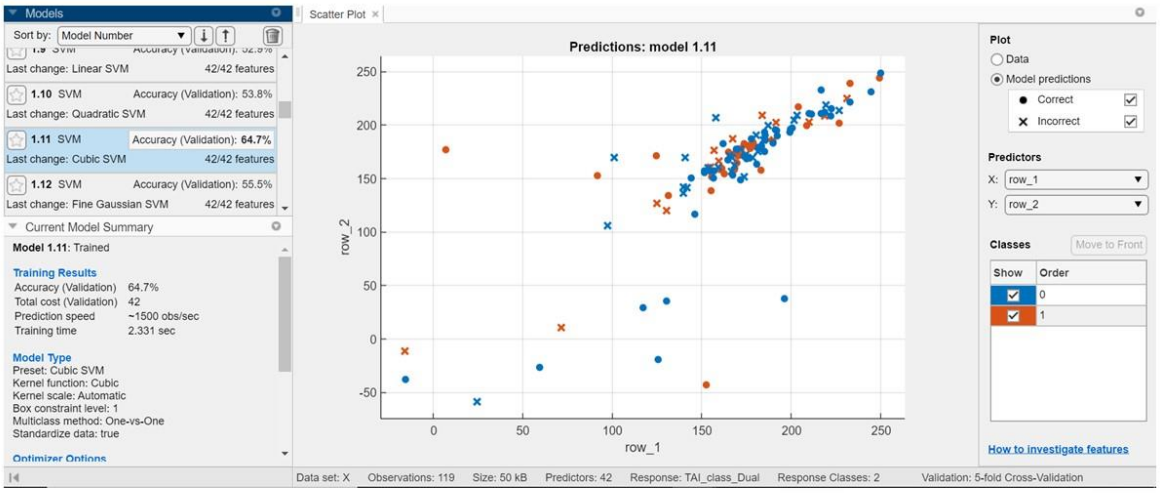

Figure 25: TAI Classification Based on Specified Features

Resting State BDI Classification

Riemannian Feature Selection

65.5% Classification for Ensemble Subspace K-Nearest Neighbor (KNN)

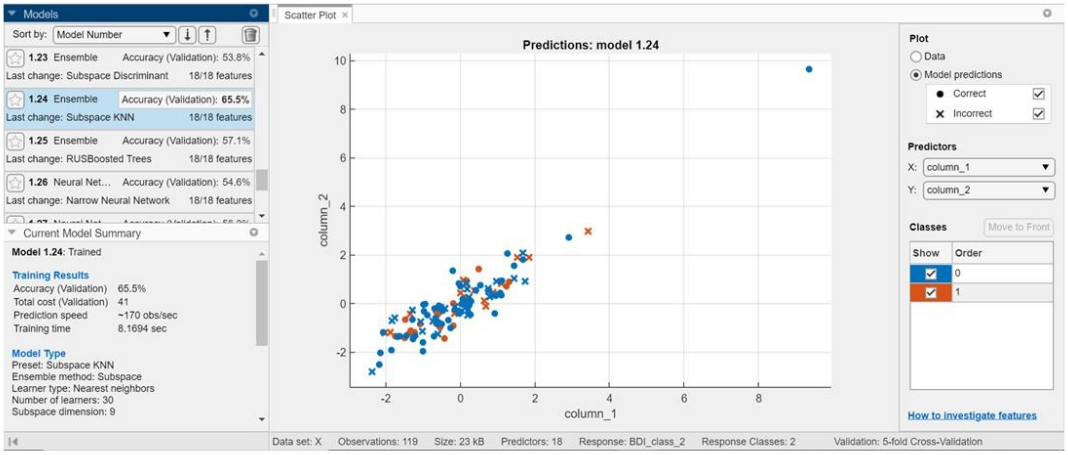

Figure 26: BDI Classification Based on Riemannian Features

Resting State TAI Classification

Riemannian Feature Selection

66.4% Classification for Ensemble Subspace K-Nearest Neighbor (KNN)

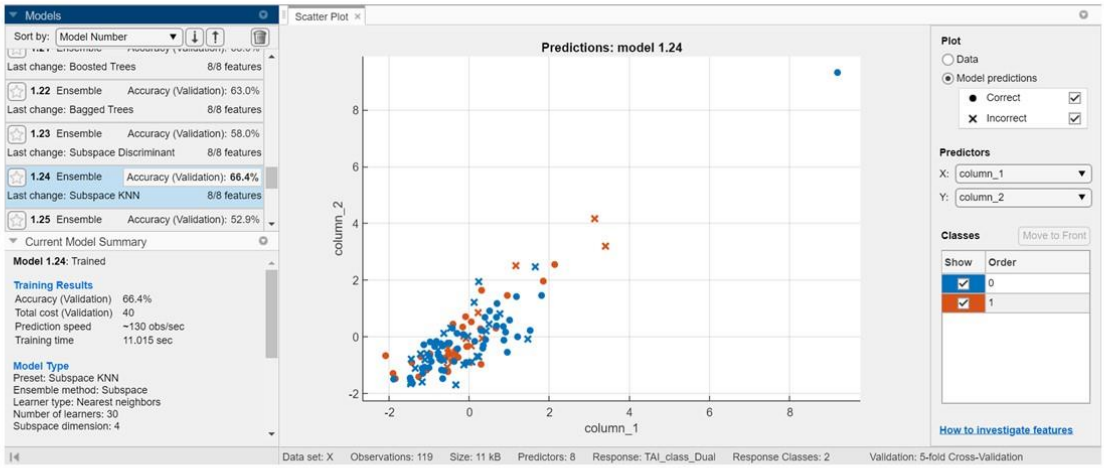

Figure 27: TAI Classification Based on Riemannian Features

Table 9: Summary of Key Classification Accuracies Based on Resting EEG Signal

Disorder	Classification Accuracy & Classifier	
	Non-Linear Features	**Riemannian Features**
Depression (BDI Score)	67.2 % (Ensemble Subspace Discriminant)	65.5% (KNN)
Anxiety (TAI Score)	64.7 % (SVM)	66.4% (KNN)

4. Discussion

4.1 Significant Features

Extracted features were used for differentiating persons with depression and anxiety from healthy controls. It was demonstrated that CD, AppEn, DFA and LE demonstrate hemispheric asymmetry differences between affected and unaffected participants. Hemispheric differences were noted, and this is due to underlying neurophysiology. Where there were differences noted in the right and left hemispheres and not in the right and left prefrontal cortex, it can be concluded that the asymmetry originates from the posterior portion of the brain (mainly the parietal region). Due to electrode detection limitations, activity is detected that is transmitted to the cortex as the depth is limited to several centimeters. The underlying structures can influence the signals detected from the cortex.

Several studies have reviewed the influence on lateralization of the hemispheres on mood in a similar way in which language is associated with the left hemisphere due to the identified Broca's and Wernicke's areas (Catrin Blank et al., 2002). Generally, the right PFC is responsible for negative emotions and the left PFC manages positive ones. However, it is a controversial topic in literature with no conclusive link either way due to conflicting evidence. Emotion does impact the elicited brain regions resulting in activation of specific areas. Emotion facilitates learning and memory including memory consolidation in the amygdala, memory encoding and learning in the prefrontal cortex and long-term memory retention in the hippocampus (Chai et al, 2017). In addition to emotion, acute stress impairs the prefrontal cortex (McEwan, Bruce & Morrison,2013). In unaffected individuals, the left PFC inhibits negative emotions generated by the limbic system. The PFC has connections involved with the neurotransmission of dopamine, serotonin, and norepinephrine.

Trends that displayed differences between the classes of BDI and TAI were more evident in the higher frequency bands (alpha and beta). This makes sense as the beta band is associated with complex thinking and the alpha band is associated with a more calm and meditative state of mind. Apart from these standard wave associations,

the alpha and beta bands can be viewed as synergistic, and lateralization can have activating and inhibiting effects on the brain. The observations call for a re-evaluation of the role of sensorimotor rhythms. In a study where healthy volunteers imagined a motor activity, alpha band oscillatory power increased in the sensorimotor cortex and beta-band power decreased in the contralateral sensorimotor cortex (Brinkman et al., 2014). It was suggested that neural oscillations in the alpha band mediate the analytical resources by disengaging certain cortical regions and the oscillations of the beta band directly relate to the activation of motor regions. A reduction in the power frequency band can have disinhibitory (activating) effects on the cortex. Therefore, the coordination between the alpha and beta band oscillations, manifesting as asymmetry, had a mediating impact on how brain regions are elicited or may be the result of specific regions elicited, indicating across volunteers, that there exist common activations.

Many participants had comorbid presentations of depression with anxiety and in cases focusing on depression, the individuals all had some level of anxiety. Likewise, when examining the anxiety state, the participantss all had some level of depression. There were too few people that only had anxiety and no depression and vice versa to be able to run an analysis and draw representative and unbiased conclusions. Realistically, the prevalence of comorbidity is high and is representative of clinical presentations. The objective is to identify universal features that consistently demonstrate similar outcomes.

Most research to date has an exclusion criterion of individuals who are not currently taking any antipsychotics, antidepressants, or antianxiety medication as well as other drugs or substances that alter the mind such as antiepileptics, caffeine, alcohol, etc. This is due to the psychopharmacological effects these substances have on the brain. Psychotropic medications interact with neurotransmitters to directly impact the way someone thinks and feels. Caffeine's mechanism of action includes blocking $GABA_A$ receptors and adenosine receptors. Alcohol affects multiple neurotransmitters including the NMDA receptor associated with glutamate, as well as $GABA_A$ inhibition and the dopamine pathway (Meyer, 2019). In addition, hand dominance can impact the asymmetry results and has been controlled for. Usually,

studies are performed on volunteers who have a singular and known diagnosis to not convolute the results with comorbidity, however with anxiety and depression that is nearly impossible to control. Many other factors that can influence the outcome of EEG signal analysis in a group would be the average age of the participant, education level, history of trauma and other social factors. Age can be determined though EEG signals by feature selection of the following spectral features: power, relative power, entropy, edge frequency and differences between consecutive short-time spectral estimations (Al Zoubi et al, 2018). Cognitive load can be differentiated by EEG signals using entropy and the deviation of wavelet coefficients (Zarjam & Lovell, 2015). Trauma can lead to a diagnosis of post traumatic stress disorder (PTSD) which manifests itself in the EEG signals. Trying to interpret brain outputs is extremely complex and not fully understood. Attempting to rationalize and attribute signal response to a particular condition can never be certain, even under rigorous and strict study conditions. The effect of interventions on EEG signals is crucial to interpreting the results. Since signals are transient and temporally sensitive, the segment of data analyzed must be intentionally selected and common participant characteristics should be sought.

4.2 Visualization of Topographic Heat Maps

Generally, the higher frequency bands are more discriminatory. The alpha band, associated with a low level of alertness, and beta bands, associated high order thinking, can be affected by depression and anxiety. Consequently, theta and delta band dominance can help to discern and delineate imbalances in the alpha and beta bands.

Most studies have performed analysis on the resting state EEG signals or have evaluated ERP responses (Newson & Thiagarajan, 2019; Damborská et al., 2019; Koo et al, 2015). This allows for predictability, reproducibility, and reliability of the data as the testing condition can be easily recreated. Analyzing and extracting features from trial-based EEG signals for biomarkers of depression and anxiety is a novel approach to analysis. When a person is performing a task, they are exhibiting cognitive processing which would differ from the resting state. It would provide clarity on how, during an active state, connectivity is impacted by a mood disorder

and if there are discernible biomarkers. The original study by Cavanagh and colleagues (2019) examined the effect of depression and anxiety on reward response learning but did not use the data for machine learning/validation of the mood disorder based on the psychological test scores.

Several trials in the EEG signals were noted as significant event occurrences as documented by the original researchers while the participants performed the probabilistic learning task. In some individuals, over 120 trials were noted. Heat maps were generated for comparison of the trial means as well as for a singular trial. Averaging the trials can eliminate critical data that may not be an outlier but can present a representative picture of the brain over the entire period. Conversely, a single trial event is very temporally specific and may not be generalizable, however can provide insight on the individual.

In the beta band for DFA, the values at channel F8 increase with increasing BDI class (see Figure 15). Decreased activity is demonstrated by a higher correlation between regions as there are fewer activations. This is because the beta frequency band is associated with higher order thinking and decreased chaos or complexity indicates reduced activity. The frontal lobe is associated with decision making and executive control. It is the part of the brain that manages everyday situations. If a person is apathetic and not actively engaged in the task at hand, then the frontal lobe activity would certainly be reduced.

This reduced complexity is visible in these EEG signals regardless of the signal acquisition condition. This disproves and contradicts one finding presented in a paper by Sun et al. (2008) that stated only in resting state the frontal cortex is affected. The study also demonstrated that while performing a mental arithmetic task, persons with depression showed left frontal beta hyperactivity as well as interhemispheric and intra-hemispheric interdependence. Conversely, during the resting state, participants showed a left frontal beta hypoactivity. This indicates that the beta band activity is dependent on what the individual is doing. Unfortunately, this feature would not help to discriminate a diagnosis of depression from signals acquired when a person is performing a task as it implies that there will be typical EEG connectivity. This study

by Sun et al. (2008) examined dependency, which differs from the selected features for this thesis, however both describe the level of disorder or chaos of the signal.

Figure 16 shows a higher AppEn in persons who are severely depressed in the alpha band with increasing severity. This finding is supported by the known characteristic of the alpha band which is notably dominant during wakeful relaxation. A less active mental state is associated with depression (anhedonia). The exception to the increased entropy or disorder in the alpha band with increasing severity of depression occurred at one channel, P6. The parietal lobe is responsible for decision making, prediction of rewards, emotional processing, and cognitive changes, which can all be affected by depression. This indicates reduced complexity in this region, aligning with a study that found homogeneity in the right inferior parietal lobe of the brain in depressed patients. This was determined measuring blood flow using fMRI (Liang et al., 2013). Therefore, these heat plots produced using EEG signals are consistent and validate the observed reduced entropy.

Lyapunov's exponent was discriminatory for persons with depression, particularly in the alpha and theta bands (see Figure 18 and Figure 19). LE increased overall in the alpha and theta bands with increasing depression severity. This feature appears to be a reliable indicator of severity increase. This indicates that LE is non-specific to a topographic region and detects overall changes.

Figure 20 shows that at channel P8, a very minor decrease in AppEn alpha band for persons with anxiety was observed in class 3 compared to classes 1 & 2. This may be due in part to the frequency band and the function of the parietal brain region. Studies have shown hyperactivity in the parietal cortex in patients with high anxiety (Grieder et al., 2020; Nitschke et al., 1999). The inferior parietal cortex helps to control fine sensorimotor functions, decision making and the prediction of rewards. MRI scan results demonstrated inactivation of this area while people were being watched, highlighting the impacts of anxiety on the brain region (Yoshie et al., 2016). A decrease in entropy can signify reduced activity and likewise, chronic anxiety is associated with an increase in homogeneity which is indicative of a reduced learning ability (Zhang et al., 2018).

For persons with anxiety, LE decreases overall in magnitude in the alpha band (see Figure 21). Similarly, for the same feature but in the beta band, LE decreases but primarily in the left temporal and occipital regions (see Figure 22). This is consistent with research suggesting left hypoactivation in individuals with depression, which holds true for persons with anxiety in this case (Henriques & Davidson, 1991). This is validated through the EEG signals during the GO/NO GO condition as when alpha band activity decreases, generally beta activity increases (alpha dominates the resting state condition). In the theta band, there is an obvious decrease in LE overall. Finally, for the same feature in the theta band, at channels Pz and P2, the LE value is higher relative to surrounding channels but decreases with increasing anxiety from 0.935 to 0.915 (see Figure 23). Frontal theta power is associated with neuroticism and avoidance, key traits of anxiety. The midcingulate cortex, part of the limbic system, is involved in regulating behaviour in response to stress. As previously mentioned, frontal-midline theta band activity has demonstrated these adaptive behaviours (Cavanagh & Shackman, 2015).

4.2.1 Value of Heat Maps

Making results easier to interpret and gaining meaningful conclusions is a key point when designing human-computer interfaces. Numerical data or visual outputs should be produced to aid in analysis. Many interfaces are aesthetically pleasing and intuitive. Topographical brain heat maps are easily understood, and the colour distribution can be interpreted by the legend. Understanding this output is equally as valuable as a numerical output and more detailed channel information can be gleaned from this, leading to further understanding into topographic influence on mood disorders. EEG signals are transient and visually observing trends can aid in understanding the interaction of neurons in the brain relative to others as opposed to monitoring the fluctuation in values. Visual output is easily understood by a user, enhances understanding of the data and can contribute to neurofeedback practices. Topographic orientation is critical to understanding the brain and correlating results to a specific brain region.

4.3 Classification

On this dataset, few papers have been published that train the data for classifying the severity of the mood and anxiety disorder. Other research papers evaluating using machine learning techniques to classify depression and anxiety produced slightly higher accuracies. This could be due in part to their method of analyzing the data, the signal quality, and the volunteers of their studies. Nonetheless, the classification accuracies achieved indicative of the presence of a disorder but would require optimization (see section 4.6 Future Work). In addition, Riemannian analysis is not a common method used for feature extraction in EEG analysis and produced classification accuracies analogous to typical discriminant non-linear features. This demonstrates its potential and novel use for classifying mood disorders from EEG signals. The highest classification accuracies for this research consisted of SVM, KNN and ensemble subspace discriminant classifiers.

Several published studies have presented their classification accuracies for identifying depression from EEG signals. Table 10 summaries these key papers, objectives, features used and classifiers. This study selected fewer participants than the total to run the analysis which increased the classification accuracy. Most papers performed their analysis on EEG signals acquired with eyes open or eyes closed in the resting state. Mohammadi and colleagues (2015) increased their accuracy by executing their analysis on a smaller subset of people from their study. This enhances machine learning results, however reduces its applicability to a diverse group.

Table 10: Notable Studies Classifying Depression Using Machine Learning

Author	Database Description	Classification Accuracy
Hosseinifard, Moradi & Rostami (2013)	Classification of 45 unmedicated depressed patients and 45 controls	• 83.3% obtained by correlation dimension (CD) and logistic regression (LR) classifier • 90% achieved by all nonlinear features and LR classifier
Bachmann, Lass & Hinrikus (2017)	Single channel EEG analysis for detection of depression	• 76.5% accuracy for (spectral asymmetry index, SASI) • 70.6% for DFA • 91.2% due to linear combination of SASI (Spectral asymmetry index which is the relative asymmetry between the higher and lower frequency bands) and DFA
Bachmann, Päeske, Kalev, Aarma, Lehtmets, Ööpik, & Hinrikus (2018)	Resting state single channel short-term EEG signals comparing linear (spectral asymmetry index, SASI) and non-linear (DFA) features for 13 unmedicated persons with depression vs. 13 gender matched controls	• 81 % for linear features • 77 % for non- linear features (HFD, DFA, Lempel-Ziv) • 88 % for a combination of 2 non-linear features • 85 % for two non-linear features • 92 % using mixed combination of three linear and three nonlinear features
Acharya, Sudarshan, Adeli, Santhosh, Koh, Puthankatti, & Adeli (2015)	Resting state EEG signals analyzed 15 depressed and 15 unaffected people using nonlinear features for classification	• 98% accuracy using SVM for non-linear including sample entropy, DFA, LE, Hurst's exponent, higher order spectra and recurrence quantification

Cai, Qu, Li, Zhang, Hu, & Hu (2020)	EEG signals for 86 persons with depressions and 96 normal controls acquired while receiving audio stimuli (3 electrode EEG)	• 86.98% using KNN classifier and audio features
Mohammadi, Al-Azab, Raahemi, Richards, Jaworska, Smith, Knott (2015)	Classifying EEGs of 54 participants with MDD and 43 healthy volunteers	• 80 % achieved for 9 selected perons with MDD • 70 % accuracy for all participants
Saeedi, Saeedi, & Maghsoudi (2020)	Classifying 5 mins of resting EEG data for 34 MDD patients	• 91.38% achieved from gamma band with KNN classifier

4.4 Research Reproducibility and Data Limitations

The analysis was performed on a relatively large sample size on 119 participants. The age of the volunteers was between 18 to 24, potentially limiting its applicability to all age groups. However, generally mood disorders emerge in early adulthood, therefore this fact could indicate that neurological variations in early adulthood could represent applicability to all age groups. Performing this analysis on larger sample size where there are more clinically extreme cases of depression and/or anxiety could be beneficial for machine learning and classification. There were only 8 individuals classified as having severe depression, which is not enough to accurately be able to train a dataset. The EEG signals were acquired from people performing a probabilistic learning task. The activity performed during signal recording is known to elicit specific responses such as ERP's. Therefore, the reproducibility of these results may vary depending on the condition of the person (i.e., resting state, eyes, closes/opened, cognitive task, etc.). It has been shown that there is an asymmetry difference between right- and left-handed individuals (Bryden, 1982). It is not known whether the participants were right or left-handed. Since part of the analysis examined asymmetry between the left and right sides, not knowing whether all individuals were dominant on one side or not could convolute the data.

Run time for these codes using the latest version of Matlab (R2021a) took a significant amount of time. Some iterations were 8 to 16 hours in length. Due to the length of analysis, analytical software improvements are needed. There are many (in the order of hundreds) different features that can be used to evaluate the EEG signal. The selected features were chosen based on prior research and their use in identifying mood disorders. Running a code for hundreds of features would be computationally inefficient. A future challenge would be to implement a fast psychological diagnostic software into hardware devices for almost immediate results and conclusions.

A healthy or normal brain must be established for various conditions to order to aid in diagnosis of abnormalities seen. This task on its own is onerous to account for

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varying factors. Self similarity over time to track changes and/progress might be more beneficial in the interim until these controls are established.

EEG is a dynamic signal with high temporal fluctuations. By taking the mean of signals temporally, certain dynamic characteristics may be lost. In addition, from a human-computer interaction perspective and analysing real-time data, it would also be beneficial to represent the temporal changes over time to see the shifting time of specific channels for specific classes. Implementing different EEG signal decomposition methods may offer different insights for diagnosis.

4.5 Sources of Error

It is important to note, just as EEG signals are dynamic, stress is also dynamic. The TAI test was completed by participants based on how they felt in the prior two weeks, not necessarily at the time of data acquisition. Stress and anxiety are time sensitive and therefore, it can be stipulated that any variations in brain signals would also be sensitive to acute responses. Consequently, drawing conclusions and applying it to peak conditions of high cortisol inducing situations may not be representative. In addition, diagnostic clinical depression and a depressed mood may be difficult for a person to differentiate themselves. Database scores indicating high depression may be inflated due to subjective measures giving rise to why large datasets are useful here. There were interviews conducted with some individuals to perform a cross sectional validation of the psychological test scores. In conclusion, it is important to consider that analyzing and classifying the EEG signals is only as accurate as the psychological test scores.

4.6 Future Work

For this research with the objective of identifying biomarkers in EEG signals, specific analysis techniques were iterated and chosen. However, there exist numerous other signal analysis algorithms which can be applied to a database for processing. To optimize prediction and classification accuracy, future analysis could incorporate other methodologies. k fold validation evaluates machine learning models on a selected subset of data (Wong & Yeh, 2020). ‘k’ indicates the number of groups on

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which the data is validated against. Larger k values will increase the computational time. In this study, a permutation function was used to randomly train the model on 70 % of the data and test it on 30%, however a 5-fold validation can be implemented to verify whether the accuracy can be improved. Independent and identically distributed (IID) analysis is an unsupervised learning technique where each variable has the same probability distribution but is independent of each other. This method is commonly implemented in EEG signal analysis when evaluating mental state as it is transient. The cognitive activities performed during signal acquisition are lengthy and if participants become distracted, it could result in mislabeling of the dataset. The flaw of classic machine learning is that it relies on the accuracy of the labels and as well, throughout the study, the noise parameters may also change. (Görnitz and colleagues (2014) proposed a 4-step method for labeling data based on non-IID analysis. IID could be implemented on this database consisting of participants with depression and anxiety to verify the label accuracy while ensuring higher certainty at later stages of analysis. This additional analysis would help to validate the objective of this research of delineating the presence of depression compared to psychological evaluations.

Increased research investigating numerical features to detect mood and anxiety disorders will allow for the selection of the most optimal algorithms for diagnosis to be used in conjunction with visualization and classification techniques. With increased data acquired from varying conditions, specific features can be identified as evidential markers of a mental illness diagnosis.

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5. Conclusion

The objective of neurophysiological signal analysis is to be able to diagnose mood disorders and anxiety through signal detection techniques more accurately than subjective psychological tests. To date, there is a decade of research on signal analysis heterogeneity between unaffected individuals and those with mood disorders. Implementing the findings for use in patient diagnosis will require more research that is consistent, reproducible, and reliable. The features should be extracted from signals where people perform the same task and from comparable components of the signal to produce consistent results. It is not a simple objective as there are many decomposition methods, features and classifiers that can be evaluated. External factors must be controlled. External factors that may impact the signals could include age, gender, prescribed medication, recreational drug use, comorbidity, etc. Signal analysis depends on computer processing capacities. Reducing the time of analysis coupled with the progress/development of hardware devices to be used in clinical settings is also a key advancement that must be established prior to effective clinical use. In addition, the protocol for acquisition of signals should be standardized. Despite the persons' state, signal feature extraction for diagnosis must be validated. My research demonstrates that during a probabilistic learning task, discriminatory features were identifiable in the signals. Understanding the biomarkers of mood disorders in the brain and how and when different individuals present these symptoms can provide input for the development of treatment methods.

My hope for the outcome of this thesis along with other research findings is that it will contribute to psychiatric diagnosis of mood and other disorders. Ideally in the future, there will be accessible commercial devices available to the public with built in software programs including feature selection, classification and visual outputs of heat maps that provide the user with a diagnosis based on how their results compare to a large database. In the next decade there will be increased data acquisition leading to the development of a database that can be used for prediction, training, testing and validation.

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Greater support is needed for people with mood and anxiety disorders. Healthcare resources are limited, and it is dangerous for someone with a severe mood disorder to be waiting for months on end for medical care. There is a need for enhanced, widespread technology for accurate diagnosis, monitoring, and eventually, neurofeedback that can provide treatment prediction and outcome. This research is not only intended for those with severe mood disorders, but also those afflicted by mild depression and anxiety as even monitoring small fluctuations can be helpful. Having answers and a diagnosis can alleviate stress associated with a lack of understanding of oneself and emotions. In addition, by quantifying qualitative findings, I hope to contribute to eliminating stigma, doubt and judgement often associated with mood disorders.

I am grateful for the opportunity to conduct this research and to have had access to over 100 individuals' EEG data. I had the opportunity to perform biomedical signal analysis and came to appreciate its algorithmic complexities.

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