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Exploring the Relationship Between Electroconvulsive Therapy and Reward Processing in Major Depressive Disorder

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Abstract

Depression affects over ten percent of the population worldwide, with a huge toll for patients, their families, and the whole society. Around one third of patients with depression does not respond satisfactorily or at all to either pharmacological or psychological therapy. Electro-convulsive therapy (ECT) is an established treatment for severe mental illnesses, in particular treatment-resistant depression, a leading contributor to global disease. Despite its proven effectiveness in treating depression, the underlying mechanisms of ECT are not yet fully understood. This thesis examines the potential differences between patients who respond positively to electroconvulsive therapy (ECT) and those who do not, providing novel insights into their relationship with the reward processing in the brain. While this thesis expands our knowledge of ECT effect in the treatment of depression, it is important to acknowledge that the study comes with at least two major limitations. (i) The small sample size may impact on the statistical power of the study; (ii) the computer task used to assess the reward processing may not be sensitive to detect subtle differences between groups or changes over time. It is possible that other measures will provide a more comprehensive assessment of reward functions in future evaluations. Future research with larger samples and more sensitive measures could build upon these findings and further advance our understanding of the mechanisms underlying ECT and treatment response in depression.

Abbreviations

MDD – Major Depressive Disorder

TRD – Treatment Resistant Depression

ECT – Electroconvulsive Therapy

MID – Monetary Incentive Delay Task

HAM-D - Hamilton Depression Rating Scale

PHQ-9 – Patient Health Questionnaire - 9

QIDS – Quick Inventory of Depressive Symptomatology

SHAPS - Snaith-Hamilton Pleasure Scale

TEPS - Temporal Experience of Pleasure Scale

NEO – NEO Personality Inventory

ASI - Anxiety Sensitivity

CBT – Cognitive Behavioral Therapy

ROI – Region of Interest

MBCT - mindfulness-based cognitive therapy

TMS – transcranial magnetic stimulation

DBS – Deep brain stimulation

tDCS – transcranial direct current stimulation

tACS - transcranial alternating current stimulation (tACS)

FUS – focused ultrasound

FDR - false discover rate

Chapter 1

Introduction

1.1 Clinical Aspects

1.1.1 Major Depressive Disorder phenotypes of depression to better develop to improve understanding of MDD

Depression is a complex and debilitating mental health disorder that affects millions of people worldwide, regardless of whether it presents as a short-term or long-term condition (World Health Organization, 2022). It is characterized by a range of symptoms, including persistent feelings of sadness, hopelessness, and loss of interest in daily activities (American Psychiatric Association, 2013). Depression can also cause physical symptoms such as fatigue, changes in appetite, and difficulty sleeping (National Institute of Mental Health, 2021). While the severity and presentation of depression may vary, it can have a significant impact on an individual's overall well-being (World Health Organization, 2022).

The percentage of individuals with depression who respond to treatment and those who do not can vary depending on the type of treatment and the severity of the depression. According to a meta-analysis of 100 clinical trials, only approximately 50% to 60% of individuals with major depressive disorder (MDD) respond to first-line antidepressant medications (Cipriani et al., 2018). However, response rates may decrease in individuals with treatment-resistant depression (TRD), which is defined as the failure to respond to two or more antidepressant treatments (Rush et al., 2006). In individuals with TRD, only 10% to 30% may respond to subsequent treatments (Souery et al., 2019). The effectiveness of medication can vary widely from person to person. For instance, a meta-analysis of antidepressant medication found that approximately 40% to 60% of patients with depression experience symptom improvement, while 30% to 40% of patients do not respond to treatment (Cipriani et al., 2018).

Studies have also shown that psychotherapy can be a partially effective treatment option for depression, as it involves talking to a mental health professional. Cognitive-behavioral therapy (CBT) and mindfulness-based interventions are the two types of psychotherapy mainly used to help treat Depression. CBT aims to help individuals identify and change negative patterns of thinking and behavior that contribute to depression. Mindfulness-based interventions, such as mindfulness-based cognitive therapy (MBCT), aim to increase awareness and acceptance of thoughts and emotions. MBCT has been found to be minor in reducing depressive symptoms (Cuijpers et al., 2018).

Although traditional treatment modalities like antidepressant medications, cognitive-behavioral therapy (CBT), mindfulness-based interventions, and lifestyle changes have demonstrated to be effective in alleviating symptoms and preventing the development of TRD, they are not always successful. Indeed, studies show that only about half of the patients with MDD show a significant response to CBT treatment (Cuijpers et al., 2018). Similarly, mindfulness-based interventions have been found to be effective in reducing depressive symptoms and improving quality of life, but studies show that response rates can range from 39% to 71% (Hofmann et al., 2010). Lifestyle changes, such as exercise and a healthy diet, have also been found to be effective in improving depressive symptoms, but their effectiveness is limited (Richardson et al., 2021; Jacka et al., 2017). Overall, CBT and mindfulness-based interventions were shown only to be effective in reducing symptoms of depression, with response rates ranging from 50-60% for CBT and 30-50% for mindfulness-based interventions (Cuijpers et al., 2018).

The focus needs to be on the significant proportion of patients who do not respond to the conventional treatments, leading to the development of treatment-resistant depression (TRD). Therefore, there is a need for continued research into alternative and new treatments for MDD, particularly those that can provide rapid and sustained symptom relief without risks and side effects. While many patients with MDD can achieve remission with first-line treatments, including psychotherapy

and antidepressant medications, a significant number of patients do not respond adequately to treatment and develop Treatment Resistant Depression (TRD) (Fava, 2019).

While the concept of treatment-resistant depression is relatively new, there are historical instances of depression that were likely treatment-resistant, even though the first reported cases of TRD are difficult to pinpoint. One famous example is the case of Virginia Woolf, a famous British writer who experienced severe depression throughout her life. Woolf was treated with various therapies, including psychoanalysis and medications, but her depression persisted and ultimately led to her suicide in 1941. While Virginia Woolf's depression was not explicitly labeled as treatment-resistant, her case is as an example of the challenges of treating severe and persistent depression. The concept of TRD began to gain more attention in the 1980s and 1990s, as researchers and clinicians recognized that a significant proportion of patients with depression did not respond to traditional treatments. The term "treatment-resistant depression" was first coined in a paper by Thase and Rush (1995), in which they defined TRD as "the failure to achieve a satisfactory response after two or more adequate trials of antidepressant treatment".

It is important to note that the term treatment resistance refers to the condition in which depression does not show a rapid and satisfactorily response to standard treatment, rather than being untreatable altogether. Typically, treatment resistance is understood to imply a lack of response to standard drug treatment, even though drug treatment is just one of several therapeutic options available. Depression is considered treatment resistant if two attempts at drug treatment, each at an appropriate dose and duration, have failed to produce a positive outcome. The classification of treatment resistance is partially subjective, with more precise definitions considering the number of unsuccessful treatment attempts (Bschor, Bauer & Adli, 2014).

The causes of TRD are not well understood, but several factors may contribute to its development. Genetic factors, for example, may play a role in the development of TRD, and individuals with a family history of depression may be at higher risk. Other factors that may contribute to TRD include childhood

adversity, comorbid medical conditions, and stressful life events (Fabri et al., 2019).

Treatment options for TRD are limited, and the condition can be challenging to manage. In recent years, several new treatments have emerged that may be more effective in treating TRD, including ketamine infusions, electroconvulsive therapy (ECT), and transcranial magnetic stimulation (TMS). Ketamine is an anesthetic medication that has been found to have rapid antidepressant effects. It is typically administered through an intravenous infusion and has been shown to be effective in individuals with TRD who have not responded to other treatments (Zarate et al., 2012). However, ketamine can have potential side effects, including dissociation, hallucinations, and addiction. TMS is a non-invasive procedure that uses magnetic pulses to stimulate nerve cells in the brain. It has been found to be effective in treating TRD, and unlike ECT, it has minimal side effects (Dunner et al., 2014). However, the long-term effectiveness of TMS is not yet fully understood. Lastly, ECT is a non-invasive procedure that involves passing an electrical current through the brain to induce a seizure. While ECT has a controversial history, it is considered a very effective and life-saving treatment for severe depression, including TRD. However, it may have later side effects such as cognitive impairment and memory loss (Sackeim, 2018).

In conclusion, TRD is a severe form of depression that can be challenging to manage. While traditional antidepressant medications and psychotherapy may not be as effective for individuals with TRD, several emerging treatments, including ketamine, ECT, and TMS, have shown promise in treating TRD. Among all these, ECT remains the gold standard in treating severe and TRD Major Depressive Disorder. ECT has demonstrated high efficacy rates, good tolerability, and accessibility.

1.1.2 Electroconvulsive Therapy

ECT is typically used for patients with major depression who have not responded to other forms of treatment, such as medications or psychotherapy (Kellner, 2017). Electroconvulsive Therapy (ECT) has been used effectively to treat depression

since the 1930s, and it remains the golden standard for treating treatment-resistant depression. Electroconvulsive therapy (ECT) has been found to be the most effective treatment for MDD in terms of achieving rapid and robust symptom improvement (Leiknes et al., 2012). ECT involves delivering small electric currents to the brain while the patient is under general anesthesia. The response rate with ECT for major depressive disorder (MDD) is approximately 80% (Sackeim, 2018), with remission rates ranging from 50-70% (Kellner et al., 2012). Pharmacotherapy and psychotherapy are considered the initial treatment options for depression, but electroconvulsive therapy (ECT) is a well-established alternative treatment option, particularly for severe, psychotic depressive episodes, and when suicidal ideation is present. Research has shown that ECT is highly effective in rapidly alleviating symptoms of depression, especially in patients who have not responded to other treatments. A meta-analysis of randomized controlled trials found that ECT was significantly more effective than pharmacotherapy in treating severe depression (Kellner et al., 2012). Additionally, a study by Kellner et al. (2016) found that ECT was effective in reducing suicidal ideation in patients with treatment-resistant depression. While pharmacotherapy and psychotherapy are the primary treatments for depression, ECT remains a crucial and well-established alternative for cases in which other treatments are not effective.

Electroconvulsive therapy (ECT) has been found to have a success rate of ~75% in treating Major Depressive Disorder and has been shown to be more effective than other pharmacological treatments such as monoamine oxidase inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) (Mukherjee et al., 2018). The initial course of ECT is usually 3 to 4 weeks, and it can provide relief from depression symptoms within a short period of time. ECT is generally safe and well-tolerated, with mild and transient side effects such as disorientation, confusion, headache, dizziness, muscle pain, high blood pressure, and memory impairment (Bergfeld et al., 2021). ECT can prolong remission rates for up to a year, especially when combined with other medications or when administered after the initial treatment (Lisanby et al., 2016). Some patients may not show improvement after the initial

course of ECT, but a follow-up with additional treatment protocols, such as unilateral or bilateral ECT with antidepressants, can lead to a reduction in symptoms (Kellner et al., 2016). A study of 44 patients with cognitive impairments also showed that ECT improved processing speed, executive functioning, and memory (McClintock et al., 2016).

The therapeutic effects of electroconvulsive therapy (ECT) are still not completely understood. However, several theories have been proposed to explain how ECT exerts its antidepressant effects (REFS). One of the proposed mechanisms is neurotransmitter modulation, in which ECT is thought to modulate the levels of neurotransmitters such as serotonin, norepinephrine, and dopamine in the brain, leading to an improvement in mood and other symptoms of depression. Studies have shown that ECT can increase the levels of these neurotransmitters in the brain, which may explain its antidepressant effects (Kellner et al., 2012).

Another proposed mechanism of action is the activation of the NMDA (N-methyl-D-aspartate) receptors in the brain, which are involved in synaptic plasticity, learning, and memory. ECT has been shown to activate these receptors, which has been linked to its antidepressant effects (Lisanby et al., 2000). ECT has also been shown to lead to changes in the plasma levels of hormones such as cortisol and thyroid hormones, which are involved in regulating mood, stress response, and metabolism (Prudic et al., 1996). Also, ECT has been shown to promote the growth of new brain cells (Rami et al., 2018).

Other proposed mechanisms of action of ECT include changes in brain metabolism and glucose utilization in regions associated with mood regulation and anxiety, changes in gene expression in the brain, modulation of inflammatory processes, and changes in neural connectivity in regions involved in mood regulation (Kellner et al., 2010; Sartorius et al., 2016). Despite the complexity of ECT's mechanisms of action, its efficacy in treating severe depression has been well established.

With respect to reward processing, some research has indicated that ECT can increase sensitivity to positive stimuli in patients with depression. For example, patients with depression who received ECT showed increased activity in the brain regions associated with reward processing, such as the ventral striatum,

in response to positive stimuli compared to negative stimuli (Schutter, 2009). This suggests that ECT may help to improve patients' ability to experience pleasure and positive emotions, which can be a significant challenge in depression. It is important to note, however, that while some studies have reported positive effects of ECT on reward processing, others have failed to find any significant changes. The effects of ECT on reward processing can also vary between individuals and can depend on several factors, such as the severity of the depression, the frequency and intensity of the ECT treatments, and the patient's overall response to the therapy.

1.1.3 Why Choose Electroconvulsive Therapy for Major Depressive Disorder Over Emerging Innovative Treatments?

ECT is a well-established treatment for severe depression and has been used for over 80 years. Since its introduction in the 1930's it has been refined, researched, and continuously improved. This long history provides a wealth of clinical data, making it one of the most extensively studied psychiatric treatments available. One of the significant advantages of ECT is the well-established safety procedures and effective delivery. (Fink 2014).

Other modalities like TMS and ketamine are newer treatments for depression and while they show promise in treating certain types of depression, they are not as effective as ECT for severe and treatment-resistant cases (Lisanby, 2017; Short et al., 2020). ECT has some advantages over TMS and Ketamine. ECT typically requires fewer sessions than TMS and the effects of ECT can last longer than those of Ketamine (McClintock et al., 2018). A review conducted by Rasmussen comparing ECT and TMS concluded that the response rate to ECT was 58.8% whereas patients who underwent TMS only showed a response rate of 38%. TMS also cannot be applied to depressed patients suffering also with comorbid mental illnesses like bi-polar and schizophrenia (Rasmussen, 2019)

TMS stands as a recognized and well-tolerated treatment for depression, yes, its suitability with comorbidities necessitates a nuanced evaluation, a decision-making process that should be

carried out under the guidance of healthcare professionals. Firstly, the application of TMS in individuals with severe medical conditions such as cardiovascular disorders or implanted metallic devices requires a careful assessment due to the potential risks associated with a strong magnetic field used in TMS (Rossi et al., 2009). Patients with active or unstable medical conditions necessitate a thorough evaluation before deeming TMS appropriate. Secondly, for individuals with a history or predisposition to seizures, a group that may be at a higher risk, cautious consideration and monitoring are essential due to the low risk of TMS inducing seizures (Rossi et al., 2009). Thirdly, those with psychiatric comorbidities, including active substance abuse disorders or severe personality disorders, should undergo a comprehensive evaluation to assess for potential impacrs on treatment engagement and efficacy (Lefaucheur et al., 2014). Additionally, the medication regimes of patients must be scrutinized for potentials interactions with TMS, considering that certain medications may affect efficacy or safety (Lefaucher et al., 2014).

Ketamine has demonstrated a rapid antidepressant effect with variable response rates. A review article by Sanacora et al., 2017, discusses the efficacy of Ketamine highlighting its rapid onset of action but also noting that the effects may be short-lived and that not all the patients respond to it.

Deep brain stimulation (DBS) is a newer treatment that involves the implantation of electrodes in the brain to stimulate certain areas that are thought to be involved in mood regulation. DBS has been studied as a treatment for depression, but the results have been mixed (Mayberg et al., 2005; Schlaepfer et al., 2008). Some patients have experienced significant improvement in symptoms, while others have not (Mayberg et al., 2005). Mayberg et al., 2005 conducted a study to investigate whether the heightened metabolic activity in the subgenual cingulate region (Broadman area 25) would reduce the heightened activity in BA25 and consequently provide clinical relief. The finding was associated with a significant decrease in the local cerebral blood flow and alterations in the limbic and cortical regions downstream measured through positron emission tomography (PET). Schlaepfer et al.,2008, implanted bilateral DBS electrodes in the nucleus accumbens in three patients suffering from

treatment resistant depression. As a result, clinical ratings significantly improved, and FDG-PET scan illustrated changes in brain metabolism within the fronto-striatal networks. Research conducted by Alagapan et al., 2023, investigated the dynamics of the cingulate cortex in relation to the recovery process of individuals undergoing deep brain stimulation for depression treatment. The research focused on how changes in the cingulate cortex activity correlated with the alleviation of depression symptoms in patients who have undergone DBS. The findings shed light on the potential for using cingulate cortex dynamics as a valuable market to monitor and understand the progress of depression recovery in the context of DBS Therapy.

Alternatively, research studies have shown no significant response to DBS treatment. In a study conducted by (Holtzheimer et al., 2017, 90 participants were randomly assigned to six months of active (n=60) or sham (n=30) bi-lateral subcallosal cingulate stimulation. Both groups demonstrated positive changes but there was no statistical significance in the treatment response during the double-blind, sham controlled phase (Holtzheimer, 2017). A study conducted by Bergfeld 2016, used DBS to target the ventral anterior limb of the internal capsule looking into placebo effects with active and sham stimulation phases. Twenty-five patients received bilateral implants of 4 contact electrodes. Patients were randomized, double blind over 12 weeks crossover phase. Patients received active treatment and sham treatment. Out 25 patients, 10 patients responded with a decrease of more than 50 percent on the HAM-D scale. (Bergfeld et al., 2016) Lastly, research conducted by Dougherty et al., 2015 a total of thirty patients suffering with treatment resistant depression were enrolled in a sham-controlled trials, focusing on stimulation the ventral capsule/ventral striatum area. The participants were randomly assigned to either active or shame for 16 weeks followed by an open-label continuation phase. The primary outcomes were expected to be a significance in symptoms of more than 50 percent in the Montgomery-Asberg Depression Rating Scale compared to baseline assessment. The results revealed no significant difference in response rate between the active treatment group and the control group. Notably the response rates at 12, 18 and 24 months during the open-label continuation

phase were 20%, 26.7% and 23.3% respectively. DBS is a more invasive treatment than TMS or ketamine and carries the risks associated with brain surgery (Dougherty et al. 2015). While some studies have demonstrated the effectives of DBS in certain cases, other research has shown no discernible changes. Therefore, further investigation is imperative to identify more precise targets and enhance treatment outcomes using DBS.

Researchers are currently exploring the use of transcranial direct current stimulation (tDCS) and focused ultrasound (FUS) as potential treatments for depression. However, it is important to note that these methods have not yet received approval for the treatment of depression. FUS uses high intensity ultrasound waves to selectively target and modulate specific areas of the brain. FUS has been shown to be effective in treating depression in several small-size studies (Jung et al., 2019; Elias et al., 2013). Although FUS may hold promise as a novel and minimally invasive treatment option for the precise mechanisms underlying FUS's impact on depression still needs to be investigated.

tDCS has also shown promise in the treatment of depression as it modulates the activity of the prefrontal cortex, an area of the brain that is underactive in people with depression (Brunoni et al., 2016). Boggio et al., assigned 39 patients to different tDCS treatment groups. Twenty patients were given anodal left DLPFC stimulation, nine patients were given anodal left occipital stimulation and ten were given sham stimulation. In all three groups the cathodal electrode was placed over the right supraorbital region. tDCS was given 5 sessions per week for two weeks and each session consisted of 20 minutes of continuous stimulation using a 2-milliamp current. As a result, 40 percent reduction in depression scale rating for the anodal left dlPFC group, 21.3 percent for the anodal left occipital group and 10.4% for the sham group. There was a 25% remission rate for the anodal left dlPFC group (Rasmussin, 2019). Like FUS, tDCS ongoing research is needed to further understand the optimal tDCS parameters, patient selection criteria and its long-term effects.

1.1.4 Reward Processing in Depression

According to research, individuals who experience depression may face a range of mental and physical symptoms (Smith et al., 2018). One of the most common and profound symptoms associated with depression is anhedonia (Jones & Watson, 2019). Anhedonia refers to the inability to experience pleasure from activities that were previously enjoyable (Rizvi et al., 2016). It is thought that anhedonia is closely related to the brain's reward processing network (Drysdale et al., 2017).
This system is responsible for generating pleasurable feelings in response to various stimuli, such as food, sex, and social interaction (Drysdale et al., 2017). When this system is disrupted, individuals may experience a lack of enjoyment or motivation, leading to reduced participation in activities they once found pleasurable (Jones & Watson, 2019).

Moreover, anhedonia may exacerbate other symptoms of depression, such as low mood, apathy, and fatigue, which can make it even more challenging to engage in pleasurable activities (Rizvi et al., 2016). Thus, recognizing and addressing anhedonia is crucial for effectively treating depression (Smith et al., 2018).

Reward processing is a fundamental aspect of human behavior that involves the brain's response to positive stimuli (Kringelbach & Berridge, 2021). This process is crucial for motivation, decision-making, and learning (Berridge & Kringelbach, 2015). The brain's reward system involves various regions, including the ventral striatum, prefrontal cortex, and amygdala (Haber & Knutson, 2010).
When individuals experience something pleasurable, such as eating a delicious meal or engaging in social interaction, the brain releases dopamine, a neurotransmitter that plays a critical role in reward processing (Schultz, 2015). This release of dopamine reinforces the behavior that led to the positive experience, making it more likely that individuals will engage in that behavior again in the future (Berridge & Kringelbach, 2015). However, chronic exposure to certain rewards can lead to desensitization of the reward system, prompting individuals to

seek out increasingly intense or novel experiences to achieve the same level of pleasure (Kringelbach & Berridge, 2021).

When we experience a reward, such as food, drugs, or social interaction, dopamine is released in the Nucleus Acumens (NAc), which results in a feeling of pleasure and reinforces the behavior that led to the reward (Wise, 2004). Conversely, when we experience a loss or absence of reward, such as social rejection or chronic stress, the dopamine system is dysregulated, leading to anhedonia and a decreased motivation to engage in rewarding behaviors (Treadway & Zald, 2011). Dysfunctional reward processing has been implicated in several psychiatric disorders, including depression, addiction, and schizophrenia (Berridge & Kringelbach, 2015). Furthermore, research has shown that the severity of anhedonia in depressed individuals is positively correlated with the degree of reward processing deficits (Gradin et al., 2011). These findings suggest that targeting reward processing may be an effective therapeutic approach for depression. Recent research has also explored the role of reward processing in addiction, with evidence suggesting that individuals with addiction have altered reward processing that contributes to compulsive drug seeking and use (Koob & Volkow, 2016). Studies using animal models have shown that chronic drug use leads to dysregulation of the dopamine system, resulting in a blunted response to natural rewards and an increased sensitivity to drug-related cues (Koob & Le Moal, 2001).

Reward processing can be disrupted in various psychiatric and neurological disorders, such as addiction and depression (Koob & Volkow, 2016). Understanding how reward processing works in the brain can help researchers develop more effective treatments for these conditions. Additionally, by understanding the neural mechanisms of reward processing, individuals can learn to modify their behaviors and thought patterns to increase positive experiences and improve their overall well-being (Kringelbach & Berridge, 2021). The relationship between reward processing and anhedonia, or the inability to experience pleasure, is also an important area of investigation. Depression is often characterized by decreased sensitivity to positive stimuli and decreased ability to experience pleasure, and these symptoms are thought to be related to alterations in reward

processing. Understanding the neural mechanisms underlying these changes can inform the development of new treatments for depression (Eshel & Roiser, 2010). Overall, the study of reward processing and the facets of pleasure can provide valuable insight into the mechanisms underlying motivation, learning, and emotion, and has important implications for the understanding and treatment of various mental health disorders. The reward circuitry in the brain is made up of several interconnected regions, including the ventral striatum, the prefrontal cortex, and the amygdala. These regions are thought to play a role in the processing of rewards and the regulation of emotions (Haber & Knutson, 2010). Studies have shown that ECT can modulate the activity and anatomy of the reward circuitry, leading to changes in the processing of rewards and a reduction in anhedonia. For example, studies have found that ECT increases activity in the ventral striatum, a key region involved in the processing of rewards (Wang et al., 2016).

There may be also personalities differences between responders and non-responders. Research suggests that personality traits may influence an individual's response to ECT treatment in depression. For example, a study published in the Journal of Affective Disorders (Loo et al., 2008) found that higher levels of neuroticism, a personality trait characterized by negative emotionality and instability, were associated with a poorer response to ECT treatment in depression. Additionally, another study published in the Journal of Psychiatric Research (Sienaert et al., 2011) found that higher levels of extraversion, a personality trait characterized by outgoingness and sociability, were associated with a better response to ECT treatment in depression. However, more research is needed in this area to better understand the relationship between personality traits and ECT treatment outcomes in depression.

1.2 Cognitive Impairments in Depression

Cognitive impairments are a common feature of depression, and they can significantly impact an individual's quality of life. Studies have shown that individuals with depression may exhibit difficulties in several cognitive domains, including attention, working memory, decision making, and

executive functioning (Lee et al., 2017). These impairments can contribute to the development and maintenance of depressive symptoms and may also affect treatment outcomes. For example, deficits in executive functioning have been associated with poorer response to antidepressant medication (Snyder, 2013), suggesting that cognitive impairments should also be considered when planning treatment interventions for depression.

Several factors may contribute to cognitive impairments in depression, including changes in neurotransmitter systems, alterations in brain structure and function, and the effects of stress and inflammation (Roca et al., 2015). For instance, research has shown that individuals with depression have reduced volume in certain brain regions, such as the prefrontal cortex and hippocampus, which are critical for cognitive processes (Campbell et al., 2004). Additionally, inflammation has been linked to both depression and cognitive dysfunction, with some evidence suggesting that cytokines may directly affect brain function and impair cognition (Felger & Miller, 2012). Given the complex interplay between these factors, further research is needed to understand the mechanisms underlying cognitive impairments in depression and develop effective interventions for this population.

While cognitive deficits are present in both responders and non-responders to treatment, some studies have found differences in the severity of cognitive impairments between these two groups. For example, a study by Andreescu et al. (2008) it was observed that the individuals who showed positive responses to the treatment exhibited less pronounced cognitive impairments when compared to those who did not respond to the treatment. Another study by Baune et al. (2012) found that responders had better cognitive function at baseline compared to non-responders. These findings suggest that cognitive deficits may be a predictor of treatment response in TRD, and that addressing these deficits may improve treatment outcomes.

1.2.2 ECT Cognitive Side Effects

Cognitive impairment is one of the most reported side effects of ECT, with studies showing that patients can experience transient deficits in attention, memory, and executive function following treatment (Semkovska et al., 2010). However, the severity and duration of these deficits can vary widely, with some patients experiencing no significant impairment (Fink, 2007). The mechanism by which ECT causes cognitive impairment is not fully understood, but it is thought to be related to changes in cerebral blood flow and glucose metabolism, as well as alterations in neurotransmitter function (Sackeim et al., 2007). Also, the number of ECT sessions received, the electrode placement used, and the patient's age and baseline cognitive status appear to play a role (Lisanby et al., 2016).
Despite persistent endeavors to mitigate the amnesia linked to ECT it has proved to be an issue that continues to be a central concern throughout the entire ECT process. Addressing memory-related matters remains a paramount consideration. Memory related complications encompass a spectrum of manifestations such as postictal disorientation (temporary confusion following s seizure), anterograde amnesia (difficulty forming new memories), retrograde amnesia (difficulty recalling memories), and impairment of subjective memory function, which collectively affect the patient's overall cognitive experience. In response to the challenges with memory loss, there have been pharmacological interventions aimed at reducing the cognitive deficits induced by ECT. These efforts seek to find ways to preserve cognitive function and minimize memory-related concerns in individuals undergoing ECT. (Rasmussen, 2019)

Several investigations have studied the specific cognitive deficits associated with ECT treatment. A meta-analysis by Semkovska and McLoughlin (2010) found that ECT was associated with deficits in autobiographical memory, verbal fluency, and attention in the immediate post-treatment period. Deficits in executive functioning and visuospatial memory were also reported, although the evidence was less consistent. Thomsen and Kessing (2012) found that ECT led to impairments in cognitive flexibility, verbal memory, and learning, which

persisted for up to 6 months after treatment. Other studies have reported that ECT may be associated with deficits in working memory, attention, and processing speed (Haq et al., 2015).
Cognitive deficits associated with ECT are typically transient, with most patients experiencing a return to baseline cognitive function within a few weeks or months after treatment. However, in some patients, cognitive deficits may persist for a longer period, particularly in those with pre-existing cognitive impairments or those who receive multiple courses of ECT (Lisanby et al., 2016).
The ethical considerations surrounding ECT should also be considered given its invasive nature and potential impact on individuals well-being. Ethical concerns primarily revolve around issues of involved consent, as patients undergoing ECT should be adequately informed about the procedure, its potential risks, benefits, and alternatives. The capacity for autonomous decision-making during a depressive episode raises questions about the validity of consent, emphasizing the need for a comprehensive assessment of the patients understanding and voluntariness (Lisanby et al., 2009; Fink, 2001). Additionally, the potential for side effects, such as memory impairment, underscores the importance of ongoing monitoring and transparency in the consent process (Sackeim, 2018). Furthermore, ethical guidelines emphasize the necessity of ensuring that ECT is administered judiciously, with a clear clinical indication, particularly considering its use as a last resort for treatment-resistant cases (American Psychiatric Association, 2001). Ethical principles of beneficence, autonomy and justice underscore the importance of balancing potential therapeutic benefits with the preservation of patients' autonomy and protection from unnecessary harm, reinforcing the need for careful ethical scrutiny in the use of ECT in psychiatric practice.
While it is essential to acknowledge the potential cognitive side effects associated with the therapy it is equally imperative to recognize that for many individuals the benefits of ECT outweigh the risks.

1.3 Neurobiological Aspects

1.3.1 The Neurobiological Understanding in Depression

By identifying brain regions and networks that are altered in MDD patients, neuroimaging studies may also help to guide the development of new treatments and interventions that target these neural circuits (Phillips et al., 2008). Neuroimaging has played a crucial role in advancing our understanding of depression and has the potential to improve the diagnosis, treatment, and outcomes for individuals suffering from this debilitating condition (Cope et al., 2019). Thus, the use of neuroimaging in the study of depression is an important tool that can aid in the development of effective interventions and therapies for individuals with MDD.

Neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), have provided valuable insights into the neural mechanisms underlying depression and the effects of various treatments on the brain. Through neuroimaging, researchers can observe changes in brain activity and connectivity that occur in patients with major depressive disorder (MDD) both before and after treatment with electroconvulsive therapy (ECT) or other interventions (Dukart et al., 2018).

The study conducted by Gong et al., hold significant in the field of depression research as it sheds light on distinct neural basis in individuals who are treatment-resistant and those who respond to antidepressant medications. This differentiation is particularly crucial in understand the heterogenous nature of depression and the varied neural mechanisms underlying treatment response. By identifying neural differences between the drug resistant and non-drug resistant individuals, the research contributes valuable insight that can inform treatment approaches. Such findings have the potential to guide clinicians in tailoring interventions based on the neural profiles of patients ultimately advancing the development of more effective and targeted therapeutic strategies for individuals with treatment-resistant depression. The study underscores the importance of considering neurobiological factors in the understand and treatment of

depression, paving the way for more precise and individualized approaches to address this complex mental health condition.

Several studies have used neuroimaging techniques to investigate the brain anatomical, metabolic, and functional alterations underlying Major Depressive Disorder (MDD). Structural MRI studies have shown that individuals with MDD have reduced volume in the hippocampus, which is involved in memory processing, and the amygdala, which is involved in emotion regulation (MacQueen and Frodl, 2011). Functional MRI (fMRI) studies have revealed altered patterns of brain activity in MDD patients, particularly in regions associated with emotion processing and regulation, such as the amygdala, prefrontal cortex, and anterior cingulate cortex (Seminowicz et al., 2004). Positron emission tomography (PET) studies have shown that individuals with MDD have reduced availability of certain neurotransmitter receptors, such as serotonin and dopamine receptors, in the brain (Drevets et al., 1999). Magnetic resonance spectroscopy (MRS) studies have demonstrated reduced levels of N-acetylaspartate (NAA), a marker of neuronal integrity, in the prefrontal cortex of MDD patients (Hasler et al., 2007).

Depression has been associated with changes in activity levels and/or structural abnormalities in the subgenual anterior cingulate cortex (sgACC). Some studies have shown that patients with depression have higher activity levels in the sgACC compared to healthy individuals, while others have shown decreased activity levels. Additionally, studies the volume of the sgACC was shown to be reduced in individuals with depression (Korgaonkar et al., 2013). The sgACC is thought to play a role in regulating mood, emotional processing, and stress responsiveness, and has been implicated in the development and maintenance of depression. It is also connected to other regions of the brain that are involved in reward processing, including the ventral striatum and the prefrontal cortex (Drevets et al., 2008).

In addition, the structure and function of the hippocampus, a key brain region involved in regulating mood and emotions, may be altered in depression (Campbell et al., 2004; Videbech & Ravnkilde, 2004). Specifically, individuals with depression have been found to have a reduction in the size of the hippocampus,

and this change has been linked to the development of depressive symptoms (McKinnon et al., 2009; Sheline et al., 1999). These findings suggest that changes in the structure and function of the hippocampus may play a critical role in the development of depression.

Some of the key brain regions that are involved in depression include the prefrontal cortex, hippocampus, amygdala, basal ganglia, and anterior cingulate cortex (ACC) (van der Meer et al., 2020; Wei et al., 2020). The prefrontal cortex, involved in regulating mood, attention, and decision-making, has been found to be dysfunctional in patients with depression (Dichter et al., 2012; Hasler, 2019). The hippocampus, a region of the brain that regulates mood, memory, and emotions, has been found to have a reduced volume as well as functional alterations in depressed patients, that are reverted by effective pharmacological treatment, psychotherapy or mindfulness meditation(van der Meer et al., 2020; Wei et al., 2020). The amygdala regulates emotions, particularly fear and anxiety, and may show an increased activity in depression, associated with increased anxiety and negative emotions (van der Meer et al., 2020; Wei et al., 2020). The basal ganglia are involved in regulating movement, mood, and reward processing, and individuals with depression may have changes in their activity, leading to changes in motivation, pleasure, and reward-seeking behavior (van der Meer et al., 2020). The ACC, involved in regulating attention, decision-making, and emotions, may undergo functional alterations in depressed individuals that may contribute to changes in mood regulation and attention (Hasler, 2019).

There is no single cause of depression, as it is a complex and multifaceted condition that can arise from a combination of genetic, environmental, and psychological factors (Kendler et al., 2011). Depression is associated with alterations in the connectivity patterns of different brain regions (van der Meer et al., 2020; Wei et al., 2020). Connectivity refers to the communication and interactions between different brain regions and is crucial for optimal cognitive functioning, including, mood and emotion processing. Studies have shown that individuals with depression have changes in the way different brain regions communicate with each other (Hasler, 2019). For example, there

may be a reduction in connectivity between the prefrontal cortex and other brain regions involved in regulating mood, such as the hippocampus and amygdala (van der Meer et al., 2020; Wei et al., 2020). This reduction in connectivity may contribute to the development of a variety of depressive symptoms, including changes in mood, motivation, and attention. Also, depression may be associated with changes in the default mode network (DMN), a network of brain regions that is active when the brain is at rest and not focused on the external environment (Juruena et al., 2021). The DMN has been implicated in processes such as self-referential thinking, rumination, and the regulation of emotions, and changes in its activity and connectivity patterns have been linked to depression (Juruena et al., 2021). Finally, research has shown that depression is associated with changes in the way the brain processes information about reward and punishment, which is thought to play a role in the development of anhedonia, a core symptom of depression that refers to the inability to experience pleasure and enjoyment (Hasler, 2019). Overall, depression is associated with alterations in the connectivity patterns of different brain regions, which may contribute to the development of depressive symptoms. Further research is needed to fully understand the changes in brain connectivity that underlie depression and develop new and more effective treatments for this condition.
Depression is also associated with changes in the way the brain processes information about reward and punishment, which is thought to play a role in the development of anhedonia, a core symptom of depression referring to the inability to experience pleasure and enjoyment. These alterations in brain connectivity patterns may contribute to the development of depressive symptoms. Further research is needed to fully understand the changes in brain connectivity that underlie depression and develop new and more effective treatments for this condition. A review by Juruena et al. (2021) discussed the current understanding of the neural circuits underlying depression and identified potential future directions for research in this area.

The Ventral Tegmental Area (VTA), a key area in the brain involved in reward processing and mood regulation, has been found to play a crucial role for the development of

depression and the effectiveness of antidepressant treatments (Keedwell et al., 2005; Schmaal et al., 2016; Hernandez & Kourrich, 2016). Keedwell et al. (2005) found that increases in the volume of the VTA can differentiate between responders and non-responders to antidepressant treatment. Schmaal et al. (2016) investigated the functional and structural brain changes in major depressive disorder and the implications for cognitive-emotional symptoms of depression. They found that changes in the VTA and other brain regions could lead to the development of depression. Hernandez and Kourrich (2016) emphasized the role of the VTA in both reward processing and depression, highlighting its importance in understanding the mechanisms underlying these conditions.

The amygdala, a small almond-shaped structure located in the brain's temporal lobe, is involved in processing emotions, particularly fear and anxiety, and has been implicated in several psychiatric disorders, including depression (Kumar et al., 2018). Individuals with depression have been found to have abnormal activity in the amygdala, with increased activity in response to negative stimuli and decreased activity in response to positive stimuli (Kumar et al., 2018). This abnormal activity in the amygdala is thought to play a role in the development and maintenance of depression, particularly in cases where depression is characterized by anhedonia and decreased reward responsiveness (Dichter et al., 2015).

Research suggests that the amygdala may play a critical role in the development of learned helplessness, a phenomenon frequently observed in individuals with depression, characterized by a feeling of helplessness and hopelessness in response to repeated negative events (Maier & Watkins, 2010). The amygdala is connected to other brain regions, including the prefrontal cortex and the hippocampus, that are implicated in emotional regulation and memory, and these connections may contribute to the amygdala's involvement in depression (Cavanna & Trimble, 2006).

Depression is associated with alterations in the production, regulation, and utilization of neurotransmitters, such as serotonin and norepinephrine, in the brain. Serotonin is essential in regulating mood and can impact the activity of brain

regions that regulate mood (Harmer, 2012). Norepinephrine, which is involved in alertness and arousal, has also been implicated in depression, and low levels of norepinephrine have been associated with depressive symptoms (Ressler & Nemeroff, 2000). Inflammation in the brain has also been linked to depression, and chronic inflammation can lead to alterations in the functioning of brain regions involved in mood regulation (Felger & Miller, 2012).

1.3.2 The Neurobiological Understanding of Reward Processing

Reward processing is controlled by the mesolimbic dopamine system, which includes the ventral tegmental area (VTA), the nucleus accumbens (NAc), and the prefrontal cortex (PFC) (Nestler & Carlezon, 2006). The role of reward processing in depression has been extensively studied, with evidence suggesting that individuals with depression have blunted responses to rewarding stimuli, which is thought to contribute to the anhedonia and low motivation characteristic of the disorder (Pizzagalli, 2014). Studies using functional magnetic resonance imaging (fMRI) have shown that depressed individuals have reduced activation in the NAc and PFC in response to rewarding stimuli, compared to healthy controls (Knutson et al., 2008). Individuals with MDD have alterations in brain activity and connectivity within these circuits, which may contribute to the decision-making difficulties commonly seen in depression (Murray et al., 2018). By tracking the changes in reward processing circuits before and after treatment, fMRI can determine whether treatments such as ECT or other therapies are effective in reversing these changes and improving decision-making ability in patients with depression (Liu et al., 2017).

Studies using fMRI have shown that also individuals with addiction exhibit reduced activation in the Nucleus Accumbens (NAc) in response to natural rewards (Joutsa et al., 2012). These findings suggest that targeting reward processing may also hold promise for the treatment of depression, which is

associated with reduced reward sensitivity (Pizzagalli, 2014). To this end, new interventions such as transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) have been developed to modulate reward processing in individuals with addiction, and early studies have demonstrated their potential for reducing drug cravings and promoting abstinence (Shen et al., 2016). Given the similar changes observed in the NAc of individuals with depression and addiction, these interventions may offer a novel approach for the treatment of depression as well.

Reward processing also involves the evaluation and anticipation of rewards and the experience of pleasure or positive affect (Berridge & Kringelbach, 2015). Dysfunction in reward processing is a core feature of depression, with reduced sensitivity to rewards and decreased motivation to engage in pleasurable activities (Pizzagalli, 2014). This is often referred to as anhedonia, which is defined as the loss of pleasure or interest in previously enjoyable activities (Rizvi et al., 2018). Anhedonia is a symptom of both acute and chronic depression and is a predictor of poor treatment response and functional outcome (Treadway & Zald, 2011).

The neural mechanisms underlying reward processing involve several interconnected brain regions, including the prefrontal cortex, striatum, and limbic system (Berridge & Kringelbach, 2015). The prefrontal cortex is involved in the cognitive and evaluative aspects of reward processing, while the striatum and limbic system are involved in the motivational and emotional aspects of reward processing. Neuroimaging studies have identified dysfunction in these regions in depression, particularly in the processing of rewards that involve social and interpersonal experiences (Knutson et al., 2008).

Several studies have examined the impact of ECT on reward processing using fMRI. One such study found that ECT led to increased activation in the ventral striatum, in response to reward cues (Liu et al., 2016). Another study found that ECT improved the ability of depressed patients to learn from positive feedback, suggesting that it may have a positive impact on reward-based learning (Kaiser et al., 2018). A third study found that ECT was associated with increased connectivity between

the ventral striatum and the prefrontal cortex, which may play a role in regulating reward processing (Bartova et al., 2019).
Reward processing plays a significant role in decision making and plays a critical role in several neuropsychiatric disorders, including depression. The Monetary Incentive Delay Task (MID) is a commonly used paradigm for studying reward processing in the brain. According to the reward processing model, this task measures different stages of reward processing, such as reward prediction, anticipation, outcome processing, and consumption under various conditions (Knutson et al., 2001). As already mentioned, patients with depression often exhibit impairments in reward processing and decision making, which can negatively impact their quality of life. For example, depression may be associated with a reduced sensitivity to rewards or an increased sensitivity to punishments, which may affect decision-making abilities (Eshel and Roiser, 2010). Therefore, understanding how depression affects reward and punishment sensitivity and decision making is crucial for the development of effective interventions. As depression often worsens with age, it is essential to understand how depression affects decision-making processes, which can decline due to changes in functional networks (Mather and Carstensen, 2005).
The MID paradigm is useful for investigating reward processing and its relationship with depression. By using the MID task, researchers can gain insights into the different stages of reward processing and how these stages are affected by depression. This information can help researchers better understand how depression affects reward-based learning and decision making and provide a basis for developing more effective treatments for depression.

1.3.3 The neurobiological understanding of ECT

Electroconvulsive therapy (ECT) is a treatment modality for depression that has been found to have significant effects on various brain regions, neurotransmitters, and neural connections associated with depression. Neuroimaging studies have demonstrated alterations in cerebral blood flow and glucose metabolism in the brain following ECT (Bajbouj et al.,

2019). ECT has been shown to modulate the neurotransmission process in the brain, leading to changes in the levels of various biochemical mediators and neurotransmitters, including serotonin, dopamine, acetylcholine, and others (Rami-González et al., 2020). Moreover, ECT has been found to lead to neuroplastic changes in the brain and trigger both neuroprotection and increased neuronal proliferation. A single ECT session can lead to the proliferation of neurons in the dentate gyrus of the hippocampus, and these newly formed neurons can persist for months (Marano et al., 2019). Studies have also shown that ECT leads to changes in the volume of various brain structures, such as gray matter and white matter (Yip et al., 2019). These neuroplastic changes induced by ECT may underlie the therapeutic effects of the intervention in depression.

The amygdala and hippocampus are two key regions that have been shown to be involved in the outcome of depression and ECT. A study by Doesschate et al. (2014) found that pre-treatment amygdala volume may predict response to ECT, with larger amygdala volumes being associated with lower scores on the Montgomery-Asberg Depression Rating Scale (MARS). Other studies have shown that specific sub-regions of the hippocampus, such as the dentate gyrus, might be more sensitive to ECT than others. A study by Marta Cano et al. (2019) showed that right unilateral ECT and bitemporal ECT might have different volumetric outcomes, with bitemporal ECT leading to gray matter increases in both the right and left limbic systems, while right unilateral ECT only led to gray matter increases in the right hemisphere.

According to Lisanby (2018), ECT has been shown to modify the critical brain regions and networks associated with depression, including neurotransmitters and neural connections. ECT alters resting-state functional connectivity in specific brain networks, including those linked with decision making and reward processing (Abbott et al., 2014). Moreover, intra-network connectivity is also impacted by ECT, with increased connectivity observed in brain regions such as the posterior cingulate cortex, the right posterior intraparietal sulcus, the right anterior prefrontal cortex, the dorsal medial prefrontal cortex

(mPFC), the left anterior prefrontal cortex, and the left anterior cingulate cortex (Sartorius et al., 2016).
Even though ECT still remains a very effective, life-saving treatment for severe depression, little is known on its potential effects on the reward processing in the brain. Several studies have examined the impact of ECT on reward processing using fMRI. One such study found that ECT led to increased activation in the ventral striatum, a key component of the brain's reward circuitry, in response to reward cues (Liu et al., 2016). Another study found that ECT improved the ability of depressed patients to learn from positive feedback, suggesting that it may have a positive impact on reward-based learning (Kaiser et al., 2018). A third study found that ECT was associated with increased connectivity between the ventral striatum and the prefrontal cortex, which may play a role in regulating reward processing (Bartova et al., 2019). One method for investigating these effects is the monetary incentive delay (MID) task, which has been used in neuroimaging studies to measure the neural response to rewards and losses (Murray et al., 2015). By examining the effects of ECT on the neural circuits underlying reward processing, researchers may be able to better understand the mechanisms through which ECT exerts its therapeutic effects and identify potential avenues for optimizing its use in the treatment of depression.

The goal of this thesis is to explore the impact of electroconvulsive therapy (ECT) on reward processing in the brain. To pursue this aim, the Monetary Incentive Delay Task (Knutson et al., 2000) will be employed as a tool to assess reward processing, with behavioral and brain activity measures obtained in patients with depression before and after ECT treatment. Additionally, the study will investigate differences between patients who respond to ECT treatment and those who do not. Furthermore, the investigation of the correlation between behavioral measures and brain activation during the task may uncover new information about the relationship between brain function and behavior in patients with depression.

In summary, the following are the main expectations from this study:

1. ECT treatment will lead to a 50%-reduction in depression severity to patients who responded, as measured by HAM-D, QIDS, and PHQ-9 scores, as well as improvements in anhedonia (TEPS), pleasure (SHAPS), positive affect (PANAS), and personality traits (NEO) associated with depression.
2. ECT treatment will have a differential effect on the neural processing of reward, punishment, and neutral cues in the MID task. Specifically, we predict that there will be a significant interaction between ECT treatment and trial type (reward, punishment, neutral) on brain activation in regions involved in reward processing. I expect to see a greater increase in activation to reward cues, a decrease in activation to punishment cues, and no significant change in activation to neutral cues after ECT treatment compared to pre-treatment.
3. ECT treatment in depressed individuals will modulate brain activation in reward, punishment, and neutral cues during the Monetary Incentive Delay (MID) task. Specifically, we predict that ECT treatment will lead to increased activation in reward-related brain regions, such as the ventral striatum, prefrontal cortex, and insula, and decreased activation in punishment-related brain regions, such as the amygdala and anterior cingulate cortex, compared to pre-treatment levels. These changes in brain activation will be assessed by ROI analysis.
4. Within the non-responder group to electroconvulsive therapy (ECT), characterized by patients experiencing less than a 50 percent decrease in depressive symptoms, it is hypothesized that ECT will not significantly impact depression severity. Additionally, smaller improvements in anhedonia, pleasure, positive affect, and relevant personality traits are anticipated compared to the responder group. The study also posits that there will be differential effects of ECT on neural processing in non-responders during the Monetary Incentive Delay (MID) task, predicting specific changes in brain

activation patterns to reward, punishment, and neutral cues. Furthermore, the hypothesis extends to the modulation of brain activation within the non-responder group, foreseeing significantly less impact on activation in reward-related regions and decreased activation in punishment-related areas, as assessed through Region of Interest analysis.

Overall, this study aims to contribute to a deeper understanding of the mechanisms underlying ECT treatment and its effects on reward processing, which may ultimately help to optimize treatment strategies for patients with depression.

Chapter 2

Materials and Methods

2.1 Experimental protocol

2.1.1 Study design

This study was conducted at a single site, where patients with MDD were assessed at four different time points: twice within a period of 10 days before the first ECT session, once after the third ECT treatment, and the final visit within 10 days after completing the acute ECT course. Each visit comprised clinical and behavioral assessments and lasted approximately four hours. fMRI scan exam also was performed at each visit (see table 1).

	Pre-ECT Visit 1	Pre ECT Visit 2	3rd Session ECT Visit 3	Post-Acute ECT Visit 4
Behavioral Measures	X		X	X
fMRI Scan	X	X	X	X
Computer Task	X	X	X	X

Table 2.1. Study Design. Outlines of the study design, conducted at a single site, for patients diagnosed with Major Depressive Disorder (MDD). The assessments occurred at four distinct time points: firstly, twice within a 10-day period before the first Electroconvulsive Therapy (ECT) session (Visit 1 and Visit 2); secondly, once after the completion of the third ECT treatment (Visit 3); and finally, within 10 days after finishing the acute ECT course (Visit 4). Each visit, lasting approximately four hours, included clinical and behavioral assessments. Additionally, functional Magnetic Resonance Imaging (fMRI) scan examinations were performed at each visit, as detailed in Table 1. This table serves as a chronological reference for the study, emphasizing key moments in the treatment process and providing

insights into the patients' clinical, behavioral, and neural status across the study period.

2.1.2 Participants

The study encompassed four key time points for each participant: two assessments within a 10-day span preceding the first Electroconvulsive Therapy (ECT) session (Visit 1 and Visit 2), one assessment after the third ECT treatment (Visit 3), and a final assessment within 10 days following the conclusion of the acute ECT course (Visit 4).

For the analysis of behavioral assessments, our study engaged a cohort of 18 participants. A comprehensive dataset was meticulously compiled during Visit 1, Visit 3, and Visit 4, except for Visit 2.

For the analysis of functional Magnetic Resonance Imaging (fMRI) data, the study included 17 participants who completed the scans at each visit. All the subjects were recruited at the Massachusetts General Hospital ECT service. All patients had a diagnosis of Major Depressive Disorder either isolated or in comorbidity with other conditions, as listed in Table 2. Psychiatric diagnoses were established using clinical interview and the Mini-International Neuropsychiatric Interview 6.0 (MINI) (Sheehan et al., 1998). All patients signed an informed written consent to the study. The study was conducted under a Review Board approved by the ethical committee at Harvard University Medical Center.

Subjects	Sex F:M	Age at Study	Diagnosis	ECT Electrode Placement	Responder not responder R:NR	Days Between V4 & Last Treatment
1	M	38	MDD, Suicidality, Social Phobia/Anxiety, GAD	RUL	Non-responder	-1

2	F	48	MDD	RUL	responder	3
3	F	48	MDD, Panic Disorder, Social Phobia/Anxiety, GAD	RUL	Non-responder	18
4	M	54	MDD	RUL	responder	9
5	F	63	MDD, Suicidality, Panic Disorder	RUL	responder	2
6	M	32	MDD, Social Phobia/Anxiety, Bipolar II, PTSD, Alcohol Dependence, Suicidality	RUL	Non-responder	8
7	F	65	MDD, Mania, Bipolar I	RUL	responder	6
8	F	42	MDD, Suicidality, PTSD, GAD	RUL	responder	6
9	F	30	MDD, Suicidality, Panic Disorder, GAD	RUL, BF	responder	2
10	M	63	MDD, Bipolar II, PTSD, Substance Dependence, GAD	RUL,	responder	2
11	F	28	MDD, Bipolar II	RUL, BF	responder	2
12	F	53	MDD, Suicidality, Panic Disorder	RUL, BF, BL	responder	9
13	M	40	MDD, Suicidality, Hypomanic Disorder, Bipolar I, Panic Disorder, GAD, Substance Abuse	RUL	responder	6
14	M	55	MDD	RUL	responder	2
15	F	30	MDD	RUL, BL	Non-responder	97

16	F	18	MDD	RUL	Non-responder	6
17	F	64	MDD	RUL, BF	Non-responder	5
18	M	25	MDD, Anorexia	RUL, BF	Non-responder	22
	(F:M)11:7	44.2 (SD:14.9)			R:NR (11:7)	

Table 2.2. Demographics based on Behavioral Measures and Completers. Demographic information for study participants based on behavioral measures and treatment completion. The table includes the subject ID, sex, age at study, diagnosis, ECT electrode placement, responder or non-responder status, and days between the last treatment and the fourth visit. The gender ratio of females to males was 11:7, and the average age of participants was 44.22 years (SD: 14.92). The ECT electrode placement was predominantly right unilateral (RUL), with some participants also receiving bilateral (BL) or bifrontal (BF) placement.

Subjects	Sex F:M	Age at Study	Diagnosis	ECT Electrode Placement	Responder not responder R:NR	Days Between V4 & Last Treatment
1	F	48	MDD	RUL	responder	3
2	F	48	MDD, Panic Disorder, Social Phobia/Anxiety, GAD	RUL	Non-responder	18
3	M	54	MDD	RUL	responder	9
4	F	63	MDD, Suicidality, Panic Disorder	RUL	responder	2
5	M	32	MDD, Social Phobia/Anxiety, Bipolar II, PTSD, Alcohol Dependence, Suicidality	RUL	Non-responder	8
6	F	65	MDD, Mania, Bipolar I	RUL	responder	6
7	F	42	MDD, Suicidality, PTSD, GAD	RUL	responder	6
8	F	30	MDD, Suicidality, Panic Disorder, GAD	RUL, BF	responder	2
9	M	63	MDD, Bipolar II, PTSD, Substance Dependence, GAD	RUL,	responder	2
10	F	28	MDD, Bipolar II	RUL, BF	responder	2
11	F	53	MDD, Suicidality, Panic Disorder	RUL, BF, BL	responder	9
12	M	40	MDD, Suicidality, Hypomanic Disorder, Bipolar I, Panic	RUL	responder	6

			Disorder, GAD, Substance Abuse			
13	M	55	MDD	RUL	responder	2
14	F	30	MDD	RUL, BL	Non-responder	97
15	F	18	MDD	RUL	Non-responder	6
16	F	40	MDD, Suicidality	RUL, BF	Non-responder	7
17	M	29	MDD, Agoraphobia, Social Phobia, PTSD, Alcohol Abuse, GAD,	RUL, BF	Non-responder	4
	(F:M)11:6	43.4, SD: 14.1			R:NR (11:6)	

Table 2.3. Demographics based on Available fMRI data and Completers. Demographic information for study participants based on available fMRI data and treatment completion.

Demographics/Depression Scores	Responders (n=11)	Non-Responders (n=7)
Age	45.25(SD=12.18)	44.57 (SD=18.43)
Gender F:M Ratio	2:5	3:5
Mean HAM-D	Pre ECT 25.36(SD=5.18) Post ECT 7.9 (SD=4.11)	Pre ECT 24.57 (SD=5.94) Post ECT 20 (SD=3.51)
Mean PhQ-9	Pre ECT 20.45 (SD=2.01) Post ECT 6.0 (SD=3.25)	Pre ECT 14.85(SD=5.40) Post ECT 12.857 (SD=5.34)
Mean QIDS	Pre ECT 23.38(SD=3.78) Post ECT 7.25 (SD=4.30)	Pre ECT 16.9(SD=6.04) Post ECT 14.1 (SD=5.01)

Table 2.4. Demographic Characteristics and Depression Scores of Responders and Non-Responders, the first column shows the demographic and depression score information, while the second and third columns show the corresponding values for responders and non-responders, respectively. The age of participants was similar between groups, with a mean age of around 45 years. The gender distribution was also similar between groups, with a slightly higher proportion of females in the responders group. The table also shows the mean scores on the Hamilton Depression Rating Scale (HAM-D), Patient Health Questionnaire-9 (PHQ-9), and Quick Inventory of Depressive Symptomatology (QIDS) before and after ECT for each group. Responders had higher pre-ECT scores on these measures compared to non-responders, but achieved much lower post-ECT scores, indicating a more significant reduction in depression symptoms.

2.1.3 Data Collection

Demographic information, clinical data, and psychometric data were collected from each participant. Demographic information included age, gender, race, and education level. Clinical data included diagnosis, medication status, and duration of illness. Psychometric data was collected using behavioral measures and analyzed with IBM® SPSS® Statistics using nonparametric tests.

2.1.4 Computer Task

To evaluate reward processing, participants completed a modified version of the card guessing task, which was originally created by Delgado and Fiez (Delgado et al. 2000). The task was administered using E-Prime® Psychology Software Tools software on a computer. Each trial of the task lasted up to 2500 ms and involved participants guessing whether a number on a card was greater or less than 5 by pressing one of two buttons on a response box. The card could contain any number from 1 to 9, and after the participant responded or the 1500 ms time limit was reached, feedback was presented for 1000 ms. Feedback consisted of indicating whether the trial was a reward, loss, or neutral trial by displaying a green up arrow with "$1" for reward trials, a red down arrow next to "-$0.50" for loss trials, or the number 5 and a gray double-headed arrow for neutral trials. The task was separated into blocks of 8 trials, with each block being either mostly reward or mostly loss. Each block contained either 6 reward trials pseudo-randomly interleaved with either 1 neutral and 1 loss trial, 2 neutral trials, or 2 loss trials, or 6 loss trials pseudo-randomly interleaved with either 1 neutral and 1 reward trial, 2 neutral trials, or 2 reward trials. Each of the two runs of the task had 2 mostly reward and 2 mostly loss blocks, which were interleaved with 4 fixation blocks lasting 15 seconds each. During the inter-trial interval (ITI) between trials, which lasted 1000 ms, a fixation cross was displayed.

2.1.5 ECT Treatment Parameters

Seventeen patients diagnosed with depression received ultra-brief and brief pulse ECT treatment using a MECTA spECTrum 5000Q machine (Portland, Oregon). Between Visits 3 and 4, all patients, except for seven, received right unilateral (RUL) electroconvulsive therapy (ECT) treatment, while the remaining participants underwent a combination of RUL, bifrontal (BF), and/or bitemporal (BL) ECT electrode placement.

The anesthesia for the procedure was administered using methohexital (0.8-1.2 mg kg−1) for induction and succinylcholine (0.5-1 mg kg−1) for muscle relaxation. The stimulus dose was titrated by determining the seizure threshold, with the initial dose starting at 19 millicoulombs for women and 38 millicoulombs for men. Subsequent treatments were conducted at six times the estimated seizure threshold. During the acute course of ECT, patients received treatment three times a week, every other day.

2.1.6 Behavioral Measures

Participants completed a battery of behavioral measures to assess mood, personality, and social and emotional functioning. The battery of measures included in this study are detailed in the figure and cover a range of constructs such as trait anxiety, emotional intelligence, self-esteem, and social support, among others. The measures were selected based on their relevance to the study's research questions and were administered to participants prior to any experimental procedures. The battery of behavioral measures provided a comprehensive assessment of participants' psychological functioning and allowed for a more nuanced understanding of the relationships between various constructs and the experimental outcomes.

All participants underwent a clinical evaluation utilizing the Quick Inventory of Depressive Symptomatology (QIDS)

(Rush et al., 2003) to assess the severity of the disorder and the Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995) to evaluate anhedonia symptomatology. A clinical response was defined as a reduction of 50% or more across scores on the PhQ-9 QIDS and HAM-D. Additionally, the Temporal Experience of Pleasure Scale (TEPS) (Gard et al., 2006) was employed to assess both anticipatory and consummatory subconstructs of reward processing. The NEO personality assessment and the Anxiety Sensitive Score was also administered. Remission was defined as a reduction in score of 50% or more in rating scores, and partial response as a reduction of 25-49%.

Measure	Description
Hamilton Depression Rating Scale (HAM-D)	A widely used clinician-administered measure of depression severity, the HAM-D assesses 17 symptoms of depression, including mood, sleep, appetite, and energy level.
Patient Health Questionnaire-9 (PHQ-9)	A self-report measure of depression severity, the PHQ-9 assesses the frequency and severity of nine symptoms of depression, such as sadness, fatigue, and suicidal ideation.
NEO Personality Inventory	A self-report measure of personality, the NEO assesses the five-factor model of personality, including openness, conscientiousness, extraversion, agreeableness, and neuroticism.
Snaith-Hamilton Pleasure Scale (SHAPS)	A self-report measure of anhedonia, the SHAPS assesses the ability to experience pleasure in everyday activities.
Temporal Experience of Pleasure Scale (TEPS)	A self-report measure of anhedonia, the TEPS assesses the ability to experience pleasure in various domains, such as social, recreational, and sensory experiences.
(QIDS)Quick Inventory of Depressive Symptomatology	A self-report measure of depression severity, assessing the severity of depressive symptoms
Anxiety Sensitivity Index (ASI)	The Anxiety Sensitivity Index (ASI) is a psychometric self-report assessment tool designed to measure an individual's level of anxiety sensitivity

Table 2.4. Behavioral Measures for Assessing Mood, Personality, and Social and Emotional Functioning. List of behavioral measures to assess their mood, personality, and social and emotional functioning. The Hamilton Depression Rating Scale (HAM-D) is a widely used clinician-administered measure of depression severity, while the Patient Health Questionnaire-9 (PHQ-9) is a self-report measure of depression severity. The NEO Personality Inventory is a self-report measure of personality, assessing the five-factor model of personality, and the Snaith-Hamilton Pleasure Scale (SHAPS) and Temporal Experience of Pleasure Scale (TEPS) are self-report measures of anhedonia, assessing the ability to experience pleasure in everyday activities and various domains, respectively. The Quick Inventory of Depressive Symptomatology (QIDS) is also included as a self-report measure of depression severity.

2.2 Image Acquisition and Preprocessing

(T1) Each patient underwent four scans: two conducted prior to the initial electroconvulsive therapy (ECT) session, one after the third ECT session, and another upon completion of the acute ECT course. Imaging was performed using a 3.0-T Siemens Prisma scanner, equipped with a 64-channel phased-array head/neck coil. The imaging parameters included a repetition time (TR) of 2400 ms, an inversion time (TI) of 1060 ms, an echo time (TE) of 2.24 ms, a flip angle (FA) of 8 degrees, 0.8 mm isotropic voxels, 208 slices per slab, GRAPPA acceleration factor of 2, and an acquisition time of 6 minutes and 38 seconds.

(Functional) The functional MRI (fMRI) acquisition protocol for the Human Connectome Project (HCP) on a Siemens Prisma scanner is characterized by a repetition time (TR) of 720 ms, an echo time (TE) of 33.1 ms, and a flip angle of 52 degrees. The imaging parameters include a voxel size of 2.0 mm isotropic, a field of view measuring 208 x 180 mm, and a matrix size of 104 x 90. The phase encoding direction is set to Posterior to Anterior (PA), with a slice thickness of 2.0 mm and a total of 72 slices acquired. Employing a multi-band acceleration factor of 8, each run of the resting-state fMRI (rs-fMRI) sequence lasts 5 minutes and 12 seconds. The entire acquisition consists of four runs, providing a comprehensive dataset for functional connectivity analyses.

The preprocessing steps used in this study were implemented using *fMRIPrep* (NeuroImaging PREProcessing toolS) application (www.nipreps.org), which is a widely used open-source software tool for fMRI data preprocessing. The preprocessing steps included standard steps such as skull stripping, motion correction, field map distortion correction, slice-timing correction, spatial smoothing, and normalization to a standard MNI brain template, denoising and brain masking.

2.2.1. Region of interest (ROI)

AFNI_17.1.12 software package was used to analyze regions of interest. Anatomical masks from the Harvard/Oxford cortical and subcortical atlases were used to define regions of interest (ROIs). The ROIs included in the analysis are the left and right thalamus, left and right caudate, left, and right hippocampus, left and right amygdala, left and right nucleus accumbens, left and right putamen, frontal medial cortex, paracingulate gyrus, as well as posterior and anterior cingulate gyrus, anterior and posterior parahippocampal gyrus, and the superior and middle frontal gyrus.

2.2.2 Neuroimaging Analysis and statistics

All data analyses were conducted using AFNI and IBM® SPSS® Statistics software. The primary outcome measures for the study were changes in brain activation and reward processing before and after ECT treatment. Brain activation was measured using fMRI and analyzed using standard methods, including t-tests, general linear modeling, and region-of-interest analyses. Changes in depression severity and behavioral function were also analyzed using descriptive statistics. To assess changes over time, a repeated-measures design was used, with visit as a within-subjects factor. Linear mixed-effects models were used to analyze fMRI data, with visit as the independent variable and brain activation as the dependent variable. The models included participant-level random effects to account for individual differences in brain activation. The primary outcome measure for the card guessing task was response time, which was defined as the time from the onset of the card to the participant's button press. In addition, accuracy, and the number of missed trials were recorded. The primary analyses focused on the response time data, which was averaged across trials for each participant. A mixed-effects model was used to analyze the data, with trial type (reward, loss, neutral) and block type (mostly reward, mostly loss) as within-subjects factors, and sex as a between-subjects factor. Post-hoc analyses

were conducted to examine the effects of sex on the primary outcomes.

The statistical methods used in this study involved analyzing demographic, clinical, and psychometric data using nonparametric tests in SPSS. Specifically, the psychometric data was analyzed using nonparametric tests, while ANOVA with post-hoc tests were used to analyze behavioral measures. In addition, the fMRI data was analyzed using the RegANA approach in the AFNI software package, and ROI (region of interest) analysis was performed to identify brain regions involved in the task or condition of interest. The use of nonparametric tests allowed for robust analysis of data that may not be normally distributed, while ANOVA and ROI analysis provided additional insight into the relationship between

Chapter 3

Electroconvulsive Therapy (ECT): Evaluating Treatment Response and Clinical Outcomes in Major Depression

3.1 Behavioral Measures Analysis

3.1.1 Evaluation of ECT Treatment Response and Clinical Outcomes in Patients with Major Depression

In this study, I examined the response to ECT treatment and clinical outcomes in 18 patients who had been diagnosed with major depressive disorder. We utilized the Hamilton Rating Scale for Depression (HAM-D), PHQ-9 and QIDS scores to measure the response at three different time points: prior to ECT, after the third ECT visit, and following the fourth and final visit post-acute ECT treatments. After the ECT treatment, the average HAM-D score significantly decreased from 25.2 at baseline to 20.6 at Visit 3 ($p<0.001$) and 12.6 at Visit 4 ($p<0.001$). The mean PhQ-9 score significantly decreased from 18.2 at baseline to 14.3 at Visit 3 ($p=.003$) and to 8.4 at Visit 4 ($p<0.001$). Finally, the mean QIDS score significantly decreased from 19.7 at baseline to 17.4 at Visit 3 ($p=.006$) and to 11.1 after the last ECT session ($p<0.001$). The HAM-D and PhQ-9 scores indicated a response rate of at least 50%. There was no significant change in scores between Visit 1 and Visit 3.

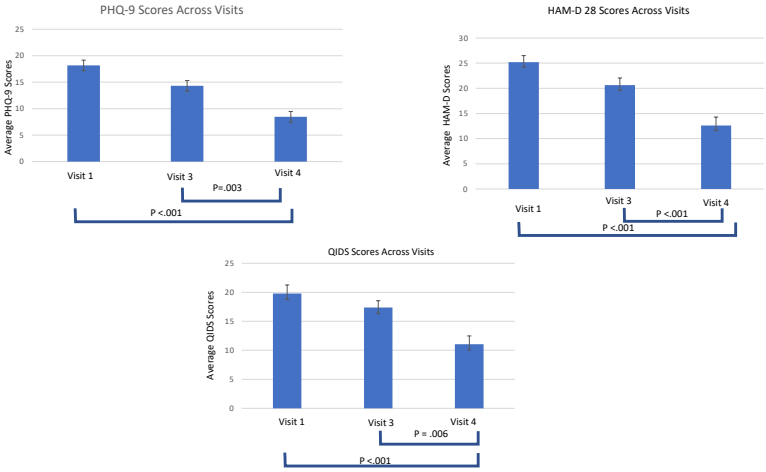


Figure 3.1. **Depression Score Changes Across Visits.** Changes in depression scores for patients undergoing electroconvulsive therapy (ECT) over the course of their treatment visits. The graph shows a significant drop in depression scores between the initial visit and subsequent visits, indicating a positive response to ECT treatment. The changes in depression scores are particularly noticeable between the first and fourth visit, with a smaller but still significant drop between visits three and four. Bars represent the mean scores. Errorbar is the SEM.

Significant scores fluctuations on the Temporal Experience of Pleasure Scale (TEPS; Figure 3.2A), and the Snaith-Hamilton Pleasure Scale (SHAPS; Figue 3.2B) where found throughout the course of electroconvulsive therapy (ECT). Specifically, we found that TEPS-ANT showed a strong effect between visit 3 and visit 4, whereas there were no significant differences between visit 3 and visit 4 in TEPS-CON. These findings suggest that certain dimensions of anhedonia may be more responsive to ECT treatment than others. On the other hand, the analysis of SHAPS scores reveals significant changes across all three visits suggesting that ECT treatment may have a more generalized effect on anhedonia, regardless of the specific dimensions

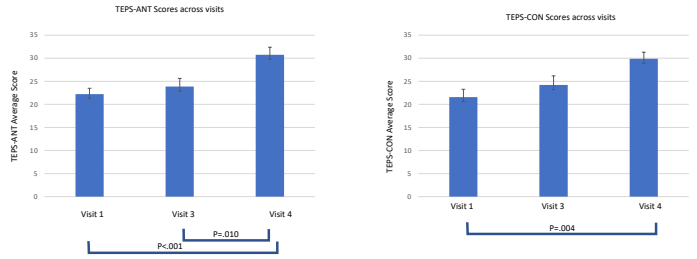
measured by the scale. This highlights the potential of ECT as a broad-spectrum treatment for depression, capable of improving a range of symptoms, including anhedonia.

Moreover, we found a significant difference in PANAS positive score between Visit 1 and Visit 3 ($p=.013$) and between Visit 3 and Visit 4 ($p=.019$), with no significant difference observed between Visit 3 and Visit 4 (Figure 3.2.B). On the other hand, there was a significant difference in PANAS negative score between Visit 1 and Visit 4 ($p=.008$) and between Visit 3 and Visit 4 ($p=.008$), with no significant difference observed between Visit 1 and Visit 3 (Figure 3.2.B). These finding suggest that ECT treatment may initially help with positive affect and then negative affect, indicating that different emotional aspects respond differently to ECT treatment. A significant increase in PANAS positive score indicates that the patients reported experiencing more positive emotions, such as joy, excitement, enthusiasm, and contentment, after the ECT treatment compared to their baseline levels. These results suggest an improvement in the patients' overall emotional state following the ECT treatment, which may be indicative of a reduction in depressive symptoms and an improvement in emotional well-being - one of the intended outcomes of ECT treatment for major depression. Additionally, a significant decrease in PANAS negative score indicates that the patients reported experiencing fewer negative emotions, such as sadness, fear, anger, and guilt, after the ECT treatment compared to their baseline levels. This result suggests an improvement in the patients' overall emotional state following the ECT treatment, which may be indicative of a reduction in depressive symptoms and an improvement in emotional well-being. Importantly, a significant decrease in PANAS negative score indicates that the ECT treatment may have been effective in reducing negative emotions associated with depression.

However, our investigation did not reveal any significant changes in NEO scores or Anxiety Sensitivity Index (ASI) scores over the course of ECT treatment. While the lack of results in the NEO may seem discouraging at first glance, they are quite important. The lack of significant changes in NEO scores

suggests that personality traits may not be a major factor in predicting treatment outcomes for depression. This could be a valuable finding as it may help to dispel some common misconceptions about the role of personality in mental health treatment, and instead focus on other factors that may be more directly related to treatment response. The lack of change in ASI scores may be concerning for patients with comorbid anxiety. Anxiety sensitivity is the fear of anxiety-related sensations and can be a major issue for patients with comorbid anxiety and depression. It is possible that some patients in our sample may have had comorbid anxiety, and the lack of change in ASI scores may indicate that ECT treatment did not effectively address their anxiety symptoms. This could have implications for the long-term treatment outcomes of these patients and may require further investigation. Furthermore, the lack of change in ASI scores may suggest that ECT treatment may not be as effective for patients with comorbid anxiety and depression as it is for those with depression alone. This finding could inform the development of more targeted treatment approaches that address both depression and anxiety symptoms in patients with comorbid conditions.

A



B

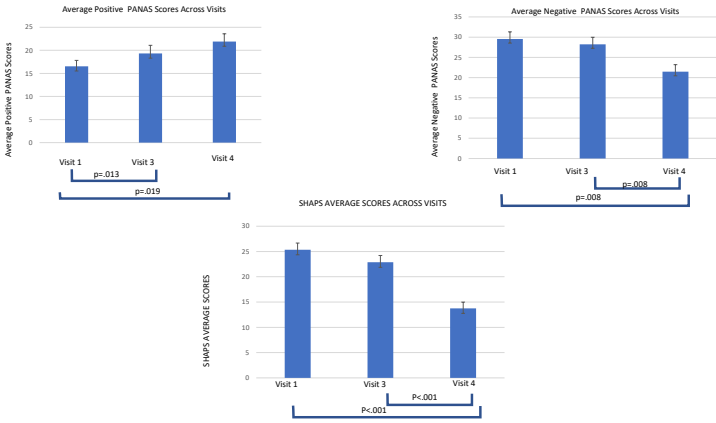


Figure 3.2. Changes in Measures Related to Anhedonia and Pleasure: TEPS-ANT and TEPS-CON displays. A) Changes in measures related to anhedonia and pleasure in patients undergoing electroconvulsive therapy (ECT). Specifically, it shows changes in scores on the TEPS-ANT (Temporal Experience of Pleasure Scale - Anticipatory subscale) and TEPS-CON (Temporal Experience of Pleasure Scale -Consummatory subscale) between pre-treatment and post-treatment visits. The graph indicates that there was a significant change in TEPS-ANT scores between visits 3 and 4, with little change observed in TEPS-CON scores over the same period. B) Changes in Measures Related to Anhedonia and Pleasure: SHAPS, PANAS-POS & PANAS-NEG. These results suggest that ECT treatment may have a more specific effect on anhedonia compared to general affective symptoms of depression. Bar represent mean scores. Errorbar is the SEM.

3.2. Brain activity during the Monetary Incentive Delay Task as measured by fMRI scan examination.

3.2.1 Three-way Analysis of Variance

The AFNI (Analysis of Functional Neuroimages) software's 3dANOVA3 command was utilized to perform a comprehensive three-way mixed ANOVA analysis. This analysis aimed to explore brain activation patterns in response to reward, punishment, and neutral stimuli across the different times of ECT treatment (visit 1, visit 3, and visit 4) within a cohort of 17 participants. Employing a random-effects model, the subjects were considered a random factor, while the fixed variables encompassed the different treatment visits and the three distinct stimuli employed in the MID task. Contrasts were conducted to investigate the influence of time and task on brain activation, as well as to uncover dissimilarities and resemblances between the reward, punishment, and neutral conditions at different time points. F-tests were carried out across three dimensions: factor A, symbolizing visit 1, visit 3, and visit 4; factor B, corresponding to reward, punishment, and neutral stimuli; and the interaction arising from the interplay between factors A and B. Further analyses included the examination of contrasts among the distinct time points of treatment. These contrasts encompassed the pre-treatment and post-treatment phases, the pre-treatment and visit 3 stages, and comparisons between visit 3 and visit 4. Furthermore, a specific focus was placed on examining variations tied to the presence of rewards or punishments between different visits. Overall task activation produced distinct clusters. Positive clusters in key regions including the left supplementary motor area (SMA), the right middle frontal gyrus and the left insula lobe. Conversely, negative clusters were observed in the supramarginal gyrus and the left caudate nucleus. All regions were statistically significant at the level of $p<.001$. Table 3, Figure 3 illustrates the results. For a visual representation of these findings, please refer to Table 3 and Figure 3.

In response to reward stimuli, robust neural activations were observed, marked by significant positive and negative clusters reaching the threshold of $p < .001$. Positive clusters were evident in key regions including the left supplementary motor area (SMA), the right and left insula, the right middle frontal gyrus, and the right hippocampus. Conversely, negative clusters exhibited activations in the left supramarginal temporal gyrus, left hippocampus, left superior frontal gyrus, and left middle frontal gyrus. Similarly, neural response to punishment stimuli also displayed substantial activations, characterized by significant positive and negative clusters achieving significance at $p < .001$. Positive clusters emerged in the right insula lobe, right middle frontal gyrus, and the left SMA. Additionally, positive clusters were observed in the right middle frontal gyrus. Conversely, negative clusters manifested in the right superior temporal gyrus, right middle temporal gyrus, right SMA, left middle temporal gyrus, and left superior temporal gyrus. For a visual representation of these findings, please refer to Tables 5 and 6 and Figures 4 and 5.

The contrasts between pre- and post-ECT conditions revealed multiple activations characterized by significant positive and negative clusters ($p < .001$). Positive activations were observed in the right middle frontal gyrus and the left middle frontal gyrus, while negative clusters emerged in the left putamen and the right putamen. When comparing visit 1 and visit 3, significant activations were identified exclusively in the form of significant positive clusters, surpassing the threshold of $p < .001$. No negative clusters were detected in this comparison. Specifically, positive activations were evident in the right middle frontal gyrus, right inferior temporal gyrus, left supramarginal gyrus, left insula lobe, left superior medial gyrus, and right superior frontal gyrus. Contrasting visit 3 and visit 4, significant activations were observed, encompassing both positive and negative clusters reaching the threshold of $p < .001$. Positive activations included the right middle frontal gyrus, left superior medial gyrus, left middle frontal gyrus, and the left supplementary motor area (SMA). Additionally, a single negative cluster activation was identified in the left putamen.

For a visual representation of these findings, please refer to Tables 7, 8 and 9 and Figures 6, 7 and 8.

Significant contrasts between reward and punishment were observed, surpassing the threshold of $p < .001$. Positive cluster activations were identified in the left middle frontal gyrus and the right caudate nucleus. However, no negative clusters were found in relation to the differences between reward and punishment. Similarities between the neural responses to reward and punishment also reached the significance level of $p < .001$. Positive clusters were present in the right insula lobe and the right middle cingulate cortex. Notably, no negative clusters were detected in relation to the shared aspects of reward and punishment processing. For a visual representation of these findings, please refer to Tables 10 and 11 and Figures 9 and 10.

Significant contrasts in the responses to reward stimuli before and after treatment manifested as positive clusters with a significance level of $p < .001$, localized in the left supplementary motor area (SMA) and the left anterior cingulate gyrus. Conversely, no negative clusters were discerned in this context. For punishment stimuli responses, disparities before and after treatment were characterized by positive clusters with a significance level of $p < .001$, observed in the left superior medial gyrus and the left hippocampus. As for the reward stimuli findings, no negative clusters were identified in the case of punishment stimuli changes before and after treatment. For a visual representation of these findings, please refer to Tables 12 and 13 and Figures 11 and 12.

Noticeable disparities in the reactions to reward stimuli between visit 1 and visit 3 were observed, yielding significant positive clusters at a significance level of $p < .001$ in the left putamen, right putamen, and the left supplementary motor area (SMA). No negative clusters emerged in this context. Similarly, substantial differences in the response to punishment stimuli between visit 1 and visit 3 were observed, with positive significant ($p < .001$), specifically centered in the left hippocampus. No negative clusters were triggered in relation to

the alterations in punishment stimuli responses between these visits. For a visual representation of these findings, please refer to Tables 14 and15 and Figures 13 and 14.

Evident discrepancies were observed in the responses to reward stimuli between visit 3 and visit 4, resulting in noteworthy significant positive clusters at a significance level of $p < .001$ in the left supplementary motor area (SMA). Intriguingly, no significant negative clusters were activated in this comparison. On the other hand, notable variations were identified in the response to punishment stimuli between visit 3 and visit 4, primarily manifested in negative clusters within the left putamen at a significance level of $p < .001$. It's important to note that no significant positive clusters were discerned in this specific context. For a visual representation of these findings, please refer to Tables 16 and17 and Figures 15 and 16.

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Left SMA	255 voxels	[-3.5, -17.5, 49.5]
Right Middle Frontal Gyrus	137 voxels	[-41.5, 39.5, 29.5]
Left Insula Lobe	135 voxels	[32.5, -19.5, 11.5]
Negative Clusters		
Supramarginal Gyrus	239 voxels	[-47.5, 30.5, 25.5]
Left Caudate Nucleus	42 voxels	[2.5, -17.5, -2.5]

Table 3.5: Overall Neural response during the MID Task.

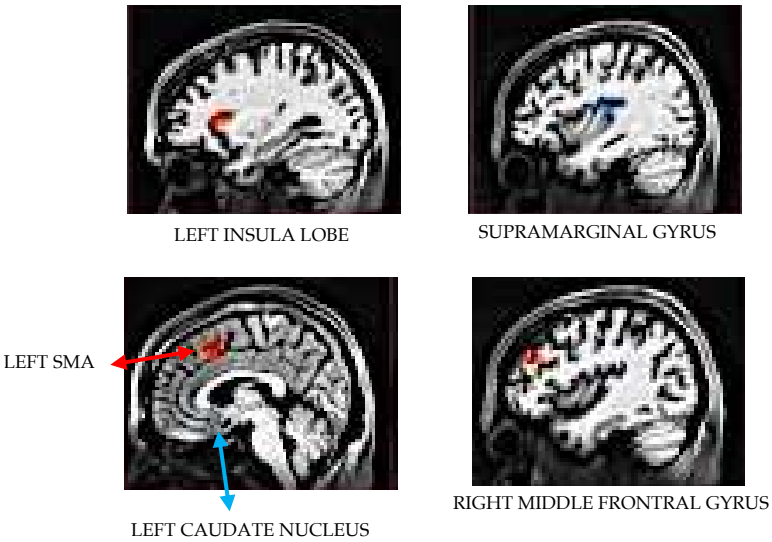


Figure 3.3: Overall brain activation during the MID Task.

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Left SMA	443 voxels	[-3.5, -9.5, +49.5]
Right Insula Lobe	366 voxels	[-31.5, -23.5, 9.5]
Left Insula Lobe	305 voxels	[32.5, -19.5, 11.5]
Right middle frontal gyrus	114 voxels	[-47.5, -33.5, 21.5]
Right Hippocampus	69 voxels	[-23.5, 26.5, -6.5]
Negative Clusters		
Right SMA	162 voxels	[-3.5, 16.5, 51.5]
Left Supramarginal Temporal Gyrus	139 voxels	[62.5, 32.5, 15.5]
Left Hippocampus	114 voxels	[24.5, 20.5, -16.5]
Left Superior Frontal gyrus	95 voxels	[42.5, 14.5, -2.5]
Left middle frontal gyrus	65 voxels	[26.5, -31.5, 49.5]

Table 3.6: Brain response to positive stimuli during the MID Task.

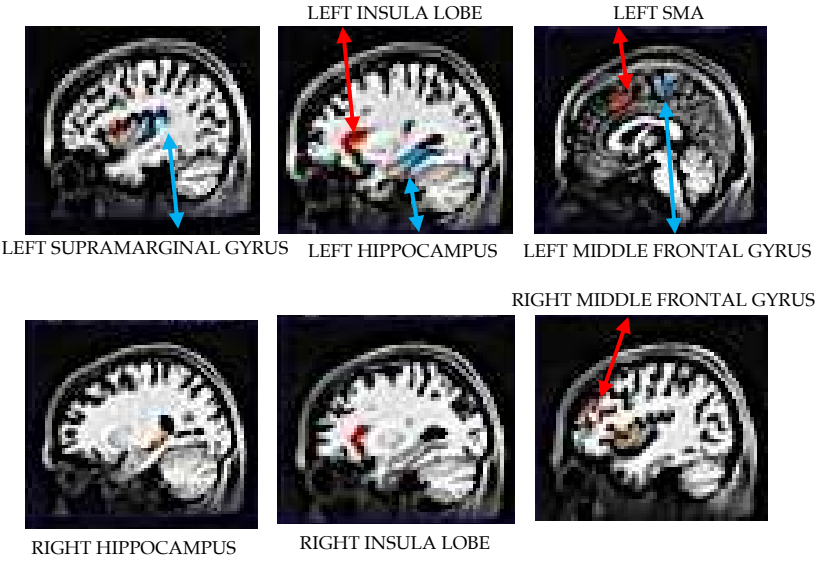


Figure 3.4: Brain regions involved in response to positive stimuli.

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Right Insula Lobe	413 voxels	[-31.5, -21.5, 9.5]
Right Middle Cingulate Cortex	238 voxels	[-7.5, -25.5, 35.5]
Right Middle Frontal Gyrus	145 voxels	[-43.5, -31.5, 21.5]
Left_SMA	81 voxels	[6.5, -9.5, 47.5]
Left Insula Lobe	56 voxels	[32.5, -19.5, 11.5]
Negative Clusters		
Right Superior Temporal Gyrus	1168 voxels	[-65.5, 25, 5.5]
Right Middle Temporal Gyrus	146 voxels	[-63.5, 4.5, -14.5]
Right SMA	90 voxels	[-3.5, 16.5, 51.5]
Left Middle Temporal Gyrus	55 voxels	[62.5, 6.5, -12.5]
Left Superior Temporal Gyrus	55 voxels	[44.5, 34.5,13.5]

Table 3.7. Brain response to negative stimuli during the MID Task.

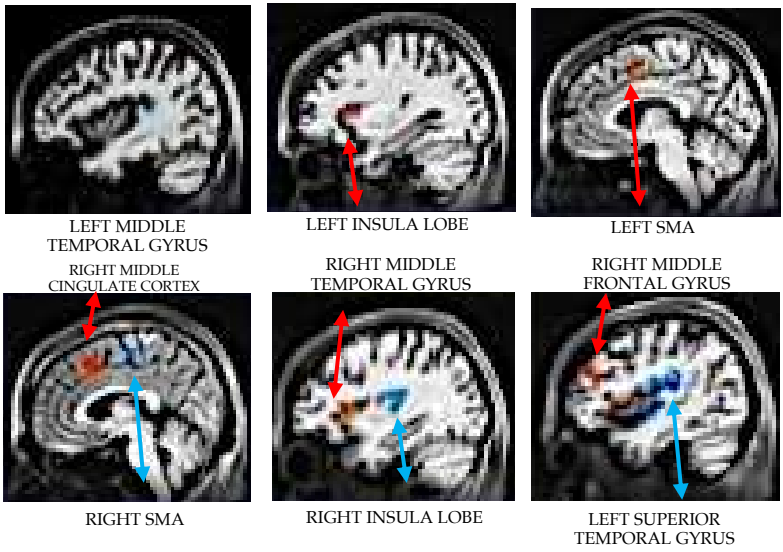
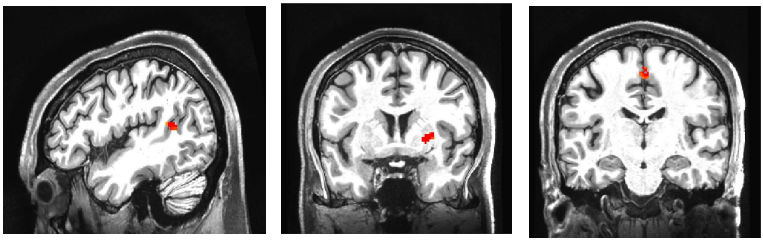


Figure 3.5. Brain regions involved in response to negative stimuli.

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Left Middle Temporal Gyrus	84 voxels	[46.5, 52.5, 15.5]
Right Putamen	51 voxels	[-23.5, -3.5, 1.5]
Left SMA	42 voxels	[0.5, 18.5,61.5]

Table 3.8: Brain activation patterns before and after ECT Treatments



LEFT MIDDLE TEMPORAL GYRUS

RIGHT PUTAMEN

LEFT SMA

Figure 3.6. Brain activation patterns between V1 and V4 and following ECT treatments.

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Left Middle Frontal Gyrus	55 voxels	[32.5, -39.5, 29.5]
Right Middle Frontal Gyrus	50 vox	[-47.5, -41.5,13.5]
Left Superior Frontal Gyrus	43 voxels	[16.5, -21.5, 63.5]
Left Inferior Frontal Gyrus	40 voxels	[50.5, -5.5, 23.5]
Left Superior Medial Gyrus	40 voxels	[10.5, -31.5, 59.5]

Table 3.9: Brain activation patterns between V1 and V3 of ECT Treatment

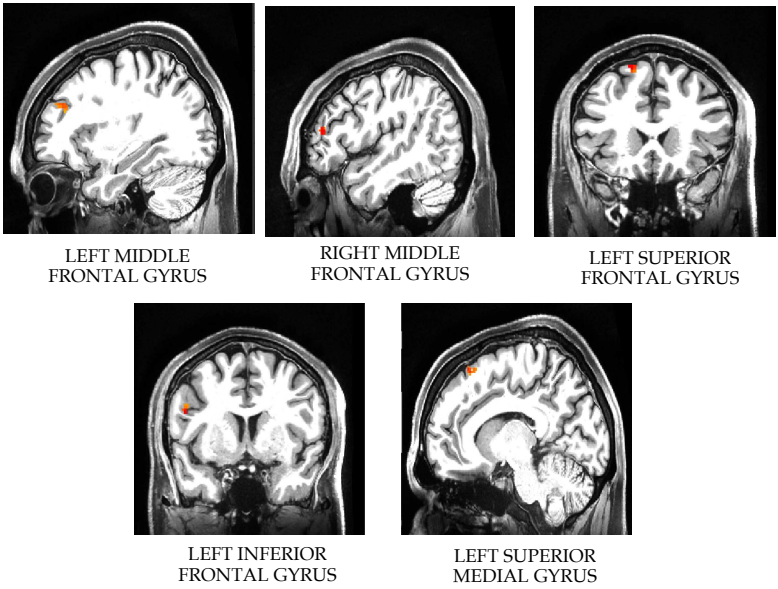


Figure 3.7. Brain activation patterns between Visit 1 and Visit 3 of ECT Treatment

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Right Middle Frontal Gyrus	52 voxels	[-29.5, -57.5, 1.5]
Negative Clusters		
Left Middle Occipital Gyrus	68 voxels	[50.5,70.5, 13.5]
Left Putamen	42 voxels	[28.5, -3.5, 3.5]

Table 3.10. Brain activation patterns subsequent Visit 3 and Visit 4 of ECT Treatment

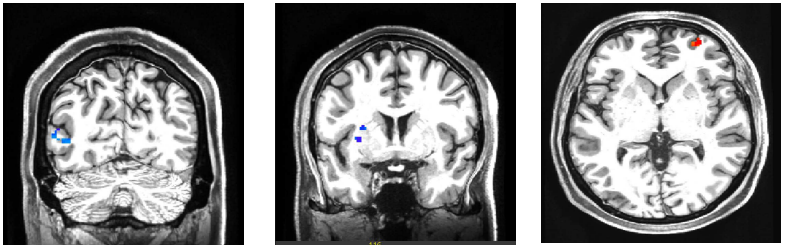
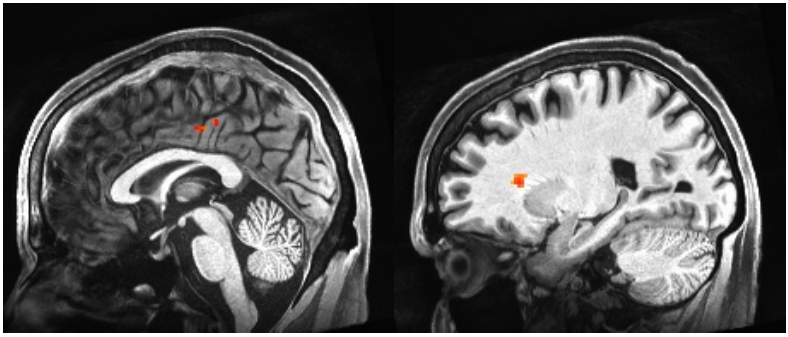


Figure 3.8. Illustrates activation patterns after Visit 3 and Visit 4 of ECT Treatment

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Left Middle Cingulate Cortex	83 voxels	[4.5, 16.5, 39.5]
Right Caudate Nucleus	44 voxels	[-23.5, -23.5, 9.5]

Table 3.11. Differences in Brain Activation between Reward and Punishment



LEFT MIDDLE CINGULATE CORTEX RIGHT CAUDATE NUCLEUS

Figure 3.9: Differences in Brain Activation between Reward & Punishment

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Right Insula Lobe	341 Voxels	[33.5, 23.5, 9.5]
Right Middle Cingulate Cortex	118 Voxels	[-5.5, -25.5,35.5]

Table 3.12: Similarities in Brain Activation between Reward and Punishment

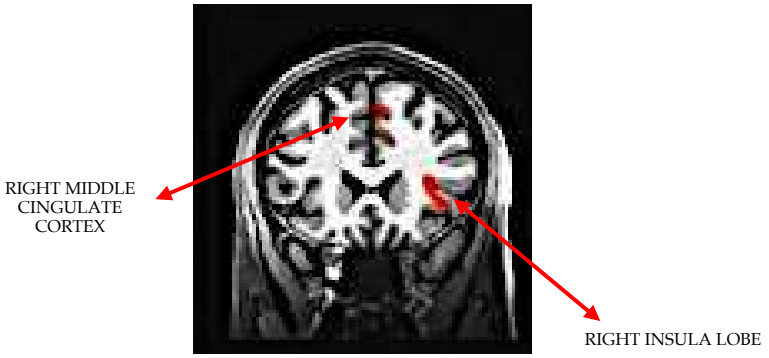


Figure 3.10: Similarities in Brain Activation between Reward and Punishment

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Left SMA	146 Voxels	[2.5, -13.5, 51.5]
Left Anterior Cingulate Gyrus	115 Voxels	[8.5, -29.5, 21.5]
Right Putamen	47 voxels	[-27.5, -9.5, 1.5]

Table 3.13: Clusters of significant activation in the Baseline vs Post @ Reward

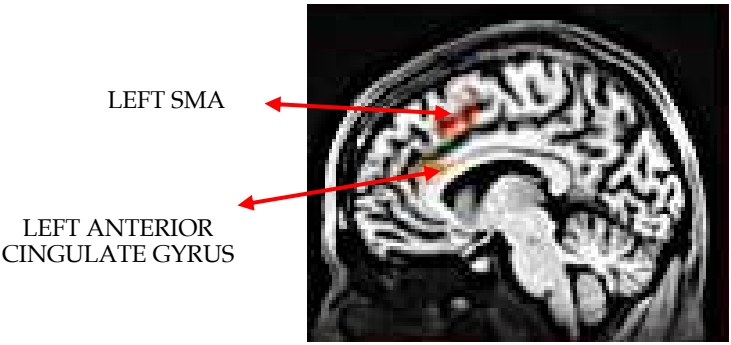
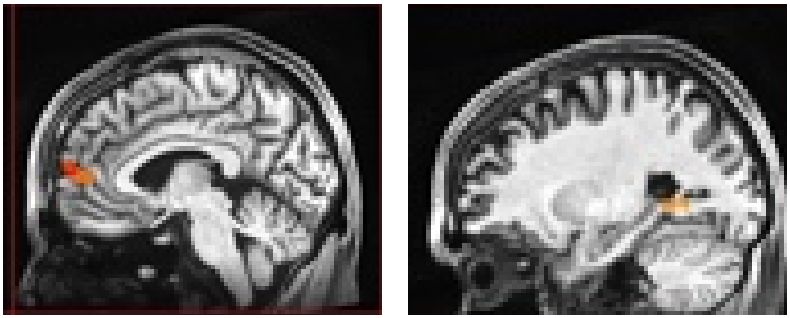


Figure 3.11: Brain response in the Baseline vs Post @ Reward

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Left Superior Medial Gyrus	181 voxels	[4.5, -59.5, 9.5]
Left Hippocampus	105 voxels	[18.5, 32.5, -0.5]

Table 3.14. Clusters of significant activation in the Baseline vs Post @ Punishment



LEFT SUPERIOR MEDIAL GYRUS LEFT HIPPOCAMPUS

Figure 3.12. Brain response in the Baseline vs Post @ Punishment

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Left Putamen	116 Voxels	[26.5, -3.5, 7.5]
Right Putamen	94 Voxels	[-25.5, -1.5, -0.5]
Left SMA	40 Voxels	[8.5, -9.5, 49.5]
Negative Clusters	-	-

Table 3.15. Clusters of significant activation in the Baseline vs Visit 3 @ Reward

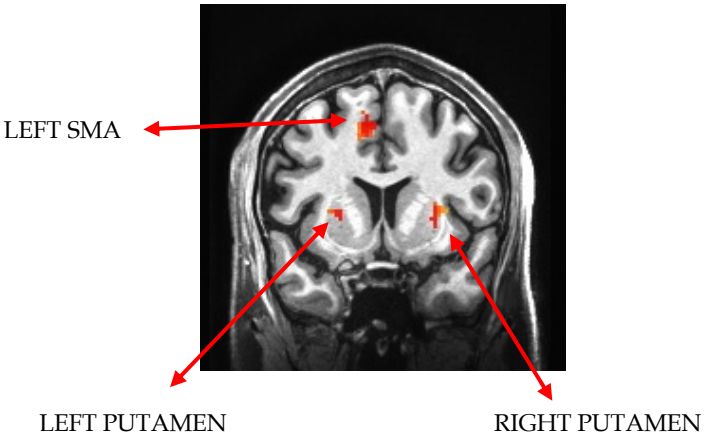
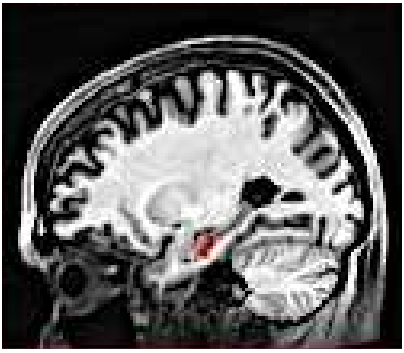


Figure 3.13. Brain response in the Baseline vs Visit 3 @ Reward

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Left Hippocampus	41 Voxels	[14.5, 14.5, -18.5]

Table 3.16. Clusters of significant activation in the Baseline vs Visit 3 @ Punishment

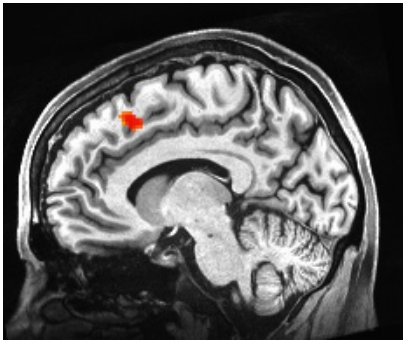


LEFT HIPPOCAMPUS

Figure 3.14. Brain response in the Baseline vs Visit 3 @ Punishment

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Left SMA	76 Voxels	[8.5, -23.5, 47.5]

Table 3.17. Visit 3 vs Visit 4 @ Reward

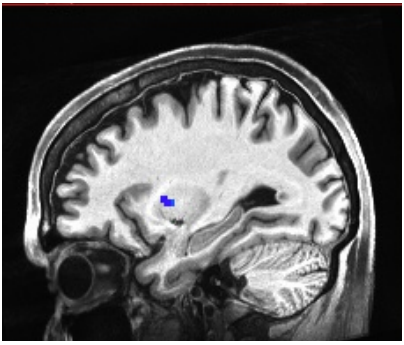


LEFT SMA

Figure 3.15. Visit 3 vs Post @ Reward

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters	-	-
Negative Clusters		
Left Putamen	45 Voxels	[30.5, -3.5, 3.5]

Table 3.18: Visit 3 vs Post @ Punishment



LEFT PUTAMEN

Figure 3.16: Visit 3 vs Visit 4 @ Punishment

3.2.2 Region of Interest (ROI) Analysis

Within the framework of this study, the conducted ROI analysis aimed to assess alterations in ROI activation in response to both reward and punishment stimuli across various visits during ECT treatment. The Harvard-Oxford Atlas (Gorgolewski et al., 2015) was employed to delineate distinct regions of interest (ROIs) for specific brain areas. These included the left and right thalamus, left and right caudate, left and right putamen, left and right hippocampus, left and right amygdala, left and right nucleus accumbens, frontal medial cortex, paracingulate gyrus, as well as posterior and anterior cingulate gyrus, anterior and posterior parahippocampal gyrus, and the superior and middle frontal gyrus. This atlas-based approach facilitated a comprehensive analysis of ROI activations and their responses to different stimuli across varying stages of ECT treatment.

Employing a rigorous threshold adjusted to counteract potential issues stemming from multiple comparisons, and applying false discovery rate (FDR) correction, only a few regions survived as statistically significant. Over the course of various time points, discernible task-induced activation materialized in response to reward stimuli, localized within distinct regions of interest (ROIs). These ROIs encompassed the right hippocampus, middle frontal gyrus, and left putamen, as visually illustrated in Figure 18. These outcomes underscore the consistent involvement of these brain regions in processing reward-related stimuli throughout the study.

Parallel observations were made in the context of punishment stimuli. The analysis unveiled task-related activation patterns within specific ROIs. Notably, the ROIs comprised the right caudate, right putamen, and right superior frontal gyrus, as highlighted in Figure 19. This robust pattern signifies that these brain regions consistently exhibited activity when processing punishment-related stimuli across the study's duration.

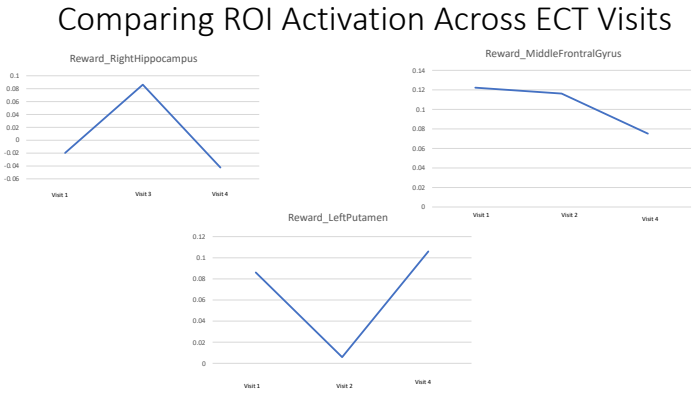


Figure 3.17. Comparison of changes in region of interest (ROI) activation in response to reward stimuli across ECT Visits.

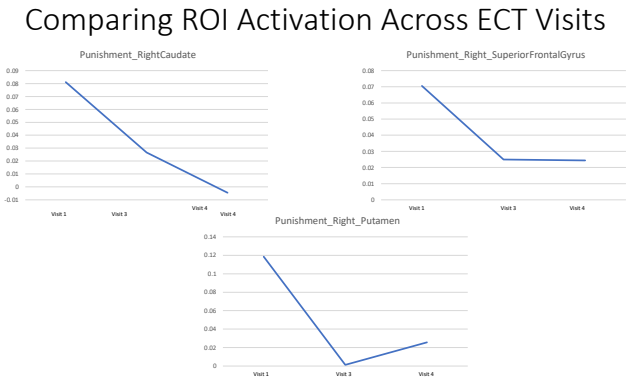


Figure 3.18. Comparison of changes in region of interest (ROI) activation in response to punishment stimuli across ECT Visits.

Chapter 4

Exploring Disparities: Responders and Non-Responders to Electroconvulsive Therapy (ECT) Treatment in Major Depression

4.1 Behavioral Measures Analysis

4.1.1 Evaluation of ECT Treatment Response and Clinical Outcomes in Patients with Major Depression- Depressive Scores

In Chapter 4, I illustrated a noticeable 50 percent decrease in depression scores among patients who underwent ECT treatment. To further gain a better understanding of the mechanism behind ECT I wanted to discern pattern differences between patients who positively responded to ECT and those who did not. For the non-responder group the categorization was based on patients who exhibited at least a 50 percent improvement, as indicated by their respective questionnaire scores. I employed the Hamilton Rating Scale for Depression (HAM-D), PHQ-9, and QIDS scores to assess treatment responses at three key time points: prior to the commencement of ECT, following the third ECT session, and after the fourth and final post-acute ECT treatment session. Upon close examination, it becomes evident that the patients classified as non-responders did not exhibit a significant decrease of at least 50 percent in depression scores across all the three depression questionnaires as below in Figure 19, 20, and 21. The variation in QIDS scores between individuals who responded to ECT treatment and those who did not, as observed across multiple visits, highlights a clear distinction (Figure 5.1). Notably, the responder group demonstrated substantial and statistically significant improvements throughout the course of treatment. Their average mean scores decreased significantly at Visit 1 (23.37, $p < 0.001$), Visit 3 (18, $p < 0.001$), and Visit 4 (7.25, $p < 0.01$), indicating a remarkable positive response to ECT therapy. Conversely, the non-responder group did not exhibit significant

score reductions across the visits. Their scores remained relatively stable at Visit 1 (16.9), Visit 3 (16.67), and Visit 4 (14.1), indicating a lack of substantial improvement in their depressive symptoms throughout the treatment period. Similarly, both the HAM-D and PHQ showed a similar pattern between responders to ECT and non-responder to ECT. The difference in HAM-D scores between individuals who positively responded to ECT treatment and those who did not, as assessed across multiple visits, presents a clear demarcation. Significantly, the responder group showcased substantial and statistically meaningful progress during their treatment. Their average mean scores witnessed a notable decline at Visit 1 (25.36, $p < 0.001$), Visit 3 (20.4, $p < 0.001$), and Visit 4 (7.9, $p < 0.001$), underscoring a remarkable positive response to ECT therapy. In contrast, the non-responder group did not display noteworthy reductions in scores across the visits. Their scores maintained relative stability at Visit 1 (24), Visit 3 (22), and Visit 4 (20), indicating a lack of significant improvement in their depressive symptoms over the treatment duration. The variance in PHQ-9 scores between individuals who positively responded to ECT treatment and those who did not, as observed across multiple visits, underscores a distinct contrast. Remarkably, the group of responders exhibited significant and substantial enhancements during the entire treatment journey. Their average mean scores experienced a noteworthy reduction at Visit 1 (20.4, $p < 0.001$), Visit 3 (14.4, $p < 0.001$), and Visit 4 (6.0, $p < 0.001$), signifying a remarkable and favorable response to ECT therapy. Conversely, the non-responder group did not show significant score reductions across the visits. Their scores remained relatively stable at Visit 1 (14.857), Visit 3 (14.16), and Visit 4 (12.857), indicating a lack of substantial improvement in their depressive symptoms throughout the treatment period. Figure 5.1 visually demonstrates the variations in mean PHQ-9 Depression Scores among patients who exhibited a significant response to ECT, characterized by a minimum of a 50 percent improvement in their scores. Significant changes were observed in the responder group across all ECT visits, while no significant changes were detected in the group of individuals who did not respond to ECT.

In Figure 4.2, I showed the variations in mean HAM-D Depression Scores among patients who exhibited a significant response to ECT, characterized by a minimum of a 50 percent improvement in their scores. Significant changes were observed in the responder group across all ECT visits, while no significant changes were detected in the group of individuals who did not respond to ECT.

Finally, Figure 4.3 illustrates the variations in mean HAM-D Depression Scores among patients who exhibited a significant response to ECT, characterized by a minimum of a 50 percent improvement in their scores. Significant changes were observed in the responder group across all ECT visits, while no significant changes were detected in the group of individuals who did not respond to ECT.

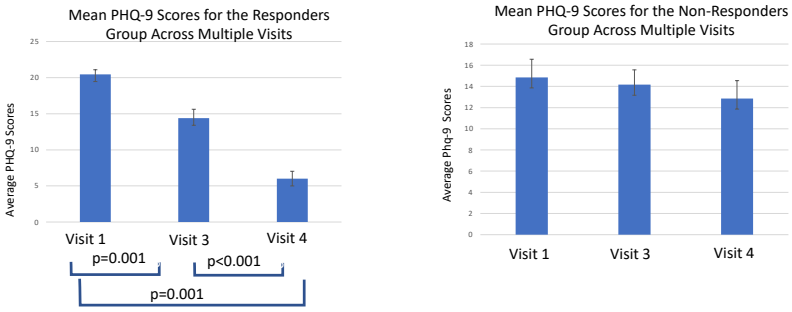


Figure 4.1. Assessing Changes in Mean Change in PHQ-9 Depression Questionnaire Scores between ECT Treatment Responders and Non-Responders. Bars represent mean scores. Errorbar represent the SEM.

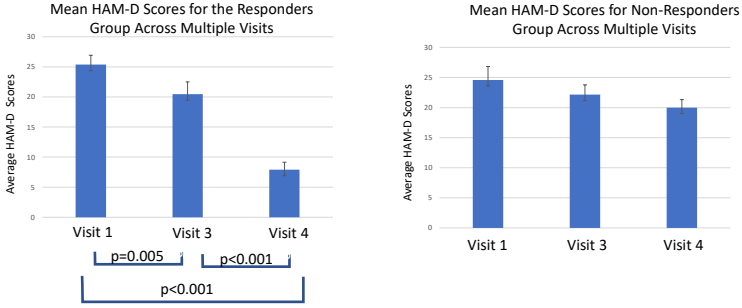


Figure 4.2. Assessing Changes in Mean Change in HAM-D Depression Questionnaire Scores between ECT Treatment Responders and Non-Responders. Bars represent mean scores. Errorbar represent the SEM.

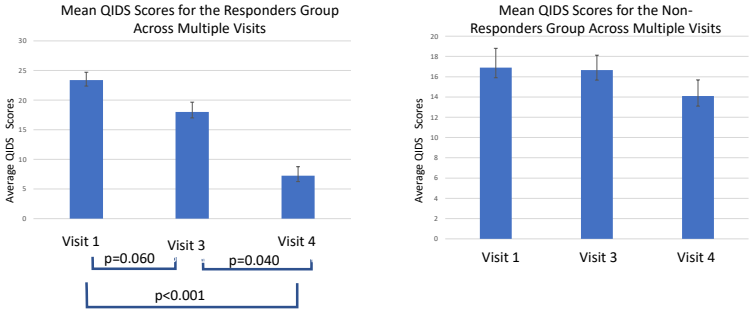


Figure 4.3. Assessing Changes in Mean Change in QIDS Depression Questionnaire Scores between ECT Treatment Responders and Non-Responders. Bars represent mean scores. Errorbar represent the SEM.

4.1.2 Evaluation of ECT Treatment Response and Clinical Outcomes in Patients with Major Depression – Anhedonia and Pleasure Behavioral Measures

Despite ECT not leading to a significant change in overall depression levels in the non-responder group, I analyzed changes in pleasure and anhedonia scores on both the Snaith-Hamilton Pleasure Scale (SHAPS), Temporal Experience of Pleasure Scale (TEPS) and the Positive and Negative Affect Schedule (PANAS). Specifically, among non-responders to ECT treatment, there were significant changes in the TEPS-ANT measure across multiple visits, with scores at Visit 1 (21.9), Visit 3 (22.2), and Visit 4 (27.6). The observed change in scores from 21.9 to 27.6 represents a statistically significant change ($p = 0.026$). On the other hand, the TEPS-CON measure across multiple visits yielded scores of Visit 1 (21.4), Visit 3 (23.8), and Visit 4 (27.2). The recorded shift in score from 21.4 to 27.2 demonstrates a statistically significant change ($p = 0.029$). It's worth noting that for both TEPS-ANT and TEPS-CON, there were no significant alterations observed between Visit 1 and Visit 3, or between Visit 3 and Visit 4.

Figure 4.4 displayed below, presents a comparative analysis of mean changes in Pleasure Scale Questionnaire scores, specifically TEPS-ANT (Anticipatory) and TEPS-CON (Consummatory), between individuals categorized as ECT treatment responders and non-responders. The data illustrates significant variations in the responses of these two groups across multiple assessment visits.

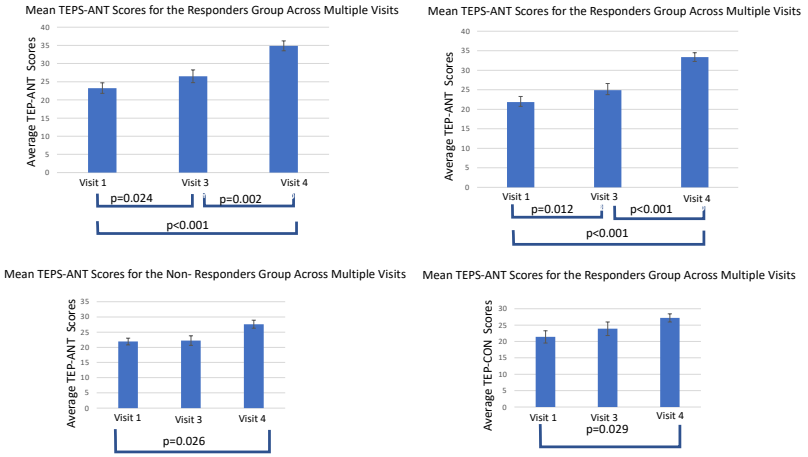


Figure 4.4. Evaluating Differences in Mean Changes of Pleasure Scale Questionnaire Scores (TEPS-ANT & TEPS-CON) between ECT Treatment Responders and Non-Responders. Bars represent mean scores. Errorbar represent the SEM.

When analyzing the responses of both the responder and non-responder groups to the SHAPS questionnaire, significant score changes were evident between Visit 1 and Visit 4, as well as between Visit 3 and Visit 4. Notably, there were no statistically significant score changes observed between Visit 1 and Visit 3. Within the non-responder group, we observed significant

differences in scores between Visit 1 and Visit 4 ($p = 0.007$) and between Visit 3 and Visit 4 ($p = 0.009$). Overall, there was a change in mean scores across all visits, with Visit 1 (24.11), Visit 3 (23.63), and Visit 4 (15.33). Within the responder group, a notably more significant statistical change in scores was evident between Visit 1 and Visit 4 ($p < 0.001$), as well as between Visit 3 and Visit 4 ($p = 0.001$). When considering the mean scores across visits, there was a pronounced shift from Visit 1 (26.75) to Visit 3 (22.12) and finally to Visit 4 (12).

Figure 4.5 shows that both ECT treatment responders and non-responders exhibited similar score changes. Significant overall changes were observed at Visit 3 and Visit 4, as well as between Visit 1 and Visit 4, respectively.

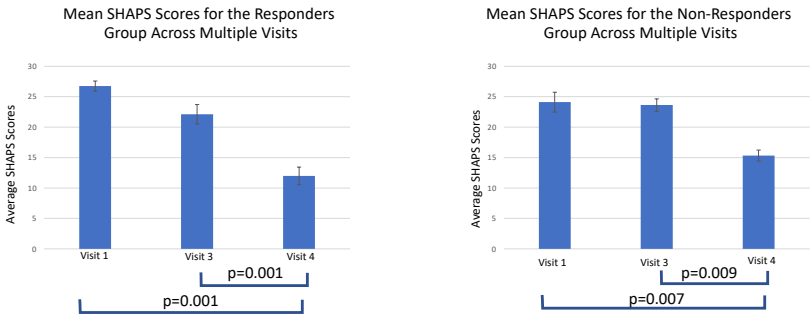


Figure 4.5. Differences in Mean Changes of SHAPS Questionnaires between ECT Treatment Responders and Non-Responders. Bars represent mean scores. Errorbar represent the SEM.

The responses to the PANAS questionnaire were categorized into two distinct aspects: positive affect and negative effect. In the non-responder group, statistically significant changes were observed only in the realm of negative affect, occurring between Visit 1 and Visit 4 ($p = 0.049$). The scores exhibited the following variations across visits: Visit 1 (28), Visit 3 (26), and Visit 4 (21). Notably, PANAS positive affect within the non-responder group did not yield statistically significant results across the ECT visits, with scores remaining relatively constant at Visit 1 (17), Visit 3 (19), and Visit 4 (21).

On the other hand, in the responder group, negative affect did not reach statistical significance, but responses did show proximity to statistical significance between Visit 1 and Visit 4 ($p = 0.088$) and between Visit 3 and Visit 4 ($p = 0.061$). Changes in scores were observed as Visit 1 (31), Visit 3 (30), and Visit 4 (22). Remarkably, the mean average scores for positive affect in the responder group demonstrated statistical significance between Visit 1 and Visit 3 ($p = 0.034$) and came close to statistical significance between Visit 1 and Visit 4 ($p = 0.060$). These changes were reflected in scores as Visit 1 (16), Visit 3 (20), and Visit 4 (24). Figure 4.6 provides a visual representation of the Disparities in Mean Changes of PANAS (Positive and Negative Affect Schedule) Score Questionnaires between ECT Treatment Responders and Non-Responders. The PANAS scores are divided into two categories: PANAS Positive and PANAS Negative Effect. Within the responder group of ECT, positive PANAS scores exhibited changes between Visit 1 and Visit 3, as well as between Visit 1 and Visit 4. Negative PANAS scores showed changes between Visit 3 and Visit 4, and an overall change from Visit 1 to Visit 4. In the non-responder group, positive PANAS scores experienced changes only between Visit 1 and Visit 3, while negative PANAS scores displayed an overall change before and after treatment, as well as between Visit 3 and Visit 4.

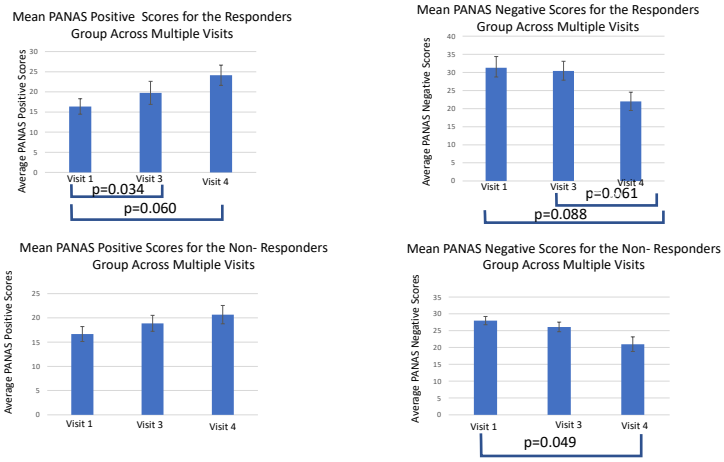


Figure 4.6. Differences in Mean Changes of PANAS Score Questionnaires between ECT Treatment Responders and Non-Responders. Bars represent mean scores. Errorbar represent the SEM.

4.1.3 Three-way Analysis of Variance

In this study, we aimed to investigate whether there were any differences in brain activity between patients who responded to Electroconvulsive Therapy (ECT) and those who did not respond to ECT. To achieve this, we conducted a 3dttest analysis in AFNI to compare the brain activation patterns of responders and non-responders. Responders were defined as patients who showed a clinical improvement of at least 50% on the HAM-D rating scale after receiving ECT. The results of the analysis did not show any significant clusters of brain activation at the level of $p<.001$. However, we did observe significant activation at a less stringent threshold of $p=.001$. These findings suggest that there may be some differences in brain activity between responders and non-responders to ECT, although the differences are not strong enough to reach statistical significance at a more stringent threshold (Figure 4.1).

It is important to note that these findings should be interpreted with caution, as the sample size in this study was relatively small. Additionally, there may be other factors that contribute to the differences in response to ECT that were not measured in this study. Further research with larger samples and more comprehensive measures may be needed to fully understand the differences in brain activity between ECT responders and non-responders.

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Right Middle Cingulate Cortex	52 voxels	-5.5, -13.5, +43.5
Negative Clusters		
Left Supramarginal Gyrus	40 voxels	+40.5, 0.5, -14.5
Right Middle Cingulate Cortex	41 voxels	-9.5, 16.5, 45.5
Left Anterior Cingulate Cortex	47 voxels	0.5, -41.5, -0.5
Right Middle Temporal Gyrus	50 voxels	-61.5, 6.5, -12.5

Table 4.1. Visit 1 Baseline Activation Non-Responders to ECT Treatment

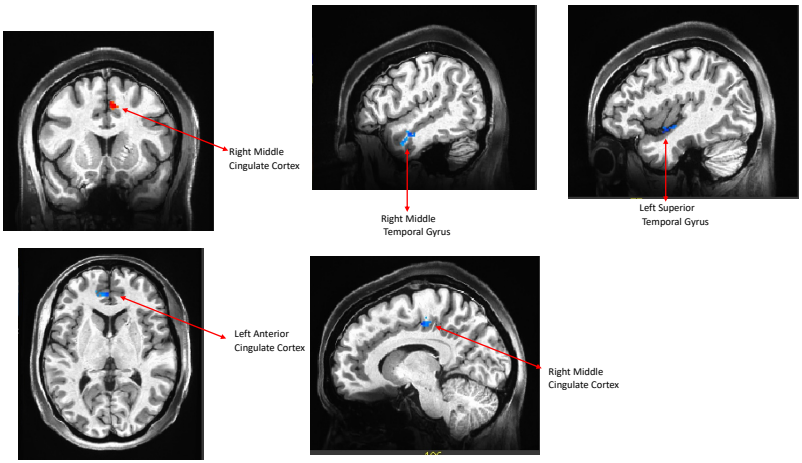


Figure 4.1. Visit 1 Baseline Activation Non-Responders to ECT Treatment: brain activations.

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Right Middle Cingulate Cortex	52 voxels	-5.5, -11.5, +45.5
Negative Clusters		
Right Insula Lobe	135 voxels	-41.5, 14.5, -4.5
Left Superior Medial Gyrus	85 voxels	4.5, -63.5, 25.5
Right SMA	60 voxels	-3.5, 16.5, 51,5
Left Anterior Cingulate Cortex	40 voxels	0.5, -31.5, 17.5

Table 4.2. Visit 4 Post ECT Non-Responders to ECT Treatment

Figure 4.2. Visit 4 Post ECT Non-Responders to ECT Treatment: brain activation.

Region	Cluster Size	Peak Activation Coordinates
Negative Clusters		
Right Middle Temporal Gyrus	104 voxels	-61.5, 8.5, -10.5
Left Anterior Cingulate Cortex	95 voxels	2.5, -45.5, 3.5
Left Superior Temporal Gyrus	94 voxels	44.5, 12.5, -2.5
Left Caudate Nucleus	62 voxels	6.5, -15.5, 1.5
Right SMA	51 voxels	-3.5, 16.5, 51.5
Right Superior Frontal Gyrus	45 voxels	-23.5, -35.5, 43.5
Positive	-	-

Table 4.3. Reward and non-responder to ECT Treatment

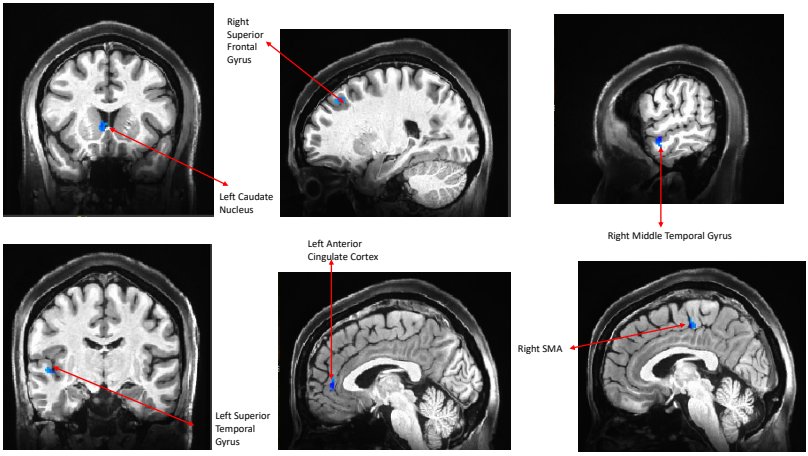


Figure 4.3. Reward and non-responder to ECT Treatment. Neural activation patterns associated with individuals identified as non-responders in the context of reward processing during Electroconvulsive Therapy (ECT) treatment. The data presented in this figure captures the intricate interplay between reward stimuli and the neural responses of participants who did not exhibit a positive

response to ECT. By focusing on the relationship between reward processing and non-responsiveness, the figure provides a visual representation that enhances our understanding of the neural dynamics in individuals who may not benefit optimally from ECT. This visual analysis contributes valuable insights into the complexities of treatment outcomes, aiding in the identification of neural markers associated with non-responsiveness and potentially informing future therapeutic strategies.

In response to overall activation to reward stimuli no significant positive clusters were identified. Overall, the right insula lobe, the right middle temporal gyrus, left anterior cingulate cortex, left temporal gyrus, left caudate nucleus, right SMA, and right superior frontal gyrus in response to reward stimuli in the non-responder group.

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Right Superior Frontal Gyrus	102 voxels	-31.5, 2.5, 59.5
Right Inferior Temporal Gyrus	41 voxels	-55.5, 32.5, -16.5
Left SMA	40 voxels	6.5, -7.5, 55.5
Negative Clusters	-	-

Table 4.4. Punishment non-responder to ECT

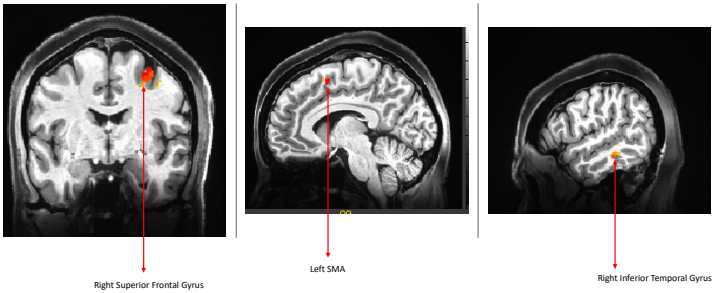


Figure 4.4. Punishment non-responder to ECT. Visual representation of neural activation patterns in individuals identified as non-responders within the context of punishment processing during Electroconvulsive Therapy (ECT) treatment. The data presented in this figure delineate the intricate relationship between punishment stimuli and the neural responses of participants who did not exhibit a positive response to ECT. By homing in on the connection between punishment processing and non-responsiveness, the figure provides a visual narrative that deepens our understanding of the neural dynamics in individuals who may not respond favorably to ECT. This visual analysis contributes crucial insights into the nuances of treatment outcomes, aiding in the identification of neural markers associated with non-responsiveness and potentially informing future therapeutic strategies.

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Right Inferior Frontal Gyrus	50 voxels	-45.5, -37.5, 3.5
Right Middle Frontal Gyrus	59 voxels	-43.5, -45.5, 15.5
Negative Clusters		
Right Superior Temporal Gyrus	67 voxels	-53.5, 46.5, 21.5

Table 4.5. Difference in Mean Activation between Visit 1 and Visit 4 to ECT Non-Responders. \

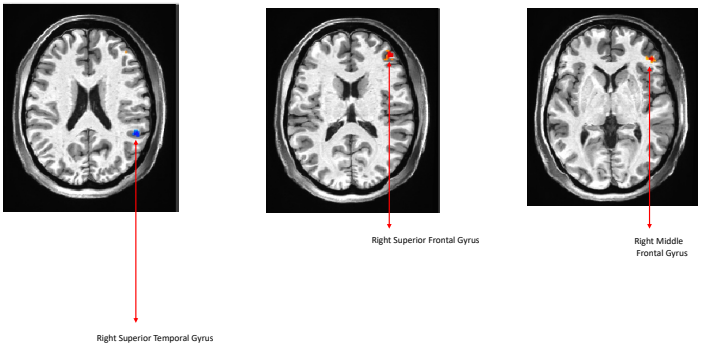


Figure 4.5. Difference in Mean Activation between Visit 1 and Visit 4 to ECT Non-Responders. Neural activation patterns in individuals identified as non-responders within the context of punishment processing during Electroconvulsive Therapy (ECT) treatment. The data presented in this figure delineate the intricate relationship between punishment stimuli and the neural responses of participants who did not exhibit a positive response to ECT. By homing in on the connection between punishment processing and non-responsiveness, the figure provides a visual narrative that deepens our understanding of the neural dynamics in individuals who may not respond favorably to ECT. This visual analysis contributes crucial insights into the nuances of treatment outcomes, aiding in the identification of neural markers associated with non-responsiveness and potentially informing future therapeutic strategies.

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters		
Left Middle Frontal Gyrus	50 voxels	46.5, -53.5, -4.5
Negative Clusters	-	-

Table 4.6. Differences Visit 1 vs Visit 4 @ Reward ECT Non-Responder to ECT

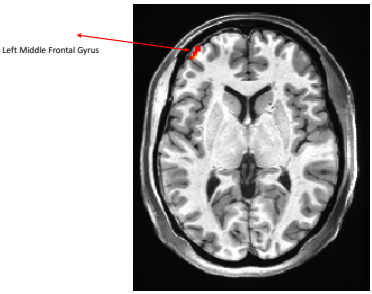


Figure 4.6. Differences Visit 1 vs Visit 4 @ Reward ECT Non-Responder to ECT. Variations in average neural activation levels among individuals identified as non-responders across the initial and final phases of Electroconvulsive Therapy (ECT) treatment. The data showcased in this analysis delineate the changes in neural response patterns, offering insights into the evolving neural dynamics over the course of the ECT intervention for participants who did not display a positive treatment response. By comparing the mean activation between Visit 1 and Visit 4, the analysis provides a visual representation that enhances our understanding of the neurobiological shifts associated with non-responsiveness to ECT. This visual exploration contributes valuable information for discerning patterns and potential markers, facilitating a more nuanced comprehension of treatment outcomes and aiding in the optimization of therapeutic approaches for individuals who may not exhibit the desired response to ECT.

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters	-	-
Left Superior Medial Gyrus	56 voxels	0.5, -35.5, 55.5
Negative Clusters	-	-

Table 4.7. Visit 1 vs Visit 4 @ Punishment ECT Non-Responder to ECT

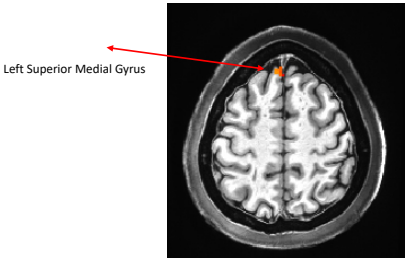


Figure 4.7. Visit 1 vs Visit 4 @ Punishment ECT Non-Responder to ECT. Neural activation patterns in individuals identified as non-responders to Electroconvulsive Therapy (ECT) during two crucial time points—Visit 1 and Visit 4. Specifically, the focus of this analysis is on the processing of punishment stimuli within this subgroup. The presented data unveil the evolving neural responses to punitive stimuli across the initial and final phases of ECT treatment, providing nuanced insights into the changing neurobiological dynamics within the brains of participants who did not exhibit a positive response to ECT. By scrutinizing the contrast between Visit 1 and Visit 4 regarding punishment stimuli, this analysis offers a visual narrative that deepens our understanding of the complex neural mechanisms associated with non-responsiveness to ECT. These insights contribute valuable information for discerning patterns and potential markers, fostering a more detailed comprehension of treatment outcomes and guiding the refinement of therapeutic strategies for individuals who may not manifest the desired response to ECT.

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters	-	-
Negative Clusters		
Left Gyrus	41 voxels	58.5, -25.5, 19.5

Table 4.8. Reward vs Neutral Stimuli @ Baseline ECT Non-Responder to ECT

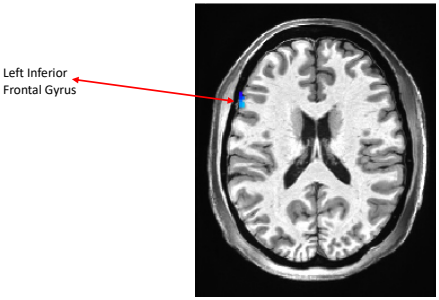


Figure 4.8. Reward vs Neutral Stimuli @ Baseline ECT Non-Responder to ECT. Neural activation patterns in individuals identified as non-responders during the baseline phase of Electroconvulsive Therapy (ECT). The specific focus of this analysis is the comparison between the processing of reward stimuli and neutral stimuli in this subgroup. The data presented in this analysis unravel the distinctive neural responses to rewarding and neutral stimuli, providing insights into the intricate neural dynamics within the brains of participants who did not exhibit a positive response to ECT at the outset. By examining the contrast between reward and neutral stimuli at the baseline stage, this analysis offers a visual narrative that deepens our understanding of the neurobiological intricacies associated with non-responsiveness to ECT. These insights contribute valuable information for discerning patterns and potential markers, fostering a more nuanced comprehension of treatment outcomes and guiding the refinement of therapeutic strategies for individuals who may not demonstrate the desired response to ECT.

Region	Cluster Size	Peak Activation Coordinates
Positive Clusters	-	-
Negative Clusters		
Right Posterior Cingulate Gyrus	42 voxels	-1.5, 42.5, 7.5

Table 4.9. Punishment vs Neutral Stimuli @ Post ECT Non-Responder to ECT

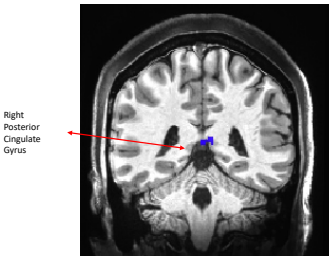


Figure 4.9. Punishment vs Neutral Stimuli @ Post ECT Non-Responder to ECT. Neural activation patterns in individuals identified as non-responders during the post-treatment phase of Electroconvulsive Therapy (ECT). Specifically, the analysis focuses on the comparison between the processing of punishment stimuli and neutral stimuli in this subgroup. The data presented in this analysis unravel the distinct neural responses to punitive and neutral stimuli, shedding light on the nuanced interplay within the brains of participants who did not exhibit a positive response to ECT. By scrutinizing the contrast between punishment and neutral stimuli at the post-treatment stage, this analysis provides a visual narrative that enhances our understanding of the neurobiological dynamics associated with non-responsiveness to ECT. These insights contribute valuable information for discerning patterns and potential markers, fostering a more detailed comprehension of treatment outcomes and guiding the refinement of therapeutic strategies for individuals who may not manifest the desired response to ECT.

4.1.4 Region of Interest (ROI) Analysis

In this Chapter the ROI analysis aimed to assess alterations in ROI activation in response to both reward and punishment stimuli across various visits during ECT treatment in the non-responder group. The Harvard-Oxford Atlas (Gorgolewski et al., 2015) was employed to delineate distinct regions of interest (ROIs) for specific brain areas. Like in Chapter 6, the ROI's included the left and right thalamus, left and right caudate, left, and right putamen, left and right hippocampus, left and right amygdala, left and right nucleus accumbens, frontal medial cortex, paracingulate gyrus, as well as posterior and anterior cingulate gyrus, anterior and posterior para-hippocampal gyrus, and the superior and middle frontal gyrus. This atlas-based approach facilitated a comprehensive analysis of ROI activations and their responses to different stimuli across varying stages of ECT treatment in patients who did not respond to ECT treatment.

The ROI analysis revealed the activation of two regions, the right hippocampus, and the right putamen, in response to stimuli associated with reward and punishment. The right hippocampus exhibited activation in response to reward stimuli during two intervals, between Visit 1 and Visit 3 ($p=0.082$) and Visit 3 and Visit 4 ($p=0.080$) as illustrated in Figure 25. These results although not statistically significant. While the findings did not reach statistically significant, they do demonstrate a trend. It is important to acknowledge that the right hippocampus hold a significant relevance in the context of depression.

Significant activation in the right putamen was observed in response to both reward and punishment stimuli, between Visit 1 and Visit 4 ($p=0.04$) in response to reward stimuli and Visit 1 and Visit 3 in response to punishment stimuli, as depicted in Figure 26.

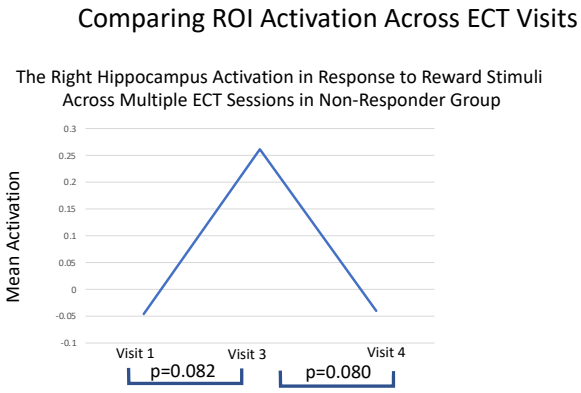


Figure 4.10. Comparison of changes in the Right Hippocampus Activation in Response to Reward Stimuli across ECT Visits in the Non – Responder Group.

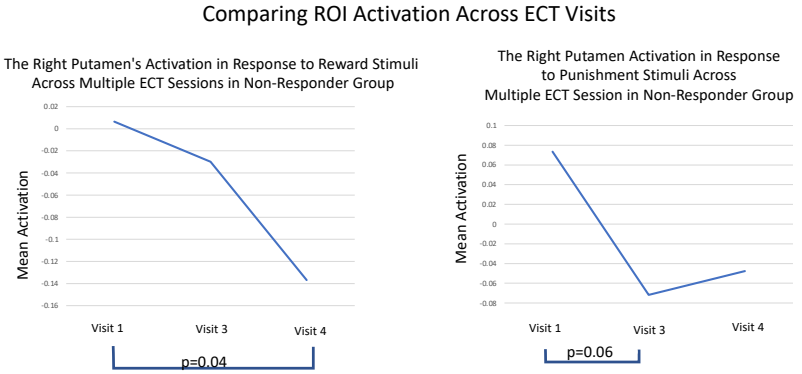


Figure 4.11. Comparison of changes in the Right Putamen Activation in Response to Punishment and Reward Stimuli Across ECT Visits in the Non-Responder Group.

Chapter 5

Discussion

The aim of this study was to investigate the way the brain processes reward and punishment stimuli prior, during and after ECT treatment in patients with treatment-resistant depression. We employed functional magnetic resonance imaging (fMRI) to assess brain activity in patients with major depressive disorder (MDD). Additionally, the cohort was further split into two subgroups to assess the differences between patients who responded to ECT and patients who did not respond to ECT treatment. Specifically, all the comparisons were made before and after electroconvulsive therapy (ECT) treatment, between visit 1 and visit 3, and between visit 3 and visit 4. Then we examined any potential differences in behavioral measures related to reward and punishment processing and compared them to the observed brain activation. By examining the participants' responses to several questionnaires related to reward and punishment processing, we aimed to gain insights into the underlying mechanisms of these processes and to identify any potential links between the behavioral and neural responses. Lastly, we investigated changes in region of interest (ROI) activation responses to positive and negative stimuli across ECT visits. The use of fMRI allowed us to identify the specific brain regions that were activated in response to reward and punishment stimuli, and to examine any differences in the patterns of activation between these conditions. Meanwhile, the inclusion of behavioral measures, such as questionnaires related to reward and punishment processing, provided insights into the subjective experience of these stimuli and how they might relate to the observed patterns of brain activation.

The results of this study indicate that ECT causes changes in behavioral measures as well as in brain patterns of response to positive and negative stimuli and ECT affects brains regions associated with depression.

5.1 Behavioral Measures

5.1.1 Depression Measures

For this study the HAM-D, Phq-9, QIDS were used to measure the degree of depression before ECT, at the third visit and after the 4th visit of ECT. The key findings amongst the depression measures, either self-reported or conducted by a clinician, yielded significant results. It is worth noting that significant results were yielded between Visit 1 and Visit 4 and between Visit 3 and Visit 4. While the initial results between Visit 1 and Visit 3 did not reach statistical significance it opens the door to exploring the dynamic relationship between the effectiveness of ECT treatment and its influence on neurological changes during the early stages of intervention. This exploration could pave the way for considering adjustments in the timing and location of ECT treatment during the early stages of treatment.

5.1.2 Measures related to Anhedonia & Pleasure

A) PANAS

The PANAS questionnaire yielded notable outcomes for both positive and negative effects. In both cases, there were significant changes observed before and after ECT treatment. Particularly, the PANAS negative subscale exhibited slightly more pronounced significant outcomes compared to the positive subscale. This discrepancy potentially indicates that ECT might exert a relatively greater impact on diminishing negative affect compared to enhancing positive affect. Notably, positive affect scores demonstrated an increase, while negative affect scores displayed a decrease.

Moreover, there were intriguing temporal patterns observed. The PANAS positive subscale indicated a noteworthy reduction in scores between visit 1 and visit 3, whereas the PANAS negative subscale exhibited a significant decline in scores

between visit 3 and visit 4. This observation is significant because it suggests a potential temporal sequence in the effects of ECT treatment on emotional states. The initial changes in positive affect could potentially trigger subsequent alterations in negative affect as the course of treatment unfolds. This sequence highlights the dynamic nature of emotional responses during the treatment process and underscores the intricate interplay between positive and negative affective states in response to ECT.

B) TEPS

The TEPs questionnaire comprises two distinct subgroups, TEPS-ant and TEPS-con. The TEPS-con which gauges the ability to derive immediate pleasure from experiences, demonstrated statistically significant changes only between Visit 1 and Visit 4. In contrast, TEPS-ant which assesses the capacity to anticipate positive emotions with future events illustrated significant changes between Visit 1 and Visit 4, as well as statistically significant changes between Visit 3 and Visit 4. These results shed light on the dynamic effects of ECT treatment on pleasure-related experiences and anticipation of positive emotions.

The statistically significant changes observed in response to questions associated with TEPS-con component are noteworthy. The changes seen points toward the possibility of ECT inducing rapid alterations in the hedonic aspects of emotional experiences. This suggests that ECT might have a relatively rapid influence on the ability to experience immediate pleasure, potentially indicating an improvement in one's responsiveness to positive stimuli.

Conversely, the TEPS-ant component, which measures the capacity to anticipate positive emotions associated with future events, revealed a more intricate pattern of changes. Statistically significant changes were illustrated between Visit 1 and Visit 4 which suggests impact on the anticipation of positive emotions. Furthermore, the statistically significant changes

between Visit 3 and Visit 4 add depth to our understanding, indicating a dynamic process over the course of ECT treatment.

The findings related to the TEPS-ant component hold intriguing implications. The substantial changes in anticipatory pleasure, at Visit 1 and at Visit 4, highlight how the treatment might influence the individual's ability to anticipate and look forward to positive emotions associated with future events. Moreover, the significant variation between visits 3 and 4 suggests that ECT might have a nuanced impact on the anticipation of positive emotions over the course of treatment. This temporal evolution could indicate a more intricate mechanism at play, where the treatment's effects on anticipatory pleasure unfold and evolve progressively.

C) SHAPS

The findings from the SHAPS questionnaire revealed a notable reduction in scores, demonstrating significant outcomes between Visit 1 and Visit 4. Additionally, a significant variation in scores was observed between visit 3 and visit 4. This pattern of results highlights a consistent trend of decreasing scores across these time points, indicating a potential influence of ECT on the measured construct.

The SHAPS questionnaire, designed to assess anhedonia or the diminished ability to experience pleasure, captured a meaningful change in participants' responses. The significant decrease in scores before and after ECT implies that the treatment might have a substantial impact on mitigating anhedonia symptoms. This aligns with the notion that ECT could contribute to alleviating the reduced capacity to derive pleasure, resulting in a more favorable emotional experience.

Furthermore, the significant score variation between visit 3 and visit 4 underscores the nuanced nature of the observed changes. This suggests that the effects of ECT on anhedonia might unfold progressively during treatment, potentially reflecting a dynamic

process in which an individual's ability to experience pleasure continues to evolve over time.

Overall, these results from the SHAPS questionnaire provide valuable insights into the potential efficacy of ECT in addressing anhedonia, a core symptom of depressive disorders. The observed decreases in scores imply a positive impact on participants' pleasure-related experiences, and the temporal variations suggest a complex interplay between ECT and the modulation of anhedonia symptoms throughout the treatment trajectory.

D) NEO-Personality & ASI

The results indicate that electroconvulsive therapy (ECT) did not have a noticeable impact or bring about any significant changes in the NEO-Personality questionnaire or the ASI (Anxiety Sensitivity Index). This lack of substantial change suggests that specific personality traits, as measured by the NEO-Personality questionnaire, and anxiety sensitivity, as assessed by the ASI, may not be strongly influenced, or altered by ECT in the context of depression. Additionally, the findings imply that ECT might not lead to significant improvements in alleviating anxiety symptoms that are specifically linked to depression. It suggests that the therapeutic effects of ECT, as observed in this study, may be more specific to certain aspects of depression rather than exerting a broad impact on personality traits or anxiety sensitivity.

E) 3dAnova3

The significance of the neural response patterns before the initiation of ECT, as revealed by the MID task, lies in the distinct clusters associated with positive and negative stimuli. Positive stimuli triggered positive clusters in critical regions such as the left SMA, right middle frontal gyrus, and left insula lobe. These areas are integral to emotional regulation, decision-making, and sensory processing. The activation of these regions

suggests a heightened engagement in processes related to reward anticipation.

Conversely, negative stimuli induced negative clusters in the supramarginal gyrus and left caudate nucleus, pointing to reduced engagement in cognitive and emotional processes associated with aversive stimuli. The involvement of the supramarginal gyrus is particularly noteworthy, as it is linked to cognitive functions such as language processing and emotional empathy.

Before the commencement of ECT, the distinctive clusters in response to positive stimuli, involving the Left SMA, Right Insula lobe, Left Insula lobe, right middle frontal gyrus, and right hippocampus, indicate a widespread activation of regions associated with emotional processing, sensory integration, and memory. On the other hand, negative stimuli evoked negative clusters in areas like the right SMA, left supramarginal temporal gyrus, left hippocampus, left superior frontal gyrus, and left middle frontal gyrus. The negative clusters point towards reduced engagement in processes related to aversive stimuli and emotional regulation.

Pre-ECT, the neural response to negative stimuli during the MID task exhibited further complexity, with positive clusters in the right insula lobe, right middle frontal gyrus, and left SMA. This suggests that even within negative contexts, certain cognitive and emotional processes might be heightened in specific brain regions.

Punishment stimuli consistently evoking positive clusters in the left SMA, and right middle frontal gyrus underscore the involvement of these regions in processing aversive stimuli. The varied patterns across positive and negative stimuli indicate the intricate interplay of neural circuits related to reward and punishment processing before ECT.

The analysis of neural differences across various conditions and stages revealed consistent patterns and noteworthy disparities. Positive clusters in the right middle frontal gyrus and left middle

frontal gyrus were a recurrent finding, indicating potential involvement in diverse cognitive and emotional processes. In the context of electroconvulsive therapy (ECT), distinct positive clusters in the right middle frontal gyrus and left middle frontal gyrus suggested changes in neural activity associated with ECT treatment, while negative clusters in the left putamen and left supplementary motor area (SMA) indicated alterations in engagement within these regions.

Examining responses to reward and punishment stimuli uncovered specific positive clusters in the left middle cingulate cortex and right caudate nucleus, emphasizing their roles in processing these stimuli. Commonalities between responses to reward and punishment stimuli, marked by positive clusters in the right insula lobe and right middle cingulate cortex, further highlighted the involvement of the middle cingulate cortex in both scenarios.

Contrasting baseline and post-treatment responses to reward stimuli indicated positive clusters in the left supplementary motor area (SMA), left anterior cingulate gyrus, and right putamen, suggesting ECT-induced alterations in neural activation associated with reward processing. Comparisons between baseline and post-ECT treatment revealed a positive cluster in the left superior medial gyrus and left hippocampus, emphasizing changes in neural dynamics post-treatment.

Distinct positive clusters in the left putamen, right putamen, and left SMA characterized disparities between baseline and visit 3 responses to reward stimuli, signifying potential shifts in neural engagement. Similarly, differences in response to punishment stimuli between baseline and visit 3 showcased a positive cluster in the left hippocampus.

When scrutinizing visit 3 and visit 4 disparities, a positive cluster in the left SMA indicated ongoing changes in neural activation. However, in the same context, the absence of a positive cluster and the presence of a negative cluster in the left putamen suggested nuanced alterations in specific brain regions during this treatment phase.

The observed neural differences across various conditions and stages provide valuable insights into the complex interplay of cognitive and emotional processes, particularly in the context of electroconvulsive therapy (ECT). The recurrent positive clusters in the right middle frontal gyrus and left middle frontal gyrus suggest their pivotal roles in diverse cognitive and emotional functions. Notably, the distinct positive clusters in these regions during ECT treatment imply alterations in neural activity associated with the therapeutic intervention, potentially contributing to the observed changes in depressive symptoms.

Examining responses to reward and punishment stimuli revealed specific positive clusters in the left middle cingulate cortex and right caudate nucleus, emphasizing their significance in processing rewarding and aversive stimuli. The shared positive clusters in the right insula lobe and right middle cingulate cortex during both reward and punishment scenarios highlight the crucial involvement of the middle cingulate cortex across different emotional processes.

Contrasting baseline and post-treatment responses to reward stimuli uncovered positive clusters in the left supplementary motor area (SMA), left anterior cingulate gyrus, and right putamen, indicating ECT-induced alterations in neural activation related to reward processing. Similarly, the positive cluster in the left superior medial gyrus and left hippocampus following ECT treatment suggests changes in neural dynamics post-treatment, potentially contributing to improved emotional regulation.

Distinct positive clusters in the left putamen, right putamen, and left SMA during baseline and visit 3 responses to reward stimuli signify potential shifts in neural engagement associated with ECT. Moreover, the positive cluster in the left hippocampus during punishment stimuli between baseline and visit 3 highlights specific changes in the neural response to aversive stimuli over the treatment course.

Scrutinizing visit 3 and visit 4 disparities, the positive cluster in the left SMA indicates ongoing changes in neural activation

during this treatment phase. The absence of a positive cluster and the presence of a negative cluster in the left putamen suggest nuanced alterations in specific brain regions, adding complexity to the evolving neural dynamics during ECT.

5.2 ROI Discussion

5.2.1 Comparing changes in region of interest (ROI) activation in response to reward stimuli across ECT Visits.

Using the Harvard/oxford atlas the right hippocampus, the middle frontal gyrus and the left putamen showed changes across all visits after ECT Treatment. the significance of the right hippocampus is pivotal in contextual processing. A decrease in its activation may imply a decreased role of the hippocampus in associating rewarding stimuli with their contextual settings or in establishing context-dependent reward associations. (Dickinson & Balleine, 2016; Shohamy & Adcock, 2010). Furthermore, the right hippocampus's linkage with habituation or satiation bears importance. Repeated exposure to rewarding stimuli might engender habituation or satiation effects within this region, signifying a gradual waning of the brain's responsiveness to positive stimuli over time. (Berridge & Robinson, 2016; Preston & Eichenbaum, 2013)

Turning to the middle frontal gyrus, recognized for its involvement in altered reward processing, the decline in activation bears implications. This region's function in evaluating and integrating reward-related information is salient (Kringelbach & Rolls, 2004). A reduction in its activation suggests a potential attenuation in the engagement of cognitive control processes associated with reward anticipation and decision-making (Aarts et al., 2010). Additionally, the reduced activation might underscore a diminished involvement of cognitive control mechanisms during reward processing, impacting attention regulation, impulsive restraint, and top-down behavioral control (Bari & Robbins, 2013). This diminution could point towards compromised regulation of responses to rewarding stimuli. Lastly, the diminished activation of the

middle frontal gyrus could also correlate with decreased motivation or interest in response to rewards, given its role in generating and maintaining goal-directed behavior (Wallis, 2012).

The enhanced reward processing associated with the left putamen is noteworthy. The observed surge in activation may signify an intensified participation of reward processing mechanisms (Haber & Knutson, 2010). Operating as a pivotal element within the brain's reward circuitry, the left putamen significantly contributes to the processing and integration of reward-related information (Haber & Knutson, 2010). This heightened activation implies an escalated involvement of the putamen in responding to rewarding stimuli, potentially indicating an elevated reactivity to positive outcomes (Knutson & Greer, 2008).

5.2.2 Comparing changes in region of interest (ROI) activation in response to negative stimuli across ECT Visits.

Using the Harvard/Oxford Atlas the right caudate, the right superior frontal gyrus and the right putamen showed changes. A reduction in activation was observed in the right caudate in response to punishment stimuli. This reduction can imply a potential attenuation in the engagement or activation of the right caudate, a cerebral region intricately linked to the processing of reward signals (Berridge & Robinson, 1998; Haber & Knutson, 2010). This decline in activation could signify a dampened sensitivity or diminished responsiveness to stimuli associated with punitive consequences, suggesting a possible mitigation in the reactivity to aversive cues (Berridge & Robinson, 1998; Haber & Knutson, 2010).

With regards to the right putamen, the observed decrease in activation may signal the initiation of regulatory mechanisms designed to suppress or inhibit responses to adverse stimuli (Etkin, Egner, & Kalisch, 2011). These regulatory processes might encompass sophisticated cognitive control mechanisms or strategies geared towards modulating emotional responses

(Etkin, Egner, & Kalisch, 2011). Additionally, the investigation into the superior frontal gyrus reveals a reduction in its activation. This decline could indicate the implementation of cognitive reappraisal strategies, a technique involving the reinterpretation or reframing of the cognitive significance attributed to aversive stimuli (Ochsner & Gross, 2005). This strategic cognitive reappraisal could potentially lead to a reduction in emotional reactivity (Ochsner & Gross, 2005). The implication of the superior frontal gyrus in cognitive reappraisal processes underscores the possibility that its decreased activation may reflect the effective deployment of such strategies to modulate emotional responses (Ochsner & Gross, 2005).

5.3 Responders vs Non-Responders - ECT Treatment Response and Behavioral Measures.

5.3.1 Depression Scores

While the non-responder group did not exhibit a statistically significant reduction of at least 50 percent in depression scores across the assessed questionnaires, it is crucial to acknowledge the discernible trend toward a decrease in scores. This nuanced observation suggests that, despite not meeting the predefined threshold for a clinically significant improvement, there might still be notable changes in depressive symptoms among non-responders. This trend prompts a more nuanced interpretation of treatment outcomes, emphasizing the importance of considering sub-threshold improvements that may contribute to a broader understanding of the impact of Electroconvulsive Therapy (ECT) on depressive symptoms.

Understanding and recognizing these trends in depressive scores among non-responders is significant for several reasons. Firstly, it highlights the complexity of treatment response and underscores that therapeutic benefits may manifest in varying degrees. Even if the stringent criteria for a 50 percent reduction in scores are not met, the observed trend may signify a partial response or the initiation of a positive trajectory in the treatment journey. Such insights are valuable in informing clinicians about

the diverse ways individuals may experience and respond to ECT.

Furthermore, the identification of a trend toward decreased depressive scores in non-responders has implications for treatment planning and patient management. It suggests that individuals who do not meet the conventional criteria for a significant response may still experience meaningful changes in their depressive symptoms over time. This information can guide clinicians in refining and tailoring treatment approaches for non-responders, perhaps by adjusting the treatment protocol, considering adjunctive interventions, or extending the treatment duration to capture the potential for further improvement.

In conclusion, while the non-responder group did not meet the stringent criteria for a 50 percent reduction in depression scores, the observed trend toward a decrease in scores is a noteworthy finding. This trend sheds light on the nuanced nature of treatment response, emphasizing the importance of considering sub-threshold improvements and the potential for meaningful changes in depressive symptoms among individuals undergoing ECT. These insights contribute to a more comprehensive understanding of the therapeutic landscape and can inform personalized and adaptive approaches to treatment for individuals with depression.

5.3.2 TEPS

The results pertaining to pleasure and anhedonia scores among non-responders to Electroconvulsive Therapy (ECT) carry considerable importance and significance despite the absence of a significant change in overall depression levels. The analysis of these specific dimension's sheds light on nuanced aspects of treatment response that extend beyond conventional measures of depression.

The observed significant changes in the Temporal Experience of Pleasure Scale (TEPS) - specifically, the TEPS-ANT (Anticipatory Pleasure) and TEPS-CON (Consummatory Pleasure) measures - are particularly noteworthy. These scales capture distinct facets of pleasure experience, allowing for a more granular understanding of the impact of ECT on specific components of anhedonia.

The statistically significant increase in TEPS-ANT scores from Visit 1 (21.9) to Visit 4 (27.6) indicates a notable improvement in anticipatory pleasure among non-responders. Anticipatory pleasure involves the ability to experience pleasure in anticipation of future events or activities. The observed change suggests that, despite the lack of significant improvement in overall depression levels, there is a positive impact on the anticipatory aspect of pleasure, potentially influencing individuals' capacity to derive joy from future experiences.

Similarly, the statistically significant change in TEPS-CON scores from Visit 1 (21.4) to Visit 4 (27.2) signifies an improvement in consummatory pleasure, which relates to the pleasure experienced in the moment. This finding suggests that, even in the absence of a marked reduction in overall depressive symptoms, ECT may contribute to enhancing the immediate pleasure experienced by individuals during various activities.

These results are significant as they highlight the nuanced effects of ECT on specific dimensions of pleasure and anhedonia, providing a more comprehensive understanding of the treatment's impact. The ability of ECT to bring about positive changes in anticipatory and consummatory pleasure, even in the absence of a significant overall improvement in depression levels, underscores the complexity of treatment response and the importance of considering multiple dimensions of mental well-being. This nuanced perspective contributes valuable insights to the broader conversation on the therapeutic mechanisms and outcomes of ECT, guiding clinicians in tailoring interventions to address specific aspects of individuals' emotional experiences.

5.3.3 SHAPS

The results derived from the analysis of both responder and non-responder groups to the Snaith-Hamilton Pleasure Scale (SHAPS) questionnaire offer valuable insights into the nuanced impact of Electroconvulsive Therapy (ECT) on anhedonia, a key aspect of depressive symptomatology.

The observed significant score changes between Visit 1 and Visit 4, as well as between Visit 3 and Visit 4, within both groups are of considerable importance. These changes signify alterations in the individuals' ability to experience pleasure over the course of ECT treatment. The absence of statistically significant score changes between Visit 1 and Visit 3 adds an additional layer of complexity, suggesting that the observed improvements in anhedonia are more pronounced in the later stages of the treatment.

Within the non-responder group, the significant differences in scores between Visit 1 and Visit 4, as well as between Visit 3 and Visit 4, highlight a meaningful positive shift in anhedonia symptoms. This finding is particularly noteworthy as it suggests that ECT may exert a positive influence on specific depressive symptom domains even in cases where the overall depressive symptomatology remains relatively stable.

5.3.4 PANAS

The analysis of responses to the PANAS questionnaire unveils intriguing patterns in both positive and negative affect, providing nuanced insights into the emotional experiences of both responder and non-responder groups undergoing Electroconvulsive Therapy (ECT).

In the non-responder group, a significant finding emerges in the realm of negative affect, indicating a notable reduction in negative emotional experiences. This statistically significant change occurred between Visit 1 and Visit 4, with scores decreasing from 28 to 21. The observed decline in negative affect

suggests that, despite the absence of a substantial overall improvement in depression scores, ECT may have a discernible impact on mitigating negative emotional states among non-responders. This finding is significant as it emphasizes the potential of ECT to influence specific emotional dimensions, contributing to a more comprehensive understanding of its therapeutic effects.

Conversely, within the non-responder group, PANAS positive affect scores remained relatively stable across ECT visits. The lack of statistically significant changes suggests that ECT may not exert a pronounced influence on positive emotional experiences among non-responders. While the absence of statistical significance should be noted, this observation still contributes valuable information about the selective impact of ECT on different affective dimensions in this subgroup.

In summary, the results from the PANAS questionnaire underscore the differential impact of ECT on positive and negative affect in both responder and non-responder groups. The observed reduction in negative affect among non-responders and the enhancement of positive affect among responders contribute important nuances to our understanding of the emotional dimensions influenced by ECT, further guiding the development of targeted interventions for individuals with depression.

5.4 3dANOVA3 non-responders

The observed changes in neural activation patterns before and after Electroconvulsive Therapy (ECT) treatment provide valuable insights into the dynamic effects of ECT on specific brain regions associated with depression. Before treatment, depressed individuals exhibited a complex pattern of abnormalities, including a significant positive cluster in the right middle cingulate cortex (rMCC) and negative activations in the left supramarginal gyrus (lSMG), right middle cingulate cortex, left anterior cingulate cortex (lACC), and right middle temporal gyrus (rMTG). These findings indicated disruptions in cognitive processes, emotional regulation, and memory functions,

contributing to the intricate interplay between cognitive and emotional factors in depression.

After ECT treatment, notable alterations were observed, with the rMCC showing positive activation. This positive change in rMCC suggests a potential normalization or enhancement in emotional regulation and cognitive processing post-ECT, aligning with the anticipated therapeutic effects on mood disorders. Conversely, negative activations in the right insula, left superior medial gyrus, right supplementary motor area (SMA), and left anterior cingulate cortex (lACC) post-ECT raise intriguing questions.

The negative activation in the right insula implies potential downregulation or alterations in emotional processing, essential for understanding how ECT influences regions associated with emotional functioning and potential adaptations in neural networks. The negative activations in the left superior medial gyrus prompt exploration into changes in various cognitive functions associated with this region, contributing to a nuanced understanding of ECT's effects on different aspects of neural functioning. Similarly, the negative activation in the right SMA raises questions about its impact on motor-related functions, providing insights into how ECT modulates neural circuitry beyond emotional and cognitive domains. Lastly, the negative activation in the left ACC introduces complexities in understanding how ECT influences emotional regulation and cognitive control in this crucial region, necessitating further investigation into the nuanced effects of ECT on the anterior cingulate cortex, integral to mood disorders. Collectively, these findings underscore the intricate neural changes associated with ECT, offering a comprehensive view of its impact on the complex interplay of cognitive and emotional factors in individuals undergoing treatment for depression.

The absence of significant positive clusters in response to reward stimuli in the non-responder group is important as it suggests a lack of robust neural activation associated with reward processing. In a healthy neural response to rewards, one would typically expect the activation of specific brain regions, such as

the ventral striatum and prefrontal cortex. The identified regions in the non-responder group, including the right insula lobe, right middle temporal gyrus, left anterior cingulate cortex, left temporal gyrus, left caudate nucleus, right SMA, and right superior frontal gyrus, might indicate an altered or insufficient response to rewarding stimuli. This lack of significant activation in key reward-related regions could be indicative of dysfunction in the brain's reward circuitry in non-responders. In the context of depression, an impaired reward system is a common feature, contributing to anhedonia, a core symptom characterized by a reduced ability to experience pleasure. Understanding the neural correlates of reward processing in non-responders provides valuable insights into the mechanisms underlying their resistance to treatment. It also emphasizes the need for targeted interventions that address specific dysfunctions in reward-related brain regions to improve treatment outcomes for individuals with depression who do not respond to conventional therapies. The observed differences in mean activation between Visit 1 and Visit 4 in Electroconvulsive Therapy (ECT) Non-Responders reveal distinct patterns in specific brain regions. Positive clusters, including the left superior medial gyrus, right inferior frontal gyrus, right middle frontal gyrus, and right thalamus, indicate notable increases in activation over the treatment period. The left superior medial gyrus, associated with various cognitive functions, may suggest enhanced cognitive processing. The right inferior frontal gyrus and right middle frontal gyrus, implicated in emotional regulation and decision-making, may signify improvements in these domains. The right thalamus, known for its role in sensory and motor signal relay, suggests heightened neural activity in response to ECT. Conversely, the negative cluster in the right superior temporal gyrus indicates a decrease in activation, potentially reflecting alterations in auditory and social processing. Understanding these regional changes contributes to a nuanced interpretation of treatment effects, offering insights into the neural dynamics associated with ECT non-responsiveness.

The differences in brain activation between Visit 1 and Visit 4 in ECT Non-Responders, specifically in response to reward stimuli,

reveal a noteworthy pattern. In this analysis, no negative clusters were identified, indicating the absence of decreased activation in any region. However, a positive cluster was observed in the left superior medial gyrus. The positive activation in this region, associated with various cognitive functions, suggests an increase in neural activity related to reward processing over the course of ECT treatment. While the absence of negative clusters implies no decline in activation, the presence of a positive cluster in the left superior medial gyrus signifies a potential enhancement in cognitive aspects associated with reward responsiveness in ECT Non-Responders from Visit 1 to Visit 4.

The comparison of brain activation between Visit 1 and Visit 4 in ECT Non-Responders, specifically in response to punishment stimuli, reveals a distinct pattern. In this analysis, no negative clusters were identified, indicating the absence of decreased activation in any region. However, a positive cluster was observed in the left superior medial gyrus. The positive activation in this region, associated with various cognitive functions, suggests an increase in neural activity related to the processing of aversive stimuli over the course of ECT treatment. While the absence of negative clusters implies no decline in activation, the presence of a positive cluster in the left superior medial gyrus signifies a potential enhancement in cognitive aspects associated with the perception of punishment in ECT Non-Responders from Visit 1 to Visit 4. Understanding these regional changes provides valuable insights into the neural dynamics of aversive stimulus processing during ECT treatment in non-responsive individuals. In examining the brain activation differences between Visit 1 and Visit 4 in ECT Non-Responders, both in response to reward and punishment stimuli, a consistent pattern emerges. Notably, no negative clusters were identified in either case, indicating a lack of decreased activation in any region. However, a positive cluster was consistently observed in the left superior medial gyrus. This region, associated with various cognitive functions, showed increased neural activity over the course of ECT treatment, suggesting heightened cognitive engagement in both reward and punishment processing. The absence of negative clusters implies a sustained level of activation, while the presence of positive clusters

signifies a potential enhancement in cognitive aspects associated with both reward and aversive stimulus responsiveness. These consistent findings underscore the importance of the left superior medial gyrus in the cognitive dynamics of ECT Non-Responders, shedding light on neural adaptations during reward and punishment processing in this population. Understanding these shared regional changes provides valuable insights into the nuanced neural dynamics associated with ECT treatment in non-responsive individuals.

In ECT Non-Responders, distinct neural patterns emerge during Reward vs Neutral Stimuli at baseline and Punishment vs Neutral Stimuli post-ECT, revealing specific implications. The absence of positive clusters in baseline reward processing highlights a deficiency in neural responses to rewarding stimuli, with reduced engagement in the left superior medial gyrus, indicating a baseline deficit in cognitive aspects related to reward responsiveness. Post-ECT, stability in neural responses to punishment cues is observed, evidenced by the absence of significant changes and a solitary negative cluster in the right posterior cingulate cortex. This suggests resistance to alteration in certain neural circuits associated with punishment processing, emphasizing the nuanced and individualized nature of treatment-resistant depression. These findings underscore the need for targeted interventions tailored to the complex neural dynamics of non-responsive individuals undergoing ECT.

5.5 Non-Responder ROI Analysis

In this chapter, the focus was on utilizing ROI analysis to investigate alterations in region activation in response to reward and punishment stimuli throughout various visits during Electroconvulsive Therapy (ECT) treatment, specifically within the non-responder group. The utilization of the Harvard-Oxford Atlas (Gorgolewski et al., 2015) allowed for the delineation of distinct regions of interest (ROIs) across various brain areas. These included the left and right thalamus, left and right caudate, left and right putamen, left and right hippocampus, left

and right amygdala, left and right nucleus accumbens, frontal medial cortex, paracingulate gyrus, as well as posterior and anterior cingulate gyrus, anterior and posterior parahippocampal gyrus, and the superior and middle frontal gyrus. This comprehensive atlas-based approach enabled a thorough examination of ROI activations and their responses to diverse stimuli throughout different stages of ECT treatment among non-responders.

The ROI analysis illustrated the activation of two specific regions, namely the right hippocampus and the right putamen, in response to stimuli associated with both reward and punishment. Notably, the right hippocampus exhibited activation in response to reward stimuli during two specific intervals, between Visit 1 and Visit 3 ($p=0.082$), and Visit 3 and Visit 4 ($p=0.080$), as depicted in Figure 25. Despite not reaching statistical significance, these findings reveal a discernible trend. It is paramount to note that the right hippocampus holds significant relevance in the context of depression, emphasizing the potential importance of these observed trends in understanding the neurobiological underpinnings of treatment response. Additionally, the analysis demonstrated significant activation in the right putamen in response to both reward and punishment stimuli. Specifically, a significant response to reward stimuli was observed between Visit 1 and Visit 4 ($p=0.04$), and in response to punishment stimuli between Visit 1 and Visit 3, as illustrated in Figure 26.

While some results did not attain statistical significance, the identified trends in the right hippocampus and the significant activation in the right putamen underscore the potential neurobiological changes occurring during ECT treatment in non-responders. These findings contribute to the evolving understanding of the neural correlates associated with treatment response and pave the way for further exploration into the intricate mechanisms underlying the effects of ECT on specific brain regions implicated in depression.

Chapter 6

Limitations and Future Implications

6.1 Limitations

It is possible that our study was limited by factors such as the sample size or experimental design. The current study focused primarily on the neural responses to reward and punishment stimuli and did not consider the behavioral or subjective responses to these stimuli. Future research could benefit from exploring these aspects more thoroughly, which may help to clarify any potential differences in how the brain processes reward and punishment stimuli. Despite these limitations, the findings of this study have important implications for our understanding of reward and punishment processing in the brain. Our results suggest that the brain may use similar neural mechanisms to process these two types of stimuli, and that the distinction between reward and punishment may not be as clear-cut as previously thought. Further research is needed to explore this topic in more detail, including investigations of the neural and behavioral responses to different types of rewards and punishments, as well as the potential interactions between these processes.

When an experiment does not reveal significant differences between reward and punishment, there are several possible explanations. First, the task or stimuli used may not have been strong enough to elicit a robust response from the reward or punishment systems in the brain. For instance, the magnitude of the reward or punishment may have been too small to produce a noticeable effect on behavior or brain activity. A study by Seymour et al. (2007) found that the perceived magnitude of a reward or punishment can modulate the neural response to that outcome in the striatum.

Second, individual differences in sensitivity to reward and punishment may have masked any group-level differences. Research has shown that some individuals may be more

motivated by the prospect of rewards, while others may be more sensitive to punishments (Knutson et al., 2001). These differences in personality traits and motivation can influence how an individual responds to reward and punishment.

Third, there may have been confounding variables or factors that influenced the results of the experiment. For example, if the reward and punishment conditions differed in some other way (e.g., difficulty level of the task), this could have affected the results. A study by Kim et al. (2018) found that task difficulty can modulate the neural response to reward and punishment in the striatum and prefrontal cortex.

Finally, it is possible that the reward and punishment systems in the brain are more closely linked than previously thought. Research has shown that both reward and punishment processing involve similar neural pathways and regions in the brain, such as the ventral striatum and prefrontal cortex (Delgado, 2007). This suggests that the differences between these systems may not be as distinct as previously believed.

In summary, when an experiment does not show significant differences between reward and punishment, it is important to consider alternative explanations such as differences in stimuli or individual differences in sensitivity, confounding variables, or the possibility of these systems being more closely linked than previously thought. Further investigation is necessary to fully understand the underlying mechanisms of reward and punishment processing in the brain.

The idea that reward and punishment stimuli may be more closely linked than previously thought is supported by research showing that these processes involve similar brain regions and neural pathways. According to a study by Haber and Knutson (2010), both reward and punishment processing involve the ventral striatum and prefrontal cortex, suggesting that these two processes share some common neural mechanisms.

This similarity between reward and punishment processing may be since both processes serve to motivate behavior and guide

decision-making. As noted by Berridge and Kringelbach (2015), the anticipation of a reward can increases the likelihood of engaging in a particular behavior, while the anticipation of a punishment can decreases the likelihood of engaging in that behavior. Similarly, the experience of a reward or punishment can influence learning and memory, helping to reinforce or avoid certain behaviors in the future.

The idea that the distinction between reward and punishment may be more arbitrary than previously believed is also supported by research. For example, a study by Delgado et al. (2008) found that the same neural circuitry is involved in processing both reward and punishment feedback. This suggests that some stimuli may be both rewarding and punishing depending on the context or individual interpretation, which could help to explain why some studies have failed to find clear differences between reward and punishment processing in the brain.

Reward processing is an essential process that allows individuals to engage in goal-directed behaviors and make decisions that lead to long-term benefits. However, individuals with depression can experience various limitations in reward processing, leading to difficulties in engaging in goal-directed behavior and making advantageous decisions. It is therefore essential for individuals with depression to receive appropriate treatment, including therapy, medication, and lifestyle changes, to help improve their reward processing and overall well-being.

There are several limitations to reward processing that can impact the ability of individuals with depression to engage in goal-directed behavior and make decisions that are advantageous in the long term. One of these limitations is individual differences. People respond to rewards differently, and this can influence how they perceive and value rewards. For example, some individuals may value social rewards more than monetary rewards, while others may prefer tangible rewards. Contextual factors can also have a significant impact on how rewards are perceived and valued. The way rewards are presented, the context in which they are presented, and the

timing of the reward can all influence how they are perceived and valued. For instance, a reward presented in a stressful situation may not be as effective as the same reward presented in a relaxed environment. Past experiences with rewards can influence the way rewards are perceived and valued in the future. This learning history can impact how individuals with depression perceive and value rewards, leading to difficulties in engaging in goal-directed behavior and making advantageous decisions. The complexity of reward processing is another limitation. Reward processing involves multiple brain regions, and the interactions between these regions are not yet fully understood. The neurobiological underpinnings of reward processing can also vary between individuals and can be influenced by factors such as age, genetics, and disease state. The temporal resolution of current imaging techniques used to study reward processing is also limited, making it difficult to study the dynamics of the process in real-time. There are also several methodological challenges associated with studying reward processing, including the use of appropriate control conditions, controlling for extraneous variables, and ensuring that participants are motivated to engage in the task. These limitations highlight the need for continued research to better understand the complexities of reward processing and how it can be influenced by various factors. Depression can impact reward processing in various ways, leading to limitations in reward-related behaviors and decision-making. One of the key symptoms of depression is anhedonia, the inability to experience pleasure or joy from activities that were previously enjoyable. This can lead to a reduced response to rewards, making it difficult for individuals with depression to find motivation or engage in goal-directed behavior. Dopamine is a key neurotransmitter involved in reward processing and motivation. Research suggests that in depression, there may be changes in dopamine signaling, leading to a reduction in the perception of reward. This dysregulated dopamine signaling can lead to a decreased ability to experience positive reward. Depression is often characterized by negative biases in attention and memory, resulting in an over-representation of negative events and an under-representation of positive events. This negative bias can lead to a reduced ability to experience positive reward and an

increased sensitivity to punishment. Depression can also affect decision-making, particularly in situations involving reward and punishment. Individuals with depression may struggle with making decisions that are advantageous in the long term due to a decreased ability to weigh the potential rewards and consequences.

While the idea that reward and punishment stimuli may be more closely linked than previously thought is an intriguing area of research, there are also some limitations to consider.

Firstly, many of the studies in this area have focused on specific brain regions or neural pathways and may not fully capture the complexity of reward and punishment processing in the brain. For example, a study by Fliessbach et al. (2007) found that different brain regions are activated during anticipation of reward and punishment, suggesting that these processes may be more distinct than previously believed.

Secondly, much of the research in this area has relied on simple laboratory tasks or paradigms, which may not fully capture the complexity of reward and punishment processing in real-world situations. For example, a study by Hare et al. (2008) found that social and emotional factors can influence reward and punishment processing in the brain, highlighting the need for more ecologically valid research designs.

Finally, individual differences in reward and punishment sensitivity may also be an important factor to consider. For example, a study by Pizzagalli et al. (2008) found that individuals with depression show reduced reward processing in the brain, while punishment processing remains intact. This suggests that individual differences in brain function may contribute to differences in reward and punishment processing.

In conclusion, limitations in reward processing can impact the ability of individuals with depression to engage in goal-directed behavior and make advantageous decisions. Appropriate treatment, including therapy, medication, and lifestyle changes, can help improve reward processing and overall well-being in

individuals with depression. Further research is necessary to better understand the complexities of reward processing and how it is influenced by various factors.

Overall, the idea that reward and punishment stimuli may be more closely linked than previously thought has important implications for understanding the underlying mechanisms of these processes in the brain. By gaining a better understanding of how reward and punishment interact and influence behavior, researchers may be better able to develop interventions and treatments for a range of disorders and conditions.

6.2 Future Implications

Research on the neural mechanisms underlying reward and punishment processing in major depressive disorder (MDD) has important implications for the development of novel treatments for this condition. The current findings suggest that there may be similarities in the neural processes underlying reward and punishment processing in MDD patients. This has important implications for the development of treatment approaches that target these processes, such as cognitive-behavioral therapy and transcranial magnetic stimulation.

Future studies could build on these findings by examining the role of specific brain regions in reward and punishment processing in MDD patients. For example, recent research has suggested that the ventral striatum may play a key role in reward processing in MDD patients. Similarly, the amygdala and anterior cingulate cortex may be particularly important for punishment processing.

In addition, future research could explore the relationship between reward and punishment processing in MDD patients and other related conditions, such as anxiety and substance use disorders. Understanding the similarities and differences in the neural mechanisms underlying these processes could provide important insights into the shared and distinct features of these conditions, as well as the development of targeted treatments.

Finally, future studies could explore the potential of using real-time fMRI neurofeedback to modulate reward and punishment processing in MDD patients. By providing patients with real-time feedback on their neural activity, this approach could help individuals learn to regulate their own reward and punishment processing, leading to improved treatment outcomes. Neuromodulation technologies, such as transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS), have shown promise in treating patients with major depressive disorder (MDD) by modulating neural activity in key brain regions involved in reward processing. These technologies work by delivering electrical or magnetic pulses to specific areas of the brain, effectively altering neural activity in those regions.

Recent studies have explored the potential of these technologies in modulating reward processing in patients with MDD. For example, some studies have shown that TMS can enhance reward processing in patients with MDD, leading to improvements in mood and overall functioning. Similarly, DBS has been shown to modulate activity in reward-related brain regions and improve depressive symptoms in some patients.As these technologies continue to be refined and optimized, they hold great potential for improving the treatment of MDD by targeting the specific neural circuits involved in reward processing. However, more research is needed to fully understand the underlying mechanisms of these technologies and to identify the most effective stimulation parameters for treating MDD.

In the future, it is possible that these technologies could be combined with other therapeutic approaches, such as cognitive behavioral therapy or pharmacotherapy, to provide a more comprehensive and personalized treatment plan for patients with MDD. Additionally, the development of non-invasive neuromodulation techniques, such as transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS), could make these technologies more accessible and affordable for a wider range of patients with MDD.

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