# EFFECTIVE CONNECTIVITY MODEL DIFFERENCES OF EMOTION REGULATION IN MAJOR DEPRESSIVE DISORDER: DYNAMIC CAUSAL MODELING ANALYSIS

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF INFORMATICS OF
THE MIDDLE EAST TECHNICAL UNIVERSITY
BY

MUSTAFA ÖZAYDIN

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

IN

THE DEPARTMENT OF COGNITIVE SCIENCE

SEPTEMBER 2021

**EFFECTIVE CONNECTIVITY MODEL DIFFERENCES OF EMOTION REGULATION IN MAJOR DEPRESSIVE DISORDER: DYNAMIC CAUSAL MODELING ANALYSIS**

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**I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.**

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## ABSTRACT

EFFECTIVE CONNECTIVITY MODEL DIFFERENCES OF EMOTION REGULATION IN MAJOR DEPRESSIVE DISORDER: DYNAMIC CAUSAL MODELING ANALYSIS

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September 2021, 47 pages

Major Depressive Disorder (MDD) is a mental disorder and one of the most critical and prevalent disorders in the world. Unlike other diseases, the diagnosis of mental disorders does not easily conform to objective tests. Medical experts consider several indicators to be able to distinguish a depressed person from a normal individual, and finding robust markers to aid diagnosis is still an active area of research. The recent proliferation of neuroimaging methods has brought up new opportunities in that regard. This study aims to contribute to these efforts by investigating the utility of Dynamic Causal Modeling (DCM) based effective connectivity measures for distinguishing MDD patients and healthy controls based on their responses to emotional stimuli. The analysis was conducted over an open fMRI dataset, including the brain responses of MDD patients and healthy controls to an emotional musical stimuli task. The results of the DCM effective connectivity model reveal an increasing sgACC to Amygdala connectivity and reduced dlPFC to Amygdala connectivity in the healthy controls compared to MDD patients. Thus, the findings of this study suggest that such differences in effective connectivity patterns in response to emotional stimuli can be useful in distinguishing MDD cases from healthy subjects.



Keywords: Major Depressive Disorder, effective connectivity, fMRI, Dynamic Causal Modeling

# ÖZ

MAJÖR DEPRESİF BOZUKLUKTA DUYGU DÜZENLEME FARKLARINA YÖNELİK ETKİLİ BAĞLANTI MODELİ: DİNAMİK NEDENSEL MODELLEME ANALİZİ

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Eylül 2021, 47 sayfa

Majör Depresif Bozukluk (MDB) ruhsal bir bozukluktur ve dünyada görülen en kritik ve yaygın rahatsızlıklardan biridir. Diğer hastalıklardan farklı olarak ruhsal bozuklukların teşhisi objektif testlerle doğrulanmamaktadır. Depresyonda olan bir kişiyi, normal bir bireyden yalnızca alanda uzmanlaşmış kişiler ayırabilmektedir. Ancak beyin aktivitesindeki ve beyin bölgeleri arasındaki bağlantılardaki farklılıklar beyin görüntüleme teknikleri ile gözlemlenebilmektedir. Bu çalışmada, Dinamik Nedensel Modelleme (DCM) yöntemi ile bir fMRI verisindeki etkin bağlantı nöral modelleri test edilmiştir. fMRI verileri duygusal müzikal uyaranları kullanılarak MDB hastalarından ve sağlıklı bireylerden toplanmıştır. DCM etkin bağlantı modelinin sonuçlarına göre, MDB hastalarına kıyasla sağlıklı bireylerde artış gösteren bir sgACC - Amigdala bağlantısı ve azalan bir dlPFC - Amigdala bağlantısı bulunmuştur. Elde edilen sonuçlarla bu çalışma, duygusal uyaranları işleyen nöral yollardaki farklılıklara dayanarak MDB hastalarının sağlıklı bireylerden ayırt edilmesi için faydalı bilgiler elde edilebileceğine işaret etmektedir.

Anahtar Sözcükler: Majör Depresif Bozukluk, etkin bağlantı, fMRI, Dinamik Nedensel Modelleme

*To my family and my beloved wife*

## ACKNOWLEDGMENTS

First of all, I would like to express my sincere gratitude to my supervisor Assist. Prof. Dr. Murat Perit Çakır for his guidance, support, suggestions, and incredible patience during the Covid-19 pandemic throughout this thesis. He always encouraged me with his positivity when I felt desperate. I was very lucky to have him as my mentor.

I am also incredibly grateful to Assist. Prof. Dr. Burcu Ayşen Ürgen with her critical guidance when I couldn't easily progress with my thesis. I would also like to thank Assoc. Prof. Dr. Cengiz Acartürk for his very useful comments.

Moreover, I would like to thank my family and my beloved wife for their endless support. Making them proud was my biggest motivation in this process.

And lastly, many more thanks to Gülşah Kurt, Ozan Bıçakcı, Ahmet Furkan Özkan, Furkan Dinçel, Salih Fırat Canpolat, Elis Güngör, Utku Baydan, Simla Kötüz Çiftcioğlu, Melek Sak, Ahmet Tıraş, Gökalp Doğukan Demirbaş, who were by my side and supported me throughout this thesis process.

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| | |
|---|---|
| **ACC** | Anterior Cingulate Cortex |
| **AFNI** | Analysis of Functional NeuroImages |
| **ANOVA** | Analysis of Variance |
| **BA** | Brodmann areas |
| **BDI** | Beck Depression Inventory |
| **BMA** | Bayesian Model Averaging |
| **BMR** | Bayesian Model Reduction |
| **DCM** | Dynamic Causal Modeling |
| **DLPFC** | Dorso-Lateral Pre-Frontal Cortex |
| **DMPFC** | Dorso-Medial Pre-Frontal Cortex |
| **DTI** | Diffusion Tensor Imaging |
| **EEG** | Electro-Encephalography |
| **FFX** | Fixed Effects Analysis |
| **fMRI** | Functional Magnetic Resonance Imaging |
| **fNIRS** | Functional Near-Infrared Spectroscopy |
| **FWE** | Family-wise Error |
| **FWHM** | Full Width at Half Maximum |
| **GLM** | General Linear Model |
| **MDD** | Major Depressive Disorder |
| **MNI** | Montreal Neurological Institute |
| **ND** | Never-depressed |
| **OFC** | Orbito-Frontal Cortex |
| **PEB** | Parametric Empirical Bayes |
| **PFC** | Prefrontal cortex |
| **PPI** | psycho-physiological interactions |
| **rfMRI** | resting-state fMRI |
| **RFX** | Random Effects Analysis |
| **ROI** | Region of Interest |
| **rACC** | Rostral Anterior Cingulate Cortex |
| **SEM** | Structural equation models |
| **sMRI** | Structural Magnetic Resonance Imaging |
| **sgACC** | Subgenual Anterior Cingulate Cortex |
| **SPM** | Statistical Parametric Mapping |
| **TR** | Repetition time |
| **vACC** | Ventral Anterior Cingulate Cortex |

# CHAPTER 1

## INTRODUCTION

In today's world, depression (also referred to as Major Depressive Disorder or MDD) is one of the most critical and prevalent disorders in the world, according to the World Health Organization. MDD, usually seen in young adults, is prevalent in 13.1% of individuals aged 18-25 years and 7.7% of individuals aged 26-49 years (The National Institute of Mental Health, 2018). MDD is defined as a mental disorder caused by biological, environmental, and genetic factors. It is related to emotional irregularities, loss of energy or interest, and low self-esteem, according to the Diagnostic and statistical manual of mental disorders – DSM (5th ed.) (American Psychiatric Association, 2013). Such symptoms cause severe problems in a person's daily life, work-life, and social relationships. One of the most critical symptoms of depression is thoughts of death and suicide. Although it is a disorder related to the mind, due to these symptoms, MDD causes an increased rate of morbidity and mortality. In up to 8% of MDD cases, depression leads the patient to commit suicide (Strakowski & Nelson, 2015). Thus, depression requires special attention.

Unlike other physical or neurological diseases, the diagnosis of mental disorders does not conform to objective tests like a blood test or brain imaging. Diagnosis of MDD is based on the specified diagnostics criteria in the DSM (American Psychiatric Association, 2013) and mental health professionals' evaluation of symptoms. However, according to Regier et al. (2013), the inter-rater reliability of MDD diagnoses is questionable (Kappa coefficient = 0.25). After being diagnosed by mental health professionals, the treatment process begins. Treatment of MDD commonly relies on antidepressant drug therapy and psychotherapy. It is known that psychotherapy is more effective than medication in the long term but using both is accepted as the most effective way to treat MDD (Brownawell & Kelley, 2011). However, psychotherapy is not an affordable option in Turkey, especially for people with low or middle income. Hence, antidepressants are preferred for the treatment. On the other hand, MDD has a broad spectrum in its effects, and each individual suffers from these effects at different levels. The level of the disorder is difficult to determine only by listening to the client's history. Also, since the treatment requires long-term use, and the rate of maintaining adherence to antidepressants is low (Martin-

Vazquez, 2016). Therefore, in most cases, antidepressants were unsuccessful. In order to eliminate these problems, the precise diagnosis of the disorder is of great importance.

Like other mental disorders, MDD is related to abnormalities in the brain. Therefore, exploring these abnormalities is crucial when studying MDD. Neuroimaging studies show that brain abnormalities related to MDD can be observed through emotional regulation processing of the brain. Dealing with emotion recognition tasks causes different brain activation patterns across specific brain areas in depressed patients than never-depressed healthy controls. In the literature, such differences in brain activation patterns are usually attributed to MDD patients' negative perceptions of their environment, which is called the *negativity bias* (Bouhuys, Geerts, & Gordijn, 1999; Gur et al., 1992). Most of the studies use emotional tasks to enhance or reduce the activities in the brain related to depression. These activations are generally observed in several brain regions, including the prefrontal and cingulate cortex, hippocampus, striatum, Amygdala, and thalamus (Nestler et al., 2002). However, the findings obtained from neuroimaging studies may not have the methodological power to make causal interpretations about the changes in the brain. Instead, they only show the statistical differences or relations in related brain areas. Although the findings in these studies provide valuable insights about neural correlates of depression, they are not sufficient to understand the processes underlying MDD because they do not explicitly focus on how different brain regions affect each other. In order to overcome this situation, connectivity analysis is one of the methods that can be used.

Neural activity can be examined in two ways: functional segregation and functional integration (Friston, 1994). Functional segregation depends on spatially distributed brain regions as distinct processing modules. However, this approach does not consider the degree of communication between different brain regions/modules. On the other hand, the functional integration approach investigates the information transfer between different brain regions. Connectivity analyses rely on the functional integration approach, where the focus is on examining the changes in the relationships among brain regions due to experimental stimuli. In the last two decades, connectivity analyses have attracted interest due to their potential for developing and evaluating inferences about how the brain works (Friston, 2011; Kahan & Foltynie, 2013). Especially the findings from studies focusing on connectivity models of MDD patients have provided important insights into how MDD patients may differ from healthy controls (Cheng et al., 2018; Goulden et al., 2012; Musgrove et al., 2015; Perlman et al., 2012; Schlösser et al., 2008; Wenjie et al., 2016).

The aim of this study is to create an effective connectivity model based on an open-access fMRI dataset by Lepping et al. (2016). This connectivity model is intended to contribute to the findings of this study by exploring whether MDD patients and healthy control subjects exhibit distinguishable connectivity profiles in response to emotional stimuli.

In the first part of the thesis, a review of related literature and the goals and motivations of the study will be provided. In this part, firstly, the neurobiology of depression was investigated for a better understanding of MDD. After that, the connectivity studies and how they should be studies were investigated. With the guideline of these information,

current limitations and the purpose of this study will be given. Following that, the materials and methods employed in the study will be introduced. Lastly, the results and a discussion of the main findings will be presented.

# CHAPTER 2

# LITERATURE REVIEW

## 2.1. Neurobiology of Depression

Even if symptoms and causes can be examined from behavioral and environmental aspects, mental disorders, especially MDD, are also physically related to brain dysfunctions. Many studies have been conducted to identify the differences between depressed patients and healthy controls in terms of their brain activity. Such efforts mainly focused on the emotion regulation processes in the brain to identify neural correlates of MDD (Fitzgerald, Laird, Maller, & Daskalakis, 2008; Rive, et al., 2013). However, the lack of consistency of emotional tasks and the neuroimaging methods used to detect depression makes it difficult to conduct replication studies and thus reduces the reliability of the findings (Juckel, 2013; Rive et al., 2013; Won & Kim, 2018). According to a meta-analysis on neuroimaging-based biomarkers of depression, MDD patients were distinguished from healthy individuals with 77% sensitivity and 78% specificity based on data from various neuroimaging modalities such as functional magnetic resonance imaging (fMRI), resting-state fMRI (rfMRI), diffusion tensor imaging (DTI) and structural magnetic resonance imaging (sMRI) (Kambeitz et al., 2017). Although these accuracy rates indicate a distinction between depressed and healthy brains, they are not considered strong enough to inform clinical practice (Won & Kim, 2018).

Furthermore, Phillips and his colleagues (2008) proposed a neural model to describe the emotion regulation system in the brain. This model has also targeted psychiatric disorders that have problems in emotion regulation, such as MDD, bipolar disorder, and schizophrenia. Emotion regulation is defined as how one experiences, expresses, and regulates his/her emotions (Gross, 1998). On the other side, emotion dysregulation is defined as poorly modulated emotional responses that are not within the range of accepted emotional responses, which is one of the most prominent features of MDD (Ochsner & Gross, 2007). This neural model divides brain functions into two categories, which are based on the ventral and dorsal systems. The ventral system includes the Amygdala,

insula, ventral anterior cingulate gyrus, ventromedial prefrontal cortex (PFC), medial orbitofrontal cortex, whereas the dorsal system includes the hippocampus, dorsal anterior cingulate gyrus, and dorsal PFC. The ventral system is related to an automatically generated emotional state, and the dorsal system is related to a voluntarily generated emotional state. Phillips et al. (2008) divided emotion regulation into six psychological subprocesses by combining emotion regulation strategies (behavioral, attentional, and cognitive processes) with automatic and voluntary systems. In order to assess each emotion regulation subprocesses, different emotional tasks were used. Processes in which a person is not directly aware of the emotional stimulus are considered automatic. In voluntary processes, however, the emotional stimulus is the main focus of the task, and there is an effortful attempt to regulate emotion.

Rive and her colleagues (2013) conducted a systematic review of this emotion regulation model to find its neural correlates in MDD. According to the results, significant differences between MDD patients and healthy people were primarily seen in automatic regulation paradigms. Differences were found in the ventral tegmental area during automatic behavioral control, the parietal and lateral PFC during automatic attentional control, and dorsolateral PFC & ventrolateral PFC during automatic cognitive control. Also, significant connectivity results were found in Amygdala, PFC, OFC, ACC (Carballedo et al., 2011), and sgACC (Ho et al., 2014; Perlman et al., 2012) during emotional information processing.

This systematic review argued about several methodological limitations of studies that aimed to determine neural correlates of MDD. These limitations were basically stated as small sample sizes, medication use, comorbidity, depression severity, different task designs and different data analysis strategies. Considering these limitations, Rive and her colleagues suggested using unmedicated MDD patients and focusing on brain networks instead of distinct brain regions in future studies.

It is important to note that these results were found between medicated MDD patients and healthy controls. However, the lateral prefrontal hyperactivity, which is mainly observed in automatic cognitive control tasks, was found in both medicated and unmedicated MDD patients (Grimm et al., 2008; Rosenblau et al., 2012). Consequently, this difference does not seem to arise from drug use, but due to the pathophysiology of MDD.

In addition to emotional information processing, Schmaal et al. (2016) conducted a large-scale study including 1728 MDD patients and 7199 healthy controls from 15 research samples worldwide. The study investigated MRI images to identify differences in subcortical brain volumes, currently offering the best available empirical evidence focusing on structural brain volume changes in MDD. In their univariate analyses, only hippocampal volume was found to be significantly decreased in MDD (Cohen's d of 0.17). On the other hand, the classification accuracy of this result was found to be 52%, which is slightly above chance (Fried & Kievit, 2016). Therefore, the structural brain volume differences among MDD patients and healthy controls that can be measured with the

current state-of-the-art neuroimaging techniques have not yet provided clinically significant differences.

To conclude, focusing on brain activities during specific emotional tasks is considered a more promising approach rather than focusing on differences in brain structures. In other words, emotional information processing has a critical role that can show neural abnormalities in depression and therefore needs to be considered when examining the neurobiology of depression.

### 2.2. Connectivity Approaches in Depression Neurobiology

Although there are significant neurobiological differences between depressive patients and healthy individuals in the literature, these results are generally inconsistent. Different levels of MDD make it difficult to differentiate depressive patients from healthy people. In addition, the tasks used to observe depression are often different from each other, and each different task is directed towards a different neurological structure of depression. Also, most studies use small samples for traditional statistical methods. This reduces the effect size and the generalizability of the findings. The inconsistencies between the results are mostly due to such limitations. In order to eliminate these limitations, more robust connectivity analysis methods should be used.

Connectivity analyses use different methods such as structural connectivity (used mostly in structural neuroimaging studies), functional connectivity, and effective connectivity (used mostly in functional neuroimaging studies). Functional connectivity describes statistical dependencies between different brain regions. In this method, the correlations between different brain regions' neural activity are typically examined. On the other hand, effective connectivity describes the causal influence of one brain region over another. Therefore, effective connectivity methods can give more interpretable results (Friston, 2009).

There are several algorithms for computing effective connectivity, such as psycho-physiological interactions (PPI), structural equation models (SEM), and dynamic causal models (DCM). According to Friston and his colleagues (2011), DCM has advantages over other methods with more robust results and the ability to test connectivity direction while avoiding some of the limitations of other methods.

In the current literature, many studies have previously been conducted to explore the connectivity among different regions in the brain during an emotional processing task. Although the vast majority of these studies were not conducted with depressed people, they are helpful in identifying the emotion regulation pathways in healthy people. Previous studies reported a significant level of functional connectivity among the Amygdala (as a seed region) and the prefrontal cortex (dorsolateral, dorsal medial, anterior cingulate, orbital) in emotion regulation tasks (Banks, Eddy, Angstadt, Nathan, & Luan Phan, 2007; Wenjie et al., 2016).

Studies with MDD patients also found significant connectivity pathways. Almost all of the studies use Amygdala as a central region of connectivity models. Cheng and her colleagues (2018) found that the Amygdala region had inhibitory functional connectivity with the OFC and temporal lobe areas. Moreover, Carballedo et al. (2011) found significant functional connectivity in Amygdala, OFC, ACC and PFC. They found a lower level of connectivity in patients compared to controls from Amygdala to OFC, and a higher level of connectivity from PFC to OFC. Also, a significantly lower degree of connectivity was observed in patients along the pathways from the right Amygdala to ACC and from the ACC to PFC. Lastly, significantly lower connectivity was found in controls for the pathway from the ACC to Amygdala (Carballedo et al., 2011).

In addition to functional connectivity, there are various studies examining effective connectivity in depression with the DCM method. A study that uses DCM found no significant differences among the depressed patients and controls with effective connectivity pathways of dorsal ACC and dlPFC regions (Schlösser et al., 2008). However, Schlösser et al. did not use an emotional task; instead, they used a Stroop Color-Word Test.

Another study that used DCM, focusing on emotional labeling of happy and sad faces, significant differences were found between control and depressed subjects (Almeida et al., 2009). Effective connectivity of the left orbitomedial prefrontal cortex and the left Amygdala was found to be different among MDD and control groups in this study. In another study that used the emotion face matching paradigm, it was found that depressed subjects had significantly weaker effective connectivity from Amygdala to sgACC (Musgrove et al., 2015).

### 2.3. Negativity Bias in Depression

In his depression theory, Beck defines one of the most critical symptoms of MDD as the negative view of one's self and his/her environment (Beck, 1967). Moreover, the vast majority of our interactions with our environment are social relationships. Social interactions include facial expressions that are a powerful non-verbal way of reflecting emotions. This negativity in depression can lead to a negative perception of facial expressions and may cause people with depression to misjudge facial emotions. Studies show that depressed people are more likely to categorize neutral or ambiguous facial expressions as sad than healthy people (Gollan, Pane, McCloskey, & Coccaro, 2008; Ito et al., 2017). Also, depressed people have significantly lower valence rating scores when evaluating sad faces, and they had slower responses for neutral and happy facial expressions (Dai, Wei, Shu, & Feng, 2016). In another study, it was found that the intensity of the expression should be greater in order for depressed patients to evaluate a happy facial expression as happy. It was also found that MDD related negativity bias in facial emotion perception reflects the current state of MDD instead of a stable depressive trait (Münkler, Rothkirch, Dalati, Schmack, & Sterzer, 2015). These studies provided important empirical evidence for the strong effect of negativity bias on depressed patients.

Consequently, detecting the negativity bias has an essential role in the diagnosis stage of depression.

The negativity bias is often used in the literature with various tasks such as using emotional faces, emotional words, or emotional pictures. Groenewold and her colleagues (2013) conducted a meta-analysis of neuroimaging studies investigating emotion processing in MDD. They examined fMRI studies which use positive, neutral, and negative emotions on facial or non-facial visual stimuli as an emotional processing task. According to their results based on 44 studies, depressed patients display hyperactivity in the Amygdala, striatum, anterior cingulate cortex when processing negative stimuli and hypoactivity in the same areas when processing positive stimuli. Also, it was found that depressed patients display hypoactivity in the left dorsolateral PFC when processing negative stimuli and hyperactivity in the orbitofrontal cortex when processing positive stimuli. The authors also made a follow-up analysis by separating facial and non-facial data to eliminate task-specific effects. This separation leads to a result in which depressed patients showed increased activation in the pregenual anterior cingulate cortex during the processing of facial stimuli and decreased activation during the processing of non-facial stimuli.

In conclusion, the negativity bias is frequently used in classification studies because of its ability to highlight brain abnormalities in depressed patients. Neuroimaging studies using negativity bias have shown significant findings. However, many studies use standard group comparison statistics. Although these methods give insightful information about the activities and connections in the brain, they lack the prediction ability to make causal interpretations about the results. Like the famous quote, “Correlation does not mean causation”, findings acquired from these methods do not have the power of causation. Therefore, there is a need for more robust computational tools such as connectivity analysis to explore the neural mechanisms underlying depression.

### 2.4. Current Limitations in The Related Literature

The meta-analyses reviewed have identified several limitations that are common to several studies in the related literature on MDD. The first and foremost limitation is the issue of medication use. It is known that pharmacological treatment methods change the neuromolecular activities (Barsaglini, Sartori, Benetti, Pettersson-Yeo, & Mechelli, 2014), and when compared to psychotherapy, more substantial changes are observed in pharmacotherapy (Boccia, Piccardi, & Guariglia, 2016). Therefore, it is essential to use unmedicated participants or separate medicated and unmedicated participants from patient and control groups.

Clinical variables such as gender, age at onset, and duration of illness are also often neglected in many studies. When the blood oxygen level-dependent fMRI activities of facial emotion processing were examined, it was found that the frontal and temporal areas of female MDD patients were generally more hyperactive (Jenkins et al., 2018). Also, significant differences were found between early-onset and late-onset in terms of brain

volumes (Kemp et al., 2013; Usher, Leucht, Falkai, & Scherk, 2010). Furthermore, the symptoms and brain activities of a patient who has just started taking medication and a patient who has been taking medication for a long time will differ (Kim & Na, 2018). Thus, clinical variables have effects on structural brain abnormalities and should be considered.

It was also noted that MDD has many comorbidities, such as anxiety disorders, bipolar disorder, substance use disorder, and post-traumatic stress disorders. Due to these different disorders that overlap with MDD, exploring MDD and different patient groups rather than distinguishing the MDD group and healthy controls were suggested (Kambeitz et al., 2017). However, since it is expensive and difficult to find volunteer participants from each patient group, there has been little progress in this area.

Different neuroimaging modalities have been used in the studies conducted to determine the neurological biomarkers of MDD, such as fMRI, rfMRI, DTI, and sMRI. Although these methods give significant results, they are expensive compared to self-assessment questionnaires. The accuracy levels of self-assessment questionnaires (~80% according to Aalto, Elovainio, Kivimäki, Uutela, & Pirkola, 2012) are close to the accuracy levels of MDD neuroimaging studies (~75% according to Kambeitz et al., 2017). However, neuroimaging studies give considerable additional data about the brain. In order to use such methods in clinical practice and eliminate their disadvantage in cost-effectiveness, it is important to extract more information from these data.

### 2.5. Purpose of this study

The main purpose of this study is to try to explore if MDD patients can be distinguished from healthy individuals by comparing their effective brain connectivity models by using the Dynamic Causal Modeling (DCM) method with Parametric Empirical Bayes (PEB) approach. This dataset was contributed to the open-fMRI repository by Lepping and her colleagues (2016). In the original study, Lepping et al. employed the emotional musical and nonmusical stimuli task to explore the differences between MDD and healthy controls. Although the study focused on the comparison of MDD and healthy controls, the authors only investigated differences among the activation maps of the brain. Therefore, the main contribution of this thesis study will be to improve upon Lepping et al.'s results by investigating the discriminative significance of contrasting the effective connectivity models of MDD and healthy controls based on DCM. In other words, the current study tests the hypothesis that whether an effective connectivity model can distinguish MDD cases from healthy subjects based on the differences in neural pathways processing emotional stimuli.

# CHAPTER 3

# MATERIALS and METHODS

## 3.1. Data

The data used in this study is an open-access fMRI dataset contributed by Lepping et al. (2016) to the Open Neuro repository (https://openneuro.org/datasets/ds000171/versions/00001). All subjects went through one fMRI session with five different functional runs and an anatomical scan. Anatomical images were high-resolution T1-weighted images with 2300 ms repetition time (TR). Functional images were acquired with five gradient echo blood oxygen level-dependent (BOLD) sequences with 50 interleaved oblique axial slices (TR = 3000 ms, echo time = 25 ms, 105 data points for each run). The data is retrieved as unprocessed, raw data and arranged by Brain Imaging Data Structure (BIDS) standards. Further details about the dataset can be found in Lepping et al. (2016).

In this study, 20 never-depressed (ND) control subjects and 19 MDD patients' fMRI scans were collected. ND subjects were chosen among volunteers who had no history of depression or any other psychological disorder and had Beck Depression Inventory (BDI) scores below 18. The ND group included 9 males and 11 females, with an average age of 28.50 (*SD*=11.14, *Range*= 18-59). The MDD subjects were unmedicated and currently experiencing depressive symptoms. They had no manic episodes or anxiety that showed comorbidity. The MDD patients' mean age was 33.53 (*SD*=13.72, *Range*= 18-56) and consisted of 8 males and 11 females. All subjects were right-handed. No significant differences were found between their age, education, and years of musical training, $p > .05$.

In fMRI scanning sessions, subjects listened to emotional (positive and negative) musical and nonmusical (sound) stimuli. In the functional runs of the data, subjects listened to positive music, negative music, positive non-music, negative non-music, and neutral tones

(as a baseline). In 3 of these 5 different functional runs, the subjects listened to positive and negative music, while in 2 of them, they listened to positive and negative sounds (non-music). The stimuli were presented to each participant in counterbalanced order to mitigate any ordering effects. In each run, some subjects first listened to positive stimuli and some of them first listened to negative stimuli. The stimulus type was also counterbalanced, where some subjects first listened to 3 runs with a musical stimulus, while others started with 2 runs of sound stimulus first. After each emotional stimulus, subjects gave a response for the emotional valence and arousal level of that stimuli. In each run, all subjects listened to neutral tones after positive or negative stimuli in order to neutralize the effect of the emotional valence of stimuli. An example functional run taken from the original study can be seen in Figure 1.

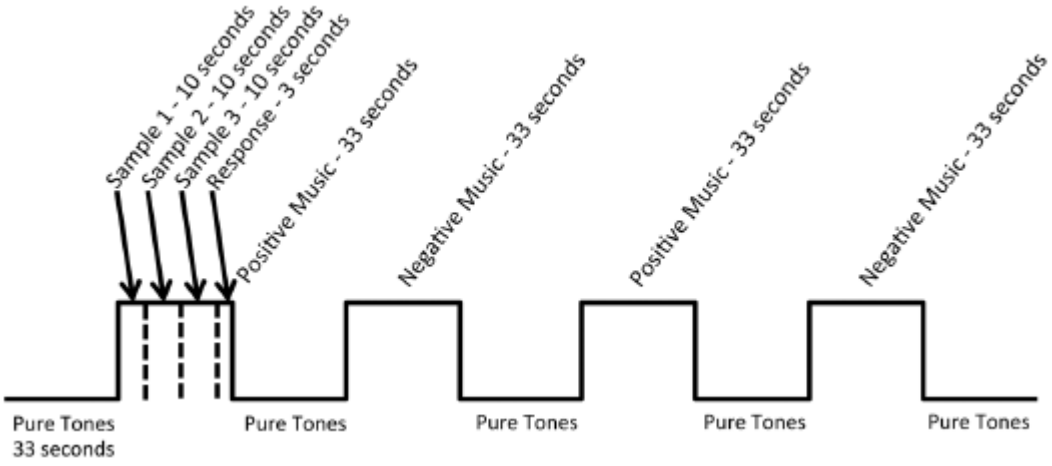


*Figure 1.* Example functional run with musical stimuli (Positive first)

Lepping and her colleagues (2016) first preprocessed the collected raw fMRI data with Analysis of Functional NeuroImages (AFNI) statistical package. The preprocessing of the data included motion correction, smoothing, resampling, realignment of the anatomical and functional images, and normalization.

After preprocessing steps, they analyzed the activation maps of the functional data with statistical parametric methods. They investigated the main effect of valence (positive-negative stimuli), the main effect of stimulus type (musical-nonmusical), and the interaction effect of valence and stimulus type in ND subjects with whole brain and region of interest (ROI) analysis. Also, these analyses were conducted in order to compare MDD and ND subjects. In their study, they focused on the anterior cingulate cortex (ACC) and striatum. Therefore, the authors created an ROI mask with those brain regions (ACC/striatum) which are anatomically defined in Talairach template masks.

After these analyzes, Lepping and her colleagues found significant differences in whole-brain activations of ND subjects with both main effects (valence and stimulus type). Although there are significant interaction effects of valence and stimulus type in whole-brain activations of ND subjects, these results were found in the auditory cortex rather

than the brain areas related to the emotional process. Also, within the ACC/striatum ROI mask, they found significant differences of positive and negative stimuli in ventral ACC (vACC) and subgenual ACC (sgACC).

Whole-brain comparison results of MDD and ND subjects revealed that there were no significant differences of group by valence (2x2) interaction effect. However, they found a significant interaction effect of group by stimulus type (2x2) in ACC and dlPFC areas. Also, no significant interaction effect of group by valence by stimulus type (2x2x2) was found in whole-brain analysis.

Lepping et al. (2016) found significant differences in ROI analysis for the interaction effect of group and valence. These differences were found in sgACC and rostral ACC (rACC) areas. It was found that in these areas, MDD and ND subjects show significantly different BOLD activations. ND subjects show more activations in positive>baseline contrast than MDD subjects in sgACC and rACC. However, no difference was found between groups in negative>baseline contrast.

### 3.2. Preprocessing

In this thesis study, MATLAB R2020b and Statistical Parametric Mapping (SPM) software were used to analyze the fMRI data. Since the data analysis was initiated with the raw fMRI data, necessary preprocessing steps were planned and conducted. The preprocessing pipeline includes realignment, slice-timing correction, coregistration, segmentation, normalization, and smoothing steps, respectively.

The realignment step consists of estimate and reslice operations, estimating how much alignment change occurs in each volume and reslicing each volume (105 volumes for each run) into alignment. In the estimation step, the estimation quality was set to 0.9 out of 1, which refers to higher quality, and more voxels were selected for the realignment process. The resampling distance for the reference mean volume was set to 2.5 mm. After the transformation parameters were estimated, images were realigned (reslice) to the mean image. 4th-degree B-Spline interpolation method was used in this reslicing procedure. An example result of a realignment step for the first functional run of the first participant in the ND group can be seen in Figure 2.

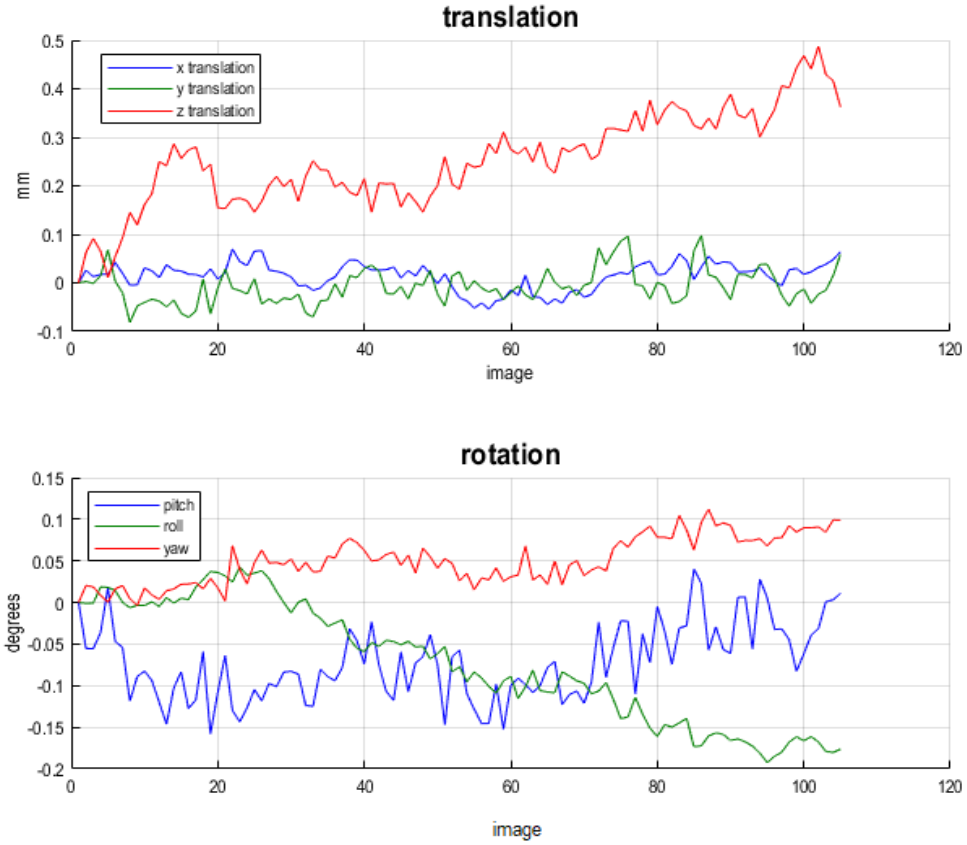


*Figure 2.* The realignment preprocessing step results of the first run of the first ND participant that show translation and rotation amounts in mm.

Since the time series of the data is critical for creating a model, the slice-timing correction has to be done. There were 50 slices in each volume with a TR of 3 seconds. Slice-timing values were provided by the owners of the data (Lepping et al., 2016).

In order to ensure that each subjects' functional images were aligned to their anatomical images, coregistration was done. Also, a segmentation step was performed on anatomical images to align different tissue types with a more precise normalization step. Normalization of the data was done with 2x2x2 voxel resolution to get a higher resolution of the data.

Lastly, smoothing was performed to eliminate any noise or other signal artifacts. 4 mm Full Width at Half Maximum (FWHM) Gaussian smoothing kernel is used for smoothing. An example illustrating the functional images of smoothing can be seen in Figure 3.

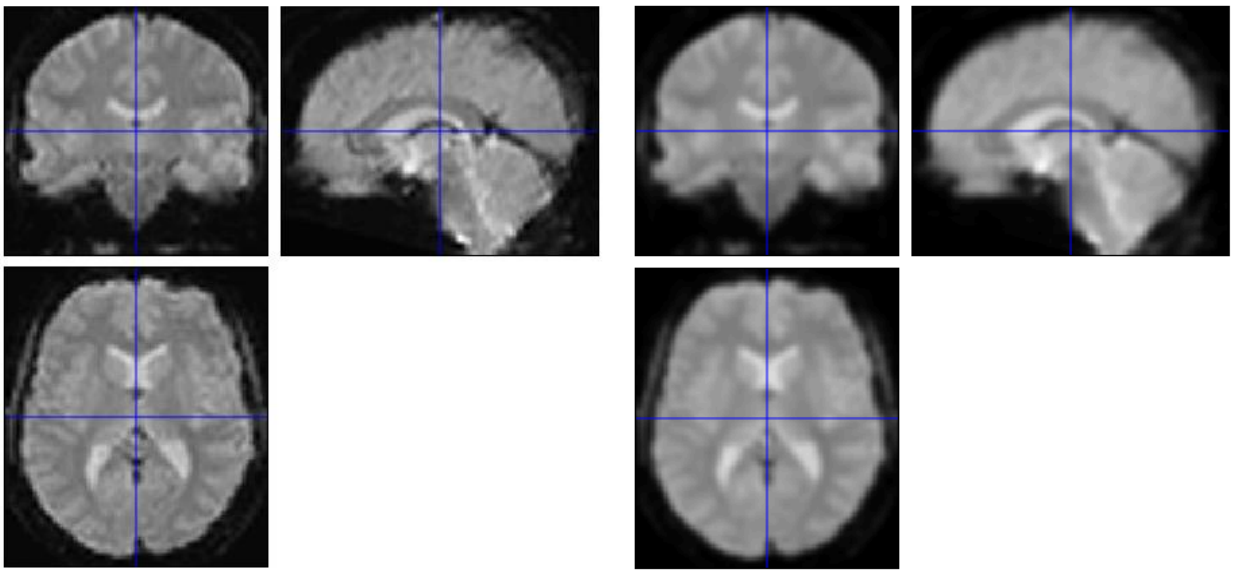

*Figure 3.* Smoothing preprocessing step results of the first ND participant's first functional volume that show before (left) and after (right) smoothing.

### 3.3. First Level (Within-Subject) General Linear Model Analysis

After the preprocessing steps were complete, each subject's functional data were fitted into first-level general linear model (GLM) to specify and estimate the conditions of the data on each participant. Parameters of each BOLD data were convolved with the canonical hemodynamic response function with 128 seconds high-pass filter cut-off. There were five different functional runs in each experiment, but in order to make it easier to extract the time series data of each participant, these five runs were combined (concatenated) into a single dataset. The counterbalanced functional runs were re-ordered before concatenation to ensure that each participant's time-series data reflected the same order of conditions. Each functional run has 105 volumes with a TR of 3 seconds, spanning a total time period of 315 seconds. The onsets and durations of 5 different conditions (positive music, negative music, positive non-music, negative non-music, neutral tones) were provided by Lepping et al. (2016). According to the provided information, a functional run consisted of 5 neutral tones, where the first of one lasted 33 seconds and the others lasted 31.5 seconds. Similarly, emotional musical or nonmusical stimuli lasted for 31.5 seconds. Onsets of the conditions, however, were changed when combining all runs into one. Since each run lasted 315 seconds total, onset times of each run were summed with multiples of 315 (0, 315, 630, 945, 1260). An example addition for onset times of emotional stimuli was shown in table 1.

*Table 1.* Example change in emotional stimuli onset times of first ND participant

| Functional runs | Emotional stimuli | Original onset times | Addition | Final onset times |
|---|---|---|---|---|
| 1. Run | Positive music | 105 | 0 | 105 |
| | Positive music | 243 | | 243 |
| | Negative music | 36 | | 36 |
| | Negative music | 174 | | 174 |
| 2. Run | Positive music | 36 | 315 | 351 |
| | Positive music | 174 | | 489 |
| | Negative music | 105 | | 420 |
| | Negative music | 243 | | 558 |
| 3. Run | Positive music | 105 | 630 | 735 |
| | Positive music | 243 | | 873 |
| | Negative music | 36 | | 666 |
| | Negative music | 174 | | 804 |
| 4. Run | Positive non-music | 36 | 945 | 981 |
| | Positive non-music | 174 | | 1119 |
| | Negative non-music | 105 | | 1050 |
| | Negative non-music | 243 | | 1188 |
| 5. Run | Positive non-music | 105 | 1260 | 1365 |
| | Positive non-music | 243 | | 1503 |
| | Negative non-music | 36 | | 1296 |
| | Negative non-music | 174 | | 1434 |

The 8th participant in the ND group and the 5th participant in the MDD group could not complete all emotional tasks. However, they only missed one emotional stimulus in only one functional run. Therefore, they were not excluded from the analysis. Instead, their onset times and durations were calculated manually, and their first-level GLM's were specified similarly to other subjects. An example within-subject GLM design matrix and positive music condition regressors plot can be seen in Figure 4.

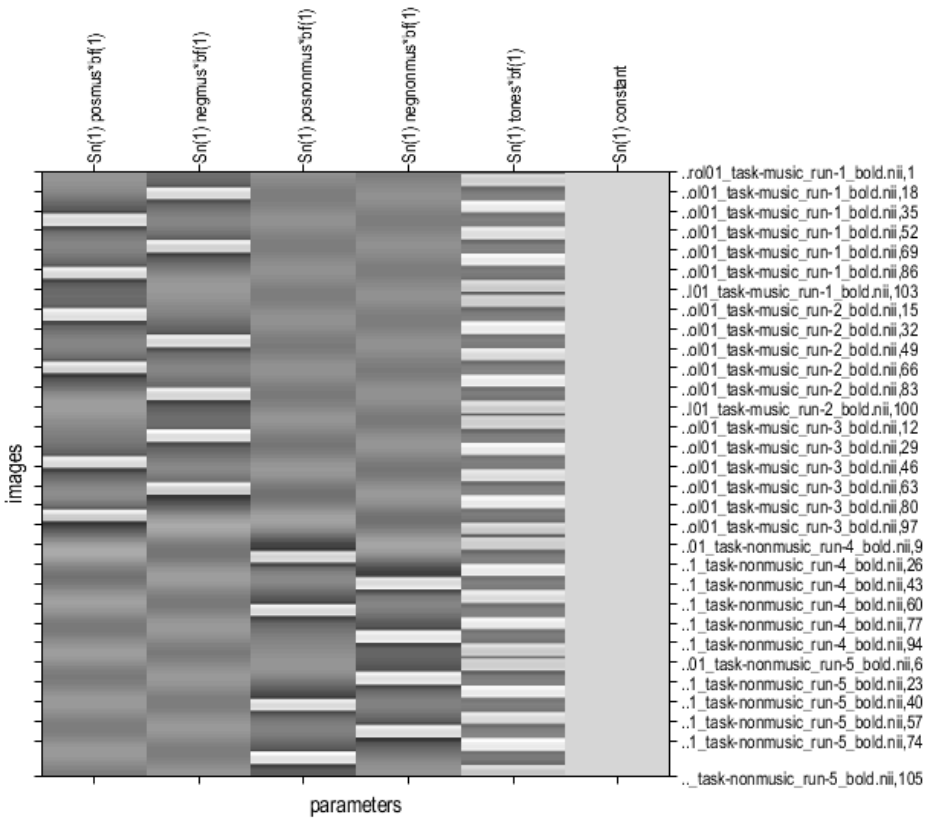


*Figure 4.* Design matrix example of first-level GLM. The y-axis represents the images run-1 through run-5. The first column represents positive music conditions (white lines), the second column represents negative music conditions, the third column represents positive non-music conditions, the fourth column represents negative non-music conditions, and the fifth column represents neutral tones. The constant parameter of GLM is shown in the last column.

### 3.4. Second Level (Group-level) Analysis

Second-level analyses were conducted to observe the effects of emotional conditions on the brain activation patterns of participants in different groups. Significant activations on each subject were calculated as a group. Beta values of each subject's contrast were averaged with random effects analysis (RFX). This averaging can be done with either fixed effects analysis (FFX) or RFX analysis. In FFX analysis, the variability does not stem from the variance between subjects; instead, the within-subject variability is taken into account. In RFX analysis, on the other hand, the variability stems from the variance between subjects. There are two methods within the RFX; namely, the hierarchical and summary statistics approach. These two methods can give the same results if the within-subject variance (first level design) is the same for all subjects. SPM uses a summary statistics approach with the less computationally demanding model. With the summary statistics approach, a one-sample t-test was conducted to create the group-level designs.

The analyses use contrast images created from the first level GLMs. For each group (MDD and ND), group-level analyses were made with two contrast images which are positive>baseline and negative>baseline contrasts (Figure 5). Therefore, 4 different group-level designs were created. These contrasts were then examined in different ROI's to see whether there is a significant difference among conditions. Amygdala, orbito-frontal cortex (OFC), dorsolateral prefrontal cortex (dlPFC), subgenual anterior cingulate cortex (sgACC), and anterior cingulate cortex (ACC) were selected to examine the differences. ROI's were extracted with the WFU PickAtlas (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003) toolbox in MATLAB. Regions were selected based on the Talairach Daemon database (Lancaster, Summerln, Rainey, Freitas, & Fox, 1997) and dilated with 1-layer 3d dilation. Brodmann areas (BA) 10 and 11 were selected for the OFC mask, BA 25 was selected for the sgACC mask, BA 32-33 were selected for the ACC mask, and BA 9-46 were selected for the dlPFC mask. Rendered images of masks can be seen in Figure 6. The contrast threshold was selected as 0,05 with family-wise error (FWE) correction for this one sample t-test analysis.

After examining the contrast images of selected ROI's for two groups separately, independent samples t-test was conducted for both positive>baseline and negative>baseline contrasts. Same ROI's were used in these analyses for masking. FWE corrected p values were evaluated within a 4 mm small volume area at the peak level.

ROI's were extracted with WFU PickAtlas (Maldjian et al., 2004, 2003) toolbox in MATLAB. Regions were selected based on the Talairach Daemon database (Lancaster et al., 1997) and dilated with 1-layer 3d dilation. Brodmann areas (BA) 10 and 11 were selected for the OFC mask, BA 25 was selected for the sgACC mask, BA 32-33 were selected for the ACC mask, and BA 9-46 were selected for the dlPFC mask. Rendered images of masks can be seen in figure 6.

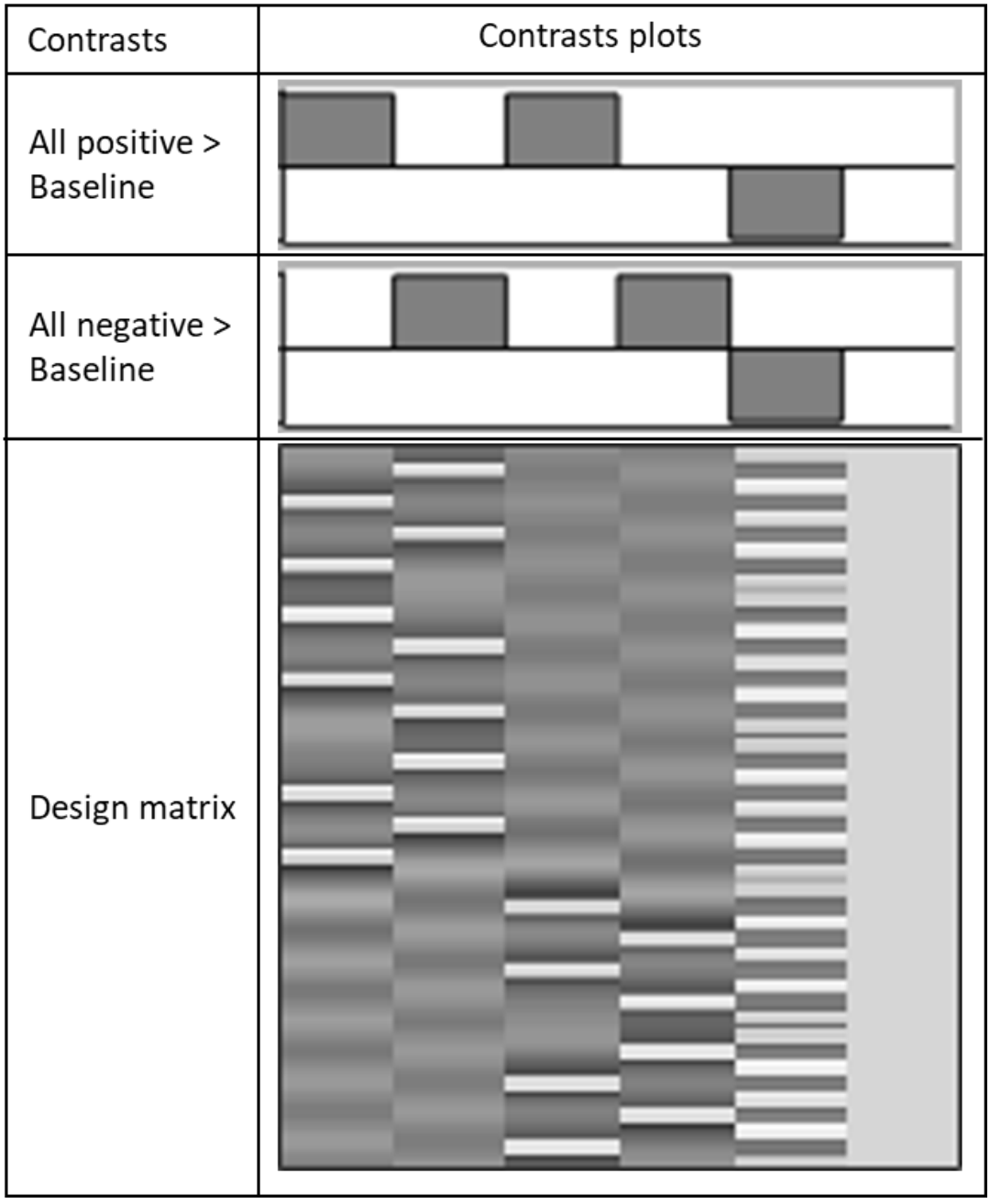


*Figure 5.* Positive>baseline and negative>baseline contrast plots.

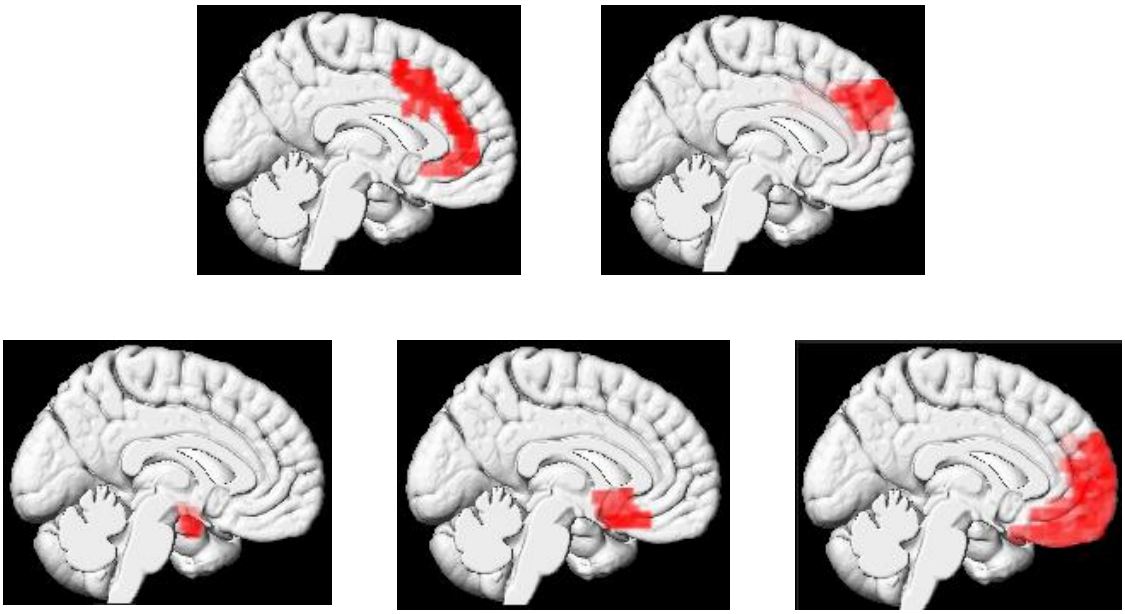

*Figure 6.* Rendered images of ROI masks. Amygdala (lower-left), sgACC (lower-middle), OFC (lower-right), ACC (upper-left), dlPFC (upper-right). Images were generated by xjView toolbox (www.alivelearn.net/xjview/)

### 3.5. Dynamic Causal Modeling (DCM) for Effective Connectivity

In order to carry out a DCM analysis for effective connectivity networks for different subjects, neural models should be specified. Neural models contain different brain regions (ROI's), connections (pathways), and modulatory conditions (stimuli). With the evidence from both the support of the literature and the second level analysis results, Amygdala, sgACC, dlPFC, and OFC brain regions were critical in emotion regulation, and the connectivity between these regions can be impaired in MDD. Thus, the neural effective connectivity models to be tested will be created with the specified ROI's. Causal inferences among those ROI's were estimated with DCM.

In order to conduct a DCM analysis, time-series data of each condition for all selected ROI's should be extracted for each subject. ROI masks were then used to extract time-series data of selected voxels in each region. These masks were applied to every subject's first-level GLM results on each region separately. After specifying an uncorrected threshold (p = ,001), beta-values from the voxels were extracted. To acquire the time-series data, SPM's eigenvariate function was used. This function conducts a principal component analysis (PCA) and takes the first component of beta-values from a selected number of voxels. Although each mask contains a certain number of voxels (Table 2), this PCA method only applied to the voxels that exceeded the threshold of 0.001. An example plot of the first ND subject's sgACC time-series can be seen in Figure 7. In this example, out of 146 total voxels in sgACC ROI, only 19 voxels have exceeded the threshold of 0.001, and the first component of PCA explains 61.08% of the variance of these time-series data. Although each subject have a different number of voxels with this method, by selecting the voxels in which the experimental effect was seen, only the useful information

in the determined ROI's for each participant was obtained. Extracted time-series data were then used to conduct the DCM analysis.

*Table 2.* Total voxel sizes of selected ROI's

| **ROI's** | **Total no. of voxels** |
|---|---|
| Amygdala | 980 |
| Left Amygdala | 492 |
| Right Amygdala | 488 |
| dlPFC | 9431 |
| Left dlPFC | 4454 |
| Right dlPFC | 4977 |
| OFC | 12034 |
| Left OFC | 5959 |
| Right OFC | 6075 |
| sgACC | 1467 |
| ACC | 5740 |

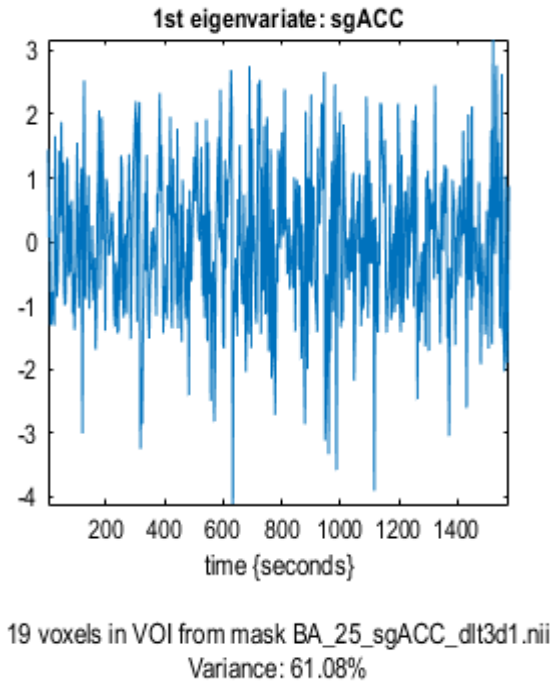


*Figure 7.* PCA extracted time-series data plot for 1st ND subject in sgACC ROI.

To establish a connectivity model, inputs and connections should be determined. There are two different types of input that DCM accepts, modulatory and driving inputs. Modulatory inputs are specified as external stimuli that can regulate the connections. The positive and negative stimuli are determined as modulatory inputs. These inputs are linked to the selected regions rather than connections between them. On the other hand, driving inputs were the selected brain regions: the Amygdala, sgACC, dlPFC, and OFC. 4 models

were created with different combinations of these regions and can be seen in Figure 8. The first model contains all of the selected ROI's while the other three models contain the Amygdala and two of the remaining ROI's. The Amygdala remains constant in each model due to its major role in emotions and decision making (Beck, 2008; Nestler et al., 2002).

Although the first model includes all the connections, certain regions are removed one by one in the other three models, and their effects on other regions are examined. In some effective connectivity studies, this is usually done by switching off the connections between modulatory or driving inputs to see whether a certain region (or external stimuli) represses or boosts the connectivity (Dima, Stephan, Roiser, Friston, & Frangou, 2011; Musgrove et al., 2015; Zeidman, 2019). With this approach, regions or stimuli remain constant while the different connections constitute different models. Among these models, the model that best explains the connectivity can be found. However, the groups are tested separately from each other, and the comparison between the groups is made on independent models.

On the other hand, testing each model within itself allows to include the group effect as a variable like a regressor in the regression analysis. Therefore, in order to examine both the group differences and the effect of brain regions on other regions, four different models were created. Each connectivity model is then specified for a single subject and replicated through each subject.

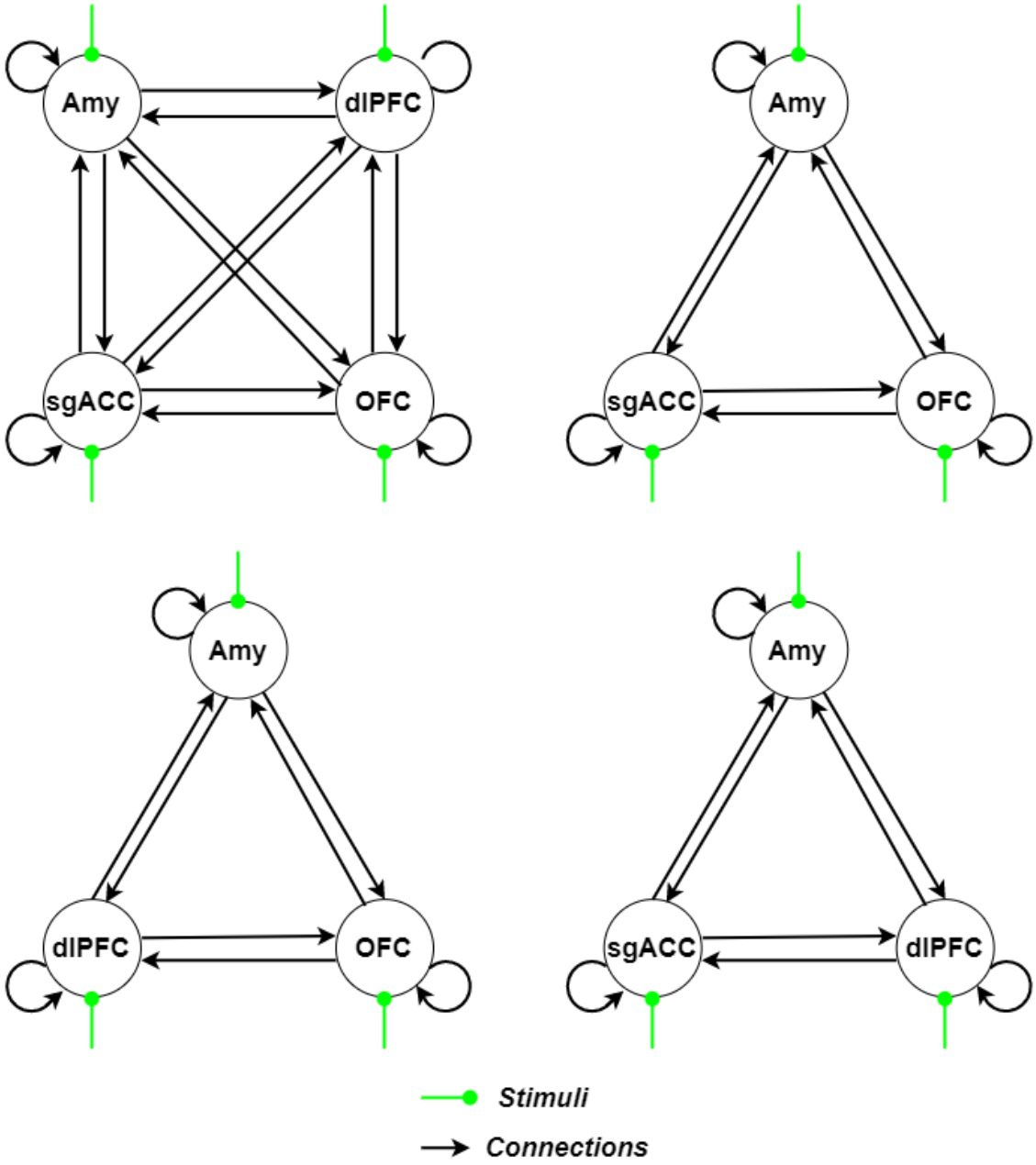


*Figure 8.* Connectivity models for different regions. Circles are ROI's, the black arrows represent between and within region connectivity. Modulation (stimuli) is denoted by red lines with circled end-points. Top-left model has 4 ROI's and 16 connection parameters, whereas the other models have 3 ROI's and 9 connection parameters.

### 3.6. Group-Level Analysis for DCM

DCM analysis was conducted to create individual-level connectivity models. However, one cannot make inferences for a group of subjects from such models. Therefore, the Parametric Empirical Bayes (PEB) framework was used to quantify the differences across

subjects. Similar to the summary statistics approach, PEB uses probability parameters from subject-level connectivity models (DCM's). The PEB approach is used to test hypotheses where the strength of connections differs in a specific DCM model. This DCM model should have the same structure in each subject. Specified PEB models are then estimated with a design matrix that contains the group effect (depression). This design matrix contains the commonalities (the average among all subjects) and the group effect contrast (ND subjects coded as 1 and MDD subjects coded as -1). To test the estimated PEB models, Bayesian Model Reduction (BMR) was used with an automatic search form. Similar to the post-hoc tests following analysis of variance (ANOVA), the BMR method searches over different PEB models that are reduced from the original model. This reduction is made by switching off connections between regions with all possible combinations. This is an exploratory approach to prune away any parameter (ROI connections) that does not contribute to the model. Among all models, the BMR method reduces them to the best models, which have the highest posterior probabilities. The connection strengths among the best models are then averaged with Bayesian Model Averaging (BMA). Since it is a Bayesian analysis, instead of significance, the results were reported as posterior probabilities for each possible connectivity pathway. The values are evaluated as suggested by Kass and Raftery (1995). The labels for posterior probabilities are as follows:

- 0.5 to 0.75 → Not worth more than a bare mention

- 0.75 to 0.95 → Positive

- 0.95 to 0.99 → Strong

- > 0.99 → Very strong

First level analysis (DCM) and second-level analysis (PEB) were conducted and interpreted in reference to the DCM PEB guideline (Zeidman, 2019; Zeidman, Jafarian, Corbin, et al., 2019; Zeidman, Jafarian, Seghier, et al., 2019).

# CHAPTER 4

# RESULTS

## 4.1. Group-level ROI Analysis Results

The results of second-level group analysis show significant differences in both positive-baseline and negative-baseline contrasts. It is found that there are significant differences between positive stimuli and baseline in ND subjects (Table 3). Within the (left & right) Amygdala, left dlPFC, (left & right) OFC and sgACC masks, positive stimuli show significantly greater activation than baseline ($p_{\text{corrected}} < .01$). On the other hand, in ACC and right dlPFC masks, no significant differences were observed ($p_{\text{corrected}} > .05$).

It can be seen from Table 4 that the results of contrast between negative stimuli and baseline in ND subjects reveal significant differences in (left & right) Amygdala, left dlPFC, and left OFC ($p_{\text{corrected}} < .05$). In right dlPFC, right OFC, sgACC and ACC masks, negative stimuli and baseline contrasts do not show any significant difference ($p_{\text{corrected}} > .05$).

MDD subjects, however, show less significant differences than ND subjects in selected ROI masks. Table 5 shows that only in left and right Amygdala masks, MDD subjects have significantly more activation in positive stimuli than baseline ($p_{\text{corrected}} < .01$). Also, negative stimuli have greater activation than baseline in MDD subjects in the (left & right) Amygdala, left dlPFC, and left OFC (Table 6).

*Table 3.* Results of Positive>Baseline contrast for ND subjects

| | Peak level MNI coordinates (mm) | | | | |
|---|---|---|---|---|---|
| | x | y | z | t | p* |
| Amygdala | | | | | |
| Left Amygdala | -22 | -10 | -14 | 14.20 | **.000** |
| Right Amygdala | 26 | -6 | -16 | 8.45 | **.007** |
| dlPFC | | | | | |
| Left dlPFC | -6 | 56 | 28 | 9.54 | **.001** |
| Right dlPFC | 14 | 42 | 26 | 6.51 | .282 |
| OFC | | | | | |
| Left OFC | -40 | 32 | -14 | 9.67 | **.001** |
| Right OFC | 40 | 32 | -14 | 8.33 | **.008** |
| sgACC | 4 | 14 | -10 | 10.03 | **.000** |
| ACC | -4 | 38 | -12 | 7.03 | .100 |

* All p values were FWE corrected. Bold p values were below 0.05 significance level

*Table 4.* Results of Negative>Baseline contrast for ND subjects

| | Peak level MNI coordinates (mm) | | | | |
|---|---|---|---|---|---|
| | x | y | z | t | p* |
| Amygdala | | | | | |
| Left Amygdala | -28 | -4 | -28 | 7.84 | **.020** |
| Right Amygdala | 30 | -4 | -24 | 7.86 | **.021** |
| dlPFC | | | | | |
| Left dlPFC | -8 | 54 | 28 | 8.66 | **.005** |
| Right dlPFC | 48 | 36 | 12 | 6.63 | .224 |
| OFC | | | | | |
| Left OFC | -40 | 34 | -14 | 8.07 | **.014** |
| Right OFC | 42 | 38 | -14 | 7.19 | .073 |
| sgACC | -4 | 0 | -6 | 6.60 | .236 |
| ACC | 14 | 18 | 42 | 5.90 | .704 |

* All p values were FWE corrected. Bold p values were below 0.05 significance level

*Table 5.* Results of Positive>Baseline contrast for MDD subjects

| | Peak level MNI coordinates (mm) | | | | |
|---|---|---|---|---|---|
| | x | y | z | t | p* |
| Amygdala | | | | | |
| Left Amygdala | -24 | -8 | -16 | 11.50 | **.000** |
| Right Amygdala | 22 | -6 | -14 | 10.46 | **.000** |
| dlPFC | | | | | |
| Left dlPFC | -54 | 30 | 16 | 5.37 | .954 |
| Right dlPFC | 8 | 58 | 30 | 5.67 | .851 |
| OFC | | | | | |
| Left OFC | -38 | 38 | -12 | 5.83 | .724 |
| Right OFC | 32 | 34 | -14 | 7.01 | .140 |
| sgACC | 6 | 2 | -8 | 6.46 | .409 |
| ACC | -8 | 8 | 22 | 3.83 | 1.000 |

* All p values were FWE corrected. Bold p values were below 0.05 significance level

*Table 6.* Results of Negative>Baseline contrast for MDD subjects

| | Peak level MNI coordinates (mm) | | | | |
|---|---|---|---|---|---|
| | x | y | z | t | p* |
| Amygdala | | | | | |
| Left Amygdala | -24 | -10 | -16 | 11.72 | **.000** |
| Right Amygdala | 24 | -6 | -10 | 12.07 | **.000** |
| dlPFC | | | | | |
| Left dlPFC | -54 | 30 | 10 | 8.76 | **.020** |
| Right dlPFC | 50 | 36 | 0 | 5.44 | .909 |
| OFC | | | | | |
| Left OFC | -26 | 32 | -12 | 8.70 | **.007** |
| Right OFC | 226 | 24 | -16 | 7.26 | .086 |
| sgACC | -4 | 0 | -8 | 7.15 | .107 |
| ACC | 8 | 32 | -2 | 5.57 | .856 |

* All p values were FWE corrected. Bold p values were below 0.05 significance level

Independent samples t-test was conducted to compare MDD and ND subjects' positive > baseline and negative > baseline contrasts on specific brain regions. It is seen from Table 7 that no significant difference was found between MDD and ND subjects' negative > baseline contrast images ($p_{corrected} > .05$). However, there are significant differences between positive > baseline contrast images that can be seen from Table 8. It is found that, in the left & right dlPFC, left & right OFC, sgACC and ACC regions, ND subjects have significantly more activation in positive > baseline contrast ($p_{corrected} < .05$).

*Table 7.* Independent samples t-test results of Negative > Baseline contrast

| | Peak level MNI coordinates (mm) | | | | |
|---|---|---|---|---|---|
| | x | y | z | t | p* |
| Amygdala | | | | | |
| Left Amygdala | -22 | 2 | -24 | 1.69 | .300 |
| Right Amygdala | 26 | -2 | -28 | 1.70 | .299 |
| dlPFC | | | | | |
| Left dlPFC | -46 | 28 | 16 | 2.52 | .099 |
| Right dlPFC | 58 | 0 | 22 | 2.54 | .095 |
| OFC | | | | | |
| Left OFC | -4 | 60 | 20 | 2.15 | .174 |
| Right OFC | 4 | 60 | -6 | 2.13 | .179 |
| sgACC | 0 | 12 | -12 | 2.21 | .160 |
| ACC | 6 | 22 | 44 | 2.21 | .161 |

* All p values were FWE corrected with peak level 4 mm sphere small-volume.

*Table 8.* Independent samples t-test results of Positive > Baseline contrast

| | Peak level MNI coordinates (mm) | | | | |
|---|---|---|---|---|---|
| | x | y | z | t | p* |
| Amygdala | | | | | |
| Left Amygdala | -18 | -4 | -12 | 2.39 | 1.000 |
| Right Amygdala | 30 | -6 | -22 | 1.94 | 1.000 |
| dlPFC | | | | | |
| Left dlPFC | -46 | 26 | 22 | 4.63 | **.001** |
| Right dlPFC | 8 | 44 | 24 | 3.43 | **.019** |
| OFC | | | | | |
| Left OFC | -8 | 46 | -6 | 4.78 | **.000** |
| Right OFC | 2 | 38 | -10 | 4.16 | **.003** |
| sgACC | 14 | 24 | -16 | 3.64 | **.010** |
| ACC | 0 | 38 | -8 | 4.97 | **.000** |

* All p values were FWE corrected with peak level 4 mm sphere small-volume. Bold p values were below 0.05 significance level

### 4.2. Group-level DCM Analysis Results

After creating DCM effective connectivity models for each subject, the PEB framework and the BMR method were used to analyze the effect of the group to see whether depression makes any difference in selected connectivity networks. In this step, each model was tested and reported separately.

#### 4.2.1. Amygdala – sgACC – dlPFC – OFC Connectivity

Firstly, "Amygdala – sgACC – dlPFC – OFC" connectivity model was tested with PEB. BMR results are summarized in Figure 9 and Table 9. The results show that there are significant connection differences between MDD and ND subjects. There is very strong

evidence that ND subjects differ from MDD subjects in OFC to OFC self-connection (posterior probability > 0.99). Also, there is positive evidence that ND subjects differ from MDD subjects in sgACC to Amygdala connection (pp = 0.79) and dlPFC to Amygdala connection (pp = 0.94) (Figure 9 and Table 9). These results can be interpreted as PEB parameters that survive the threshold are related to the group difference. Since ND subjects were coded as 1 and MDD subjects were coded as -1 in the design matrix, in the ND subjects, OFC was more inhibited by self-connection than MDD subjects. Also, there is an increasing sgACC to Amygdala connectivity and reduced dlPFC to Amygdala connectivity in the ND subjects compared to MDD subjects.

*Table 9.* Bayesian Model Reduction for PEB model of Amygdala – sgACC – dlPFC – OFC

| **Source ROI** | **Target ROI** | **Connectivity value** | **Posterior probability** |
|---|---|---|---|
| Amygdala | Amygdala | .002 | .00 |
| Amygdala | sgACC | -.003 | .00 |
| Amygdala | dlPFC | .000 | .00 |
| Amygdala | OFC | -.003 | .00 |
| sgACC | Amygdala | .051 | .79 |
| sgACC | sgACC | .048 | .66 |
| sgACC | dlPFC | -.001 | .00 |
| sgACC | OFC | -.003 | .00 |
| dlPFC | Amygdala | -.068 | .94 |
| dlPFC | sgACC | .002 | .00 |
| dlPFC | dlPFC | .000 | .00 |
| dlPFC | OFC | .040 | .65 |
| OFC | Amygdala | -.004 | .00 |
| OFC | sgACC | .002 | .00 |
| OFC | dlPFC | -.001 | .00 |
| OFC | OFC | .160 | 1.00 |

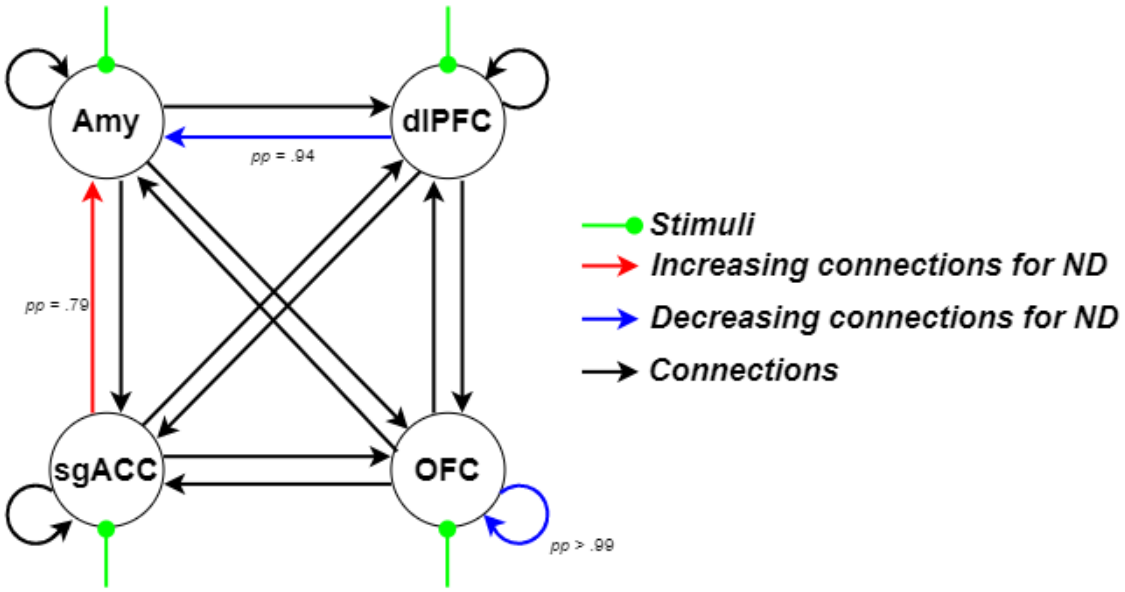


*Figure 9.* BMA connectivity results of Amygdala – sgACC – dlPFC – OFC model with posterior probabilities greater than 0.75.

### 4.2.2. Amygdala – sgACC – OFC Connectivity

After the first model with 4 ROI's, the dlPFC region was taken out from the model, and a new connectivity model with "Amygdala – sgACC– OFC" regions was tested with PEB. The BMR results can be seen in Figure 10 and Table 10. The results show that there are significant connection differences between MDD and ND subjects. There is very strong evidence that ND subjects differ from MDD subjects in Amygdala to Amygdala self-connection (pp > 0.99), OFC to OFC self-connection (pp = 0.98), and OFC to Amygdala connection (pp > 0.99). Also, there is positive evidence that ND subjects differ from MDD subjects in Amygdala to OFC connection (pp = 0.92) (figure 10 and table 10). These results suggest that in the ND subjects Amygdala and OFC were more inhibited by self-connections than MDD subjects. Also, in ND subjects, there is an increasing Amygdala to OFC and OFC to Amygdala connectivity compared to MDD subjects.

*Table 10.* Bayesian Model Reduction for PEB model of Amygdala – sgACC – OFC

| Source ROI | Target ROI | Connectivity value | Posterior probability |
|---|---|---|---|
| Amygdala | Amygdala | .205 | 1.00 |
| Amygdala | sgACC | .051 | .71 |
| Amygdala | OFC | .056 | .92 |
| sgACC | Amygdala | .000 | .00 |
| sgACC | sgACC | .063 | .68 |
| sgACC | OFC | -.004 | .00 |
| OFC | Amygdala | .122 | 1.00 |
| OFC | sgACC | -.060 | .68 |
| OFC | OFC | .190 | .98 |

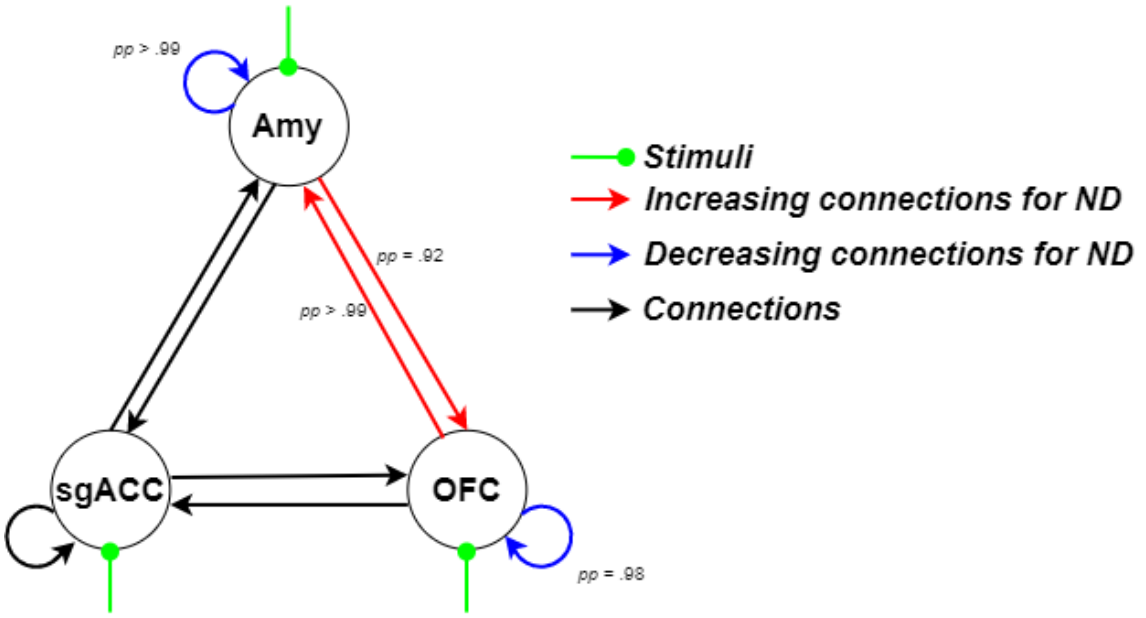


*Figure 10.* BMA connectivity results of Amygdala – sgACC – OFC model with posterior probabilities greater than 0.75.

### 4.2.3. Amygdala – dlPFC – OFC Connectivity

Without the sgACC region, the Amygdala – dlPFC – OFC connectivity model was tested with PEB. The BMR results can be seen from Figure 11 and Table 11. The results show that there are significant connection differences between MDD and ND subjects. There are very strong evidence that ND subjects differ from MDD subjects in Amygdala to OFC self-connection (pp > 0.99) and dlPFC to OFC to connection (pp > 0.99). These results can be interpreted as there is an increasing Amygdala to OFC connectivity and reduced dlPFC to OFC connectivity in ND subjects than MDD subjects.

*Table 11*. Bayesian Model Reduction for PEB model of Amygdala – dlPFC – OFC

| Source ROI | Target ROI | Connectivity value | Posterior probability |
|---|---|---|---|
| Amygdala | Amygdala | .043 | .67 |
| Amygdala | dlPFC | -.001 | .00 |
| Amygdala | OFC | .092 | 1.00 |
| dlPFC | Amygdala | .002 | .00 |
| dlPFC | dlPFC | .002 | .00 |
| dlPFC | OFC | -.125 | 1.00 |
| OFC | Amygdala | .002 | .00 |
| OFC | dlPFC | .000 | .00 |
| OFC | OFC | .048 | .62 |

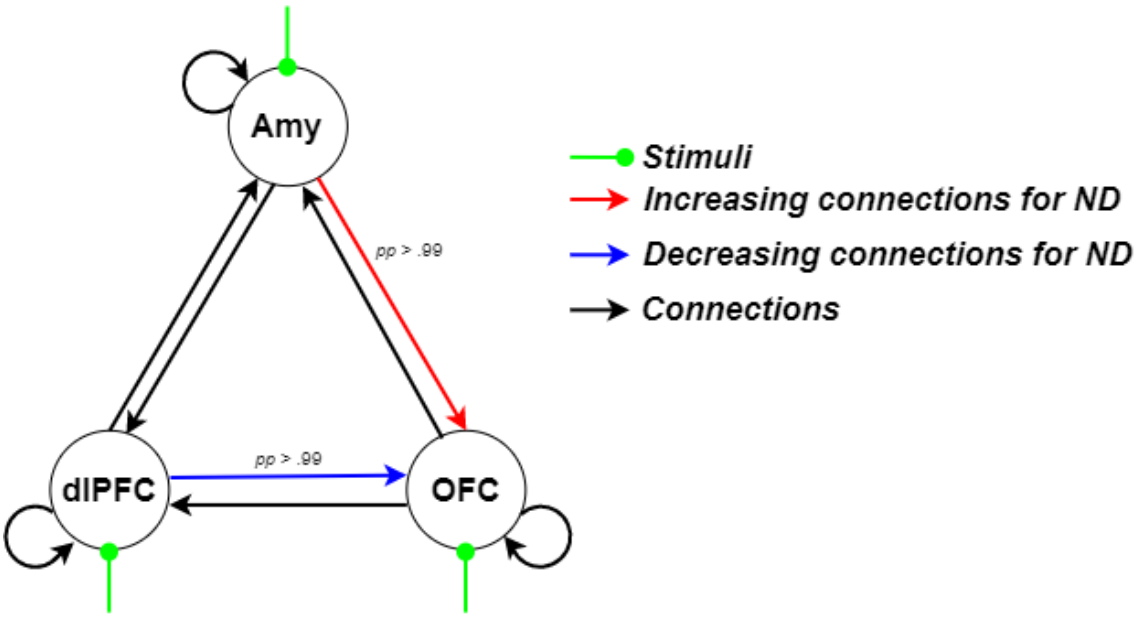


*Figure 11*. BMA connectivity results of the Amygdala – dlPFC – OFC model with posterior probabilities greater than 0.75.

### 4.2.4. Amygdala – sgACC – dlPFC Connectivity

Without the OFC region, the Amygdala – sgACC – dlPFC connectivity model was tested with PEB. BMR results can be seen in Figure 12 and Table 12. The results show that there is positive evidence that ND subjects differ from MDD subjects in Amygdala to sgACC connection (pp = 0.86), dlPFC to sgACC connection (pp = 0.91), and Amygdala to Amygdala self-connection (pp = 0.78). These results can be interpreted as there is an increasing dlPFC to sgACC connectivity and reduced Amygdala to sgACC connectivity in ND subjects than MDD subjects. Also, in ND subjects Amygdala was more inhibited by self-connection.

*Table 12.* Bayesian Model Reduction for PEB model of Amygdala – sgACC – dlPFC

| Source ROI | Target ROI | Connectivity value | Posterior probability |
|---|---|---|---|
| Amygdala | Amygdala | .061 | .78 |
| Amygdala | sgACC | -.055 | .86 |
| Amygdala | dlPFC | -.002 | .00 |
| sgACC | Amygdala | .017 | .40 |
| sgACC | sgACC | .000 | .00 |
| sgACC | dlPFC | .003 | .00 |
| dlPFC | Amygdala | .001 | .00 |
| dlPFC | sgACC | .085 | .91 |
| dlPFC | dlPFC | -.001 | .00 |

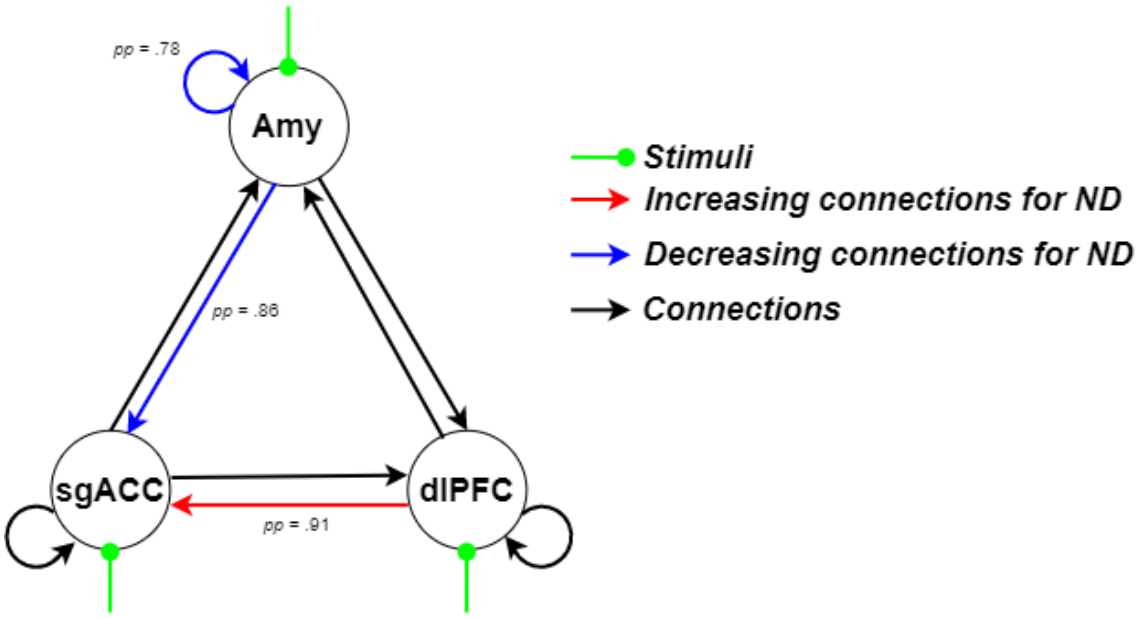


*Figure 12.* BMA connectivity results of the Amygdala – sgACC – dlPFC model with posterior probabilities greater than 0.75.

### 4.2.5. Amygdala – sgACC – dlPFC – OFC Connectivity with Positive Stimuli

Since group-level ROI analysis results revealed significant differences among groups for positive musical and nonmusical stimuli, a connectivity model with only positive stimuli was also tested. In this model, all 4 regions were used. BMR results are summarized in Figure 13 and Table 13. The results show that there are significant connection differences between MDD and ND subjects. There is very strong evidence that ND subjects differ from MDD subjects in Amygdala to dlPFC connection (pp > 0.99), OFC to dlPFC connection (pp > 0.99), sgACC to dlPFC connection (pp > 0.99) and dlPFC to sgACC connection (pp > 0.99) (Figure 9 and Table 9). These results can be interpreted as in the presence of positive stimuli, there are increasing dlPFC to sgACC and sgACC to dlPFC

connectivity in ND subjects than MDD subjects. Also, reduced Amygdala to dlPFC and OFC to dlPFC connectivity in the ND subjects compared to MDD subjects.

*Table 13.* Bayesian Model Reduction for PEB model of Amygdala – sgACC – dlPFC – OFC with positive stimuli

| Source ROI | Target ROI | Connectivity value | Posterior probability |
|---|---|---|---|
| Amygdala | Amygdala | .002 | .00 |
| Amygdala | sgACC | -.111 | .74 |
| Amygdala | dlPFC | -.227 | 1.00 |
| Amygdala | OFC | -.002 | .00 |
| sgACC | Amygdala | .001 | .00 |
| sgACC | sgACC | .001 | .00 |
| sgACC | dlPFC | .340 | 1.00 |
| sgACC | OFC | .001 | .00 |
| dlPFC | Amygdala | -.107 | .73 |
| dlPFC | sgACC | .249 | 1.00 |
| dlPFC | dlPFC | -.127 | .71 |
| dlPFC | OFC | -.002 | .00 |
| OFC | Amygdala | -.001 | .00 |
| OFC | sgACC | .000 | .00 |
| OFC | dlPFC | -.260 | 1.00 |
| OFC | OFC | -.001 | .00 |

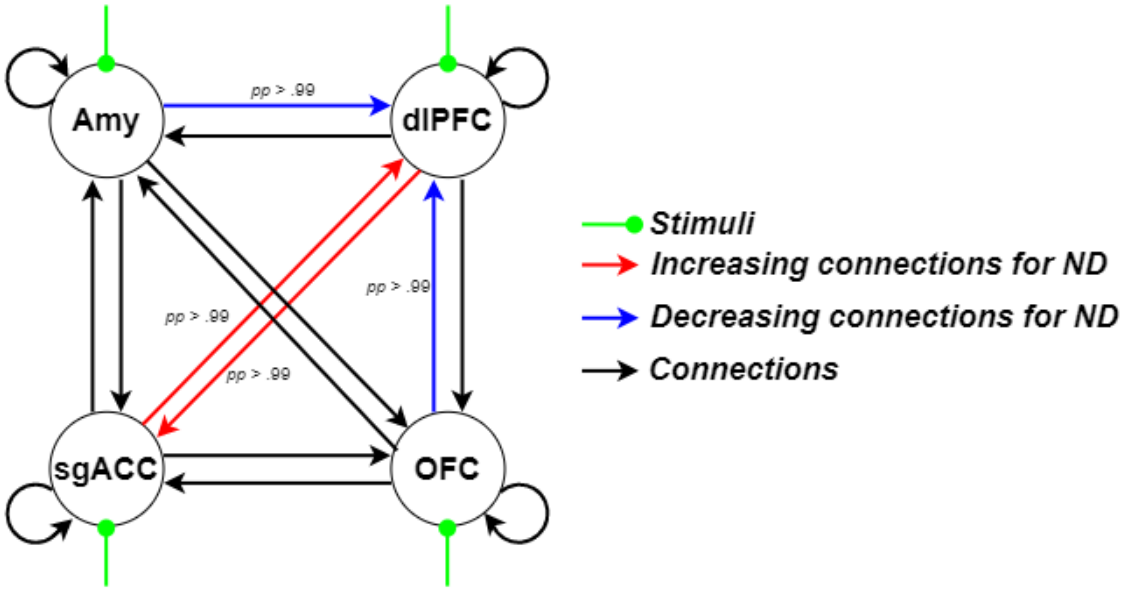


*Figure 13.* BMA connectivity results of Amygdala – sgACC – dlPFC – OFC model with positive stimuli and with posterior probabilities greater than 0.75.

# CHAPTER 5

# DISCUSSION

This thesis study aimed to model the emotion regulation process with an effective connectivity approach in Major Depressive Disorder (MDD) patients and never depressed (ND) controls. Dynamic Causal Modeling (DCM) method was used to create the connectivity models. These connectivity models are intended to identify different brain connectivity pathways in MDD patients. The fMRI dataset used in this thesis is obtained from Lepping and her colleagues' study (2016). MDD patients and ND subjects' fMRI data were collected with an emotional musical task in that study. The collected data was investigated by comparing whole-brain and ROI activation maps. This thesis tried to replicate their findings and also improve what they found with a DCM effective connectivity analysis.

This study consists of two parts. First, ROI analyses were made to compare the results with Lepping et al.'s findings. Then, effective connectivity analyses were performed to distinguish MDD subjects based on the differences in neural pathways processing emotional stimuli. The selected ROI's were Amygdala, OFC, sgACC, ACC and dlPFC for ROI analyses. The connectivity models however, were created using only Amygdala, OFC, sgACC and dlPFC. The specified brain regions were selected based on both Lepping et al.'s study and the literature review about the neurobiology of MDD and emotion regulation networks.

## 5.1. ROI Differences

The results obtained from this study revealed that there are significant activations for both positive and negative emotions in MDD and ND subjects' ROI activation maps. When comparing the BOLD activations of positive stimuli and baseline neutral tones, ND subjects have greater activation in the regions of Amygdala, left dlPFC, OFC and sgACC. However, MDD subjects' BOLD activation differences for positive-baseline contrast can be seen only in the Amygdala. The comparison of MDD – ND subjects reveals that dlPFC,

OFC, sgACC, and ACC regions, ND subjects have significantly more activation than MDD subjects in positive > baseline contrast.

In addition to that, the contrast between negative stimuli and baseline show no difference between MDD and ND subjects. In both groups, negative stimuli have greater activation than baseline in the Amygdala, left dlPFC and left OFC regions.

It is known that these ROI activations may alter when the person is in a depressive state (Bürger et al., 2017; Diener et al., 2012; Drevets, Price, & Furey, 2008; Fitzgerald et al., 2008; Groenewold et al., 2013; Grotegerd et al., 2014; Hamani et al., 2011; Kambeitz et al., 2017; Rive, et al., 2013). Therefore, these findings also support the results of other previous studies in the literature. The different effects of positive stimuli in depressed people support the negativity bias theory. While stimuli containing positive emotions cause activation in the Amygdala, dlPFC, OFC and sgACC regions in ND subjects, MDD subjects' activations were only observed in the Amygdala region. These results can be interpreted as positive stimuli cause less BOLD activation in depression. However, the fact that both groups have the same activation patterns in negative stimuli can be interpreted as MDD participants do not perceive negative emotions differently than ND subjects.

These findings also show similarities to the dataset's original study (Lepping et al., 2016). The authors found significant differences in ACC and sgACC areas for positive stimuli and no group difference for negative stimuli. The same pattern can be observed in this study as well. Moreover, significant results were obtained in the Amygdala, dlPFC, and OFC brain regions. Although the original study did not perform an ROI analysis on the frontal cortex, their analyses on the Amygdala did not yield significant results. However, in this study, significant differences were found in the Amygdala region. This difference may be due to methodological differences in the two studies.

These methodological differences arise from the examined contrast differences and the differences in the program used for analysis. The original study used the Analysis of Functional NeuroImages (AFNI) statistical package. In this study, Statistical Parametric Mapping (SPM) software was used. The examined contrast differences were the main difference of activation analyses between the original research and this study. They made their analysis with three variables which are the group (MDD and ND), valence (positive and negative), and stimulus type (musical and nonmusical). This study tried to focus on the effect of emotion. Therefore, instead of finding the contrast of different emotional valence (positive and negative), emotional stimuli and non-emotional stimuli comparisons were made in this study. With this approach, positive and negative stimuli were regarded as emotional stimuli and compared with baseline neutral tones. Thus, in addition to finding similar results with the original study, these new findings allowed a more comprehensive assessment of the emotional differences in depression.

## 5.2. Effective Connectivity Models

The brain consists of different regions that are in constant communication with each other. Although the ROI activation maps provide interpretable results, it does not provide any information on the connections between the activated regions. Identifying relationships between brain regions may better explain the neural correlates of depression.

The effective connectivity analyses were found to be able to model the contrast of MDD and ND subjects. The results were interpreted with the help of Zeidman's DCM PEB guideline (Zeidman, 2019). Four different models were tested, and all of them yielded significant results. Within these models, the first model that contains all four regions (Amygdala, dlPFC, sgACC and OFC regions) reveals that there is an increasing sgACC to Amygdala connectivity and reduced dlPFC to Amygdala connectivity in the ND subjects compared to MDD subjects.

In addition to this first model, three additional models were tested to determine how the connectivity would change in the absence of each of the other three regions while keeping the Amygdala region constant. This decision was made in this study because the most effective connectivity models for MDD and emotions in the literature use the Amygdala region, although other regions may not be examined in such studies.

When the dlPFC region was removed from the model, it was found that self-inhibition for Amygdala and OFC can be seen in ND subjects more than MDD subjects. Also, compared to MDD subjects, there is an increasing Amygdala to OFC and OFC to Amygdala connectivity in ND subjects. However, in the absence of the dlPFC region, no differences were observed between groups in the connectivity of the sgACC with other regions (Amygdala and OFC).

When the sgACC region was removed from the model, an increasing Amygdala to OFC connectivity and reduced dlPFC to OFC connectivity were found in ND subjects than MDD subjects. Without including the sgACC, the connectivity between the Amygdala and dlPFC did not differ between the two groups.

Lastly, when the OFC region was removed from the model, there was an increasing dlPFC to sgACC connectivity and reduced Amygdala to sgACC connectivity in ND subjects than MDD subjects. Also, in ND subjects Amygdala was more inhibited by self-connection. In this last model, same as the previous model, without including the OFC, the connectivity between the Amygdala and dlPFC did not differ between the two groups.

Apart from these models, the first model was also modified with the inputs. ROI analysis showed that positive musical or nonmusical stimuli had more impact on the difference between ND and MDD subjects. Therefore, investigating the effect of positive stimuli only revealed important results as well. It was found that when only the positive stimuli have entered the model, sgACC and dlPFC areas show greater increased connectivity between each other in ND subjects. Also, it was found that the connectivity of the

Amygdala to dlPFC and OFC to dlPFC have been significantly reduced in the presence of positive stimuli among ND subjects. In other words, in MDD subjects, the dlPFC region is more affected by Amygdala and OFC. As can be seen, different results were found in the model tested with only positive stimuli. Finding different results from the first model can be interpreted as the differences in response to emotional stimuli between MDD and ND subjects also vary according to the type of emotion.

As a consequence, this study reveals the significant effective connectivity network alterations between MDD and ND subjects. Obtaining different results in all four models tested proves that a single brain region (sgACC, dlPFC and OFC in this study) can affect the relationships between other regions. The presence or absence of these brain regions in the models affects the connections between other regions. Therefore, the evaluation of the first model in which all regions are included will give more meaningful results.

This study tests the hypothesis of whether an effective connectivity model can distinguish MDD cases from healthy subjects based on the differences in neural pathways processing emotional stimuli. These results suggest that the effective connectivity models developed in this study were able to distinguish MDD subjects from ND subjects based on emotional musical or nonmusical stimuli. Thus, the hypothesis of this study is supported by the data.

These models also show similarities and differences with other studies in the literature as well. The result of reduced dlPFC connectivity to the Amygdala in MDD subjects contradicts the study of Jamieson et al. (2021). This difference may be due to the emotional task and contrast differences. They used an emotional face processing task and created connectivity models for sad and happy faces separately. However, in this study, musical stimuli were used, and the connectivity models were built with the whole BOLD activations in task since all subjects were exposed to the same stimuli and the effect of emotion type could be controlled.

On the other hand, increasing Amygdala to OFC connectivity in ND subjects is consistent with the results from the study of Carballedo et al. (2011). Also, Ho and her colleagues found increased sgACC to Amygdala connectivity in depressed adolescents (Ho et al., 2014). This result is also consistent with our findings over the first model.

### 5.3. Contributions

The findings of this study suggest that there are distinct effective connectivity neural pathways between depressed and never-depressed subjects. The connectivity studies in the literature mostly examined functional connectivity networks. This study contributes to the limited effective connectivity literature that investigates depression by using DCM models. Using effective connectivity allows more interpretable results when investigating the brain network differences in MDD. In addition to contributing to the literature, the neurological structure of depression identified in this study may enable a more effective diagnosis and treatment of depression.

This study used open fMRI data collected for another study (Lepping et al., 2016). Sharing the collected data has enabled much more information to be drawn from the same data. Especially in neuroimaging studies, since a vast amount of data can be collected than the purposes of the study, the obtained data may not be evaluated with 100% efficiency. This study shows how important it is to share open data collected for other neuroimaging studies. When data collection becomes difficult due to COVID-19, more contributions can be made to the literature thanks to the availability of open data sets.

### 5.4. Limitations and Suggestions for Future Studies

The use of open data comes with many disadvantages and limitations as well. Since the data collection process was not carried out specifically for this study, it is limited to the characteristics of the participants and data collection methods. The data has a small sample size and is limited to the emotional task. Although depressed and healthy participants were not significantly different with demographic information, this data uses adults with a wide age range. However, adolescent and adult depression may work in different ways. Using the same task on other age groups and examining the results of these groups separately may provide more valuable results.

In addition to these methodological limitations, there are other limitations in the preprocessing of this data. These limitations were First of all, in the realignment step of preprocessing, functional scans were realigned with the estimated transformation parameters. These parameters should later be added into the analysis as a covariate since they may have an effect on the results. Also, the task includes a response period after listening to emotional or non-emotional sounds where subjects gave a response for the emotional valence and arousal level of that stimuli. These periods last 3 seconds and there are four response periods in every run. However, they were included in the analysis as they were part of that stimuli. Because the onset times and durations were drawn from the supplementary data that the authors of the original study provided and these onset and duration times include these response periods. These limitations occurred because all preprocessing steps were attempted to be similar to the original study from which the data were obtained.

The emotional task used in this study contains musical stimuli. Although music and harmony are universal, the perception of music can vary according to different cultures. Therefore, this emotional task may not yield the same results in studies with people from different cultures. This emotional musical task should be validated in other countries and cultures in future studies.

This study is also limited to the brain regions that were tested. Although the analyzed brain regions were selected with support from the literature, different brain regions may be associated with depression. Future studies should include other relevant brain regions in their analysis.

Although studies on the neurobiology of depression have found very inspiring results, a large number of similar studies need to be made before these findings can be used for diagnostic purposes in practice. For this reason, continuing studies in this field may lead to discoveries that will be very helpful, especially in the psychiatric diagnosis of depression and other psychiatric disorders.

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**TEZİN ADI /** TITLE OF THE THESIS (**İngilizce** / English) : EFFECTIVE CONNECTIVITY MODEL DIFFERENCES OF EMOTION REGULATION IN MAJOR DEPRESSIVE DISORDER: DYNAMIC CAUSAL MODELING ANALYSIS

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