2017

Pattern separation and frontal EEG change as markers for responsiveness to electroconvulsive therapy

https://hdl.handle.net/2144/23748

Boston University
Thesis

PATTERN SEPARATION AND FRONTAL EEG CHANGE AS MARKERS FOR RESPONSIVENESS TO ELECTROCONVULSIVE THERAPY

by

KATHRYN GORDON DAVIS

B.S., Bates College, 2015

Submitted in partial fulfillment of the requirements for the degree of Master of Science 2017
Approved by

First Reader

Roberta White, Ph.D.
Professor of Neurology
Chair of Environmental Health, School of Public Health

Second Reader

Michael Henry, M.D.
Psychiatrist
Director of Somatic Therapy, Massachusetts General Hospital
ACKNOWLEDGMENTS

Over the past year I’ve been fortunate enough to meet so many admirable people while working towards the completion of my thesis. I would like to extend my deepest gratitude towards my primary thesis reader, Dr. Roberta White, a truly remarkable woman who has inspired me with her stories and positivity. Her empathy, warmth, and encouragement were a constant comfort, particularly on those endless, coffee-fueled nights of research. I would also like to thank my secondary thesis reader and primary thesis mentor, Dr. Michael Henry, the man who does it all, and who has taught me a great deal about being confident, resourceful, and persistent in pursuit of all that I set out to do. And of course one cannot forget the unforgettable Michelle Collins-Butman and Jessenia Urquiza, who both went above and beyond to offer me help whenever they could. I will always appreciate their kindness, good humor and willingness to show me all the ins and outs of the ECT department of Psychiatry at MGH. I would also like to give a special thanks to David Zhou, who helped me navigate through the mysteries and complications of coding and Matlab. As always, I’d like to give a tremendous thank you to my parents, who listened patiently to all my explanations, plights, excitement, and doubts, and who always had faith in me. Your support in my academic efforts continues to drive me towards my greatest aspirations. Last, but not least, thank you to my friends who offered me their kindness and support. Thank you.
PATTERN SEPARATION AND FRONTAL EEG CHANGE AS Markers for
RESPONSIVENESS TO ELECTROCONVULSIVE THERAPY
KATHRYN GORDON DAVIS

ABSTRACT

There is still a great deal that is unknown about various depressive conditions, though it is a very common affliction and cause of disability throughout the world. Not only do the underlying mechanisms of various types of depression remain uncertain, but the mystery of how different treatment options work and who will respond to them also persists. The aim of this study was to identify potential non-invasive biomarkers, to predict responsiveness to electroconvulsive therapy. Two hypotheses were investigated in this study. The first was that patient improvement from baseline on the neurocognitive, computer based pattern separation task prior to the third ECT treatment will correlate with a clinical antidepressant response. The second was that increased prefrontal slowing relative to baseline will correlate with a decrease in depressive symptoms. As a first step to validate this approach, a healthy control group performed both the pattern separation and EEG tasks once per week over the course of three weeks. Patient participants completed both tasks before their first ECT treatment, prior to their third treatment, and prior to their last treatment. A spectral analysis of EEG data was then conducted. Results indicated good test-retest reliability for the pattern separation task and EEG measurements across all three trials in the healthy control group. Results from patient data are inconclusive, but indicates that there is a change from baseline to subsequent trials for at least the EEG measurements. However, a larger sample size is needed to
determine this. The limited results from this small patient sample suggest that these measurements may have clinical value in refining ECT treatment, and merit further study.
# TABLE OF CONTENTS

TITLE........................................................................................................i

COPYRIGHT PAGE....................................................................................ii

READER APPROVAL PAGE....................................................................iii

ACKNOWLEDGMENTS ........................................................................ iv

ABSTRACT ...............................................................................................v

TABLE OF CONTENTS ........................................................................ vii

LIST OF TABLES ..................................................................................... x

LIST OF FIGURES ................................................................................... xi

LIST OF ABBREVIATIONS .......................................................................xii

INTRODUCTION ..................................................................................... 1

**Depression: Impact and Prevalence** .......................................................1

**Neurocircuitry of Mood Disorders** ......................................................2

**A Closer Look at the Hippocampus and its Role in Depression** ..........6

**BDNF and Depression** ......................................................................7

**Pharmacological Interventions and the Rise of Treatment Resistant Depression** ..................................................................................9

**Electroconvulsive Therapy for Treatment-Resistant Depression** ......11

**Mossy Fiber Sprouting: Indicative of Positive or Negative Changes?** 15
Pattern Separation Scores in Healthy Controls and Patients..................44
Relationship between the QIDS-SR and the Pattern Separation Task........46
Relationship between the QIDS-SR and the EEG Task..........................47
EEG Measurements and Laterality in Healthy Controls and Patients.......48
Limitations and Future Suggestions..................................................51
REFERENCES..................................................................................56
CURRICULUM VITAE........................................................................66
<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Demographic Data</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>Mean and Standard Deviation Scores of EEG Measurements in Healthy and Depressed Participants</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>Mean and Standard Deviation Scores of Pattern Separations Scores for Healthy Participants</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>Measures of Test-Retest for Pattern Separation Scores in Healthy Participants</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>Measures of Test-Retest for EEG Measurements in Healthy Participants</td>
<td>37</td>
</tr>
<tr>
<td>Figure</td>
<td>Title</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>1</td>
<td>Pattern Separation Scores for Healthy Controls Compared to Patient Participants</td>
<td>40</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

BDNF ......................................................................................... Brain Derived Neurotropic Factor
CA3 ............................................................................................. Cornu Ammonis 3
CGI ............................................................................................... Clinical Global Impression Scale
CIDI .......................................................... Composite International Diagnostic Interview
DG .................................................................................................... Dentate Gyrus
ECS .............................................................................................. Electroconvulsive Shock
ECT .............................................................................................. Electroconvulsive Therapy
FEAST ........................................................ Focal Electrically Administered Seizure Therapy
fMRI ........................................................ Functional Magnetic Resonance Imaging
HPA ............................................................................................... Hypothalamic-Pituitary-Adrenal
HRSD ............................................................................................ Hamilton Rating Scale for Depression
IDS ................................................................................................. Inventory of Depressive Symptomatology
LCPST ........................................................ Limbic-Cortical-Striatal-Pallidal-Thalamic
MINI ........................................................ Mini International Neuropsychiatric Interview
MRI ............................................................................................... Magnetic Resonance Imaging
OMPFC ........................................................ Orbital and Medial Prefrontal Cortex
PET ........................................................ Positron Emission Tomography
QIDS-SR ........................................................ Quick Inventory of Depressive Symptomatology
WHO ........................................................ World Health Organization
YMRS ........................................................ Young Mania Rating Scale
INTRODUCTION

Depression: Impact and Prevalence

Depression is one of the most common of human afflictions (Rotheneichner et al., 2014). Approximately 350 million individuals worldwide are affected by depression, including conditions such as major depressive disorder, bipolar disorder, dysthymia, cyclothymic disorder, seasonal affective disorder, as well as depression associated with illness (WHO, 2016; Mayo Clinic, 2016). Of these people, 10-15% will experience recurrent depression throughout their entire lifetime, leading to a deep socioeconomic strain (Silverstein et al., 2015; Joshi et al., 2016). Consequences of chronic, moderate to severe depression have profound effects in the psychological, physical, and socioeconomic functioning of the individual (WHO, 2016). In addition to being the second leading cause of disability throughout the world, it is also a risk factor for ischemic heart disease and is associated with an increased risk of suicide (Silverstein et al., 2015; Ferrari et al., 2013). Tragically, more than 800,000 people each year die from suicide, and is one of the leading causes of death in individuals between 15 and 29 years old (WHO, 2016). Depression is a major source of disability, illness, and death across the globe (Nordanskog et al., 2010).

There are a variety of treatment options for those affected by depression, including cognitive behavioral therapy, antidepressant medication, and neuromodulation. However, due to severity and heterogeneity of the illness, insufficient numbers of trained
professionals and resources for treatment, and social stigma, over half of the afflicted individuals worldwide are untreated (WHO, 2016). Additionally, the rates of various depressive conditions, like major depressive disorder and bipolar disorder, along with other mental health conditions, have been increasing across the globe, and yet, knowledge of the pathogenesis of major affective illness is still limited (WHO, 2016; Drevets, Price, and Furey, 2008).

**Neurocircuitry of Mood Disorders**

Early studies hypothesized that particular neurochemicals and peptides were responsible for the underlying pathology of major depression (Mayberg, 2003). However, as more research has been conducted, models for depression have become increasingly more complex, with data suggesting that the disorder cannot be pinpointed to any one particular structure or neurotransmitter system in the brain (Mayberg, 2003). Current theories now look at depression as a multifaceted disorder that involves dysfunction of distinct, yet connected, pathways within the brain, as well as multiple neurotransmitter systems. In the face of this dysfunction, the remaining systems within the brain are unable to compensate for a decline in emotional regulation during times of stress (Mayberg, 2003). This model of neurocircuitry is consistent with data from post mortem studies, as well as studies involving neuroimaging, particularly fMRI (Drevets et al., 2008; Zhong, Pu, Yao, 2016). These models have indicated that both structural and
functional abnormalities influence the development of mood disorders (Drevets et al., 2008).

Both major depressive disorder and bipolar disorder usually involve major depressive episodes, which are believed to involve various brain systems that regulate mood, attention, expression of emotions, reward processing, motivation, social awareness, response to stress, and other functions like sleep or appetite (Drevets et al., 2008). Although the disturbances affecting these brain systems are not yet clear, genetics, injury during development, temperament, and environmental stress are all thought to play a role (Mayberg, 2003). Furthermore, studies have found abnormal neurophysiology, neurochemistry, and neuropathology in patients suffering from both major depression and bipolar depression (Drevets et al., 2008).

A meta analysis by Seminowicz et al., (2004) found that many studies have reported frontal and cingulate changes in depressed patients as well as other limbic and subcortical structures, though these are reported less frequently. Abnormalities of these structures found during the pretreatment state were often normalized upon antidepressant treatment, thus providing evidence for their role in various depressive conditions (Seminowicz et al., 2004). These studies suggest that there are complex interactions between these brain areas, types of treatment, and responsiveness of the brain to treatment (Seminowicz et al., 2004). Further neuroimaging, neuropathological assessments, and lesion studies have suggested that emotional behavior is regulated in part by the limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuit. This circuit includes connections between brain structures such as the amygdala, hippocampus, orbital and
medial prefrontal cortex (OMPFC), ventromedial striatum, ventral pallidum, and mediodorsal and midline thalamic nuclei (Drevets et al., 2008; Zhong et al., 2016).

The LCSPT circuit was initially believed to have a role in emotional regulation due to connections to structures such as the hypothalamus and periaqueductal gray, both of which are involved in controlling emotional expression (Drevets et al., 2008; Price and Drevets, 2010). Both human and animal models have found associations between emotional expression and regulation and structures within this brain circuitry, particularly with the orbital frontal cortex, medial prefrontal cortex, and the anterior cingulate cortex (Murrough, Iacoviello, Neumeister, Charney, and Iosifescu, 2011). Lesion studies involving the LCSPT circuit have supported its hypothesized role in mediating emotional behavior and expression. For example, early lesion studies in monkeys examining the lateral temporal cortex and medial temporal lobe structures, such as the hippocampus and amygdala, showed that such lesions produced an apathetic response in the animals (Kluver and Bucy, 1939). Imaging studies of older adults with lesions in, or connected to, this circuitry have been carried out in patients with degenerative basal ganglia disorders, such as Parkinson’s and Huntington’s disease, and in individuals with cerebrovascular injury to their striatum and orbital cortex (MacFall, Payne, Provenzale, and Krishnan, 2001; Folstein, M. F., Robinson, Folstein, S., and McHugh, 1985). These patients had an increased risk of experiencing a major depressive episode. In particular, deep white matter lesions in the orbital cortex were associated with the severity of depression (MacFall et al., 2001). Furthermore, a meta-analysis exploring the association of the LCSPT circuit in depression by Zhong et al., found that drug-naïve patients with major
depression had decreased fMRI activation within this circuit (2016). This suggests that this neurocircuitry may be a directly involved in the mechanism of depression, rather than a target of the effects of antidepressant pharmacological treatment (Zhong et al., 2016). Furthermore, fMRI studies of patients with major depressive disorder have found decreased activity particularly within the dorsolateral prefrontal cortex, a structure included in the LCSPT circuitry. This area has been linked to cognition, regulation of mood, and decision-making, and is one of the most consistently detected regions of abnormality in patients with major depression (Zhong et al., 2016).

It is thought that modifying this circuit is important for remission of mood disorders, and certain pharmacological, deep brain stimulation, and surgical treatments help to inhibit abnormal activity within extended cortical circuits that connect with the LCSPT circuit (Mayberg, 2003; Drevets et al., 2008). Neuroimaging studies have also found that these extended cortical circuits play a role in anxiety disorders that often accompany depression (Drevets et al., 2008). As research continued to build upon knowledge of the limbic system and its projections to other brain areas, investigators have hypothesized that the medial prefrontal cortico-striato-pallido-thalamic circuit was vastly intertwined with the amygdalo-striato-pallido-thalamic circuit, and to constitute the main circuitry involved in mood disorders (Price and Drevets, 2010).

Consistent with the above functional abnormalities, patients with mood disorders have often been found to have volumetric irregularities in their ventral and medial frontal cortices as well as in their hippocampus and other visceromotor network structures, such as the amygdala (Mayberg, 2003). However, the degree and location of abnormal
morphology depends on factors such as age at onset, genetic predisposition, and whether the patient experiences mania or psychosis associated with their depression (Drevets et al., 2008). For example, those who develop major depressive disorder and bipolar disorder later in life, tend to show non-specific atrophy. However, those who experience early onset, non-psychotic, major depressive disorder or bipolar disorder are often found to have abnormal volumes in their prefrontal cortex, cingulate, and structures in their temporal lobe (Drevets et al., 2008).

A Closer Look at the Hippocampus and its Role in Depression

The hippocampus is a structure within the medial temporal lobe of the brain involved in forming, storing, and retrieving memories, as well as applying memories to new situations (Kirwan et al., 2012; Yassa and Stark, 2011). Despite its well known role in declarative memory, evidence has also shown an association between the hippocampus and mood disorders, such as depression. Abnormalities in the hippocampus have been found to be associated with depressive episodes (Abbott et al., 2014). Cellular apoptosis, decreased neurogenesis, a lower number of glial cells in the hippocampus, atypical hippocampal connections, and smaller volumes have been associated with depressive disorder (Abbott et al., 2014). Postmortem and neuroimaging research have provided evidence for decreased gray matter volume, glial cells, and neuron size, associated with the cellular and structural alterations found in depressed patients (Canali et al, 2014). The loss of volume in the hippocampus, determined by clinical imaging studies, not only
seems to relate to the depressive state of the individual, but also to the duration and number of episodes (Nordanskog, Larsson, M.R., Larsson, E.M., and Johanson, 2014). In addition, post mortem studies have shown a relationship between stress, depression, and a lack of neuroplasticity in the hippocampus (Nordanskog et al., 2014). The hypothalamic-pituitary-adrenal axis (HPA) is associated with the body’s management of stress (Nemeroff, 1998). Overall, patients with depression have been found to have a hyperactive HPA axis causing increased levels of hormones, particularly cortisol (Nemeroff, 1996). Observations in animal models demonstrate that high levels of cortisol are associated with damage to the hippocampus. Consistent with these findings, human imaging studies have shown that, compared to healthy controls, depressed patients have smaller hippocampus volumes (Nemeroff, 1998). However, the increased activity of the HPA axis in depressed patients tends to normalize towards that of healthy controls upon treatment, such as medications or ECT (Nemeroff, 1996). Therefore, it is thought that antidepressants and neuromodulation may have a role in stopping these negative changes within the brain, and possibly improving symptoms through neurogenesis and repair activities (Canali et al, 2014).

**BDNF and Depression**

Preclinical studies have shown that interventions that increase plasticity in the hippocampus have led to an antidepressant effect in animals. However, clinical studies have had mixed results. One theory on remission of depression is that increased plasticity
allows the neural networks to be repaired, leading to a response to pharmacological
treatment (Lee, Park, Um, and Kim, 2014). Of current interest is brain-derived
neurotropic factor (BDNF) and its potential as a biomarker for depression. BDNF is
important for neuronal growth, survival, and differentiation, as well as neurogenesis and
plasticity (Molendijk et al., 2011). BDNF has also been found to be related to
maintaining neurons within brain circuitry involved in emotion, learning, memory,
appetite and sleep (Molendijk et al., 2011). Many recent studies have indicated a role for
BDNF in depression and have led to the suggestion that this disorder occurs due to a
stress related deficit in BDNF (Kurita, Nishino, Kato, Numata, and Sato, 2012; Lee et al.,
2014; Molendijk et al., 2011). Some studies have found that in patients suffering from
major depression, both plasma and serum BDNF levels are lower than normal, with lower
levels associated with greater severity of the disorder. In addition, it has been found
through postmortem studies that suicide victims show lower BDNF levels within their
prefrontal cortex and hippocampus than controls (Kurita et al., 2012). Clinical studies
have found that treatment with antidepressants normalizes serum BDNF levels to those of
healthy individuals (Kurita et al., 2012; Lee et al., 2014). Furthermore, some studies have
found an increase in serum and plasma BDNF after 6-8 weeks of treatment in responders
to treatment, leading to the possibility that BDNF levels could be used to predict
individual treatment outcome (Lee et al., 2014). However, the association between BDNF
levels and depression are still unclear. Though some studies have found promising
results, others have found that BDNF levels had no association with depression severity
(Rapinesi et al., 2015). Furthermore, it remains controversial as to whether BDNF levels
are associated with a response to pharmacological treatment or neuromodulation, as several studies have found that BDNF levels remain unchanged after ECT or certain SSRIs (Zhou et al., 2017; Rapinesi et al., 2015).

**Pharmacological Interventions and the Rise of Treatment Resistant Depression**

In previous years, mood disorders, like depression, were thought to be due only to a neurochemical abnormality. However, newer evidence suggests that structure and neuroplasticity also play a role in the disorder and that these two potential underlying causes may be overlapping (Nordanskog et al., 2014; Drevets et al., 2008). For example, within the brain circuitry thought to be very involved in mood disorders, abnormalities in dopaminergic, noradrenergic, serotonergic, cholinergic, GABA-ergic, glutamatergic, glucocorticoid and petidergic systems have been associated with depression. Many antidepressants are believed to alter these systems. It has been hypothesized that since antidepressant medications have a delay in manifesting their effects on mood, there are other mechanisms involved, such as a change in plasticity or gene expression (Drevets et al., 2008). In addition, there has been some evidence that suggests that pharmacological interventions are protective against depression-related hippocampal volume loss (Joshi et al., 2016). However, others have found no correlation between volume of the hippocampus and an improvement in depressive episodes (Nordanskog et al., 2014).

Despite the significant advance that antidepressant medications represent in the treatment of depression, as many as one-third of those diagnosed with depression are
unresponsive to first line pharmacologic interventions (Joshi et al., 2016). Following the use of second line treatment options, one third of patients utilizing these options do not respond (Joshi et al., 2016). When patients are unable to attain remission of their symptoms, despite treatment with interventions that have been shown to be effective for their disorder, they are considered to be treatment-resistant (Magnezi, Aminov, Shmuel, Dreifuss, and Dannon, 2016). In addition, some patients may show response to treatment, without being able to fully achieve remission. Any symptoms that are still experienced after the course of treatment then becomes a risk factor for future relapse (Fava, 2003). Treatment-resistant depression appears to be an increasing problem, with recent estimates of up to 40% of depressed patients suffering. In the past, this estimate was only approximately 10-15% (Taylor, 2008). One possibility for such a large increase in patients suffering from treatment resistant depression could be increased public health measures and awareness, as well as a possible inadequacy in the diagnostic validity of the new DSM-V. An analysis by Wakefield (2012), suggested that for depression and grief disorders, the DSM-V was lacking in its ability to completely distinguish between normal and disordered, increasing the risk of false diagnoses. Further studies are needed to confirm the validity of the DSM-V.

In 1997, Thase and Rush proposed a system for staging treatment resistant depression (Thase and Rush, 1997). In the first stage, the patient does not respond to first line treatment options. The second stage occurs when the patient fails to respond to a different class of drug than was previously tried. In stage three, the patient also fails to respond to a tricyclic antidepressant. Stage four is characterized by failure of the patient
to respond to a monoamine oxidase inhibitor. Stage five is when the patient cannot respond to any of the above treatment options or to electroconvulsive therapy (Thase and Rush, 1997). Although this model is helpful in the classification of treatment resistant depression, it does not take into account the dose or duration of treatment. Additional paradigms staging treatment resistant depression have been developed and expanded upon (Fava, 2003).

**Electroconvulsive Therapy for Treatment-Resistant Depression**

With awareness of treatment resistant depression on the rise, it has become increasingly more urgent to utilize treatment options for patients that are not only effective, but can induce a faster remission than traditional pharmacological agents. The induction of seizures to treat psychiatric conditions dates back to as early as the 1500s, with instances of physicians treating mania by instructing patients to ingest camphor (Rudorfer, Henry, and Sackeim, 2003). However, modern use of convulsive therapy first occurred in the 1930s after neuropsychiatrist Ladislas Joseph von Meduna used camphor oil to successfully treat a patient suffering from catatonia. After this success, he continued to use convulsive therapy to treat individuals suffering from schizophrenia (Rudorfer, et al., 2003). Interestingly, additional studies during the time found that schizophrenic patients who developed epilepsy experienced an improvement in their symptoms (Kimball, 2016). In 1938, the pharmacologic approach to inducing seizures was improved upon by using electricity to initiate them (Kimball, 2016). Clinicians
Cerletti and Bini, after first conducting the procedure in animals, tested the efficacy of electrically induced seizures in a delusional patient. The patient showed immediate improvement and, after eleven more treatments, recovered (Rudorfer et al., 2003).

Soon after, ECT was used for the treatment of mood disorders and underwent great refinement in technique and patient comfort (Kimball, 2016; Rudorfer et al., 2003). ECT is now considered to be the most potent biologically based treatment for individuals with treatment resistant depression, as well as other psychiatric disorders (Tendolkar et al., 2013; Ende, Braus, Walter, Weber-Fahr, and Henn, 2000). Consistent with this viewpoint, a meta-analysis from the UK ECT Review Group (2003) found that ECT was significantly more effective in improving symptoms of unspecified depression diagnoses than pharmacological agents. In addition, they found that patients electing to receive ECT as part of their care were less likely to discontinue treatment compared to those using medications alone (UK ECT Review Group, 2003). Although one study found that relapse rates between those using only medications and those using ECT were not significantly different, ECT ultimately had both faster response and remission rates (Kellner et al., 2006; Taylor, 2008). Despite some patients’ resistance to other methods of treatment, ECT has led to a 50-70% improvement for patients who fall into the treatment-resistant category (Tendolkar et al., 2013). However, patient responsiveness to ECT also appears to depend on the duration of depressive episodes, whether or not they have psychotic depression, or whether patients have previously responded to medications (Daly et al., 2001). Nevertheless, it has been reported that depressed patients treated with
ECT rate their quality of life as being more improved than those who do not receive this treatment (McCall, 2001).

Despite the quick improvement in treatment-resistant individuals undergoing ECT, this method of treatment is often considered controversial due to potential side effects (Ende et al., 2000). Cognitive side effects of ECT can include anterograde amnesia, which is typically temporary, and retrograde amnesia, which at times can be permanent (Ende et al., 2000). Animal studies of ECS provided additional information and demonstrations of side effects associated electric shock. For example, mice trained to avoid a foot shock would lose knowledge of their training after ECS was administered (Fochtmann, 1994). In addition, the effects of ECS on memory were also tested in mice through taste aversion to a toxin put in their water. After ECS, the animal’s ability to associate water with the toxin was distorted (Fochtmann, 1994). It is also worth noting however, that electrode placement in these animals had an effect on the extent of their memory loss and that animals often showed a gradual improvement in their memory over time (Fochtmann, 1994). Despite these effects, both post mortem and brain imaging studies have shown no signs of brain damage as a result of ECT (Joshi et al., 2016). However, although there is no evidence that ECT causes obvious structural alterations when observed post-mortem, it does promote mossy fiber proliferation in the hippocampus that may be related to its antidepressant effects (Joshi et al., 2016).

Although the mechanism behind ECT is still largely unknown, there are a few theories based on clinical and pre-clinical studies on how ECT elicits its antidepressant effects (Tendolkar, 2013). For example, early pharmacological studies found that agents
that prevented reuptake or depleted monoamine stores, particularly norepinephrine and serotonin, were associated with depressive states in patients (Schatzberg, Garlow, and Nemeroff, 2002). It is theorized that ECT treatment either upregulates these neurotransmitters or changes the sensitivity of their receptors (Kellner et al., 2012). The neuroendocrine theory postulates that ECT modifies the hypothalamic-pituitary-adrenal axis in depressed patients, and the anticonvulsant theory suggests that the actual induced seizure during ECT is responsible for the improvement of symptoms (Kellner et al., 2012). Animal models of ECT have found that electroshock therapy causes increased neuro- and synaptogenesis within the hippocampus (Kellner et al., 2012). In addition, both animal and human studies have found increased BDNF after ECT treatment. From these findings, the neurotrophic theory of ECT was derived, suggesting that ECT works through increased neurogenesis and neurotrophic factors in the brain (Kellner et al., 2012). This suggests that ECT increases neuroplasticity, counteracting the volume loss and atrophy of neurons seen in patients with depression (Tendolkar et al., 2013). It is also thought that ECT may change brain connectivity (Kimball, 2016). Studies with high-resolution magnetic resonance imaging (MRI) have found abnormalities in the circuitry of frontal regions and subregions of both the hippocampus and amygdala, as well as decreased hippocampal volumes, that improve after a course of ECT (Krishnan et al., 2016; Tendolkar et al., 2013; Nordanskog et al., 2010). However, it is uncertain whether the increase in hippocampal and amygdala volume was long-lasting as these studies measured volume only the week before and the week after ECT treatment (Tendolkar et al., 2013; Nordanskog et al., 2010). The changes in plasticity invoked by ECT treatment
have been found to be associated with the patient’s clinical state and the magnitude of their response to treatment, suggesting a potential role in ECT’s mechanism of action (Joshi et al., 2016).

**Mossy Fiber Sprouting: Indicative of Positive or Negative Changes?**

One change associated with neuronal plasticity and morphology that has been studied in models of ECT and epilepsy is the sprouting of mossy fibers within the hippocampus (Vaidya, Siuciak, Du, and Duman, 1999). Mossy fibers are also known as dentate gyrus granule cells, which will reorganize their terminal axons upon certain stimuli, such as ischemia, stroke, trauma, or temporal lobe epilepsy (Scharfman, Sollas, Berger, and Goodman, 2003). Several animal studies have shown a remodeling of the hippocampus via mossy fiber changes after ECT treatments, a result that is not seen through pharmacological treatments (Ende et al., 2000; Tendolkar et al., 2013). In animal epilepsy studies involving kindling or excitotoxin treatment, not only has mossy fiber sprouting been observed, but also severe cell death and spontaneous seizures (Vaidya et al., 1999). It has therefore been suggested that this change in mossy fiber sprouting compensates for cell loss after kindling or excitotoxin treatments (Vaidya et al., 1999). Some of these modalities, such as electrical kindling, have also been found to cause a secondary or “mirror focus” lesion (Morrell, 1989; Morrell, 1959). In this condition, seizure activity arising from a location in one hemisphere of the brain may be related to additional seizure activity in a symmetrical area of the other hemisphere (Morrell, 1960).
Although these studies show a negative outlook on stimuli such as repeated electrical treatments and give reason to view mossy fiber sprouting as a sign of damage to the brain, some studies note a difference between epileptic seizures and electroconvulsive seizures (Dam, A.M. and Dam, M., 1986). For example, methods used to induce seizures in patients or animals during ECT treatment are often very different from induced seizures in epilepsy studies. Only in very rare cases do patients treated with ECT experience spontaneous recurring seizures after their treatment (Dam, A.M. and Dam, M., 1986). Despite the neuronal loss associated with epilepsy, a meta-analysis conducted by Devanand, Dwork, Hutchinson, Bolwig, and Sackeim, (1994) found that neither animal nor human studies have found evidence of structural damage or cell loss as a result of ECT treatment. A few studies have even suggested that mossy fiber sprouting may indicate a positive effect of ECT. A study by Vaidya et al., (1999) found that chronic ECS in animals generates mossy fibers in the hippocampus that help to innervate areas that were previously lacking neuronal input. Their data suggests that mossy fiber growth was not related to cell death, as the mice they treated with chronic ECS experienced no cell loss (Vaidya et al., 1999). As previously mentioned, ECT also appears to be related to an increase in BDNF, which studies have suggested may also contribute to mossy fiber sprouting (Vaidya et al., 1999). This may play a role in protecting the hippocampus by helping to increase neuroplasticity, which is typically reduced in depression (Tendolkar et al., 2013). Studies have speculated that changes in morphology, cell survival, and function of dentate granule cells may contribute to the therapeutic effects of ECT (Vaidya et al., 1999). Increased mossy fiber sprouting from the dentate granule cells after ECS
may also help the CA3 pyramidal cells of the hippocampus via increased innervation and delivery of BDNF; a process that may decrease the risk of stress-induced cell death (Vaidya et al., 1999).

**Focal Electrically Administered Seizure Therapy (F.E.A.S.T.)**

For many years, it was believed that the seizure elicited by ECT was responsible for the efficacy of treatment (Nahas et al., 2013). However, studies have found that electrode placement, type of electrical stimulus, and strength of electrical stimulation, can affect both the antidepressant response and side effects as well (Nahas et al., 2013). In addition, it has now been suggested that where the seizure is initiated is more important than where it propagates to (Sahlem et al., 2016). Through this research, a new form of ECT has been developed known as “Focal Electrically Administered Seizure Therapy” or FEAST (Sahlem et al., 2016). FEAST was designed to deliver a more focal and efficient electrical stimulus and is suggested to have lesser cognitive side effects than traditional ECT, though further studies are necessary to confirm this conclusion (Sahlem et al., 2016). One factor that may contribute to lesser side effects is that a more focalized delivery of electrical stimuli has been found to limit the induced seizure to only the prefrontal cortex (Chahine et al., 2014). In addition, FEAST has been found to be less efficacious than traditional ECT, thus with a less intense treatment, it can be expected that the side effects will be more minimal (Nahas et al., 2013).
FEAST has three distinct differences from traditional ECT: it uses unidirectional current instead of bidirectional, it uses a circular anterior electrode and an elongated oval-shaped posterior electrode, and the placement of electrodes is different than in traditional ECT (Sahlem et al., 2016). Additionally, the theory behind FEAST lies in the belief that certain neural circuitry, when altered, can help promote an antidepressant response (Sahlem et al., 2016). For example, many studies have noted prefrontal changes brought about by ECT. In one study utilizing EEG probes, it was found that increased delta waves in the prefrontal regions were associated with treatment response (Sackeim et al., 1996). Furthermore, when examined by positron emission tomography (PET), reductions in glucose metabolic rates particularly in the frontal, prefrontal, and parietal cortexes regions correlated with response to ECT, thus suggesting a prominent role for these brain regions in the antidepressant response of ECT (Nobler et al., 2001; Henry, Schmidt, Matochik, Stoddard, and Potter, 2001). Therefore, FEAST aims to contain the induced seizure to the prefrontal region in an attempt to maintain efficacy while minimizing cognitive side effects (Sahlem et al., 2016).

Some of the elements that make FEAST unique also make it potentially more efficient than traditional ECT. In an animal study comparing the two treatment methods, it was found that the unidirectional current in FEAST is more efficient at inducing seizures than bidirectional current used in traditional ECT. In addition, when comparing bilateral ECT to FEAST, the electrode placement and size in FEAST was found to be more effective by producing a lower seizure threshold (Spellman, Peterchev, and Lisanby, 2009). In a clinical study by Sahlem et al. (2016), FEAST showed adequate
efficacy, remission rates, and cognitive side effects, and was found to be both tolerable and safe. Other studies have found that although reorientation time, or the time it takes a patient to regain awareness of things such as their name, location, birthday, age, or day of the week, may be better than traditional ECT and cognitive side effects may be diminished, the efficacy may not actually be greater than other forms of ECT (Nahas et al., 2013). Further studies are needed to compare, refine, and optimize this method of treatment.

**Indicators of Responsiveness and Study Aims**

Many studies have strived to discover neurobiological indicators of responsiveness to ECT for patients with depression (Silverstein et al., 2015). One interesting finding from various studies indicates that a lower than normal hippocampal volume is a predictor of responsiveness for ECT (Silverstein et al., 2015). Despite a variety of studies, few findings have been replicated, and further research is necessary to accurately identify biomarkers that can be used clinically (Silverstein et al., 2015). This study aims to determine whether changes in EEG or pattern separation can be used as biomarkers early in treatment to indicate likely positive patient responsiveness to ECT.
Pattern Separation Task and its Relation to the Hippocampus

Pattern separation is a process in which memories are condensed into distinct and non-superimposable interpretations. It is mediated particularly by the hippocampus, though other brain structures may be involved as well. This process helps individuals recall and distinguish between memories that are very similar (Brock et al., 2012). It leads to the conclusion that a memory is either new and must be stored or is already in place and simply needs to be recalled (Das, Ivleva, Wagner, Stark, and Tamminga, 2014).

In a healthy brain, the hippocampus performs this process quickly and accurately (Kirwan et al., 2012). However, there is likely a spectrum across different individuals, since memory performance, including pattern separation by the hippocampus, is often variable and can be altered by events such as trauma, neuroplasticity, or age (Stark, S., Yassa, Stark, C., 2010).

Although computational models provided the first insight that the hippocampus engages in the pattern separation process, evidence from human neuroimaging studies as well as studies with memory impaired individuals have provided further confirmation of this hypothesis (Brock et al., 2012). For example, Hopkins and Kesner (1993) evaluated patients who acquired damage to the hippocampus through hypoxic episodes. These patients were told to remember various locations of cities on a map and then asked which cities were further north, south, east, or west. Normal control subjects were able to use the pattern separation process to delineate between cities that were close to each other in distance, while the hypoxic patients showed impairment in determining the location of
similarly placed cities (Hopkins and Kesner, 1993). Later, Kirwan and Stark (2007) conducted a study using a pattern separation task in concordance with fMRI to provide further evidence that the pattern separation process is mediated by the hippocampus. Traditionally, studies used pattern separation tasks to compare hippocampal functioning between older and younger individuals. Through studies involving hippocampal deficits in older patients and through fMRI imaging studies, researchers have been able to pinpoint the location of the pattern separation process within the hippocampus to the dentate gyrus and CA3 sub-region (Yassa and Stark, 2011; Stark, S., Yassa, Stark, C., 2010). In young individuals with healthy hippocampi, fMRI shows activation demonstrating sensitivity in the DG region of the hippocampus to “lure” objects in the pattern separation task, or objects that are similar but not quite the same as objects previously shown. Aging studies, such as the study performed by Stark, Yassa, and Stark (2010), have provided information regarding the natural changes in function to the hippocampus and how these changes impact the ability of the hippocampus to perform the pattern separation activity (Yassa and Stark, 2011; Stark, S., Yassa, Stark, C., 2010).

The pattern separation task utilized in the current study is known as the Behavioral Pattern Separation Task, or Mnemonic Similarity Task, developed by Stark Lab of Neurobiology and Behavior. The task is designed to evaluate subjects’ ability to either recognize previously seen objects or identify objects as being old, new, or similar to the initial list of objects presented to them (Stark Lab, 2013). It is believed that this assessment reflects changes in connectivity and mossy fiber remodeling in the hippocampus, a modification often seen in patients after seizures such as those induced
by ECT treatment. To determine changes in functionality of the hippocampus, this study will assess patients undergoing ECT through the use of this task at baseline, prior to the third treatment, and prior to the last treatment. We hope to determine whether this non-invasive method of measuring change in hippocampal function can be used to predict later antidepressant response for patients undergoing ECT.

**Frontal EEG and its Relation to Depression Treatments**

In addition, frontal EEG will be assessed as a non-invasive predictor of patient responsiveness to ECT treatment. EEG has been an important tool for monitoring patients undergoing ECT in particular and has been helpful in preventing prolonged seizures during treatment, which can be very unpredictable in patients (Girish, Gangadhar, and Janakiramaiah, 2002.) It has also been found that ECT treatment causes an increase in frontal activation in those with depression (Casarotto et al., 2013). Despite these findings, the relationship between EEG and clinical state remains unclear, although some studies have concluded that greater patient responsiveness is correlated with increased EEG slowing (Sackeim et al., 1996).

EEG is not only a tool used to optimize treatment practice but can also provide information on mood disorders as well. Both unipolar and bipolar depression have been found to have unique EEG characteristics compared to EEGs in healthy individuals (Tas et al., 2015). In fact, studies have reported that about 20-40% of depressed patients have altered EEG readings that are characteristic of depression (Woźniak-Kwaśniewska,
Szekely, Harquel, Bougerol, and David, 2015). For example, unipolar depressed patients tend to show increased frontal alpha power, which causes an asymmetry and a lack of synchronization in the EEG reading between the two hemispheres. This is a strong indicator of diminished activity on the left side of the brain (Tas et al., 2015). Although EEG readings have shown differences between bipolar and unipolar depressed individuals, bipolar patients’ EEG readings have similarly shown greater activity on the right side of the brain than on the left. Because some studies on depression and EEG have depicted left frontal sluggishness and overall asymmetrical waves, this EEG pattern has been thought to be a biomarker for depression (Tas et al., 2015). After pharmacological intervention, several studies have also noted a difference in theta waves in patients who responded to treatment, indicating an alteration in activity of the anterior cingulate cortex, a structure involved in emotional regulation (Wozniak-Kwasniewska et al., 2015). Studies examining patient response to emotional tasks have also found a decrease in both unipolar and bipolar patients’ frontal gamma waves, which the hippocampus also contributes to (Canali et al. 2015). Some studies have found consistently reduced gamma waves, even after patient remission, suggesting that patients’ EEG readings are not altered by treatment (Canali et al. 2015). However, other studies have found that EEG slowing, indicating increased power of delta and theta waves, usually develops during the course of ECT treatment. Variables such as age and the number of treatments may result in a greater amount of changes in EEG readings, and it has been found that change in EEG reading is transient, with patients’ EEG readings indicating no changes eight weeks post treatment (Sackeim et al., 1996). However, the EEG changes induced from treatment
imply that synchronization between neuronal groups has occurred, as well as reducing their firing rate (Sackeim et al., 1996). Despite the use of EEG as a tool to study the characteristics of depression, there are currently very few studies utilizing frontal EEG to predict responsiveness to ECT.

**Hypotheses:**

A. Depressed patients undergoing ECT have a tendency to show decreased hippocampal volumes that normalize towards that of controls after treatment. It has been found that seizures, like those induced by ECT, can cause an increase in mossy fiber sprouting within the hippocampus, which may be one of the underlying causes for the antidepressant effects of ECT. Pattern separation tasks reflect change in function of the hippocampus by observing whether patients can adequately detect items that are similar or different to objects they have previously seen. This study aims to test whether this non-invasive, computer-based task can serve as a predictor of patient responsiveness to both ECT and TMS.

Hypothesis 1: Relative to scores at baseline, patient improvement on the pattern separation task prior to the third ECT treatment, will correlate with treatment response indicated by at least a 50% decrease in QIDS-SR score at the end of their course of ECT treatment.
B. Some studies have found that antidepressant response to ECT correlates with frontal EEG changes. This study aims to test whether frontal EEG readings measured by a Sedline Monitor can be used to predict patient responsiveness to treatment early on in the patient’s course of ECT.

Hypothesis 2: Increased prefrontal slowing relative to pretreatment baseline, as measured by a Sedline Monitor, prior to the third ECT treatment will correlate with treatment response indicated by at least a 50% decrease in QIDS-SR score.
METHODS

Participants

This study planned to recruit 20 healthy volunteers through flyers posted at the Massachusetts General Hospital, as well as 20 unipolar and bipolar depressed subjects, from patients referred for ECT at MGH by the patients’ clinical treatment teams. After the treatment type was decided, patients were asked if they were interested in partaking in this research study. Participants ranged in age from 18 to 65 years old (Mean = 36, Standard Deviation = 15.92). Other demographic data is shown in Table 1. Each participant provided written informed consent, and the Partners Human Research Committee/IRB approved the experimental protocol. Inclusion criteria for healthy volunteers consisted of a minimum age of 18 years old and being able to provide informed consent. Inclusion criteria for depressed individuals included the criteria for healthy volunteers with the addition of meeting DSM-V criteria for Major Depressive Disorder or Bipolar Disorder. Exclusion criteria for this study for both healthy volunteers and depressed individuals included having electroconvulsive therapy within the past six months, inability to keep their medications stable for the duration of the study course, a significant cardiac condition, history of seizure disorders, adverse reaction to anesthesia, history of moderate to severe concussions, a metal object in their skull, history of mild cognitive impairments or dementia, and lastly a medical condition associated with increased risk for ECT. Participants were asked to complete a brief phone pre-screening to determine their eligibility for the study.
Procedure

Upon arrival to the clinic for a semi-structured clinical interview, subjects were given a copy of the study consent form to review. During the screening interview, the protocol, risks, and benefits of the study were reviewed in detail and informed consent was obtained. Study subjects then completed a brief EEG recording to observe changes in brain waves, and a short computer-based neuropsychological task to assess a subtype of memory known as pattern separation. For study subjects who enrolled in the study as a unipolar or bipolar depressed individual, four symptom rating scales were used to assess their change in mood at baseline and throughout the study: the Self Report version of the Quick Inventory of Depressive Symptomatology (QIDS-SR), the Young Mania Rating Scale (YMRS), the Clinical Global Impression Scale (CGI), and the Mini International Neuropsychiatric Interview (MINI).

Symptom Measures

Subjects enrolled in the study as depressed individuals were assessed using four symptom rating scales to confirm diagnostic impressions and determine the severity of symptoms at baseline and throughout their course of treatment with ECT.

The Mini International Neuropsychiatric Interview (MINI) was used as part of the study subject’s screening visit. Study subjects were evaluated by a board certified psychiatrist (MEH) to assess clinical history and confirm eligibility for the study. The
reliability and validity of the MINI was determined by comparing it to the Composite International Diagnostic Interview (CIDI) scale (Lecrubier et al, 1997).

The next three symptom-level scales were completed at baseline, prior to the third ECT treatment, and prior to the last treatment. Participants were assessed for manic symptoms using the 11-item Young Mania Rating Scale (YMRS), with a clinician administering the scale during a brief interview. The YMRS helps determine the severity of symptoms based on both the patient’s experience over the past 48 hours as well as the clinician’s observations of the patient (Young et al., 1978). The reliability and validity of the YMRS was determined by comparing it to the Global Rating, Petterson, and Beigel scales.

Subjects were also assessed using the Clinical Global Impression Scale (CGI). This scale is divided into three sections that evaluate severity of illness, change or improvement, and response to treatment. The first two sections are rated on a seven point Likert scale ranging from 1 (normal) to 7 (very severely ill). The third section is similarly rated on a Likert scale, ranging from 0 (improvements with no side effects) to 4 (no changes or worse with side effects more pronounced than therapeutic benefits). Generally, in clinical and research settings, the first two sections of the CGI are more widely used than the final section (Guy, 1976). As in the YMRS, the CGI was administered and rated by a clinician during an interview with the patient. Clinical drug trials have found the CGI to be an effective measure of illness severity and improvement and studies have found the CGI Global Improvement section to be comparable to changes
in the Hamilton Rating Scale for Depression (HRSD) scores (Guy, 1976; Spearing, Post, Leverich, Brandt, and Nolen, 1997).

Lastly, subjects were asked to complete the Quick Inventory of Depressive Symptomatology (16-item, self-report) to assess for Major Depressive Disorder. The QIDS-SR16 asks subjects to answer 16 questions that fall into the 9 diagnostic criteria of the DSM-IV: Sadness, concentration, suicidal ideation, self criticism, interest, sleep, fatigue, change in appetite or weight, and psychomotor changes (Rush et al., 2003). Each question has four possible responses and each response has an associated score from 0 to 3 points. Subjects are able to score from 0 to 27 total points, with a higher score associated with greater symptom severity (Rush et al., 2003). The QIDS-SR16 has been found to be comparable to the 30-item Inventory of Depressive Symptomatology (IDS-SR30) and the 24-item Hamilton Rating Scale for Depression (HRSD-24). The QIDS-SR16 was found to be highly sensitive to fluctuation of symptoms and was determined to have a high validity (Rush et al., 2003).

Measure of Memory Performance

In addition to the four symptom rating scales, we asked study subjects to engage in a computer-based task, conducted on a Hewlett Packard EliteBook laptop, to assess memory performance. This task, known as the pattern separation task, was developed by C. Stark et al (2007). It’s aim is to test short-term changes in hippocampal functional connectivity by evaluating recognition memory of the subjects. The developers of this
task have also studied it under various circumstances, and have found that prior knowledge of the task, short-term repeated testing, and most smaller set sizes do not have an effect on the results or performance of the subjects (Stark, S., Stevenson, Wu, Rutledge, and Stark, C., 2015). For each set, researchers can choose to run it as a 64-item, 32-item, a 20-item, or a 16-item. Besides the 16-item, which had a lower correlation ($R^2 = .24, p=.34$), all other set sizes showed similar positive correlations between performance and set size ($R^2$ ranged from .55 to .63, with all $p$ values <.01) (Stark et al., 2015).

There are two phases of the task: a study phase and a test phase. In both phases, objects appear on the computer screen one by one, and only remain on the screen for two seconds. During the study phase, subjects are asked to identify objects on the computer screen by pressing one of two keys on the keyboard to indicate whether the object on the screen belongs indoors or outdoors. During the test phase, subjects are again presented with objects, but now they are asked to compare this series of objects to the objects seen during the study phase. Subjects are instructed to press one of three keys to indicate whether an object is old, similar, or new compared to what they saw in the previous phase. Subjects are asked to complete this task at baseline, as well as before the third and last ECT treatments. All participants completed a 20-item set size and completed sets 1, 2, and 3 over the span of three weeks. The order of set completion was determined by an online random number generator (random.org). The entire task lasts approximately ten minutes.
Measure of Brain waves via EEG

Frontal EEG was measured using a Sedline device from Masimo Corporation (52 Discovery, Irvine, CA 92618, USA). During the measurements, subjects were asked to think of something peaceful. Both healthy volunteers and depressed individuals completed this task a total of three times. For depressed individuals, this task was completed during a baseline assessment, and then repeated prior to the third and last treatments.

EEG files were then converted from Sedline .PHY files to .EDF files via a “phy2edf” conversion program (Purdon Labs, Massachusetts General Hospital) and then run through Matlab using an edfread.m function, developed by Purdon Labs, and several functions included in the Fieldtrip Matlab Toolbox, developed by Donders Institute for Brain, Cognition and Behaviour in Nijmegen, the Netherlands (Oostenveld, Fries, Maris, Schoffelen, 2011). Analysis of these files was then conducted via spectral analysis functions provided by Chronux Matlab Toolbox, developed by Mitra Lab in Cold Spring Harbor Laboratory (Mitra and Bokil, 2008, http://chronux.org/).
RESULTS

Participant Characteristics

This study recruited ten healthy volunteers and two depressed patients (one with Bipolar Affective Disorder, the other with Major Depressive Disorder) receiving ECT treatment at the Massachusetts General Hospital. The mean ages of healthy control participants and depressed patient participants were 34.9 and 41.5 years old, respectively. 67% of participants were Caucasian, with 83% of participants having at least a college degree. See table 1 for further demographic information.

Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Healthy Volunteers</th>
<th>Depressed Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>12</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Mean Age</td>
<td>36</td>
<td>34.9</td>
<td>41.5</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>8</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>African American</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asian American</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Education Level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High School Graduate</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Some College</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>College Degree</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>
Descriptive Data, Outcome Measures

The EEG measurements and pattern separation scores for both healthy controls and depressed patients are shown in Tables 2 and 3. The overall average pattern separation score (with 100% being the highest score possible) in depressed patient participants was numerically, but not quite significantly, lower at baseline ($t(10) = 1.9023$, $p = .0863$) when compared to healthy controls. EEG measurements were made on a decibel scale with more negative scores associated with lower power and more positive scores associated with higher power.

A Shapiro-Wilk test was conducted to determine whether the variables for the healthy volunteers presented in this study were normally distributed. A normal distribution was found for each trial of the pattern separation task in healthy controls and for each observed brainwave in all five electrodes across the group of healthy controls, except for alpha waves in the FP2 electrode in trial 3, and gamma waves in the FPz electrode in trial 2. Subsequent test-retest correlations were conducted using the intraclass correlation coefficient and Cronbach’s alpha.
Due to the small sample size of the patient participants, we were unable to test whether the pattern separation results are normally distributed. This is also the case with the brainwaves across each electrode.

**Table 2.** Mean and Standard Deviation Scores of EEG Measurements in Healthy and Depressed Participants

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls</th>
<th>Depressed Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP1</td>
<td>-7.612 ±2.741</td>
<td>-7.501 ±1.332</td>
</tr>
<tr>
<td>FP2</td>
<td>-7.122 ±2.310</td>
<td>-5.939 ±0.420</td>
</tr>
<tr>
<td>FPz</td>
<td>-9.281 ±2.502</td>
<td>-6.285 ±1.126</td>
</tr>
<tr>
<td>F7</td>
<td>-2.544 ±2.888</td>
<td>-1.735 ±0.144</td>
</tr>
<tr>
<td>F8</td>
<td>-3.144 ±2.586</td>
<td>-1.800 ±0.246</td>
</tr>
<tr>
<td><strong>Beta</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP1</td>
<td>-10.990 ±2.383</td>
<td>-11.735 ±0.700</td>
</tr>
<tr>
<td>FP2</td>
<td>-10.781 ±2.316</td>
<td>-10.878 ±0.001</td>
</tr>
<tr>
<td>FPz</td>
<td>-13.744 ±1.558</td>
<td>-13.088 ±0.170</td>
</tr>
<tr>
<td>F7</td>
<td>-7.391 ±1.812</td>
<td>-7.418 ±1.752</td>
</tr>
<tr>
<td>F8</td>
<td>-8.028 ±2.105</td>
<td>-8.419 ±2.419</td>
</tr>
<tr>
<td><strong>Delta</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP1</td>
<td>-11.358 ±0.700</td>
<td>-11.375 ±0.700</td>
</tr>
<tr>
<td>FP2</td>
<td>-11.812 ±0.001</td>
<td>-10.878 ±0.001</td>
</tr>
<tr>
<td>FPz</td>
<td>-8.227 ±1.752</td>
<td>-13.088 ±1.752</td>
</tr>
<tr>
<td>F7</td>
<td>-6.445 ±2.419</td>
<td>-7.418 ±2.419</td>
</tr>
<tr>
<td>F8</td>
<td>-6.856 ±2.179</td>
<td>-7.402 ±2.179</td>
</tr>
<tr>
<td></td>
<td>Baseline (n=10)</td>
<td>1 week (n=1)</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
<td>--------------</td>
</tr>
<tr>
<td></td>
<td>FP1 Delta</td>
<td>FP2 Delta</td>
</tr>
<tr>
<td>Baseline</td>
<td>5.164 ±0.060</td>
<td>7.924 ±2.107</td>
</tr>
<tr>
<td>1 week</td>
<td>5.671</td>
<td>5.661</td>
</tr>
<tr>
<td>2 weeks</td>
<td>11.823</td>
<td>11.823</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>FP1 Theta</td>
<td>FP2 Theta</td>
</tr>
<tr>
<td>Baseline</td>
<td>-3.380 ±2.399</td>
<td>-2.903 ±2.800</td>
</tr>
<tr>
<td>1 week</td>
<td>-1.900 ±2.928</td>
<td>-2.258 ±3.279</td>
</tr>
<tr>
<td>2 weeks</td>
<td>-1.617 ±2.629</td>
<td>-2.390 ±2.698</td>
</tr>
<tr>
<td>Depressed Patients</td>
<td>FP1 Gamma</td>
<td>FP2 Gamma</td>
</tr>
<tr>
<td>Baseline</td>
<td>-13.151 ±2.442</td>
<td>-12.915</td>
</tr>
<tr>
<td>1 week</td>
<td>-13.401 ±1.522</td>
<td>-13.593</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>FP1 Gamma</td>
<td>FP2 Gamma</td>
</tr>
<tr>
<td>Baseline</td>
<td>-15.739 ±2.408</td>
<td>-14.90</td>
</tr>
<tr>
<td>1 week</td>
<td>-10.442</td>
<td>-6.733</td>
</tr>
<tr>
<td>2 weeks</td>
<td>-17.712</td>
<td>-19.081</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=10)</th>
<th>1 week (n=1)</th>
<th>2 weeks (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FP1 Delta</td>
<td>FP2 Delta</td>
<td>FPz Delta</td>
</tr>
<tr>
<td>Baseline</td>
<td>4.781 ±3.128</td>
<td>5.625 ±3.736</td>
<td>2.407 ±1.651</td>
</tr>
<tr>
<td>2 weeks</td>
<td>8.222 ±3.262</td>
<td>7.441 ±3.752</td>
<td>5.619 ±6.134</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>FP1 Theta</td>
<td>FP2 Theta</td>
<td>FPz Theta</td>
</tr>
<tr>
<td>Baseline</td>
<td>-13.151 ±2.442</td>
<td>-12.915</td>
<td>-2.910 ±1.602</td>
</tr>
<tr>
<td>1 week</td>
<td>-13.401 ±1.522</td>
<td>-13.593</td>
<td>-1.786 ±5.053</td>
</tr>
<tr>
<td>Depressed Patients</td>
<td>FP1 Gamma</td>
<td>FP2 Gamma</td>
<td>FPz Gamma</td>
</tr>
<tr>
<td>Baseline</td>
<td>-15.739 ±2.408</td>
<td>-14.90</td>
<td>0.157 ±1.158</td>
</tr>
<tr>
<td>1 week</td>
<td>-10.442</td>
<td>-6.733</td>
<td>-8.234</td>
</tr>
<tr>
<td>2 weeks</td>
<td>-17.712</td>
<td>-19.081</td>
<td>-5.051</td>
</tr>
</tbody>
</table>

35
Table 3. Mean and Standard Deviation Scores of Pattern Separations Scores for Healthy Participants (n=10, n=2)

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls</th>
<th>Depressed Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Score</strong></td>
<td>71.821</td>
<td>52.995</td>
</tr>
<tr>
<td><strong>1 week</strong></td>
<td>73.53777778</td>
<td>51.17</td>
</tr>
<tr>
<td><strong>2 weeks</strong></td>
<td>68.99444444</td>
<td>67.86</td>
</tr>
</tbody>
</table>

| T-Test for Baseline Pattern Separation Scores Between Healthy and Depressed Participants |
|---|---|
| t | 1.9023 |
| p | .0863 |

Test-Retest Reliability of the Pattern Separation Task for Healthy Controls

Intraclass correlation coefficients and Cronbach’s alpha were conducted to determine the test-retest reliability for the pattern separation task. This task was found to have high reliability. Statistical results can be found in Table 4.

Table 4. Measures of Test-Retest for Pattern Separation Scores in Healthy Participants (n=10).

| Test-retest correlation for Healthy Controls: Pattern Separation |
|---|---|
| Intraclass Correlation Coefficient | 0.92 |
| 95% confidence interval | .75 to .98 |
Test-Retest Reliability of EEG Measurements for Healthy Controls

The power of brainwaves, alpha, beta, delta, theta, and gamma, for healthy controls were recorded over the course of three separate trials in five different electrodes placed over the frontal region of the scalp. Test-retest reliability was determined for each brainwave for each electrode using intraclass correlation coefficients and Cronbach’s alpha. Brainwaves across all five electrodes were found to be reliable. In depth statistical data are shown in Table 5.

Table 5. Measures of Test-Retest for EEG Measurements in Healthy Participants (n=10).

<table>
<thead>
<tr>
<th>Test-retest correlation for Healthy Controls: EEG Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Table" /></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>r</td>
</tr>
<tr>
<td>95% confidence interval</td>
</tr>
<tr>
<td>F Value</td>
</tr>
<tr>
<td>p Value</td>
</tr>
<tr>
<td>r</td>
</tr>
<tr>
<td>95% confidence interval</td>
</tr>
<tr>
<td>F Value</td>
</tr>
<tr>
<td>p Value</td>
</tr>
<tr>
<td>r</td>
</tr>
<tr>
<td>95% confidence interval</td>
</tr>
<tr>
<td>F Value</td>
</tr>
<tr>
<td>p Value</td>
</tr>
</tbody>
</table>

**Cronbach’s Alpha**

<table>
<thead>
<tr>
<th></th>
<th>FP1 Alpha</th>
<th>FP1 Beta</th>
<th>FP1 Delta</th>
<th>FP1 Theta</th>
<th>FP1 Gamma</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>0.8</td>
<td>0.89</td>
<td>0.93</td>
<td>0.74</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>FP2 Alpha</td>
<td>FP2 Beta</td>
<td>FP2 Delta</td>
<td>FP2 Theta</td>
<td>FP2 Gamma</td>
</tr>
<tr>
<td>α</td>
<td>0.77</td>
<td>0.85</td>
<td>0.84</td>
<td>0.84</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>FPz Alpha</td>
<td>FPz Beta</td>
<td>FPz Delta</td>
<td>FPz Theta</td>
<td>FPz Gamma</td>
</tr>
<tr>
<td>α</td>
<td>0.6</td>
<td>0.82</td>
<td>0.62</td>
<td>0.55</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>F7 Alpha</td>
<td>F7 Beta</td>
<td>F7 Delta</td>
<td>F7 Theta</td>
<td>F7 Gamma</td>
</tr>
<tr>
<td>α</td>
<td>0.88</td>
<td>0.96</td>
<td>0.93</td>
<td>0.89</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>F8 Alpha</td>
<td>F8 Beta</td>
<td>F8 Delta</td>
<td>F8 Theta</td>
<td>F8 Gamma</td>
</tr>
<tr>
<td>α</td>
<td>0.93</td>
<td>0.91</td>
<td>0.93</td>
<td>0.83</td>
<td>0.86</td>
</tr>
</tbody>
</table>

### Relationship between the Pattern Separation Task and the QIDS-SR

Patient participants were asked to complete both the pattern separation task and the Quick Inventory of Depressive Symptomology (self-report) for each study visit. At this point, there are not sufficient data to conduct correlations between these variables. However, as more data are collected, and assuming a normal distribution for pattern
separation and QIDS-SR scores, a two-tailed Pearson’s correlation will be conducted to evaluate the relationship between the two variables. Current patterns in the data can be observed via Figure 1. As previously mentioned, healthy controls had reliable scores over the course of the three trials. On average, there was a slight improvement during the second trial for these participants, but overall, scores were consistent and high for the duration of the study.

The first patient participant showed no improvement in pattern separation score for the first two trials, on which he received a score of 57.78% and 53.57% respectively. However, upon the third trial, prior to the last of his ECT treatments, he received a score of 67.86%. This patient’s QIDS-SR score also substantially decreased between the first and second trials, from 18 to 3 points. However, prior to the last treatment, his QIDS-SR score increased to 8 points.

The second patient participant has yet to have her third study visit, due to difficulties with study compliance. During trials one and two, her pattern separations scores were 48.21% and 48.78%, respectively. If her scores follow the same pattern as the first patient participant, we can expect to see a large increase in her scores upon the next trial. In addition, her scores on the QIDS-SR remained in the depressed range during the first and second sessions. Her scores were 32 and 33 on trials one and two, respectively.
Relationship between EEG measurements and the QIDS-SR

As with the pattern separation task, currently there are insufficient data to conduct a correlation between EEG measurements and the QIDS-SR. However there does seem to be a pattern indicating treatment effect. As more data are collected, assuming a normal distribution of the variables, a two-tailed Pearson’s correlation will be conducted to evaluate for the associations between each brainwave measured by each electrode and the QIDS-SR scores.

For the first patient participant, a corrupted Sedline data file caused the omission of results from the second trial. However, treatment effect can be seen between baseline
and third trial measurements. The general pattern is that there is an increase in the power of the brainwaves across almost all electrodes.

As with the pattern separation trials, the second depressed patient has yet to complete the last EEG measurement trial due to the need for more ECT treatment. However, even from baseline EEG measurements to the second trial, done just before the third ECT treatment, there appears to be a treatment effect that follows the same pattern as the first patient participant. Although the changes are sometimes less pronounced than in the first participant, as would be expected since these changes were between earlier times in her course of treatment, the power of all measured brainwaves tends to increase from baseline to the second trial.
DISCUSSION

To our knowledge, this is the first study to utilize both the pattern separation computer-based task and frontal EEG, as measured by a Sedline anesthesia monitor, to predict remission of depressive symptoms prior to the end of a course of ECT. Based on the previous studies showing an effect of ECT on EEG patterns, and the hypothesis that pattern separation reflects changes in the hippocampus, this study aimed to assess the clinical utility of changes in these two non-invasive measurements to predict responsiveness to ECT. The hypotheses of this study were that: 1) relative to baseline, improvement on pattern separation scores prior to the third ECT treatment will correlate with treatment response measured by the QIDS-SR, and 2) relative to baseline, Increased prefrontal slowing, as measured by a Sedline Monitor, prior to the third ECT treatment will correlate with treatment response measured by the QIDS-SR.

General Expectations and Actual Findings

Expectations for the healthy control population were that their scores on the pattern separation task would remain approximately the same for all three trials. It was also expected that the healthy control population would have similar EEG measurements across all trials. Therefore, one of the aims of the study was to establish the reliability of these two measurements so that they could be confidently assessed in a patient population. From the results, we can see that the test-retest reliability of the pattern separation task was very good, indicating consistency of the healthy control population.
across the three trials. This finding was consistent with current literature (Stark et al., 2015).

In addition, results also demonstrated excellent test-retest reliability for each of the studied brainwaves for each of the five electrodes used during the frontal EEG task. Measurements of alpha, beta, delta, theta, and gamma waves in electrode FP1 were found to be very reliable over the course of the three trials, with theta waves, slightly less reliable than the other brainwaves measured by this electrode. All brainwaves measured by the FP2 electrode were also found to have good reliability, though slightly less than electrode FP1, across all trials. Alpha waves recorded in FP2 were found to have adequate reliability, though less so than other waves recorded with this electrode. Of all the electrodes used in this study, FPz was found to be the least consistent and reliable, possibly due to the fact that the FPz electrode is used as the ground electrode, which serves as a reference point for all other electrodes in the system and is important in reducing noise on the recordings (Light et al., 2011). Although alpha, delta, and theta waves were not found to have statistically significant reliability as measured by the FPz electrode, beta and gamma waves showed adequate test-retest reliability. The F7 electrode showed very good test-retest reliability across all brain waves measured, with gamma waves, indicating slightly less reliability that the other brainwaves measured. Lastly, the F8 electrode showed great reliability for each measured brainwave across all three trials, with theta and gamma waves slightly less reliable than the other waves measured by this electrode. In depth statistical data is shown in Table 5.
Expectations for patient participants were that their scores on the pattern separation task would increase over the course of their treatment. In addition, it was also expected that prefrontal EEG slowing, determined by an increase in power of the slow waves, theta and delta, would occur. The small sample size to date precludes a definitive analysis. Generally, there is an observable change from baseline measurements in the EEG brainwaves recorded across the five electrodes, as well as a change from baseline for pattern separation scores. Additional data is needed to apply these findings to the general population.

**Pattern Separation Scores in Healthy Controls and Patients**

To our knowledge, the pattern separation task has yet to be used for studies involving mood disorders. It has been used in several aging studies, as well as studies involving memory or damage to the hippocampus. Based on these studies, it is evident that performance on the pattern separation task is subserved by the hippocampus and by several other brain regions. Lesions or damage to the hippocampus have been found to disrupt an individual’s ability to complete the pattern separation task (Brock et al., 2012). Because this task is thought to be sensitive to changes within the hippocampus, it was used in this study to assess potential hippocampal changes brought about by ECT treatment.

As a group, the healthy control population scored an average of 71.82% at baseline, 73.54% on trial 2 and 68.99% on trial 3. Other pattern separation tasks reported
in the literature have found similar scores on healthy individuals, such as the spatial pattern separation task, which found its participants to score within a range of 74% to 93% (Holden, Hoebel, Loftis, and Gilbert, 2012). As expected, the score of the healthy controls in this study remained relatively consistent for the duration of the study (p < .01). The two patients, as a group, had much lower scores at baseline than healthy individuals, though the two groups are not quite statistically different (p = .0863). The average score for patient participants for trials 1 and 2 were 53% and 51.18%, respectively. It is worth noting however, that previous studies have found that age can have a big impact on pattern separation results (Stark, S., Yassa, and Stark, C. 2010). 60% of the healthy control group were in their twenties; therefore it’s possible that this group had a higher average score due to the affects of age, though this study will continue to recruit volunteers and attempt to control for this variable. Despite this possibility, it is also well known that depression is often associated with cognitive impairments, in domains such as memory and attention (Beblo, Kater, Baetge, Driessen, and Piefke, 2016), both of which could be the cause of the lower average pattern separation score in the patient participants.

Although the current sample size has prevented any definitive conclusions, the first depressed patient participant is interesting because of the timing of his improvement on this task. Although the first two trials appeared unremarkable, the first patient’s third trial pattern separation score increased to almost the average healthy control score. The second patient participant has yet to complete the third trial, as more ECT treatments were needed. However, she too demonstrated a similar pattern of low and consistent
scores across the first two trials. If this pattern holds true for additional patient participants, then we can expect that the greatest change occurs between the second and third study trials, or between the third and last ECT treatments. Additional trials may more closely pinpoint when the changes in pattern separation scores begin to take place, which could increase the accuracy of using this tool as a biomarker for treatment responsiveness.

**Relationship between the QIDS-SR and the Pattern Separation Task**

Although correlations have yet to be conducted until there is an increase in sample size, based on QIDS-SR scores, there does appear to be an effect of treatment on pattern separation scores. The first patient participant showed a large decrease in QIDS-SR scores between trials 1 and 2, indicating a decrease in depressive symptoms. Although his QIDS-SR score increased a little on the last trial, it was still greatly diminished from baseline. It was trial three where the greatest change in pattern separation scores occurred. Thus, perhaps improvement of pattern separation scores may be more directly correlated with mood improvement. The second patient participant remained nearly constant with her QIDS-SR scores and her pattern separation scores during the two complete trials. It is expected that when/if her QIDS-SR scores begin to decrease, her pattern separation scores will normalize towards those of controls.

It is also worth considering the possibly of different results between our two patient participants due to different baseline depression diagnoses and treatment response
rates. According to current literature, a decrease in QIDS-SR score by 50% is necessary to consider that the patient is responding to treatment. Furthermore, it was established that a score of five or less on the QIDS-SR is considered to be the remission threshold (Brown et al., 2008). The first patient in this study had a QIDS-SR score of 18 at baseline, which decreased to 3 before the third treatment. Unlike this patient, the next patient had a QIDS-SR score of 32 at baseline, which increased slightly, with a score of 33, prior to the third ECT treatment. Although this patient has shown further improvement through the course of treatment, the responsiveness to ECT for this individual has been much slower than for the first patient. It may be that her response to ECT is different from the first patient participant, and it is possible that this could be reflected in her pattern separation scores.

The first patient was diagnosed with bipolar affective disorder, and the second patient with major depressive disorder. It is possible that different types of depression can be a factor in the changes to the brain brought about by ECT, thus possibly rendering different outcomes. As more data are collected in this study, patients can also be analyzed based on their diagnoses and ECT responsiveness to see if there are particular patterns in pattern separation scores for different conditions.

**Relationship between the QIDS-SR and the EEG Task**

As with the pattern separation task, sample size is currently too small to conduct meaningful correlations between the QIDS-SR and EEG measurements. However, like
the pattern separation scores, it does appear that there was an effect of treatment on the EEG measurements. Generally all electrodes showed an increase from baseline in alpha, beta, delta, theta, and gamma power. Interestingly, for the first patient participant, delta and theta waves, which are in the slower end of the spectrum, appear to have had the largest increases in power. For the second patient, there was a pattern of increasing brainwave power, but it appears to have been more variable. For electrodes FPz, F7 and F8, delta and theta wave power seem to have increased the most in power. However for electrodes FP1 and FP2, alpha, beta, and gamma waves seem to have had the greatest increase in power. Again, this could be related to the varying rates of treatment response between the two patient participants, or may also be due to their differences in the pathophysiology of their depressive conditions. EEG measurements can be very unique and can also be sensitive to different states or conditions (Teplan, 2002).

**EEG Measurements and Laterality in Healthy Controls and Patients**

After the average power for each brainwave for each electrode was calculated, a pattern for frontal EEG was observed. In the healthy volunteers, alpha, beta, theta, and gamma waves were all found to have a more negative power at the FP1 and FP2 electrodes, which are placed directly over the left and right eyebrow. For these brainwaves, power was found to be less negative when recorded at the F7 and F8 electrodes, which are placed over the left and right temple. The opposite trend was found for delta waves. This finding was unexpected because it suggests that detection of alpha,
beta, theta, and gamma brainwaves were more pronounced in the temporal region than directly on the forehead. It is possible that this result could be due to noise of the Sedline device. However, studies have found that detection of particular brainwaves is sometimes greater over different areas of the skull, such as alpha waves, which can be detected more so in posterior and occipital regions than other areas (Teplan, 2002).

Another interesting finding of the healthy controls’ average EEG measurements is the fact that delta waves consistently had the most positive values, and thus the greatest power of all the waves. Delta waves have a frequency of about 0.5 to 4 Hz, and are considered the slowest of the five waves. They have also been associated with sleep (Teplan, 2002). In addition, during wakeful states with eyes open, beta is the dominant brainwave, but when relaxed with eyes closed, alpha power begins to increase, followed by theta and delta when tired or asleep. EEG is very sensitive to different states of alertness and can be greatly affected even by closing one’s eyes (Teplan, 2002; Strijkstra, Beersma, Drayer, Halbesma, and Daan, 2003). During this study, we asked subjects to relax, think peaceful thoughts, and sit with the lights off for the duration of the recording. Results seemed to show the effects of this environment, with beta waves being of lower power than alpha waves, delta and theta waves having the greatest power, and gamma having the lowest power. In addition, a few participants reported feeling that they were close to falling asleep.

Asymmetry of EEG also seems to be fairly common and can be related to asymmetrical skull thickness, or other factors (Teplan, 2002; Hagermann, Hewig, Walter, and Naumann, 2008). For healthy participants, asymmetry of any brainwave was not
apparent. In a few cases, there were differences of approximately 1 to 2 decibels, but this was often found only on one of the three trials, and may potentially be related to noise of the recording.

One interesting trend in healthy controls was the small but consistent difference between baseline recordings and the second and third trials. Though there was not a dramatic difference, the second and third trials on average appear have been much closer in power than baseline. This may be attributed to participants becoming more comfortable with study procedures as the study progressed. After participants knew what they could expect from subsequent study visits, they may have been more able to relax during the EEG recording, allowing for more consistent results during trials 2 and 3.

The EEG measurements for patients also demonstrated some interesting patterns. Similar to healthy controls, alpha, beta, and theta waves in patients were found to be of lesser power when measured with the FP1 and FP2 electrodes and higher when measured by F7 and F8 electrodes. As in healthy controls, delta waves appeared to have the opposite trend. Gamma waves seemed to be more consistent across all the electrodes. In addition, the power of the brainwaves measured in depressed patients, except for gamma waves, tended to be slightly higher than the healthy controls. This was most apparent in theta waves and could perhaps be accounted for by the early morning study visits, when the patients may have been very tired. However, current literature indicates that differences in theta wave activity may be related not only to antidepressant medications, but also to different activity in the anterior cingulate cortex (Woźniak-Kwasniewska et al., 2014). This area of the brain is thought to be important for emotional regulation,
learning, motivation, reward, and memory, functions which are often disrupted in depressed patients. Treatments such as antidepressants and deep brain stimulation have been found to increase cerebral blood flow to the prefrontal cortex and the anterior cingulate cortex (Mayberg et al., 2005). As in the healthy controls of this study, asymmetry of any brainwave was not apparent.

Limitations and Future Suggestions

As a preliminary study using pattern separation and frontal EEG as biomarkers to predict responsiveness to ECT, there are a number of limitations and recommendations for future studies.

Although we plan to continue collecting data from both healthy volunteers and patients suffering from major depressive disorder and bipolar disorder, the current sample size prohibits confidence in the interpretations of the results. The current demographic data shows that this study involved mostly Caucasian individuals with a college or professional level degree (see demographic data in Table 1). The aim is to continue obtaining data from a diverse group of participants that can accurately represent the general population as well as to demographically match the healthy volunteers to the depressed patient participants.

It is also worth noting that there are a number of variables related to the participant that can effect EEG measurements. For example, the methods by which EEGs are analyzed can alter the ability to observe potential EEG changes relating to sleep,
drugs, psychiatric conditions, cognitive tasks and thought processes, and even intelligence (Anokhin, Birbaumer, Lutzenberger, Nikolaev, and Vogel, 1996). This study utilized traditional methods of EEG analysis using a power spectogram to observe the frequencies of various brain waves. However, other types of EEG analysis, such as correlational dimension analysis, may potentially contribute to a deeper understanding of the meaning behind participants’ EEG measurements. For example, it has been found that this method can pick up on certain neuropsychological patterns that are not detected by traditional analysis (Anokhin et al., 1996).

It is also important to note that variations in skull thickness between participants may have had an impact on interpretation of results. One study by Hagermann et al. (2008) found greater skull thickness in the frontal region than the posterior region of the head, contributing to less detection of frontal alpha activity. Therefore, differences in the frontal skull thickness of participants had a greater effect on the ability of the EEG device to pick up alpha waves. In addition to this finding, it was observed that some participants of the Hagermann et al. study had asymmetrical skull thickness, causing greater detection of alpha waves on the side where the skull was less thick (Hagermann et al., 2008).

Theory for the effects of skull and intracranial variations on EEG is attributed to Ohm’s law, stating that the volume and conduction properties between the brain and the electrodes on the scalp have an effect on the recorded electrical potentials (Hagermann et al., 2008).

Another limitation of this study is the environment in which volunteers complete the study tasks. Though participants are asked to close their eyes and think of something
peaceful during the frontal EEG and are asked to try their best with the computer task, the rooms are not sound proof, potentially leading to distractions. This is particularly relevant for patient participants who complete the study immediately prior to receiving their treatment. Though we attempt to minimize any disturbances while they perform the two tasks, nervousness over their treatment, conversations with treatment staff, and preparations for their treatment may distract them from completing the task to the best of their ability. For this reason, as we move forward with the study, all data will be collected in the center for perioperative care at Massachusetts General Hospital so that the study environment remains consistent.

Lastly, this study is limited by the reliance on self-report questionnaires. For example, the MINI is limited mainly due to its brief nature and focuses more so on current diagnoses instead of lifetime prevalence (Lecrubier et al., 1997).

Certain obstacles also occurred while measuring participants’ EEG using the Sedline device. Though clearly the device was capable of recording EEG information in real time, the device failed to store the information correctly on a few participants’ trials, leading to corrupt files that could not be analyzed via a power spectrogram. This further reduced sample size.

Taking into account the current limitations of this study, the future of this current study involves analyzing the pattern separation task and EEG with a larger sample. Although this is currently underway, there are several other directions that could be pursued.
One possible direction would be to control for any changes in medications during treatment. It is possible that the effects of ECT may be stronger than the effects of medications. However, it may be beneficial to control for medication changes while doing the study, because medication changes might affect the EEG and pattern separation task. For example, in a systematic review conducted by Aiyer, Novakovic, and Barkin (2016), it was found that a vast range of medications can have effects on the brain waves detected by EEG. Antidepressants and mood stabilizers have been found in several studies to alter the quality and characteristics of EEG. Buproprion can cause sharp, spikey waves or focal slowing patterns on the EEG recording, SSRIs have been found to lower theta waves in responding patients, and lithium can increase beta, delta, and theta EEG activity (Aiyer et al., 2016). However, practical clinical considerations may not permit this approach.

As previously mentioned, age also appears to be a prominent factor on participant ability to do the pattern separation task and also on variations in EEG measurements. Future studies could explore if both EEG and pattern separation have clinical value for predicting remission regardless of age, or whether it is more sensitive to a particular age group.

Although further data collection is needed to draw more definitive conclusions, the available data suggests frontal EEG and pattern separation have potential to become valuable tools for clinical practice. Given the millions of individuals worldwide who suffer from various depressive conditions, such as major depression, bipolar disorder, dysthymia and postpartum depression and who are unable to obtain relief through
treatment, the ability for rapidly assessing treatment efficacy is valuable (WHO, 2017). Further studies to provide evidence that EEG recordings and/or the pattern separation task have utility as biomarkers to predict patient responsiveness to ECT should allow refinement in ECT technique that will benefit future patients.
REFERENCES


