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Neuroplasticity hypothesis of the mechanism of electroconvulsive therapy: a proton magnetic resonance and functional connectivity investigation

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NEUROPLASTICITY HYPOTHESIS OF THE MECHANISM OF ELECTROCONVULSIVE THERAPY: A PROTON MAGNETIC RESONANCE AND FUNCTIONAL CONNECTIVITY INVESTIGATION

by

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ABSTRACT

Introduction: Major depressive disorder (MDD) is characterized by ongoing feelings of guilt, sadness, and memory and cognition impairment. It is a multidimensional illness that affects many functionally integrated pathways of the brain. Understanding the underlying brain dysfunction that gives rise to this complex illness has been challenging, and by extension the search for appropriate treatments. MDD patients who are considered treatment resistant make up the primary population that receives electroconvulsive therapy (ECT). Remarkably, ECT shows a 75% remission rate in this patient population and is considered the “gold standard” treatment for major depression. Although the exact mechanism of its function is unknown, it is well accepted that the induced grand-mal seizure confers its therapeutic effect. The seizure likely has broad effect that somehow corrects the underlying dysfunction in brain circuitry. Here, we specifically examined studies of functional connectivity and metabolite changes.

Methods: Through literature search, we examined six studies in functional connectivity and four studies in magnetic resonance spectroscopy (MRS).
Results:

*Functional Connectivity:* Studies have found that after bilateral ECT treatments, patients with major depression showed reduction of functional connectivity (FC) from the left dorsolateral prefrontal cortex (DLPFC) to other cortical and limbic structures. Correlated activity between the superior frontal gyri, middle frontal gyri and angular gyri were significantly increased after ECT. Hyperdeactivation of the orbitofrontal cortex to negative emotional stimuli in patients was decreased, and it was associated with improvement in depressive symptoms. Regional activity in the subgenual anterior cingulate cortex (sgACC) and functional connectivity between the sgACC and left hippocampus in treatment naïve patients after ECT were increased and correlated to reduction of depressive symptoms. Reduced connectivity between the amygdala and sgACC and increased connectivity between the amygdala and DLPFC were found by sequential assessments over a course of ECT treatments. Lastly, ECT increased the functional connectivity between DLPFC and the default mode network.

*MRS:* Studies found decreased levels of glutamate or combined glutamate/glutamine/ GABA levels in patients in the anterior cingulate cortex and dorsolateral prefrontal cortex compared to healthy controls. Additionally, it was found that glx levels increased after ECT treatments and that this increase was only in those who responded to treatment. Lastly, GABA level increased after ECT treatment in the occipital cortex.
**Discussion:** Results from functional connectivity and brain metabolite studies in patients with major depression point to induced neuroplasticity as part of ECT’s therapeutic mechanism. Remodeling connectivity and mediating metabolite changes both will require modifications at the synaptic level. The wide spread changes seen in several different brain regions that have been implicated in depression further suggests that ECT’s effects are both highly specific and broad.

**Conclusion:** Electroconvulsive therapy has consistently demonstrated impressive efficacy among the most severely depressed patients and is known to produce widely distributed effects in the brain. However, this also makes assessing its therapeutic mechanism challenging. Magnetic resonance imaging studies assessing functional connectivity and brain metabolite levels have demonstrated that ECT likely produces neuroplastic changes to remodel aberrant connectivity and dysfunctional excitatory and inhibitory neurotransmission in cortical and limbic areas. Although these findings should be interpreted with caution, this field of research has provided an unprecedented opportunity to examine the living brain in great detail. Further studies with larger sample sizes and improved technical specifications will likely yield greater results.
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LIST OF ABBREVIATIONS

ACC............................................................................................................... Anterior Cingulate Cortex
ALFF..........................................................Amplitude of Low Frequency Fluctuation Analyses
BDNF..........................................................Brain Derived Neurotrophic Factor
BL........................................................................................................... Bilateral
BOLD ..........................................................Blood Oxygen Level Dependent
BP........................................................................................................... Brief Pulse
Cho ..........................................................Choline
Cr ........................................................................................................... Creatine
CSF ..........................................................Cerebrospinal Fluid
CT ..........................................................Computerized Tomography
DLPFC..........................................................Dorsolateral Prefrontal Cortex
DMN ..........................................................Default Mode Network
DMPFC..........................................................Dorsomedial Prefrontal Cortex
DT..........................................................Dose Titration
ECS ..........................................................Electroconvulsive Shock
ECT ..........................................................Electroconvulsive Therapy
EEG..........................................................Electroencephalogram
FC..........................................................Functional Connectivity
fMRI..........................................................Functional Magnetic Resonance Imaging
GABA ..........................................................gamma-Aminobutyric Acid
GAD..........................................................Glutamic Acid Decarboxylase
Glx .......................................................... Glutamate/Glutamine/GABA
GM .......................................................... Grey Matter
GR .......................................................... Glucocorticoid Receptor
HA .......................................................... Half Age
HAM-D .................................................. Hamilton Rating Scale for Depression
HC .......................................................... Healthy Control
HIP .......................................................... Hippocampus
HPA .......................................................... Hypothalamic Pituitary Axis
HSRD .................................................... Hamilton Rating Scale for Depression
ICA .......................................................... Independent Component Analysis
IFGOrb .................................................. Inferior Orbitofrontal Cortex
IU .......................................................... Institutional Units
IbA .......................................................... Lateraobasal Amygdala
LC .......................................................... Linear Combination
MADRS ................................................. Montgomery Asberg Depression Rating Scale
MAOI .................................................. Monoamine Oxidase Inhibitor
MDD ...................................................... Major Depressive Disorder
MFGOrb ............................................... Middle Orbitofrontal Cortex
MNI ..................................................... Montreal Neurologic Institute
MRI .................................................... Magnetic Resonance Imaging
MRS .................................................... Magnetic Resonance Spectroscopy
MTGP .................................................. Middle Temporal Gyrus
MTP ................................................................................................. Middle Temporal Pole
NAA ............................................................................................... N-acetylaspartate
NMDA......................................................................................... N-methyl-D-aspartate receptor
OFC ................................................................................................. Orbitofrontal Cortex
p_DM ............................................................................................. Posterior Default Mode
pdACC .......................................................................................... Posterior dorsal ACC
PET .............................................................................................. Positron Emission Tomography
PFC ................................................................................................. Prefrontal Cortex
pgACC .......................................................................................... Pregenual Anterior Cingulate Cortex
ROI ................................................................................................. Region of Interest
rsFC .............................................................................................. Resting State Functional Connectivity
rs-fMRI .......................................................... Resting State Functional Magnetic Resonance Imaging
RUL ................................................................................................. Right Unilateral
SCC ............................................................................................... Subcallosal Cingulate Gyrus
sf/cmA .......................................................... Superficial Centromedial Nuclei of the Amygdala
SFGorb ........................................................................................ Superior Orbitofrontal Cortex
sgACC .......................................................................................... Subgenual Anterior Cingulate Cortex
ST ................................................................................................. Seizure Threshold
STEAM .............................................................. Stimulated Echo Acquisition Mode
TCA ............................................................................................... Tricyclic Antidepressant
UBP ............................................................................................... Ultra-brief Pulse
VMHC .............................................................. Voxel Mirrored Homotrophic Connectivity
WGC ................................................................. Weighted Global Connectivity
YLD ................................................................. Years Lived with Disability
INTRODUCTION AND BACKGROUND

History of Electroconvulsive Therapy

In 1934, Ladislas Meduna, a Hungarian neuropsychiatrist, injected an extract of camphor into a patient who was considered hopeless for his catatonic schizophrenia (Fink, 2001). Forty five minutes after the injection, the patient lost consciousness and underwent a brief grand-mal seizure but survived the ordeal. Meduna continued camphor injections four more times, two days after the last convulsion, the patient came out of his catatonic state and was even able to engage in conversation. Unfortunately, this positive effect was short-lived and the patient rapidly relapsed back to a catatonic state. However, Meduna did not give up and continued treatments with camphor. He noted that with each successive treatment, the patient remitted for longer periods of time. Eventually, the patient was able to resume work and normal daily activities. The idea of inducing a grand-mal seizure as treatment for psychiatric conditions came from Meduna’s earlier work studying glial cells. In his postmortem examinations, he noted that the glial cell concentration was much higher for patients who had an epileptic disorder than those who had dementia. Additionally, patients who suffered from dementia experienced improvements in their symptom when they developed a seizure disorder. Meduna suspected that the seizures helped to increase the amount of glial cells in these patients and helped relieved their symptoms and thought that perhaps it is also helpful in schizophrenia (Fink, 2014b). Meduna
went on to treat five more patients with schizophrenia and saw improvements in all (Fink, 2001), and is regarded as the father of convulsive therapy (Bolwig, 2014).

Although camphor and Metrazol, alternative convulsive agents, were successful in inducing seizures, their reliability was low. There was a significant delay in the induced seizure with camphor injection and Metrazol frequently required multiple injections to achieve a seizure, physicians quickly looked for more reliable ways to induce convulsions (Fink, 2001). In 1938, two Italian physicians, Cerletti and Bini, successfully induced an immediate seizure using electricity by placing electrodes on the temples of a patient. By the 1950s, electroconvulsive therapy (ECT) became a principal treatment for a broad range of psychiatric illnesses (Fink, 2014; Hirshbein and Sarvananda, 2008). Although the specific mechanism for ECT was unknown, the general belief for its treatment effect was that “convulsions disrupted problems in the patient’s thinking and restored some semblance of normality” (Hirschbein and Sarvananda, 2008). Therefore, the therapeutic effect of ECT is largely dependent on the induction of a grand-mal seizure (Fink, 2001). This view is backed up by studies of incomplete seizures, where the treatments were mostly ineffective (Fink, 2001). As such, the induction of adequate seizures is guided by measurements of a seizure threshold (ST). ST is the lowest stimulation needed to induce an adequate seizure (Fink, 2008). It can be measured by two ways, a dose titration (DT) method or a half-age method (HA) (Petrides et al., 2009). The DT method
starts stimulation at a level anticipated to be below the threshold for a seizure, and stimulation is increased at fixed increments (25 or 50mC) until a seizure is induced. The HA method estimates the ST by using half of the anticipated “percent of charge” given the patient’s age as a starting point (Petrides et al., 2009).

Unfortunately, early unmodified administrations of ECT lacked standardization, was minimally supported by scientific research and came with many side effects (Hirschbein and Sarvananda, 2008). In particular, the convulsions frequently produced fractures and dislocations (Gallegos et al., 2012), hemodynamic complications and inadequate respiration. Consequently, patients were often physically restrained during treatment to prevent physical harm (Gallegos et al., 2012; Hirshbein, 2008), which induced a great deal of anxiety and fear. Patient reports at the time showed a 50% - 80% fear and anxiety rate prior to treatment (Gallegos et al., 2012). Although some physicians have thought of unmodified treatment as inhumane and degrading (Gallegos et al., 2012), ECT’s side effects were generally accepted and thought of as “unavoidable consequences of the larger fight” (Gallegos et al., 2012).

Modified ECT was introduced in the 1950s, as a way to reduce patient discomfort and improve safety (Gallegos et al., 2008). Sedatives, muscle relaxants and ventilation were given prior to treatment to replace physical restraints and improve on the cognitive side effects of post-ECT delirium,
confusion and agitation seen with unmodified ECT (Gallegos et al., 2008). However, the public perception of ECT began to shift in the 1970s, from amazement with this highly effective treatment to concerns with its wide spread use as a “magic formula that will catapult the unhappy into sudden happiness” (Hirshbein and Sarvananda, 2008) and fear based on outdated, unmodified images of ECT. These fears were exacerbated by news articles at the time that described ECT as a “violent means by which psychiatrists assumed control over their patients” and comparing ECT to the electric chair and lobotomy procedures (Hirshbein and Sarvananda, 2008). The dramatic illustration of ECT in the 1975 film, One Flew Over the Cuckoo’s Nest, further solidified the horrifying image of ECT in the public’s mind (Hirschbein and Sarvananda, 2008). Many believed that ECT caused irreversible brain damage and altered one’s personality and character (Gallegos et al., 2012).

By the middle of the 1980s, proponents of ECT began making more assertive efforts to inform the public of ECT treatment standards in the modern day (Hirshbein and Sarvananda, 2008). Notably, Drs. Max Fink and Harold Sackheim pushed for greater scientific research on the use of ECT, its efficacy and mechanism (Fink, 1978). They produced numerous evidence based publications that both acknowledged the abuse of ECT in history and its progressive present day modifications that treat specific illnesses with minimal dosing (Hirschbein and Sarvananda, 2008). Thus, early research on ECT has focused on understanding and improving its side effects.
One major concern for the use of ECT is induced brain damage through electrical stimulation (Fink, 2001). This fear largely stems from postmortem studies from the 1940 and 1950s of patients who died from complications of unmodified ECT (Devanand et al., 1994). These studies found either no pathological change in the gross or micro-structure of the brain to severe changes in both (Devanand et al., 1994). However, these studies were poorly controlled as cerebrovascular damage can be caused by preexisting conditions that are unrelated to ECT. Present day imaging studies, ranging from computerized tomography (CT) to magnetic resonance imaging (MRI) have not been able to identify consistent brain structural abnormalities in either single ECT treatment or a course of ECT (Fink, 2001; Devanand et al., 1994). It is noteworthy that early unmodified ECT without adequate ventilation caused cognitive defects in some patients, but it is difficult to directly attribute these defects to ECT alone (Fink, 2001).

Secondary to electrical stimulation, induced grand-mal seizure that is central to the therapeutic effect of ECT has also raised concern for brain damage. Studies in patients with severe epilepsy have found that they “had a lower cell density than comparison subjects, while patients with infrequent and moderately frequent seizures had neuron cell densities within the normal range” (Devanand et al., 1994). Aggregate results from epilepsy studies in animals and humans showed that “neuronal loss occurs only after dozens of closely spaced unmodified convulsions or only after several hours of continuous seizure activity
if adequate ventilation and muscle relaxation are employed” (Devanand et al., 1994). However, the seizures elicited during modern day modified ECT are far from these requirements, as they typically only last a few seconds and are modified with adequate ventilation and muscle relaxants (Devanand et al., 1994).

A consistent patient reported side effect of ECT is memory impairment, either in events that occurred prior to treatment or difficulty remembering events immediately post treatment (Fraser et al., 2008). Approximately 29% - 55% of ECT patients report memory loss, but subjective memory impairment reports are found to be longer than those reported with objective measures (Fraser et al., 2008). Memories around the time of ECT treatment are reported as especially poor. However, studies have found that patient memory impairments are usually only reported at short term follow up, while long term follow ups at 2 months have reported no difference in memory ability (Lisanby et al., 2000; Sackeim et al., 2000). Some studies have even found an improvement in memory at 1 and 6 months follow up after ECT (Calev et al., 1991). The improvement in memory is thought to be a related to post treatment improvement of depressive symptoms (Fraser et al., 2008). The difference in subjective and objective memory reports and symptom improvement may contribute to the different findings of these studies. However, they all suggest that memory impairment in ECT is unlikely irreversible.
Research to reduce memory impairment in ECT has focused on the impact of different ECT administration on memory performance. As such, bilateral (BL) electrode placement was found to produce more severe acute memory disruptions than right unilateral placement (RUL) (Sackeim, 2007; Weiner, 1986). Patients who received bilateral treatment typically perform worse on word recall tasks and event recall tasks. Additionally, traditional sine wave form was also found to produce greater cognitive impairment than brief pulse square wave (Sackeim et al., 2007; Weiner, 1986). Cognitive advantage of right unilateral electrode placement is thought to avoid direct electrical stimulation over the dominant left hemisphere (Fink, 2001). Likewise, bilateral electrode placement is typically placed over the frontal region of the brain, to directly stimulate the motor strip and avoid stimulation to memory centers to minimize disruptions of memory (Fink, 2001). However, despite these efforts to improve the side effect profile of ECT, research results on the efficacy of RUL are mixed. Most studies have found that BL treatments showed more rapid symptom improvement with fewer treatments (Abrahams et al., 1991; Kellner et al., 2010; Halliday et al., 1968); while other researchers have argued for more prevalent use of RUL as first-line treatment given its more favorable side effect profile compared to BL treatments (Sackheim et al., 2007). Both approaches aim to decrease patient suffering, either by shortening treatment duration or minimizing side effects.
A more recent modification to ECT is the introduction of ultra-brief pulse (UBP) width at 0.3 ms compared to brief pulse (BP) stimulation (0.5-1.5 ms) (Loo et al., 2012). Studies have found that BP stimulation exceeds the ideal pulse width to depolarize neurons, which is around 0.1-0.2ms (Loo et al., 2012; Tor et al., 2015). By further reducing pulse width to <0.5ms, neurons are more efficiently depolarized and “a narrower band of tissue is stimulated and areas such as the hippocampus and other temporal lobe structures may be relatively spared” (Galvez, 2015; Loo et al., 2012). This is supported by evidence from seizure threshold data that showed a lower ST in UBP ECT compared to BP ECT (Galvez et al., 2015). However, research on the efficacy and proposed side effect improvement of UBP ECT remains controversial and difficult to interpret (Spaans et al., 2013). Research efforts on electrode placement, pulse width and waveform in ECT practice further align convulsive treatments with modern day evidence based practices that seek to minimize harm and discomfort to patients, a drastic change from the early days of unmodified ECT.

As a result of the misunderstanding of ECT due to its early unmodified administration and negative media depiction in the 1970s, the use of ECT was largely restricted from, or even rejected by, patients who might have otherwise benefitted greatly. For the most part, ECT is given to patients who are severely ill or who are considered treatment resistant (failure to respond to at least two adequate trials of treatments (Rush et al., 2003)). Despite this limitation, ECT has consistently demonstrated impressive efficacy, especially in the treatment of
major depressive disorder (MDD), with a 75% remission rate (Husain et al., 2004; Hermann, 1995; Weiner, 2001). Additionally, in comparison studies of ECT, simulated ECT, and antidepressants (Tricyclic antidepressants, monoamine oxidase inhibitors, etc.), it was shown that ECT is significantly more effective than all comparison treatments (Pagnin et al., 2004). Today, ECT is considered the gold-standard treatment for depression (Spaans et al., 2013).

**Major Depressive Disorder**

Major depressive Disorder (MDD) is a debilitating psychiatric disorder with a ~14% - 16% lifetime prevalence in adults in the United and considered as a disease with one of the longest years lived with disability (YLDs) globally (Hasin et al., 2005; Kessler et al., 2003, Murray et al., 2013). By 2020, it will be the second leading cause of disability according to the World Health Organization (Blazer et al., 2000). Patients who suffer from MDD also show a high comorbidity with other mental disorders such as disorders of substance use with alcohol and drugs (Hasin et al., 2005; Kessler et al., 2003) and anxiety disorders such as panic disorder, posttraumatic stress disorder, and obsessive compulsive disorder (Drevets et al., 2008). Additionally, major depression is associated with significant cognitive impairment in memory and attention (Kessler et al., 2003; Mayberg et al., 1999). Adult patients report an average 35 days of inability to carry out their normal activities such as work and social interactions (Kessler et al., 2003). They experience depressed mood, fatigue, high anxiety, and/or
recurrent thoughts of death and suicide (Anacker et al., 2011), causing severe disruptions in personal relationships and economic productivity (Mayberg et al., 1999; Kessler et al., 2003; Bremner et al., 2002). Combined with MDD’s high prevalence, finding effective treatment to alleviate this health issue is extremely valuable.

The heterogeneity of symptoms of MDD suggests that it is a disease that involves multiple neurological mechanisms. One area of research has looked at the significant correlation between dysfunction of the hypothalamic-pituitary axis (HPA) and symptoms of depression (Anacker et al., 2011). Depression has been found to be vulnerable to stress, which perturbs normal HPA function (Luscher et al., 2011). HPA hyperactivity has been consistently demonstrated across multiple studies of depression, which leads to increased levels of cortisol regulating neuronal survival (Anacker et al., 2011; Pariante et al., 2009). It exerts neuronal excitability, neurogenesis and memory acquisition by binding to specific glucocorticoid receptors (GR) in the brain and regulating the expression of neutrophic factors such as brain derived neurotrophic factors (BDNF). These neutrophic factors have significant effects on the regulation of neuronal death and neurogenesis, especially in the hippocampus (Anacker et al., 2011). Therefore, it is hypothesized that hyperactivity of the HPA leading to abnormal rises in cortisol levels and dysfunctional GR can both contribute to functional and structural changes in the depressed brain (Sousa et al., 2008).
Studies have also shown that cortisol induces a marked increase in extracellular glutamate levels in the hippocampus, amygdala, and prefrontal cortex (PFC) (Sanacora, 2012). Glutamate is the major excitatory neurotransmitter in the brain, accounting for 85% of all synapses in the brain (Sanacora et al., 2012; Krystal et al., 2002). Cognition and emotion are largely mediated by the glutamatergic system, and it is widely accepted that memory encoding is due to glutamatergic synaptic plasticity (Sanacora et al., 2012). Structural and functional studies of patients with unipolar depression have reductions in glial and neuronal cell numbers in cortical and subcortical structures, which is correlated to glutamatergic abnormalities (Krystal et al., 2002). Glia is especially important in the normal functionality of the glutamatergic system. Disruption in glia, which contains transporters that remove glutamate from synapses, can cause toxic glutamate accumulation and prolong excitatory activation (Krystal et al., 2002; Choudary et al., 2005) and ultimately alter synaptic transmission (Sanacora et al., 2012). Additionally, glia also stimulates release of an N-methyl-D-aspartate receptor (NMDA) receptor coagonist. Loss of glia can lead to reductions in NMDA receptor function. Last but not least, glial function is also important in providing neuronal energy substrate. The combination of increased excitatory input from glutamate accumulation at the synapse and decrease in energy supply can cause neuronal atrophy and cytotoxic damage (Krystal et al., 2002; Choudary et al., 2005). In MDD, glutamate dysfunction is also associated with “maladaptive” neuroplastic
changes in excitatory signaling in response to emotional and environmental stressors (Sanacora et al., 2012). Glutamate metabolite levels has been found to be decreased in the frontal and cingulate cortex but increased in occipital and parietal regions in MDD (Sanacora et al., 2012; Sequeira et al., 2009; Auer et al., 2000). Similarly, gamma-Aminobutyric acid (GABA), the major inhibitory neurotransmitter of the brain, used by approximately 40% of all neurons, has also been implicated in mood disorders as it is closely related to glutamate metabolism (Sanacora et al., 2012; Krystal et al., 2002; Torrey et al., 2005). GABA is formed by glutamic acid decarboxylase (GAD) in GABAergic synaptic terminals using glutamate as precursor (Brambilla et al., 2003). Main effect of GABA is to “balance and fine tune excitatory neurotransmission… including monaminergic and cholinergic projections to the forebrain” (Luscher et al., 2011). In MDD, GABA has been found to be significantly reduced in occipital cortex, anterior cingulate cortex (ACC), dorsomedial/ dorsolateral PFC (Luscher et al., 2011). Given the significant alterations seen in the major excitatory and inhibitory neurotransmitter systems of the brain, the effects of antidepressant treatments on these systems cannot be overlooked.

Following the neurotoxic hypothesis, studies have looked specifically at alterations in brain volume in MDD. Several studies reported that compared to healthy controls, patients show decrease in medial orbitofrontal cortical volume (Bremner et al., 2002), decreased ACC volume (Drevets et al., 2008), significantly smaller left and right hippocampal volumes correlated to duration of
major depression (Sheline et al., 1996), and significantly smaller left hippocampal volume (Bremner et al., 2000). These studies indicated the neurotoxic role of increased cortisol levels as a possible mechanism in the neuronal loss seen in MDD patients as similar neuronal loss specifically in the hippocampus has also been reported in patients with Cushing’s syndrome (malignant elevated cortisol levels) (Bremner et al., 2000; Sheline et al., 1996). The hippocampus is the major brain center for memory (Squire et al., 1992), while prefrontal cortices are involved in emotional and visceral regulation (Bremner et al., 2002). Therefore, atrophy of the hippocampus may explain the memory defects experienced with depression (Bremner et al., 2000), and the reduction in cortical volume of prefrontal cortices reveal possible mechanism for the “deficits in emotion, mood, and social regulation” in major depression (Bremner et al., 2002).

In addition to examining the brain structural differences and molecular changes in MDD, studies have also looked at functional differences, such as cerebral blood flow, cerebral glucose metabolism and connectivity. Studies of cerebral blood flow in MDD have found conflicting results depending on the brain region under investigation (Segawa et al., 2006). The most consistent finding to date is decreased perfusion and metabolism in the frontal region of the brain and increased blood flow in the ACC, in depressed patients compared to healthy controls after corrections for brain volume (Milo et al., 2001; Bench et al., 1992; Awata et al., 2002; Drevets et al., 2008). The ACC has been shown to modulate emotional behavior, along with the medial prefrontal cortex, these brain regions
have been identified as key structures for MDD (Horn et al., 2010; Drevets et al., 2008). Changes in blood flow or metabolism level reflect regional or global neural function, and it is influenced by changes in synaptic transmission that can be associated with alterations in neurotransmitter concentration or receptor activity or with changes in synaptic connection resulting from regional brain volume changes (Drevets, 1998). It is important to note that changes in blood flow or metabolic activity can reflect either the “physiological correlates of depressive emotions and thoughts or pathophysiological changes that predispose subjects to or result from affective disease” (Drevets, 1998).

Functional connectivity and resting state magnetic resonance imaging (MRI) studies in MDD have found hyperconnectivity in regions that are part of the default mode network (DMN), especially in the subgenual ACC (sgACC) (Greicius et al., 2007; Berman et al., 2010; Zhu et al., 2012). The DMN is important

“in self-referential activities, being described as low frequency toggling between a task independent, self-referential, and introspective state and an extrospective state the ensures the individual is alert and attentive to unexpected or novel environmental events” (Zhu et al., 2012).

More specifically, the anterior region of the network is associated with self-referential processing, such as the sgACC, while the posterior region is associated with memory retrieval (Greicius et al., 2007). Greicius et al.
hypothesized that the emotional and constant self reflective tendencies seen in depressed patients is possibly related to an increase in functional connectivity in the frontal parts of the DMN, versus a reduction in functional connectivity of the posterior part of the network might be more involved in cognition and memory impairments in these patients (Greicius et al., 2007). As such, studies have found hyperactivity in the ventral medial PFC and hypoactivity in the dorsolateral PFC, which both shows trends towards normalization during remission (Koenig et al., 2009).

Although research efforts have tackled the biological underpinnings of MDD from many perspectives, the complexity of the illness prevents a single explanation for its etiology. The reduced brain volume, changes in glutamate/GABA levels, and hyperconnectivity in several brain regions consistently found in patients with depression suggests that secondary to a wide spread change in brain physiology and biochemistry, the direction of the change may be dependent on individual brain regions that have specific cognitive or emotional function. Thus, to develop more effective treatments for this pervasive and disruptive illness, a focus on treatments that target a wide range of neural circuits and are also capable of inducing circuit specific changes may yield a more immediate therapeutic effect.
Neuroplasticity Hypotheses for the Mechanism of ECT

To date, a unifying mechanism for ECT in MDD is still elusive. The complex and wide spread dysfunctions caused by the illness suggests that the mechanism is unlikely to be of a single source. However, converging evidence from several fields of research suggest that ECT’s overall effect is to correct dysfunctional activity through neuroplasticity induction.

Interestingly, albeit that ECT exerts its therapeutic effect through the induction of grand mal seizures (Fink, 2014b), it actually has anticonvulsive properties that are strongly correlated to clinical response (Sackheim, 1999). Patients on average experience a 40-100% increase in their seizure threshold over a course of treatment, consequently the patient becomes increasingly more resistant to seizure initiation (Sackeim et al., 1987; Coffey et al., 1995). This increased resistance suggests that ECT alters brain physiology, and the effect is likely wide spread (Sackeim et al., 1994). However, the alteration is not permanent, with many patients reverting back to baseline seizure threshold after discontinuation of ECT (Sackheim, 1999). It has also been demonstrated that bilateral ECT results in much greater increase in seizure threshold than RUL ECT (Sackheim et al., 1987). Therefore, a significant increase in seizure threshold is considered a marker of ECT efficacy, as only patients who responded to ECT show an increase in seizure threshold (Figure 1.) corresponding to the degree of their clinical response (Sackheim, 1999). There
are also other clinical observations that support the anticonvulsive properties of ECT. Such as a decrease in seizure duration over a treatment course, reductions in regional cerebral blood flow and metabolism, increased slow wave activity in electroencephalogram (EEG), and enhanced transmission of inhibitory neurotransmitters and neuropeptides.

Figure 1. Comparison of Seizure Threshold in Electroconvulsive Therapy Patients. Percent change in seizure threshold. Percent change in seizure threshold between responders and non-responders in two studies that compared seizure threshold between bilateral and unilateral electrode placement. Figure taken from Sackheim, 1999.

A neurotransmitter mechanism for this observed change in seizure threshold has been proposed. It has been found in animal studies that electroconvulsive shock (ECS) induced seizures through antagonism of the
GABA system (Bowery et al., 1976; Simmonds et al., 1980; Bradford et al., 1995). GABA is the most abundant inhibitory neurotransmitter in the brain, and has been shown to be dysfunctional in mood disorders (Emrich et al., 1980). Binding of GABA to GABA\(_A\) receptor enhances chloride ion channel opening, which hyperpolarized the neuronal membrane, causing an inhibitory effect (Brambilla et al., 2003). Drugs such as benzodiazepines, anticonvulsants and anesthetics bind to the GABA\(_A\) receptor to mediate their effects. MDD is especially vulnerable to the effects of chronic stress (Luscher et al., 2011). It has been shown that chronic stress reduces the level and function of GABA\(_A\) receptors in cortical and subcortical areas, and subsequent reduction in inhibitory transmission can greatly impair neurogenesis in the hippocampus (Luscher et al., 2011). Additionally, clinical response to ECT in the patient population is correlated with an increase in GABA levels (Brambilla et al., 2003), which contributes to increases in seizure threshold. Interestingly, GABA has been shown to modulate the activity of dopaminergic, norepinephrine and serotonin systems of the central nervous system (Brambilla et al., 2003), which have all been implicated as dysfunctional systems in mood disorders. Unsurprisingly, ECT also influences the glutamatergic system, and has been shown to correct deficits in patients who responded to ECT (Michael et. al., 2003; Ende et al., 2000; Pfleiderer et al., 2003). Thus the transmission of the major inhibitory and excitatory neurotransmitters, GABA and glutamate respectively, may provide a
possible platform to investigate the wide spread therapeutic mechanism and side effect profile of ECT.

Studies have also looked at the neural functional connectivity in patients with MDD compared to healthy controls. Functional connectivity represents areas of the brain that have coordinated activity during a goal-oriented task or at a resting state, these areas will show temporal correlations in blood oxygen level-dependent (BOLD) signals during functional magnetic resonance imaging (fMRI) are thought to reflect the functional interaction between different populations of neurons (Greicius et al., 2003; Honey et al., 2009; Sheline et al., 2009). These correlations demonstrate intrinsic connectivity across broad brain regions and serve important functions such as vision, hearing, language and self-referential processing (Greicius et al., 2009, Sheline et al., 2009). Evidence shows that structural connectivity of brain regions is interrelated to their functional connectivity, such that brain regions that are closer together show stronger interrelatedness (Honey et al., 2009). Therefore, functional connectivity also is reflective of the physical interactions between different neuron populations.

Functional connectivity studies began by demonstrating increased neural activity during a cognitive task compared to baseline resting state. However, a network of brain regions known as the DMN demonstrates higher activity during rest than cognitive tasks, and has been referred to as regions of deactivation during goal-oriented tasks and is thus most active during resting states (Greicius
et al., 2003; 2009). The DMN is thought to be important in processing information about the world such as “remembering the past as well as planning for the future” (Sheline et al., 2009), and the decrease in its activity during goal-oriented task is to “attenuate the brain’s self-referential activity as a means of more effectively focusing on a task” (Sheline et al., 2009). The DMN includes areas of the dorsal and ventral medial prefrontal cortices, medial and lateral parietal cortex, and part of the medial and lateral temporal cortices (Sheline et al., 2009). Structural and functional studies in MDD have revealed abnormal brain circuits involved in emotional processing that fall within the anterior DMN (Sheline et al., 2009). Such changes can be, in part, due to the DMN’s susceptibility to maladaptive changes in neural networks due to factors such as early life stress, which can cause aberrant regulation of neuronal plasticity (Sheline et al., 2009).

Research on the effects of ECT on functional connectivity shows normalization of aberrant functional connectivity in patients towards healthy controls (Abbott et al., 2013; Perrin et al., 2012). This suggests that ECT may mediate its therapeutic effects through restoring normal structural and functional connectivity in MDD. Similarly, given the importance of the glutamate/GABA system in coordinating excitatory and inhibitory activity across the brain and their implication in neuronal health and neurogenesis, the normalization of the two systems after ECT is likely correlated to the restoration of normal functional connectivity. Studies on the neuroendocrine and neurotrophic hypotheses of ECT further supports significant increases in serum BDNF post treatment, which
promotes neuronal growth, neuroplasticity (Bumb et al., 2015; Marano et al., 2007), and also regulates GABA reuptake/inactivation (Brambilla et al., 2003). Studies have also shown increased cortical and subcortical volume after ECT (Jorgensen et al., 2016; Tendolkar et al., 2013; Ota et al., 2015; Sartorius et al., 2015). Such changes have been attributed to ECT’s ability to induce neurogenesis in these structures (Tendolkar et al., 2013; Ota et al., 2015). Two regions of special interests are the amygdala and hippocampus, which have consistently been identified as centers of increased volume (Jorgensen et al., 2016; Tendolkar et al., 2013). The amygdala has modulatory effects on the activity of the hippocampus, where in early depression an increase in amygdala volume is related to an increase in functional activity that influences hippocampus activity. This hyperactivation is normalized after remission to antidepressant treatment (Tendolkar et al., 2013). Together, the evidence further suggests that ECT induces beneficial plastic changes at the neuronal level that affect both structural and functional connectivity of the brain.

In this thesis, we will review current literature on functional connectivity using fMRI and glutamate/GABA using magnetic resonance spectroscopy (MRS). We hypothesize that ECT mediates its therapeutic effect through correcting abnormal glutamate/GABA systems and restoring normal functional connectivity by remodeling brain structures involved in affective and cognitive processing.
PUBLISHED RESULTS

Functional Connectivity

Perrin et al., 2012

In a 2012 study, Perrin et al. looked at the effect of ECT on functional connectivity of the whole brain in nine patients (Perrin et al., 2012). The patients were given brief-pulse, bilateral ECT treatments twice a week, the mean number of treatments administered was 8.3. Clinical measures such as the Montgomery Asberg Depression Rating scale (MADRS) were collected within 48 hours of the first treatment, after the 4th treatment and after the last treatment. The patients were scanned before and after ECT treatments using a 3 Tesla MRI scanner. The amount of time before and after each ECT session was unclear. During the scans, each patient was instructed to perform a virtual ball passing cognitive task to help focus attention. The authors suggested that a simple cognitive task will reduce within group variance as resting state fMRI usually causes greater inter-subject variance because patients may be thinking about different things and are also prone to falling asleep (Perrin et al., 2012).

Instead of using predetermined candidate seed regions, they used weighted global connectivity (WGC) to compare before and after treatment effects. This approach allows quantification of the degree of connection between each voxel to all other voxels in the brain. They found a significant decrease in
average global connectivity in a cluster in the left dorsolateral prefrontal cortex (DLPFC), meaning that the connectivity of each voxel within the cluster to the voxels of the rest of the brain is significantly reduced (Perrin et al., 2012). This cluster was then used as a seed region to find other regions of the brain that it is functionally connected to. Results (Figure 2.) of this additional analysis showed that ECT significantly reduced connectivity between medial cortical structures, bilateral DLPFC, and left supermarginal gyrus, angular gyrus and somatosensory association cortex. Patients in this study showed significant reduction in depression symptoms after ECT.
Figure 2. Functional Connectivity of Dorsolateral Prefrontal Cortex Seed Region. Orange regions denote areas of significant connectivity with DLPFC before ECT treatment in patients with depression. Blue regions denote areas of significant functional connectivity with DLPFC that persisted after ECT treatments. Z value refers to distance in millimeters from the midline of Montreal Neurological Institute stereotaxic space. Figure modified from Perrin et al., 2012.
Another 2012 study, by Beall et al., investigated the changes in activation and connectivity during task based and resting state fMRI before and after ECT treatments in ECT naïve patients (Beall et al., 2012). Six patients with MDD or bipolar affective disorder were enrolled. Patients received an average of 9 bilateral ECT treatments and were scanned 1 week before first ECT treatment and 1 to 3 weeks after last ECT treatment using a 3 Tesla MRI scanner with a 12 channel head coil. At each scan, working memory, affective pictures and resting connectivity scans were acquired. For working memory, a 2 back spatial working memory task was used. Patients were presented with four empty boxes on a display monitor that contains a white ball in one of the boxes. They were then instructed to remember the locations of the white ball for 2 presentations. For affective pictures, patients were shown a series of neutral and unpleasant pictures, and were asked to indicate when a new picture was presented (Beall et al., 2012).

ECT effect on activation was assessed by linear correlation of activation in regions of interests (ROI) to changes in Hamilton Rating Scale for Depression (HAM-D). Mean activation values were compared in DLPFC, superior parietal lobe, superior cerebellum, posterior cingulate cortex and premotor cortex ROIs for the working memory task. Mean activation were compared in the right DLPFC, anterior cingulate cortex, medial prefrontal cortex, orbitofrontal cortex

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and inferior parietal lobe ROIs for the affective task. Mean activation changes before and after ECT in individual ROIs were then correlated to HAM-D score changes (Beall et al., 2012). It is important to note that regions of deactivation and activation are all considered “activation” to examine all significant changes in blood flow in both directions. Resting state functional connectivity (rsFC) was analyzed between ROIs. The effect of ECT on rsFC is also tested by linear correlation between changes in connectivity and HAM-D scores before and after ECT.

In the task-related activation analysis, Beall et al. found a reduction in the absolute level of activation or deactivation in most regions during working memory and affective picture tasks after ECT, with exception of increased activation (or deactivation) in the cerebellum and posterior cingulate cortex during working memory task. The greatest reduction in deactivation was in the orbitofrontal cortex in the affective task. Mean activation in orbitofrontal cortex was found to be significantly correlated to changes in HAM-D scores in patients (Beall et al., 2012).

rsFC analysis showed a decrease in the connectivity of left anterior cingulate cortex and orbitofrontal cortex and an increase in the connectivity between right ACC and orbitofrontal cortex, ACC and caudate after treatment. The most significant increase in connectivity found in the study is between the ACC, the right DLPFC and posterior cingulate cortex. No significant correlation
between connectivity change and HAM-D change survived after corrections for multiple comparisons (Beall et al., 2012).

**Wei et al., 2014**

An interesting study examining interhemispheric functional coordination modulation by ECT was done by Wei et al. in 2014. The study included 11 patients with depression and 15 group-matched healthy controls. The patients underwent a mean of 7 bifrontal ECT treatments, while the controls did not receive any. HAM-D scores were collected 12-24 hours before and 24-72 hours after ECT from patients. Both patients and healthy controls underwent resting state (rs) fMRI scans. Patients were scanned twice, 12-24 hours before and 24-72 hours after ECT, while healthy controls were scanned once. Scans were done with a 3 Tesla scanner (Wei et al., 2014).

The study used voxel mirrored homotrophic connectivity (VMHC) method to assess interhemispheric coordination effects of ECT. VMHC “indexes the resting-state functional connectivity between each voxel in one hemisphere and its mirrored counterpart in the opposite hemisphere” (Wei et al., 2014). To perform VMHC computation, a mean image of normalized gray matter images of all subjects was created and averaged to create a left-right symmetrical template. Then individual gray matter images were registered to the symmetrical template.
Comparing pre-ECT to post-ECT scans in patients, they found significantly increased VMHC in superior frontal gyri, middle frontal gyri, and angular gyri (Table 1) (Wei et al., 2014). In comparison between healthy controls and pre-ECT patients, significantly lower VMHC was reported in the middle frontal gyri and angular gyri. Comparing healthy controls to post-ECT patients, significantly higher VMHC was reported in superior frontal gyri and middle frontal gyri (Figure 3). No significant correlation was found between reductions in HAM-D score and VMHC changes in the superior frontal gyri, middle frontal gyri, or angular gyri when comparing pre-ECT and post-ECT conditions. There was also no significant correlation between the number of ECT treatments and VMHC changes in the superior frontal gyri, middle frontal gyri, or angular gyri.

Table 2. Voxel Mirrored Homotrophic Connectivity Changes Following Electroconvulsive Therapy. Three brain regions showed significant homotrophic connectivity changes (VMHC) changes after electroconvulsive therapy (ECT) during resting state (rs) functional connectivity scan. MNI coordinates refer to Montreal Neurologic Institute coordinates. MNI coordinates and t-scores are both for the peak voxel. Table modified from Wei et al., 2014.

<table>
<thead>
<tr>
<th>Brain regions</th>
<th>Voxel number</th>
<th>t-score</th>
<th>MNI coordinates (x, y, z)</th>
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<tr>
<td>Middle frontal gyri</td>
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<td>6.0747</td>
<td>±48, 15, 45</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>7.2623</td>
<td>±42, 51, -3</td>
</tr>
<tr>
<td>Angular gyri</td>
<td>97</td>
<td>6.1551</td>
<td>±48, -66, 27</td>
</tr>
</tbody>
</table>
Figure 3. Comparison of Voxel Mirrored Homotrophic Connectivity in Brain Regions. Graph demonstrates a significant increase in voxel mirrored homotrophic connectivity (VMHC) between healthy controls (HC) and patients before electroconvulsive therapy (ECT) (Pre) and after ECT (Post). ** Denotes significant difference between comparison group and healthy control. There were two clusters (clusters A and B) within the middle frontal gyri that were found to be significantly increased in VMHC after ECT in the patient group. (a) Compared to HC, patients after ECT showed significantly higher VMHC in the superior frontal gyri. (b) Compared to HC, patients before ECT showed significantly lower VMHC in the middle frontal gyri in cluster A. (c) Compared to HC, patients after ECT showed significantly higher VMHC in the middle frontal gyri in cluster B. (d) Compared to HC, patients before ECT showed significantly lower VMHC in the angular gyri. Figure modified from Wei et al., 2014.
Abbott et al., 2013

Abbott et al. (2013) examined the rsFC in four regions affected in MDD in a 2013 study. They looked at subcallosal cingulate gyrus (SCC), DMN, DLPFC and dorsomedial prefrontal cortex (DMPFC) in patients with MDD compared to age and gender matched healthy controls (Abbott et al., 2013). A total of 12 patients and 12 healthy controls were included in the study. Ten patients received brief pulse RUL ECT and 2 patients received brief pulse bitemporal ECT, on average the patients received 11 treatments. Resting state scans were acquired with a 3 Tesla scanner over a minimum of 5 minutes. Baseline clinical assessment (24 item Hamilton Depression Rating Scale (HDRS-24)) and resting state scan were done 1 to 2 days before the first ECT treatment. Post-ECT assessments and resting state scan were done at least 5 days after their last treatment.

The group performed an independent component analysis (ICA) instead of a seed based analysis (Abbot et al., 2013). Unlike seed based analysis, where one predetermines an area of interest, ICA identifies functionally connected brain regions by looking for temporal coherence in hemodynamic changes of all brain regions (Abbott et al., 2013). Therefore, ICA is thought to be less arbitrary than seed based analysis and consider all information between voxels, therefore increasing sensitivity in detecting between group differences.
Clinical assessment analysis found that responders to ECT treatment showed a significant reduction in HRDS-24 scores compared to non-responders (Figure 4) (Abbott et al., 2013). Nine patients were considered remitters. In functional connectivity analysis, components of interests were further divided into anterior default mode (a_DM), SCC, DMPFC, posterior default mode (p_DM), and right/left DLPFC (r_DLPFC, l_DLPFC). Primary analysis of longitudinal changes in functional connectivity found that correlation between p_DM and DMPFC changed from negative to positive after ECT treatment. Connectivity correlation between p_DM and l_DLPFC also changed from negative to weak positive after ECT. Secondary analysis compared pre-ECT depressed patients with healthy controls in the functional connectivity in significant network pairs identified via primary analysis. Compare to healthy controls, patients had significantly lower connectivity between p_DM and DMPFC, and pDMN and l_DLPFC. Last but not least, they also found that connectivity increased significantly in p_DM and l_DLPFC after ECT in remitters but not non-remitters (Abbott et al., 2013).
Figure 4. Functional Connectivity Comparison Following Electroconvulsive Therapy. Shown is connectivity between patient (pre/post-electroconvulsive therapy (ECT)) and healthy controls. Y axis represents direction and magnitude of functional connectivity correlation. Red solid lines – average of healthy control connectivity correlations of that region. Dashed red lines – standard errors of healthy control connectivity. DMPFC- dorsomedial prefrontal cortex. P_DM – posterior default mode network. DLPFC – dorsolateral prefrontal cortex. (A). Pre-ECT patients had significantly lower connectivity between DMPFC and p_DM compared to healthy controls. Connectivity shows a trend of normalization towards healthy control after ECT. (B). Pre-ECT patients show significantly lower connectivity between DLPFC and p_DM compared to healthy controls. Connectivity shows a trend of normalization towards healthy control after ECT. Figure adapted from Abbott et al., 2013.

Liu et al., 2015

In their 2015 study, Liu et al. hypothesized that ECT resets “regional activity and neuroplasticity of distant connectivity in the subgenual anterior cingulate cortex (sgACC)” in patients with major depression (Liu et al., 2015). They measured changes in both spontaneous whole brain activity and functional connectivity before and after ECT treatments. The study included 23 patients.
who underwent brief pulse bitemporal ECT. All patients received at least 8 ECT treatments and at most 12 treatments. They were scanned 1 day before the first session of ECT and were scanned again more than 24 hours after 8 ECT treatments. All scans were performed using a 3T MRI scanner; resting scans were acquired by instructing patients to relax with their eyes closed and staying awake. HAM-D questionnaire was given 1 day before ECT and the day after 8 ECT treatments as clinical assessment. Two types of analyses were performed, amplitude of low frequency fluctuation analyses (ALFF) and functional connectivity. Functional connectivity analyzed from a seed based approach in the sgACC (Liu et al., 2015).

The DMN showed the greatest ALFF value in both pre-ECT and post-ECT scans (Liu et al., 2015). The left sgACC, left hippocampus (HIP), bilateral orbitofrontal cortex (OFC), right pregenual (pg) ACC, and right pre-central gyrus showed a significant increase in ALFF after ECT. Significant decreases in ALFF was also observed in the middle posterior dorsal (pd) ACC (Figure 5). Functional connectivity between seed region sgACC and all other voxels in the brain showed an increase in connectivity between left sgACC and ipsilateral parahippocampal gyrus, pgACC, contralateral middle temporal pole (MTP), and OFC (Figure 6). The clinical assessment showed a negative correlation between increased activity in the left sgACC and reduced HAM-D scores. There was also a negative correlation between increased functional connectivity in the sgACC and MTP and reduced HAM-D scores.
Figure 5. Amplitude of Low frequency Fluctuation (ALFF) Analysis. L. sgACC – left subgenual anterior cingulate cortex (ACC). R. pgACC – right pregenual ACC. L HIP – left hippocampus. L.OFC – left orbitofrontal cortex. R. OFC – right orbitofrontal cortex. R. PreCG – right precentral gyrus. pdACC – posterior dorsal ACC. Figure taken from Liu et al., 2015.

Figure 6. Functional Connectivity with Subgenual Anterior Cingulate Cortex. L. Parahip – left parahippocampus. L. pgACC – left pregenual anterior cingulate cortex (ACC). L. SFGOrb – Left superior orbitofrontal cortex. R. IFGOrb – Right inferior orbitofrontal cortex. MFGOrb – Middle orbitofrontal cortex. MTGP – Middle temporal gyrus, pole. Figure taken from Liu et al., 2015.
Cano et al., 2015

Cano et al. were interested in the effect of ECT on limbic and prefrontal connectivity in treatment resistant MDD (Cano et al., 2015). In their 2015 study, they looked at how ECT affects sgACC and DLPFC to amygdala functional connectivity at different points during a course of ECT. Specifically, they looked at before ECT, after one treatment, after nine treatments and 15 days after the last ECT treatment. They tested if the connectivity from amygdala to sgACC and amygdala to DLPFC would change sequentially over a course of ECT treatment. 13 patients with treatment resistant MDD and 10 age and gender matched healthy controls were included in the study. All patients received bifrontotemporal ECT and were scanned a total of four times with a 3 Tesla MRI scanner. On average the patients received 12 ECT sessions. They were scanned 24-48 hours before the first ECT (fMRI 1), 24-48 hours after the first ECT (fMRI 2), 24-48 hours after the ninth ECT (fMRI3) and 15 days after the last ECT (fMRI 4). Healthy controls were scanned twice, 5 weeks apart. Resting state functional connectivity (FC) scans were acquired with an 8 channel head coil. ECT’s effect on FC was assessed by seed based analysis. Four ROIs were selected, left and right laterobasal amygdala (lbA) and left and right superficial-centromedial nuclei of the amygdala (sf/cmA). Left and right anatomical masks of FC target regions were generated for sgACC and DLPFC. Comparison time points were from fMRI1 to fMRI2, from fMRI1 to fMRI3 and from fMRI1 to fMRI4. Additionally, the Hamilton Rating Scale for Depression (HSRD) was used to assess clinical
response to ECT. The HSRD score was used in a PATH analysis to test the association between clinical response and FC changes. PATH analysis allows testing of the effect of both indirect and direct variables on an outcome of interest. In this study, they tested the direct and indirect effects of ECT on functional connectivity changes during early and late treatments. Additionally, they also tested the direct and indirect effects of functional connectivity changes on clinical outcome (Cano et al., 2015).

FC analysis (Figure 7) found that patients had a decreased FC between right sf/cmA and left sgACC after fMRI2 and remained significant after fMRI3. An increased FC between right sf/cmA and right DLPFC was also observed after fMRI3 (Cano et al., 2015). Healthy controls showed no significant difference in FC between their two scans. PATH analysis yielded three direct findings (Figure 8). Firstly, the decrease in right sf/cmA to left sgACC FC after fMRI2 was directly associated with the decrease in sf/cmA to left sgACC FC after fMRI3. Secondly, the decrease in sf/cmA to left sgACC FC after fMRI3 was directly associated with the increased FC in right sf/cmA to right DLPFC after fMRI3. Lastly, increased FC in right sf/cmA to right DLPFC after fMRI3 was directly correlated to clinical improvement after fMRI4. Several indirect findings were also reported (Figure 8). Decreased FC in right sf/cmA to left sgACC after fMRI2 was indirectly associated with increased FC in right sf/cmA to right DLPFC after fMRI3 and clinical improvement. Decreased FC in right sf/cmA to left sgACC after fMRI 3 was also indirectly associated to clinical improvement (Cano et al., 2015).
Figure 7. Functional Connectivity Changes in Patients. Functional connectivity was evaluated over 9 electroconvulsive therapy (ECT) sessions. fMRI2 – fMRI1: functional magnetic resonance imaging (fMRI) FC differences between before first ECT treatment (fMRI1) and after the first ECT treatment (fMRI2). fMRI3 – fMRI1: FC differences between fMRI scan after the ninth ECT treatment (fMRI3) and before the first ECT treatment (fMRI1). Color bars on the left indicate t value. (A). FC between right superficial-centromedial amygdala (sf/cmA) and left subgenual anterior cingulate cortex (sgACC) decreased (both in red). (B). FC between right sf/cmA and left sgACC decreased (red region). (C). FC between right sf/cmA and right dorsolateral prefrontal cortex (DLPFC) increased (blue region). Figure modified from Cano et al., 2015.
Figure 8. Effects of Functional Connectivity Change on Electroconvulsive Therapy Clinical Outcome. Decreased FC in right superficial - centromedial amygdala (rsf/cmA) and left subgenual anterior cingulate cortex (LsgACC) after functional magnetic resonance imaging after first ECT (fMRI2) directly correlated to decreased FC in rsf/cmA and LsgACC after fMRI after 9th ECT treatment (fMRI3). Decreased FC in rsf/cmA and LsgACC after fMRI3 is directly correlated to increased FC in rsf/cmA and right dorsolateral prefrontal cortex (rDLPFC) after fMRI3. Increased FC in rsf/cmA and right dorsolateral prefrontal cortex (rDLPFC) after fMRI3 directly correlated to clinical improvement at fMRI 15 days post last ECT treatment (fMRI4). Decreased FC in rsf/cmA and LsgACC after fMRI2 indirectly correlated to increased FC in rsf/cmA and rDLPFC after fMRI3. Decreased FC in rsf/cmA and LsgACC after fMRI3 indirectly correlated to clinical improvement at fMRI4. Figure modified from Cano et al., 2015.

Magnetic resonance spectroscopy: Glutamate and GABA

Michael et al., 2003

Michael et al. conducted a study in 2003 to look at whether ECT normalized glutamate disruptions in the left DLPFC in patients with severe
treatment resistant unipolar depression (Michael et al., 2003). Twelve patients and 12 age and gender matched controlled were included in the study. The patients were treated with brief pulse ECT and they received a mean of 10 ECT treatments in total. Magnetic resonance spectroscopy (MRS) measurements in patients were taken 2 days before the first ECT treatment and at least 30 hours after the last ECT treatment (1-3 days). Healthy controls were scanned once. Measurements were done at 1.5 Tesla field strength and single voxel stimulated echo acquisition mode (STEAM) spectroscopy was used. Post processing of MRS signals was done with linear combination (LC) model. Glutamate, GABA and glutamine concentrations were measured together as “Glx” due to the difficulty of separating these overlapping resonances at the given field strength (Table 2, Figure 9).
Table 2. Metabolite levels in Left Dorsolateral Prefrontal Cortex. Metabolite levels reported for controls, pre-electroconvulsive (pre-ECT) and post-ECT patients with major depression groups. Glx - glutamine/glutamate/GABA. CSF – cerebrospinal fluid. NAA – N-acetylaspartate – NAA. Cho – Choline. Cr - Creatine. ECT non-response patients were those who did not respond to 10 consecutive treatments. * Significantly different from controls. **Significantly different from pre-ECT measurements. Table modified from Michael et al., 2003.

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<tr>
<td>Cr (IU)</td>
<td>4.4±1.6</td>
<td>3.1±0.8</td>
<td>3.5±0.5</td>
<td>3.6±1.4</td>
</tr>
</tbody>
</table>

Figure 9. Combined Glutamine/Glutamate/GABA Level Following Electroconvulsive Therapy. Responders are patients who responded to 10 ECT treatments. Their Glx was significantly increased after treatment. Non-responders are patients who did not respond to 10 ECT treatments and showed low or good response after additional treatments. Glx increased in patients who showed response to additional treatments. Figure modified from Michael et al., 2003.
Pfleiderer et al., 2003

A study by Pfleiderer et al. in 2003 assessed Glx changes in the left ACC in patients with MDD before and after ECT (Table 3) (Pfleiderer et al., 2003). A total of seventeen patients and seventeen age and gender matched controls were included in the study. MRS measurements were taken before ECT and 24-48 hours after the last ECT in the patient group. Healthy controls underwent two MRS measurements, 5 months apart to assess the reproducibility of the Glx measurements. The patients received on average 13 ECT brief pulse treatments in either unilateral or bilateral administration. MRS measurements were done with single voxel STEAM spectroscopy at 1.5 Tesla field strength. Analyses were done with LC model program package. Similar to Michaels et al., Pfleiderer et al. also examined Glx concentration due to the difficulty of separating the overlapping resonances of glutamate, glutamine and GABA at 1.5 Tesla. The assumption is made as glutamate concentration is much higher than GABA or glutamine levels in each 1 mmol/kg of brain tissue (Figure 10) (Pfleiderer et al., 2003).
Table 3. Metabolite Changes in Anterior Cingulate Cortex Following Electroconvulsive Therapy. Voxel composition and metabolite levels (in institutional units (IU)) in the anterior cingulate cortex in patients with depression before and after electroconvulsive therapy (ECT) and healthy controls. a. Significantly different from controls. b. Significantly different from pre-ECT measurements. Glx – glutamate/glutamine/GABA. NAA – N-acetylaspartate. Cho – choline. Cr – creatine. CSF – cerebral spinal fluid. Only Glx levels significantly changed after ECT responders. Significant reduction in Glx is seen in pre-ECT patients compared to healthy controls. Table modified from Pfleiderer et al., 2003.

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Controls (n=17)</th>
<th>Patients pre-ECT (n=17)</th>
<th>ECT non-responders (n=7)</th>
<th>Patients ECT responders (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA (IU)</td>
<td>6.6±2.5</td>
<td>5.8±2.3</td>
<td>6.0±1.8</td>
<td>6.1±1.1</td>
</tr>
<tr>
<td>Glx (IU)</td>
<td>12.3±5.3</td>
<td>4.2±3.0</td>
<td>4.0±3.8</td>
<td>10.1±7.4^b</td>
</tr>
<tr>
<td>Cho (IU)</td>
<td>1.4±0.5</td>
<td>1.2±1.5</td>
<td>0.90±0.3</td>
<td>1.0±0.3</td>
</tr>
<tr>
<td>Cr (IU)</td>
<td>4.9±1.5</td>
<td>4.3±1.5</td>
<td>5.3±1.9</td>
<td>4.9±1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Controls (n=17)</th>
<th>Patients pre-ECT (n=17)</th>
<th>Patients post-ECT (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray matter (%)</td>
<td>64.7±10.0</td>
<td>61.6±6.5</td>
<td>62.3±4.2</td>
</tr>
<tr>
<td>White matter (%)</td>
<td>29.2±10.0</td>
<td>28.1±3.7</td>
<td>28.0±4.4</td>
</tr>
<tr>
<td>CSF (%)</td>
<td>6.0±4.6</td>
<td>9.9±4.3^a</td>
<td>9.6±3.4</td>
</tr>
</tbody>
</table>
Figure 10. Combined Glutamate/glutamine/GABA Level Following Electroconvulsive Therapy. * - Post-ECT. Patients before ECT showed significantly lower glutamate/glutamine/GABA (Glx) levels compared to controls. Patients who responded to ECT (response) showed a significantly increased Glx compared to pre-ECT. Levels match that of healthy controls. Figure modified from Pfleiderer et al., 2003.

Metabolite and voxel composition results are shown in Table 3. The pre-ECT patient population showed a 67% reduction in Glx levels in the left ACC compared to healthy controls (Pfleidere et al., 2003). Patients also showed a significantly higher CSF fraction than healthy controls. Grey matter (GM) fraction was not reduced in patients compared to healthy controls. Patients who was responsive to ECT treatments (n=12) showed a significant increase in Glx in the
left ACC compared to their baseline Glx level and was no longer statistically
different from healthy controls (Figure 10). In contrast, non-responding patients
did not show Glx increase. Nonresponders were given additional antidepressant
treatments and was remeasured after response. They showed significantly
increased Glx compared to baseline.

**Sanacora et al., 2003**

Sanacora et al. examined the effect of ECT on GABA levels in the
occipital lobe in depressed patients (Sanacora et al., 2003). Eight subjects with
major depression were included in this study. Patients were treated with either
bilateral (n=7) or unilateral ECT (n=1). The mean number of treatments per
patient was 8.5. MRS measurements were taken before ECT treatments and at
least 1 day after the last ECT treatment. One patient’s post-ECT MRS
measurement was made 46 days after the last ECT treatment. A 2.1 Tesla
magnet bore with a Bruker Avance spectrometer was used for MRS
measurements. GABA resonance editing was performed using a J editing pulse
sequence.

Figure 11 depicts the significantly increased GABA concentration in the
occipital lobe after ECT (Sanacora et al., 2003). Seven out of eight subjects
showed increased cortical GABA concentrations after ECT treatments, four
patients had increases of over 85%. Seven out of eight patients also showed
significantly decreased seizure duration over the course of ECT treatment.
Although two patients showed complete remission and five patients showed partial response, there was no significant correlation between clinical response and change in cortical GABA concentrations.

Figure 11. Gamma Aminobutyric Acid Level Following Electroconvulsive Therapy. GABA levels in the occipital cortex of patients before and after they received electroconvulsive therapy (ECT). Each line indicates a distinct patient. Figure taken from Sanacora et al., 2003.

Merkel et al., 2011

The 2011 MRS study by Merkel et al. looked at the absolute levels of different metabolites between patients with depression and healthy controls. They hypothesized that patients will have lower levels of glutamate and NAA at baseline compared to healthy controls and these levels will normalize after
remission (Merkl et al., 2011). A total of 25 patients and 27 age and gender matched healthy controls were included in the study. Patients were treated with right unilateral ultrabrief pulse ECT, with exception for two patients, who received bilateral and brief pulse ECT. All patients received at least 9 ECT treatments. For patients who did not show response to treatment, ECT was continued for them until clinical response is observed (continuation phase). The investigators defined response to treatment as a 50% reduction in the Hamilton Depression Rating Scale (HDRS). There were three time points where clinical and/or MRS measurements were made, at baseline (T0), after 9 ECT treatments (T_acute), and after the last continuation ECT treatment (T_1). MRS measurements were done at T_0 and T_acute in patients. Healthy controls were scanned once. All MRS measurements were made with a 3 Tesla scanner and spectroscopy was recorded from the left DLPFC and ACC (Merkl et al., 2011).

For the patient population, 32% showed clinical response after 9 ECT treatments and 68% showed response after additional continuation treatments (Merkl et al., 2011). Comparing patients at baseline to healthy control MRS data, no significant differences in metabolite levels were found in the left DLPFC (Table 5). However, patients showed a decrease in NAA and glutamate levels in the ACC compared to healthy controls (Table 4). Upon closer examination, reduction of NAA and glutamate levels in the ACC was only significant between ECT responder and healthy controls. After ECT, only responder group showed a significant decrease in NAA in the left DLPFC and an increase in NAA in the
ACC. Through a correlation analysis, they found that high baseline glutamate level was correlated to a greater reduction in HDRS score at time T_1, which implied that higher glutamate level predicted better clinical response to ECT. Lastly, glutamate levels were found to correlate positively with NAA levels in ACC and DLPFC at baseline in all subjects (patients and healthy controls) (Figure 12).
**Table 4. Metabolite Levels in Anterior Cingulate Cortex.** tCho – total choline. tCr – total creatine. NAA – N-acetylaspartate, Glu – glutamate. ECT – electroconvulsive therapy. MDD – major depression. HC- healthy control. T0 – baseline. T_acute – after 9 ECT treatments. a & b = P < 0.05. Table modified from Merkl et al., 2011.

<table>
<thead>
<tr>
<th></th>
<th>All MDD</th>
<th>ECT</th>
<th>ECT</th>
<th>All MDD</th>
<th>ECT</th>
<th>ECT</th>
<th>p Value MDD</th>
<th>p Value ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HC at T0</td>
<td>T0</td>
<td>at T0</td>
<td>Patients at T0</td>
<td>at T0</td>
<td>Patients at T0</td>
<td>Responders</td>
<td>Nonresponders</td>
</tr>
<tr>
<td>tCho</td>
<td>2.40 ± .34</td>
<td>2.44 ± .37</td>
<td>2.44 ± .39</td>
<td>2.47 ± .42</td>
<td>2.43 ± .46</td>
<td>2.4 ± .54</td>
<td>2.42 ± .43</td>
<td>.75</td>
</tr>
<tr>
<td>tCr</td>
<td>10.4 ± 1.0</td>
<td>10.6 ± 1.1</td>
<td>10.6 ± 1.1</td>
<td>10.8 ± 1.03</td>
<td>10.3 ± 1.06</td>
<td>10.3 ± 1.1</td>
<td>10.3 ± .84</td>
<td>.49</td>
</tr>
<tr>
<td>NAA</td>
<td>13.1 ± 1.1</td>
<td>12.3 ± 1.1</td>
<td>12.2 ± 1.1</td>
<td>12.4 ± 1.3</td>
<td>12.6 ± 1.7</td>
<td>12.8 ± 1.9</td>
<td>11.8 ± 1.5</td>
<td>.005</td>
</tr>
<tr>
<td>Glu</td>
<td>14.9 ± 1.3</td>
<td>13.6 ± 1.0</td>
<td>13.6 ± .8</td>
<td>13.6 ± 1.5</td>
<td>13.7 ± 1.6</td>
<td>13.6 ± 1.8</td>
<td>13.82 ± 1.2</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Table 5. Metabolite Levels in Left Dorsolateral Prefrontal Cortex.** tCho – total choline. tCr – total creatine. NAA – N-acetylaspartate, Glu – glutamate. ECT – electroconvulsive therapy. MDD – major depression. HC- healthy control. T0 – baseline. T_acute – after 9 ECT treatments. Table modified from Merkl et al., 2011.

<table>
<thead>
<tr>
<th></th>
<th>All MDD</th>
<th>ECT</th>
<th>ECT</th>
<th>All MDD</th>
<th>ECT</th>
<th>ECT</th>
<th>p Value MDD</th>
<th>p Value ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HC at T0</td>
<td>T0</td>
<td>at T0</td>
<td>Patients at T0</td>
<td>at T0</td>
<td>Patients at T0</td>
<td>Responders</td>
<td>Nonresponders</td>
</tr>
<tr>
<td>tCho</td>
<td>1.84 ± .26</td>
<td>1.78 ± .23</td>
<td>1.75 ± .25</td>
<td>1.85 ± .20</td>
<td>1.76 ± .32</td>
<td>1.71 ± .33</td>
<td>1.88 ± .25</td>
<td>.35</td>
</tr>
<tr>
<td>tCr</td>
<td>9.45 ± .96</td>
<td>9.27 ± .79</td>
<td>9.41 ± .85</td>
<td>8.96 ± .59</td>
<td>8.97 ± 1.16</td>
<td>9.06 ± 1.27</td>
<td>8.79 ± .94</td>
<td>.45</td>
</tr>
<tr>
<td>NAA</td>
<td>12.7 ± 1.4</td>
<td>12.1 ± 1.5</td>
<td>12.1 ± 1.6</td>
<td>11.9 ± .98</td>
<td>11.2 ± 1.5</td>
<td>11.3 ± 1.68</td>
<td>11.3 ± 1.6</td>
<td>.11</td>
</tr>
<tr>
<td>Glu</td>
<td>10.2 ± 1.6</td>
<td>9.85 ± 1.95</td>
<td>9.84 ± 2.09</td>
<td>9.89 ± 1.7</td>
<td>10.5 ± 2.0</td>
<td>10.4 ± 1.78</td>
<td>10.7 ± 2.7</td>
<td>.53</td>
</tr>
</tbody>
</table>
Figure 12. Correlation of Hamilton Depression Rating Scale Score and Glutamate Level. Glutamate level reported from the anterior cingulate cortex of patients. Higher glutamate levels at baseline predicted a greater reduction in the seventeen itemed Hamilton Depression Rating Scale Score (HDRS-17) score after electroconvulsive therapy (ECT). Figure taken from Merkl et al., 2011.
DISCUSSION

Major depressive disorder (MDD) is characterized by ongoing feelings of guilt, sadness and worthlessness, as well of memory, cognition, sleep and motivation impairment and even vulnerability to physical pain (Horn et al., 2010; Hecht et al., 2010). It is a multidimensional illness that affects “discrete, but functionally integrated, [brain] pathways” (Mayberg et al., 2003). Understanding the underlying brain dysfunction that gives rise to this complex illness has been challenging, and by extension the search for appropriate treatments. Currently, only about 50% of patients who suffer from major depression show a sustained response to one form of pharmacological antidepressant (Husain et al., 2002). As such, patients who fail to respond to “at least two adequate trials of medications from different classes in the current episode” (Rush et al., 2003) are considered treatment resistant. These patients may suffer from an underlying metabolic disorder that prevents pharmacological interventions from being properly dosed or that they show a much more delayed response to conventional antidepressant medications and thus failed to show response within the expected time frame (Rush et al., 2003). These patients make up the primary population that receives electroconvulsive therapy (ECT) for major depression. Remarkably, ECT shows a 75% remission rate (Husain et al., 2004; Hermann et al., 1995; Weiner et al., 2001) in this patient population and is considered the “gold standard” treatment for major depression (Abbott et al., 2013). Although the exact mechanism of its
function is unknown, it is well accepted that the induced grand-mal seizure confers its therapeutic effect (Fink, 2008). The seizure likely has broad effect that somehow corrects the underlying dysfunction in brain circuitry. Here, we specifically examined studies of functional connectivity and metabolite changes.

Perrin et al. found that after bilateral ECT treatments, patients with major depression showed an overall reduction of functional connectivity (FC) from the left dorsolateral prefrontal cortex (DLPFC) to other cortical and limbic structures. Hyperconnectivity in this area has been found in major depression, and therefore ECT may attenuate the pathological connectivity. In addition, it is interesting that their finding is localized to the left side of the brain as interhemispheric activity asymmetry is well documented in mood disorder (Hecht et al., 2010). In depression, it has been found that the right hemisphere is hyperactive, while the left hemisphere is hypoactive. This imbalance is associated with a tendency to focus attention inwards and towards fearful and sad stimuli, causing a deep sense of negativity (Hecht et al., 2010). The interesting laterality of ECT’s therapeutic effect found in Perrin et al.’s study is supported by Wei et al.’s and Beall et al.’s studies. Wei et al. found that correlated activity between the superior frontal gyri, middle frontal gyri and angular gyri were significantly increased after ECT. Increased coordination between the middle frontal gyri, an area known for emotion regulation (Wei et al., 2014), was correlated to reduction of depressive symptoms. Additionally, Wei et al. found an increased coordination in the angular gyrus after ECT, a key component to the default mode network (DMN), is in
agreement to findings of decreased metabolism, blood flow and coherence based regional homogeneity in this area in depressed patients. Beall et al. found that after ECT, hyperdeactivation of the orbitofrontal cortex to negative emotional stimuli was decreased in patients, and this decrease was also associated with improvement in depressive symptoms (Beall et al., 2012). These studies suggest that ECT’s therapeutic effect is in rebalancing the functional asymmetry between the hemispheres and normalizing hyperactive areas.

Liu et al. found increased regional activity in the subgenual ACC (sgACC) in treatment naïve patients after ECT and increased functional connectivity between the sgACC and left hippocampus that was correlated to reduction of depressive symptoms (Liu et al., 2015). Cano et al. found reduced connectivity between the amygdala and sgACC and increased connectivity between the amygdala and DLPFC in patient by sequential assessments over a course of ECT treatments (Cano et al., 2016). These results are consistent with abnormalities found in MDD. Patients show reduced activity in limbic areas, specifically reduced metabolism, grey matter volume in the sgACC (Liu et al., 2015). The sgACC has been implicated as a major area of dysfunction in major depression and is responsible for mediating emotional and autonomic responses to external stimuli (Drevets et al., 1997). Therefore, increasing deficiency activity from the sgACC might be part of the therapeutic effects of ECT. Additionally, hyperconnectivity between the amygdala and sgACC and hypoconnectivity between limbic and PFC are also well documented in depression (Cano et al.,
2016; Kupfer et al., 2012; Kaiser et al., 2015). Hypoconnectivity between limbic and PFC has been attributed to poor cognitive control seen in patients and their tendency to fall into negative ruminations (Kaiser et al., 2015). Last but not least, Abbott et al. found that ECT increased the functional connectivity between DLPFC and the default mode network (DMN) (Abbott et al., 2013). The DLPFC has been implicated in cognitive deficits observed in patients with depression (Abbott et al., 2013). The DMN includes multiple brain regions that are found to be involved in emotional processing, introspection and endocrine regulation, and hyperactivity of the DMN in depression can result in overactive rumination (Sheline et al., 2009). The increased connectivity between prefrontal areas and the DMN found in Cano et al. and Abbott et al.’s studies points to ECT’s role in the restoration of top/down, executive control of the cognitive brain over these areas (Sanacora et al., 2012). However, it is more likely that ECT confirms the involvement of both cortical and subcortical structures in the depressed state and that normalization of the connectivity in these networks conveys the therapeutic mechanism of grand-mal seizures.

The changes in connectivity observed after ECT treatments suggest its role in neuroplasticity, such that it enhances weakened connections while attenuates hyperconnectivity. Although the correlation between functional and structural connectivity is not absolute, there is evidence that areas that are closer in proximity tend to show stronger correlated functional activity (Honey et al., 2009). Therefore it is likely that a change in connectivity reflects a change in
physical connections between neurons. Given the anatomical basis for functional connectivity, it is interesting that ECT induces changes at the neuronal level. This effect can be seen in metabolite studies from magnetic resonance spectroscopy (MRS), specifically the major excitatory and inhibitory neurotransmitter systems, glutamate and GABA respectively. The use of MRS to examine total tissue metabolite levels in the brain bypasses the confounding factors usually associated with postmortem and plasma studies, and allows for direct measurement in living brain tissue (Sanacora et al., 2012).

It is well established that the brain undergoes significant synaptic remodeling during early years of development. Through learning, new experiences and emotional processing, areas of the brain is still continuously remodeled in adulthood (Sanacora et al., 2012). However, the brain is equally susceptible to changes induced by good experiences as it is by bad, such as stress. It has been shown that stress causes neuronal remodeling, atrophy and retraction, especially in early years of life (Sanacora et al., 2012). These negative neuroplastic changes likely contribute to the development of depressive disorders. In the glutamate system, it has been shown that induced stress, in the form of cortisone injection, causes excessive glutamate release in prefrontal cortices (Sanacora et al., 2012). This excessive release can cause toxic cellular neurodegeneration and contribute to grey matter volume loss observed in mood disorders (Krystal et al., 2001; Sanacroa et al., 2012; Brambilla et al., 2003).

Additionally, drastic increases in glutamate release can also cause exhaustion of
the glutamate system and lead to decrease in glutamate levels overtime (Michael et al., 2003). MRS studies of glutamate and depression consistently demonstrate reduced glutamate levels in the PFC and cingulate cortex in depressed patients (Sanacora et al., 2012). Concurrently, deficit in the GABA system has also been implicated in depression. Neuroplastic changes in the GABA transmission system have also been observed in stress models, where stress induced significant changes in the expression and function of GABA receptors in the adult brain (Luscher et al., 2011). In depression, decreased levels of GABA and downregulation of its receptors in areas of the cingulate cortex, PFC and hippocampus have been found (Luscher et al., 2011; Brambilla et al., 2003). Additionally, GABA has also been shown to modulate the activity of several major monoamine systems that have long been the targets of pharmacological antidepressant treatments, they are the dopamine, norepinehrine and serotonin systems (Luscher et al, 2011).

Therefore, we thought to examine MRS literature on ECT’s effect on brain metabolites in depression. We found that studies by Pfleiderer et al., Michael et al. and Merkl et al. all confirmed decreased levels of glutamate or glx (glutamate/glutamine/GABA) in patients in the ACC and DLPFC (Pfleiderer et al., 2003; Merkl et al., 2011; Michael et al., 2003). Additionally, Michael et al. and Pfleiderer et al. found that glx levels increased after ECT treatments and that this increase was only found in responders (Pfleiderer et al., 2003; Michael et al., 2003). These findings on the normalization of glutamate in only responders are
consistent with literature on mood disorder. Sanacora et al. found that GABA levels increased after ECT treatment in the occipital cortex (Sanacora et al., 2003). This result is consistent with both literatures on mood disorder as well as the anticonvulsive properties of ECT. Such that increases in GABA levels are associated with increased seizure threshold during a course of ECT treatment (Sackheim et al., 1999; Sanacora et al., 2003). Together, these results suggest that ECT demonstrates neuromodulatory effects on both excitatory and inhibitory synaptic transmission. These effects are likely mediated through either the direct change in neurotransmitter release, which causes downstream synaptic remodeling or through the alteration of neuronal density in these systems.

Results from functional connectivity and brain metabolite studies in patients with major depression point to induced neuroplasticity as part of ECT’s therapeutic mechanism. Remodeling connectivity and mediating metabolite changes both will require modifications at the synaptic level. The wide spread changes seen in several different brain regions that have been implicated in depression further suggests that ECT’s effects are both highly specific and broad. However, these results must be taken with caution. Since the patient population studied in ECT is often severely depressed (Kellner et al., 2015), they are likely to have been prescribed many types of pharmacotherapy and are often kept on medications while receiving ECT treatments. The effects of these medications on connectivity and metabolite changes can be complex and extremely difficult to assess. The sample sizes of these studies are often very
small, studies of larger sample sizes are needed to extrapolate these findings to the general patient population. The ECT treatment parameters across studies are also difficult to standardize, as the therapeutic effect will vary from patient to patient. Last but not least, MRS data should be interpreted with extra caution as most studies examined here were performed at relatively low field strength. Therefore, many studies examined the combined peaks of glutamate, glutamine and GABA. Although the glx signal is mostly dominated by glutamate levels, the effect of other metabolites on this signal cannot be fully discounted. Additionally, MRS measures provide the total level of the metabolites in the brain, which includes both intracellular and intercellular concentrations, therefore, conclusions about metabolite levels involved in actual neurotransmission is difficult to make. Nonetheless, consistencies shown in these studies are promising and provide a good foundation for further magnetic resonance imaging studies of ECT’s therapeutic mechanism in depression.
CONCLUSION

Depression is a multidimensional illness that affects multiple brain circuits. Early life stressors can cause maladaptive synaptic modeling that predisposes the formation of mood disorders. As such, treatments that target specific neural systems, such as monoamine based antidepressants, often produces very limited responses in patients and a high relapse rate. Development of antidepressant treatments that matches the widespread dysfunction seen in mood disorder is highly valuable. Electroconvulsive therapy has consistently demonstrated impressive efficacy among the most severely depressed patients and is known to produce widely distributed effects in the brain. However, this also makes assessing its therapeutic mechanism challenging. Magnetic resonance imaging studies assessing functional connectivity and brain metabolite levels have demonstrated that ECT likely produces neuroplastic changes to remodel aberrant connectivity and dysfunctional excitatory and inhibitory neurotransmission in cortical and limbic areas. Although these findings should be interpreted with caution, this field of research has provided an unprecedented opportunity to examine the living brain in great detail. Further studies with larger sample sizes and improved technical specifications will likely yield stronger results.
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CURRICULUM VITAE

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EDUCATION

Master of Science in Medical Sciences May 2016
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Bachelor of Arts in Neuroscience May 2011
Boston University; Boston, MA

RESEARCH EXPERIENCE

Somatic Therapies Laboratory July 2015 - Present
Department of Psychiatry, Massachusetts General Hospital

Clinical Research Coordinator (40 hours/week)

• Extracted and analyzed data from patient charts of electroconvulsive therapy (ECT) services at McLean Hospital and Massachusetts General Hospital
• Built REDCap clinical database for ECT study in catatonia. Imported patient data onto REDCap and performed data extraction for statistical analysis.
• Built REDCAP clinical database for MGH ECT patient services. Setup questionnaires for electronic administration onsite.
• Collaborated with researchers and librarians to perform a systematic review of literature on medications to attenuate hyperdynamic effects of ECT treatment.
• Managed administrative duties of the laboratory such appointment scheduling and performing period literature searches. Maintained institutional regulatory documentation.

Laboratory for Neuroimaging of Anxiety & Respiratory Psychophysiology May 2011 – June 2013
Department of Psychiatry, Massachusetts General Hospital

Clinical Research Coordinator (40 hours/week)

• Responsible for participant recruitment. Conducted over 200 phone diagnostic screen interviews. Assisted in the study of 50+ participants in challenging multiple-visit research protocols. Assisted in data collection for human studies of respiratory symptom provocation during functional magnetic resonance imaging (fMRI) at 3 Tesla and at ultra-high field strength (7 Tesla).
• Independently calibrated vital-signs and physiological monitoring equipment. Applied monitor electrodes/sensors to participants prior to experiments.
• Pre-processed and analyzed physiological and neuroimaging data with Matlab based scripts and SPM8 software on Linux workstations.
• Facilitated the successful operation of collaborative fMRI projects that involved respiratory provocation in human subjects.
• Managed administrative duties of the laboratory: scheduled participants and shared equipment resources, data management. Maintained institutional regulatory documentation.

**Neural Prosthesis Laboratory**  
**Department of Speech, Language and Hearing Sciences, Boston University**  
*Undergraduate Research Assistant*  
(20 hours/week)

• Assisted in the design of EEG/Electromyography (EMG) experiments to examine breathing patterns during covert and overt speech in patients with locked-in syndrome.
• Recruited research participants and performed pilot study in Matlab to improve protocol design and to test respiratory monitoring equipment, ancillary amplifiers and audio recordings.

**Laboratory for Developmental Studies**  
**Harvard University**  
*Undergraduate Research Assistant*  
(20 hours/week)

• Recruited and tested research participants ages 5 – 10 to study early pronoun usage in English.
• Assisted in protocol design for eye-tracking study of pronoun usage in Mandarin Chinese.
• Analyzed eye-tracking data from 22 subjects in Mandarin Chinese pronoun study and organized final laboratory presentation.

**VOLUNTEER EXPERIENCE**

**Women’s Education, Rosie’s Place**  
*Volunteer ESL Teacher*  
(5 hours/week)

• Taught basic English reading and writing skills to a class of 10 pre-literacy women biweekly.
• Independently developed teaching curriculum, in-class exercises and homework assignments through web search of free ESL resources and pre-literacy material.

**Department of Neurology,**  
**New York Presbytarian Hospital**  
May 2009 – August 2009
Volunteer (30 hours/week)

- Attended to neurology patients and family members by resolving emergency call bells and delivering basic amenities.
- Helped clean and feed patients. Learned skills for developing rapport in long-term patients via quality of life counseling sessions.

PRESENTATIONS


PUBLICATIONS


ABSTRACTS