Neural Mechanisms and Cognitive Outcomes of Electroconvulsive Therapy: A Transdiagnostic Approach

by

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Abstract

Introduction. Electroconvulsive therapy (ECT) is an effective treatment for severe mental health disorders (e.g., depression, psychosis). However, cognitive side effects and neural mechanisms underlying its therapeutic effect are not well understood. This study aims to probe the mechanisms of ECT using transcranial magnetic stimulation (TMS) and investigate cognitive outcomes in a diverse psychiatric population. Methods. Sixteen individuals receiving ECT completed three assessments (baseline/72-hrs post-/1-month post-ECT). Clinical symptoms were assessed and cognition was measured with the Montreal Cognitive Assessment (MoCA) and ElectroConvulsive therapy Cognitive Assessment (ECCA). Nine of those individuals underwent TMS to probe cortical inhibition and excitation. Results. Clinical symptoms significantly improved following ECT. MoCA scores significantly declined 72-hrs post-ECT, while ECCA scores were unchanged. Cortical inhibition significantly increased post-ECT and was correlated with cognitive and clinical changes. Conclusion. Our findings suggest that cortical inhibition is involved in the mechanisms of ECT and potentially linked to clinical and cognitive outcomes.
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1. Introduction

Around the world, mental health illnesses are extremely prevalent. Globally, in 2017, the prevalence of depression was over 264 million, with over 163 million of those diagnoses being major depressive disorder (MDD; James et al., 2018). This high prevalence has led to depression being the leading cause of disability, low quality of life, and suicide (Friedrich, 2017). In 2019, over 19 million people had a diagnosis of schizophrenia and over 45 million people had a diagnosis of bipolar disorder (James et al., 2018). Globally in 2020, rates of depression increased by 27.6% (Santomauro et al., 2021) likely due to the onset of the COVID-19 pandemic. During the COVID-19 pandemic suicidal thoughts, suicide attempts, and self-harm increased compared to pre-pandemic studies (Dubé et al., 2021). These staggering statistics highlight the importance of continuing research into mental health treatments to improve the lives of individuals living with these illnesses.

Depression can be effectively treated with antidepressants, although it can take considerable time to find the correct medication and dosage, and can take 4-8 weeks to show the full effect (Health Quality Ontario, 2016). Approximately 50% of individuals with depression fail to achieve response after one course of antidepressant treatment and 70% of individuals fail to achieve remission (Health Quality Ontario, 2016). In addition, approximately 35% of individuals still fail to achieve response after two courses of adequate antidepressant treatment (Health Quality Ontario, 2016), which is referred to as treatment resistance (Souery et al., 1999). For individuals with schizophrenia, between one fifth to one half are treatment resistant and only 30-60% of those individuals will respond to clozapine, a last line medication for schizophrenia (Nucifora et al., 2019). The standard treatment for bipolar disorder is pharmacological therapies (Harrison et al., 2016), such as mood stabilizers, atypical antipsychotics, and conventional antidepressants (Geddes & Miklowitz, 2013; McCormick et al., 2015). Although pharmacological treatments can be very helpful, some individuals may experience significant side effects and some remain treatment resistant (Harrison et al., 2016).

Depression and other severe mental health disorders are one of the main risk factors for suicide (National Institute of Mental Health, 2021), but despite high life losses, suicide mortality rate has seen little progress in many high resourced settings since
the year 2000. In fact, between 2000 and 2019 the suicide mortality rate for high income countries declined by less than 5%. In addition, the suicide rate in the Region of the Americas increased by 28% between 2000 and 2019, and the European Region still has the highest suicide death rate despite a 40% decline in the past two decades (World Health Organization, 2021). Therefore, it is crucial to provide effective treatment to diminish suicide risk and to treat populations with treatment resistant severe mental health disorders. One treatment, developed decades ago, that has shown great promise for treating severe mental health disorders and suicidal ideation is electroconvulsive therapy (ECT).

ECT can be an effective treatment for individuals who are treatment resistant and individuals with active suicidal ideation (Health Quality Ontario, 2016; Kellner, Knapp, et al., 2010; Kennedy et al., 2009; Li et al., 2020; Nucifora et al., 2019; Schoeyen et al., 2015). During ECT, a series of high frequency electrical pulses are delivered to the cortex through electrodes placed on the skull. This results in pyramidal cells firing, creating generalization of cortical activity which produces generalized tonic-clonic seizures, lasting between 30-60 seconds (Voineskos et al., 2016). Although a very promising treatment, ECT has been associated with a strong stigma (Case et al., 2013) and the mechanisms of action are not well understood. Therefore, the purpose of this study was to better understand ECT in the hopes of reducing this stigma and improving treatment outcome. Specifically, we investigated the neural mechanisms of ECT and explored the clinical and cognitive outcomes of treatment.

1.1 Electroconvulsive Therapy

1.1.1 History

The concept of ECT dates back centuries to the notion that convulsions may promote wellness (Payne & Prudic, 2009). In the 1930s, when it was discovered that individuals with a diagnosis of schizophrenia rarely experience seizures, epilepsy was induced in patients using chemicals, in an attempt to cure schizophrenia. Due to unpleasant sensations of convulsions induced by chemicals, the concept of applying electricity to the heads of people with mental health disorders was developed. In 1938, two Italian scientists successfully delivered ECT to a man with a diagnosis of schizophrenia to cure his delusions (Payne & Prudic, 2009; Suleman, 2020; Swartz,
Since then, ECT administration has seen many advancements such as shortened stimulus duration, which reduces post procedure aphasia, cognitive blunting, and recovery time, and in 1952, anesthesia was added which improved comfort and tolerability (Suleman, 2020).

### 1.1.2 Clinical Efficacy and Main Side Effects

ECT has been shown to be effective for all subtypes of MDD (Kennedy et al., 2009) including MDD with psychotic features (Petrides et al., 2001). ECT has also been shown to be effective for typical and atypical depression (Husain et al., 2008), bipolar depression (Grunhaus et al., 2002), depression with prominent suicidal ideation (Kellner et al., 2005), and is considered the most effective treatment for severe depression that has not responded to other treatments (Health Quality Ontario, 2016; Li et al., 2020). For treating schizophrenia, it has proven effective for individuals who are clozapine-resistant (Nucifora et al., 2019). ECT has also shown to be more effective than pharmacological treatments for treatment resistant depression in individuals with a diagnosis of bipolar disorder (Schoeyen et al., 2015). In addition, ECT has been indicated as a first line treatment for active suicidal ideation (Kennedy et al., 2009). ECT has also been shown to be an effective treatment for anxiety (Huang et al., 2019), although there is very limited research on the effects of ECT on anxiety. There is also very limited evidence for the effect of ECT on substance use disorders, although one study reported four out of six participants with substance use disorder, including one with alcohol use disorder (AUD), remained abstinent for over five years following ECT and chlorpromazine therapy (Roper, 1966).

Despite being considered the most effective treatment for severe depression, only around 65% of individuals with MDD will respond to ECT treatment and only about half will achieve remission (Health Quality Ontario, 2016). Response and remission rates are similar for other disorders including schizophrenia, catatonia, and mania (Rosenquist et al., 2018). In addition, there are often cognitive side effects associated with treatment, such as autobiographical memory loss (Kennedy et al., 2009; Napierala et al., 2019; Semkovska & Mcloughlin, 2010). Therefore, research into mechanisms to better understand the treatment is crucial, especially given the cognitive side effects that are associated with ECT.
1.1.3 Parameters

As mentioned, during ECT electrical pulses are sent through the cortex using electrodes placed in various locations on the individual's head. The three most common electrode placements are bilateral (or bitemporal), right unilateral, or bifrontal (Kellner, Tobias, et al., 2010), all of which have been shown to have clinically and statistically significant antidepressant effects (Kellner, Knapp, et al., 2010). Bilateral placement consists of two electrodes symmetrically placed on each temple. This placement is has been considered the most efficacious and is often used in situations that require a quick response, such as acute mania, catatonia, and high levels of suicidal ideation (Kellner, Knapp, et al., 2010; Kellner, Tobias, et al., 2010). The more severely ill (in terms of mental and physical health) a patient is, the more likely they will receive bilateral electrode placement (Kellner et al., 2012). Right unilateral ECT consists of one electrode placed on the right side of the head, near the right temple, and the second electrode is placed to the right of the middle point on the top of the skull (Kellner, Tobias, et al., 2010). This placement has been shown to be dose sensitive, meaning that a higher electrical dose provides a more rapid and more efficacious antidepressant response (Sackeim et al., 1993). Bifrontal placement is when two electrodes are symmetrically placed on the forehead and has become increasingly employed because it is thought to be efficacious (Lawson et al., 1990; Letemendia et al., 1993). Another electrode placement, called left unilateral can also be used in specific cases such as if there is a skull defect over the right hemisphere (Warnell, 2004). Another placement consisting of electrodes placed on the right frontotemporal and left frontal areas was developed to minimize the cognitive effects of ECT while maintaining efficacy (Swartz, 1994). In one study it was shown to have high efficacy (Swartz, 1994) but beyond that, this placement has very limited evidence (Kellner, Tobias, et al., 2010).

Favourable electrode placement is highly controversial due to inconsistent findings of antidepressant efficacy (Kellner, Knapp, et al., 2010). To our knowledge, only two large multicentre randomized, blinded controlled trials have directly compared the clinical efficacy of bilateral, bifrontal, and right unilateral electrode placement. In a sample of 230 individuals with a diagnosis of MDD, bipolar or unipolar depression, it was found that each electrode placement was highly effective. Specifically, right
unilateral, bifrontal, and bilateral placements led to remission rates of 55%, 61%, and 64%, respectively. The only difference observed was bilateral placement led to a more rapid decline in symptom ratings early in treatment (Kellner, Knapp, et al., 2010). Su and colleagues (2019) also compared the efficacy of the three electrode placements in a sample of 120 individuals with a diagnosis of MDD. They concluded efficacy did not differ between the three groups (Su et al., 2019).

Regardless of the electrode placement, typical ECT stimulation, also called brief pulse stimulation, has an electrical stimulus of 0.5-1.5 milliseconds (Kellner et al., 2019). A common alteration is shortening the electrical stimulus to 0.5 or 0.3 milliseconds, which is called ultrabrief pulse stimulation. This results in more focal stimulation and has shown to retain the high efficacy of standard brief pulse ECT (Kellner et al., 2019; C. Loo, 2013).

1.1.4 Typical Treatment Schedule

As with electrode placement, treatment schedule and duration are dependent on the individual receiving treatment. A typical course of ECT for depression is administered two to three times per week for up to 15-18 treatments (Voineskos et al., 2016), referred to as the acute phase of treatment. In one study, given three times a week, the mean number of right unilateral ECT treatments to achieve remission was 7.3, anywhere between 4 or fewer treatments to 10 or more were reported (Kellner et al., 2016). In another study, given three times a week, the mean number of ECT treatments in remitters was 5.9 for right unilateral, 6.2 for bifrontal, and 5.5 for bilateral (Kellner, Knapp, et al., 2010). It is common that once individuals have achieved response after their acute phase of treatment, they will receive additional ECT treatments at a decreased frequency, referred to as maintenance treatment (Rabheru, 2012). Maintenance treatment has been shown to be effective in sustaining improvement in depressive symptoms for an average of almost two years following an acute course of ECT, without adverse cognitive effects (Luccarelli et al., 2020).

1.2 Effects of ECT on Cognition

Previous studies have reported cognitive impairment as a side effect of ECT. Accordingly, several studies have investigated the impact of ECT on cognitive measures such as global cognitive function, processing speed, attention/working memory, verbal
episodic memory, visual episodic memory, spatial problem solving, executive functioning, and intellectual ability (Semkovska & McLoughlin, 2010). A meta-analysis by Semkovska and McLoughlin (2010) showed the extent of impairment differed across these cognitive domains. Medium to large deficits in episodic memory and executive functioning were quantified up to three days after treatment (Semkovska & McLoughlin, 2010). The authors reported that delayed recall was more often affected than immediate recall, and verbal memory for unstructured information (i.e., word list tests) showed higher impairment than remembering organized and textualized information (i.e., story memory tests). Processing speed, spatial problem solving, and global cognition were slightly impaired, and attention/working memory did not differ from baseline. Authors also reported that ECT had no effect on intellectual ability at any time. During short term follow up (4-15 days post-ECT), only one variable, i.e., verbal paired associates delayed recall, showed persistent small deficits. Processing speed, episodic memory, and executive functioning all showed recovery of baseline functioning at short term follow ups (4-15 days post-ECT). Results even indicated a medium improvement in the ability to learn and spontaneously recall new organized and contextualized verbal information. This meta-analysis did not find any persisting cognitive deficits beyond 15 days post-ECT and for most variables, there was a small to medium improvement beyond baseline (Semkovska & McLoughlin, 2010). A large, multi-site, prospective, naturalistic, longitudinal study of 347 patients with a diagnosis of MDD was conducted to assess the clinical and cognitive outcomes of ECT. This study measured cognitive domains such as global cognitive status, psychomotor function, attention, and anterograde learning and memory. Despite significant differences in cognitive outcomes between the different sites, they reported the greatest cognitive deficits following ECT were retention of newly learned information, global cognitive status, and simple reaction time, and that there was a significant improvement six months following ECT on all cognitive tasks measured, other than reaction time. The authors noted the difference in cognition between sites is largely due to differences in ECT techniques (Sackeim et al., 2007).

One study investigated the short and long-term effects of ECT on patients with a diagnosis of depression and also included healthy controls. They found that ECT is not associated with a significant decline in short-term or long-term cognitive performance,
and that improvement in some cognitive domains, such as processing speed and attention, may be partly due to practice effects (Vasavada et al., 2017). This study, along with others, also suggested cognitive effects related to ECT are independent of clinical outcome (Hebbrecht et al., 2020; Letemendia et al., 1993; Vasavada et al., 2017).

Studies have also reported a significant decline of autobiographical memory following ECT (Napierala et al., 2019; Sackeim et al., 2007). Autobiographical memory is the memory of an event from a person's own history (Fraser et al., 2008), such as remembering what they did on their last birthday or the name of their childhood pet. Impairments in this type of memory have been reported immediately after ECT and can persist three to six months after treatment has ended (Napierala et al., 2019; Sackeim et al., 2007). A study with 347 patients with a diagnosis of MDD reported a significant decline in autobiographical memory immediately and six months after ECT compared to baseline (Sackeim et al., 2007). Merkl and colleagues (2011) also reported a significant decline of autobiographical memory in all patients following ECT (Merkl et al., 2011). However, one retrospective study involving 48 patients receiving ECT for a major depressive episode, reported no significant differences in autobiographical memory following treatment (Jelovac et al., 2016). This may be due to lack of sensitivity of assessments used to measure autobiographical memory (Jelovac et al., 2016).

As previously discussed, research into the impact of ECT on cognition is controversial and inconsistent. This may be due to the fact there is a large variety of tools used to measure various domains of cognitive function (Semkovska & Mcloughlin, 2010). A tool commonly used to monitor global cognitive impairment is the Montreal Cognitive Assessment (MoCA). Typically the MoCA is administered at baseline and the end of treatment, or more frequently if there are cognitive concerns (Kellner et al., 2012). The Mini Mental Status Exam or short individual tasks such as the trail making test, digit span tests, figure reproduction, delayed and immediate recall, and Stroop Colour-Word condition are also commonly used (Sackeim et al., 2007; Semkovska & Mcloughlin, 2010; Vasavada et al., 2017). As autobiographical memory impairments have been reported after ECT, it is often monitored using the Autobiographical Memory Interview (AMI; or its shorter version) or the Squire Subjective Memory Questionnaire (Fraser et al., 2008; Merkl et al., 2011; Napierala et al., 2019; Sackeim et al., 2007). However, these
pose challenges since even the short version of the AMI can be very lengthy and is not always suitable for severely ill populations such as those requiring ECT. Also, since autobiographical memory questions ask about memories specific to the individual’s life, it is difficult for the individual administering the test to know if the patient’s answers are correct (Kellner, Tobias, et al., 2010). It is common to use baseline answers to score subsequent responses, but this poses challenges because when individuals are assessed at baseline, their memory is often impaired by their mental health disorder (Kellner, Tobias, et al., 2010). Further, none of these tools or tests have been developed specifically to be used in clinical ECT settings, therefore may not be sensitive enough to detect cognitive changes throughout ECT. This is why it is crucial to develop rapid and easily administrable tests to use in clinical and research settings. For tests that include an autobiographical memory section, it is also important that they include the help of a close friend or family member to verify the individual's answers to the autobiographical memory questions (Kellner, Knapp, et al., 2010; Weiner et al., 1986).

One such questionnaire is the ElectroConvulsive therapy Cognitive Assessment (ECCA; Hermida et al., 2020). The ECCA is a tool that was specifically designed to measure cognitive domains most affected by ECT. Those domains include orientation, attention, autobiographical memory, factual knowledge, and delayed verbal recall (Hermida et al., 2020). The ECCA also requires assistance from a close friend or family member to assess the accuracy of the autobiographical memory section and to answer questions regarding the patient's cognitive function from their perspective (the latter section is called the “informant subscale”). The ECCA is a promising tool to monitor the cognitive effects following ECT as it has been shown to be more sensitive to cognitive changes than the MoCA (Hermida et al., 2020). However, the ECCA is a new tool that requires further assessment by research groups and in a more diverse mental health population (Hermida et al., 2020).

1.2.1 Parameters and Cognitive Side Effects

It is reported that the degree of cognitive impairment following ECT depends on several factors including electrode placement, treatment schedule, and stimulus dose (Kellner, Tobias, et al., 2010; Porter et al., 2020; Prudic, 2008; Sackeim et al., 2007). Compared to unilateral placement, bilateral placement is thought to produce larger and
more persistent amnestic side effects (Kellner, Tobias, et al., 2010; Prudic, 2008; Sackeim et al., 2007). Adverse side effects of bilateral placement are thought to be the reason for the development of alternative electrode placements that do not involve the medial temporal structures associated with memory function (Kellner, Knapp, et al., 2010; Kellner, Tobias, et al., 2010). Bifrontal electrode placement has been shown to have less cognitive impairments compared to bilateral and right unilateral placement in some reviews (Kellner, Tobias, et al., 2010; Prudic, 2008). Although, a large multicentre randomized, double-blind, controlled trial using a total of 230 individuals with a diagnosis of bipolar or unipolar depression, directly compared bilateral, bifrontal, and right unilateral electrode placements and found no statistically significant differences in global cognitive impairment or executive function between the three electrode placements (Kellner, Knapp, et al., 2010). This study did reveal however that individuals who received bifrontal placement performed worse on two measures of anterograde memory than those who had bilateral treatment. Also, despite previous findings, right unilateral placement was not significantly superior to bilateral placements on any cognitive measures, although this may be due to the higher stimulus dose than previous studies (Kellner, Knapp, et al., 2010). Findings from another large multicentre randomized, blind, controlled trial with 120 individuals with a diagnosis of MDD found that right unilateral and bifrontal groups actually had improved cognition measured with the Mini Mental Status Exam after ECT compared to the bilateral group (Su et al., 2019).

As previously mentioned, shortening the electrical stimulus (performing ultrabrief ECT), may reduce cognitive side effects (C. Loo, 2013; C. K. Loo et al., 2008, 2014). Two studies comparing right unilateral and ultrabrief right unilateral placement demonstrated comparable efficacy, but better cognitive outcomes in individuals who received ultrabrief right unilateral placement (C. K. Loo et al., 2008, 2014). This superior cognitive outcome has also been demonstrated in ultrabrief bilateral placement, although far fewer studies assessing ultrabrief bilateral placement have been conducted (Martin et al., 2019).

Contrary to electrode placement, the number of ECT treatments has not been shown to have an effect on cognitive deficits post-ECT (Kirov et al., 2016). Therefore,
more studies examining the relationship between electrode placement, stimulation, and cognitive side effects are needed.

1.3 Mechanisms of Action

The mechanisms of action of ECT are not well understood. In other words, it is unclear how ECT affects the brain and exerts its therapeutic effects. There are many proposed biological theories which include changes in the blood brain barrier, genetics, hormones, neurotrophic factors, or structural brain changes (Ousdal et al., 2022; Singh & Kar, 2017). One theory, which was examined in this study, suggests ECT works through inhibitory and excitatory brain pathways.

Animal studies using rat models suggest that modulation of gamma aminobutyric acid (GABA) pathways in the brain are involved in the mechanisms of action of ECT (Bowdler et al., 1983; Gray & Green, 1987; Green & Vincent, 1987). Particularly, repeated ECT increased GABA concentration in the hippocampus, hypothalamus, cortex, and striatum (Bowdler et al., 1983; Green & Vincent, 1987) and increased GABA_\text{B} receptor function in mouse frontal cortices (Gray & Green, 1987).

In humans, repeated ECT has also been shown to increase serum GABA levels, hypothalamic GABA_\text{B} receptor activity (Esel et al., 2008) and increase occipital cortex GABA concentrations. Specifically, in a study with 25 in-patients with a diagnosis of depression who responded to a course of ECT, it was found that ECT significantly increased serum blood GABA levels immediately after the first treatment and remained increased after the full treatment course (Esel et al., 2008). In this study, patients and 23 matched healthy controls also received baclofen, a selective GABA_\text{B} receptor agonist which is used to explore the activity of GABA_\text{B} receptors (Cryan & Kaupmann, 2005). Baclofen was administered two days prior to the first ECT and three days after the last ECT. This administration revealed that after a course of ECT, patients had significantly increased hypothalamic GABA_\text{B} receptor activity (Esel et al., 2008). In addition, a proton magnetic resonance spectroscopy (MRS) study conducted in eight patients with a diagnosis of MDD revealed a significant increase in GABA concentrations after ECT compared to baseline (Sanacora et al., 2003). However, contrary to these findings, one study found a decrease in GABA plasma levels two hours after one to seven sessions of ECT (Palmio et al., 2005). An MRS study with 11 patients with a diagnosis of MDD or in
a depressive episode of bipolar disorder, also found no significant changes in GABA levels after ECT compared to baseline in the prefrontal cortex or occipital lobe (Knudsen et al., 2019). A similar MRS study conducted in 41 participants with a diagnosis of depression, also found no difference in GABA levels in the anterior cingulate cortex after ECT compared to baseline, regardless of clinical response (Erchinger et al., 2020). It is important to note these studies also did not observe a difference in pre-ECT GABA levels between individuals with a diagnosis of depression and healthy participants, contrary to most literature on this topic (Brambilla et al., 2003; Esel et al., 2008; H. Gerner et al., 1984; R. Gerner & Hare, 1981; Marchesi et al., 1991; Petty et al., 1993; Sanacora et al., 1999).

Studies assessing glutamate before and after ECT have found an increase in levels following ECT (Palmio et al., 2005; Zhang et al., 2013). Specifically, Zhang and colleagues (2013) found a significant increase in glutamate levels in the anterior cingulate cortex between baseline and after the sixth ECT treatment using MRS (Zhang et al., 2013). Palmio and colleagues (2005) also found plasma levels of glutamate increased six hours after one to seven ECT treatments compared to baseline (Palmio et al., 2005). However, contrary to these findings, an MRS study examining the dorsolateral prefrontal cortex (DLPFC) and cingulum in 25 patients with depression, found no change in glutamate levels after ECT compared to baseline (Merkl et al., 2011).

Both increased GABA and glutamate findings correspond with the assumption that a deficit in GABAergic and glutamatergic activity may be involved in the pathophysiology of mood disorders in humans (Esel et al., 2008; H. Gerner et al., 1984; R. Gerner & Hare, 1981; Marchesi et al., 1991; Merkl et al., 2011; Sanacora et al., 1999; Zhang et al., 2013). Specifically, GABA cerebrospinal fluid levels and GABA plasma and serum levels were typically decreased in individuals with a diagnosis of depression or mania (Esel et al., 2008; H. Gerner et al., 1984; R. Gerner & Hare, 1981; Petty et al., 1993) and that neuroimaging (Sanacora et al., 1999) and neuroendocrine studies (Marchesi et al., 1991) all reflect a decrease of GABAergic processes in depression and other mood disorders (see Brambilla et al., 2003 for review). MRS studies also revealed glutamate levels were decreased in patients with a diagnosis of depression compared to healthy controls (Merkl et al., 2011; Zhang et al., 2013).
The evidence that GABAergic pathways are involved in the mechanisms of ECT also correlates with the presumed mechanism of many pharmacological treatments for mood disorders. It has been shown that administration of mood stabilizers increase GABAergic activity in rat brains (Ahluwalia et al., 1981) and that mood stabilizers and antidepressants increase GABA concentrations in healthy controls and individuals with a diagnosis of depression (Löscher & Schmidt, 1980; Sanacora et al., 2002). It is important to note however, that there are inconsistent findings in the literature regarding the role of GABA (see Brambilla et al., 2003 for review). Studies assessing glutamate have shown conflicting results as well. Some evidence suggests antidepressant treatments decrease glutamate release and synaptic transmission (Musazzi et al., 2013) but ketamine (a quick acting antidepressant) is thought to work by increasing glutamate levels (Krystal et al., 2013).

Although this research is important in understanding ECT, most findings come from animal models, which may not be directly translated to humans (Perel et al., 2007). The research that does involve humans mainly comes from clinical molecular studies that are limited to using peripheral tissues and fluids, such as blood. Changes in these fluids may not accurately reflect the brain's environment (Ryan & McLoughlin, 2019). Further, the human studies that do directly assess brain activity, such as MRS studies, only measure global levels of biochemical changes in a specific brain area rather than receptor activity. Therefore, studies investigating GABAergic and glutamatergic receptors and pathways in humans before and after ECT are needed.

**1.3.1 Transcranial Magnetic Stimulation**

In humans, GABAergic and glutamatergic activity can be quantified using a tool called transcranial magnetic stimulation (TMS). TMS is a non-invasive tool that can be used to explore excitatory and inhibitory brain mechanisms, and has the advantage of being sensitive to the activity of specific receptors (Rossini et al., 2015). TMS produces a magnetic field that induces an electric current in the underlying tissue, depolarizing cortical neurons. When applied to the motor cortex at high enough intensities, TMS can stimulate motor cortical regions which creates a motor evoked potential (MEP) in the peripheral muscles that correspond to the stimulated region (Rogasch et al., 2014). The MEP is a result of the activation of the corticospinal tract and is recorded and quantified.
using electromyography (EMG), reflecting cortical excitability (Rogasch et al., 2014). See Figure 1. The appropriate stimulation intensity varies between individuals and is referred to as the motor threshold (MT). The MT is the lowest stimulus intensity over the motor cortex required to produce a consistent MEP of minimal amplitude in the target muscle (Rossini et al., 2015).

**Figure 1.** Path of TMS Through the Body. A: Transcranial magnetic stimulation (TMS) applied to the left motor cortex. B: TMS traveling down the corticospinal tract into the hand muscle and C: the resulting motor evoked potential (MEP). Image made by Molly Watson with Biorender.com

A variety of TMS measures stimulating the motor cortex can be used to assess GABAergic and glutamatergic systems (Rogasch et al., 2014; Rossini et al., 2015). Measures can involve single or paired pulses, with pulses sent at varying intensities and intervals. Single pulse measures consist of one pulse being sent at a time, whereas paired pulse stimulation consists of two pulses, a conditioning stimulus (CS) followed by a test stimulus (TS), sent at various inter-pulse intervals. Single and paired pulse measures are presumed to be associated with GABAergic and glutamatergic systems as demonstrated by studies using TMS measures of corticospinal excitability, and central nervous system active drugs with a well-known single mode of action. Through these studies, the effects of a drug on a given measure led to conclusions regarding the physiological mechanisms...
underlying the particular measure (Ziemann, 2015). The TMS measures focused on in this study are the cortical silent period, short and long interval intracortical inhibition, and intracortical facilitation.

The cortical silent period (CSP) is a single-pulse TMS measure that can be used to measure intracortical inhibition (Rossini et al., 2015). To quantify the CSP, a suprathreshold TMS pulse is sent to the motor cortex while the individual is slightly contracting their contralateral hand, which creates a "silent period" (i.e., no EMG activity), lasting 100-300ms. The duration of that silent period is measured (Rossini et al., 2015) and provides an index of GABAergic inhibition in the cortex (Rogasch et al., 2014; Voineskos et al., 2016); a longer silent period indicates more cortical inhibition. CSP is thought to measure GABA \(_B \) activity because the duration of the silent period has been shown to increase when administered baclofen, a GABA \(_B \) agonist (Siebner et al., 1998).

Short interval intracortical inhibition (SICI) is a paired pulse measure which consists of a subthreshold CS followed by a suprathreshold TS with an interval of 1-6ms between pulses (Kujirai et al., 1993). SICI is thought to measure GABA \(_A \) activity because when administered diazepam, a positive allosteric modulator, SICI was enhanced (Florian et al., 2008). Long interval intracortical inhibition (LICI) consists of a suprathreshold CS and TS with an interval of 50-200ms between pulses (Kujirai et al., 1993). LICI is thought to measure GABA \(_B \) activity because, similar to CSP, when administered baclofen, a GABA \(_B \) agonist, LICI was increased (Florian et al., 2008; McDonnell et al., 2006). Intracortical facilitation (ICF) consists of a subthreshold CS and a suprathreshold TS with an interval of 10-15ms between pulses. ICF is thought to measure cortical excitability and glutamatergic functioning because riluzole, a glutamate antagonist, suppressed ICF (Liepert et al., 1997; Rogasch et al., 2014; Rossini et al., 2015). Due to these measures, TMS is a promising tool to assess the mechanisms of action of ECT and its impact on the brain given that alterations in cortical inhibition and excitation are thought to be implicated in the mechanisms of ECT (Bajbouj et al., 2005, 2006; Sommer et al., 2002).

To this date, TMS has been used in a handful of human studies to assess the mechanisms of ECT and results generally point towards ECT treatments increasing intracortical inhibition in the motor cortex (Bajbouj et al., 2005, 2006; Sommer et al.,
2002). Specifically, in a case study by Bajbouj and colleagues (2005), after a successful treatment of right unilateral ECT, intracortical inhibition, measured using a paired pulse technique, was increased (Bajbouj et al., 2005). These findings were then replicated as it was found that, in a sample of 10 patients, after 10 treatments of right unilateral ECT, intracortical inhibition was significantly increased with an additional finding that the CSP duration was significantly longer compared to baseline in the motor cortex (Bajbouj et al., 2006). In a case study of a woman with a diagnosis of depression, reduced excitability of the motor cortex was found after a successful course of right unilateral ECT by measuring MEP amplitude before and after treatment (Sommer et al., 2002). However, in a prior study done by Chistyakov and colleagues (2005), in 22 patients with a diagnosis of MDD, the opposite was found. In this study, after a course of bilateral ECT a significant reduction in intracortical inhibition was found in the left hemisphere (Chistyakov et al., 2005). There are several differences between these studies including electrode placement, number of ECT sessions, and sample sizes, which may account for the contradictory findings. ICF has been shown to remain the same pre- and post ECT, reflecting no change in cortical excitability (Bajbouj et al., 2006; Voineskos et al., 2016). More research needs to be done to clarify these findings in larger, more diverse study populations using a variety of electrode placements and treatment durations.

1.4 Objectives and Hypotheses

Our first objective was to monitor the short- (72-hours post-ECT) and long-term (one-month post-ECT) effects of ECT on cognition using the MoCA and ECCA total scores. We hypothesized cognitive deficits on total ECCA scores would be present 72-hours post-ECT (Hermida et al., 2020), but would resolve one-month post-ECT (Sackheim et al., 2007). We hypothesized no cognitive deficits on total MoCA scores would be seen 72-hours or one-month post-ECT (Hebbrech et al., 2020; Hermida et al., 2020).

Additionally, we monitored the short-and long-term effects of ECT on ECCA and MoCA subscales. For the ECCA, we hypothesized there would be impairments on all subscales except orientation and factual knowledge 72-hours post-ECT, but these would resolve one-month post-ECT (Hermida et al., 2020). Autobiographical memory impairments would be present 72-hours post-ECT and one-month post-ECT (Hermida et al., 2020;
Napierala et al., 2019; Sackeim et al., 2007). We hypothesized there would not be cognitive deficits on any MoCA subscales (Hebbrecht et al., 2020; Hermida et al., 2020).

Our second objective was to monitor the short- and long-term effects of ECT on symptoms of depression, suicidal ideation, and anxiety. We hypothesized depressive and suicidal ideation symptoms would improve 72-hours and one-month post-ECT (Health Quality Ontario, 2016; Kellner, Knapp, et al., 2010; Kennedy et al., 2009; Li et al., 2020; Nucifora et al., 2019; Schoeyen et al., 2015). The effects of ECT on anxiety are not well researched, however based on Huang and colleagues' (2019) findings, we hypothesize anxiety will improve 72-hours and one-month post-ECT as well (Huang et al., 2019).

Our third objective was to investigate the short-term effects of ECT on cortical inhibition and excitation using TMS measures (CSP, SICI, ICF, and LICI). We hypothesized ECT would increase the level of cortical inhibition in the motor cortex 72-hours post-ECT measured by SICI, LICI, and CSP (Bajbouj et al., 2006; Voinèskos et al., 2016), and ICF would remain unchanged (Bajbouj et al., 2006; Voinèskos et al., 2016).

Our final objective was to determine if baseline levels and change in levels of cortical inhibition and excitation post-ECT were related to change in clinical symptoms and cognitive impairments following ECT. Due to previous research, we hypothesized cortical inhibition would correlate with change in depression, suicidal ideation, and anxiety symptoms 72-hours and one-month post-ECT. This is because cortical inhibition is presumed to be involved in the mechanisms of ECT, and ECT has been shown to improve depression, suicidal ideation, and anxiety symptoms (Bajbouj et al., 2005, 2006; Health Quality Ontario, 2016; Huang et al., 2019; Kennedy et al., 2009; Nucifora et al., 2019; Schoeyen et al., 2015; Sommer et al., 2002). To our knowledge, there are no previous studies investigating the relationship between excitability and change in clinical response, or the relationship between cognitive outcome and TMS measures of cortical inhibition and excitation, therefore there are no hypotheses for this portion of the objective.

2. Methodology

2.1 Participants

The original aim for our study was to recruit 60 participants. However, recruitment was limited due to COVID-19 restrictions. Hence, for this study, we recruited
a total of 25 in-patients staying at The Royal Ottawa Mental Health Centre (ROMHC), diagnosed with diverse mental health disorders who were prescribed ECT treatment at the ROMHC clinic. Sixteen participants completed the study. Of those 16, seven participants did not complete TMS assessments, and completed only clinical and cognitive assessments. These individuals did not complete TMS assessments due to contraindications to TMS and remote study visits while COVID-19 study restrictions were in place. Nine participants completed clinical and cognitive assessments, as well as TMS measures. Two of those individuals withdrew from the study before the final study visit. See Figure 2 for patient retention flowchart.

Participants were 18 years or older and made the voluntary and informed decision to receive ECT treatment prescribed by their treating physician. Mental health diagnosis was confirmed by Electronic Medical Records. Patients prescribed ECT treatment at the ROMHC were informed about the research study by a member of their health care team, and if interested, a referral form was sent to our research team by their physician. After participants were referred, they completed a telephone pre-screen with a study team member to ensure eligibility. If they appeared eligible for the study, participants who completed assessments remotely were asked to verbally consent to participate over the phone after study personnel read the study consent form. Participants who completed assessments in-person signed a consent form after they read it or had it read to them. This study was approved by the Research Ethics Board (REB) at the University of Ottawa Institute of Mental Health Research at The Royal, with the study #2018053.

Potential participants were excluded from the study if they had a comorbid neurodegenerative disorder, intellectual disability, borderline personality disorder and/or antisocial personality disorder that would prevent them from completing the study procedures. In addition, participants were excluded from the TMS component of the study if they completed the study assessments remotely (i.e., due to COVID-19 study restrictions), had a substance use disorder in the past six months, had a concomitant major unstable medical or neurological illness, were pregnant or breastfeeding, or had a specific contraindication for TMS, such as history of epilepsy or seizure, traumatic brain injury, metallic head implant, or pacemaker. Study participation could have been terminated by the instruction of the primary investigator for other reasons such as a high
TMS threshold (not allowing stimulation under the maximum capacity of the TMS stimulator) or noncompliance to study protocol or instructions, although this did not occur. If participants were not able to complete the TMS portion of the study for any of the above listed reasons, they were invited to complete just the clinical and cognitive portion of the study. As per current practice guidelines at the ROHMC, patients taking low-dose benzodiazepine medications (e.g., < 1.5mg Lorazepam) remained on their prescribed dose throughout ECT treatment.

### Figure 2
Participant Retention Flowchart. ECT = electroconvulsive therapy. TMS = transcranial magnetic stimulation.

#### 2.2 Procedure
Participants completed assessments at three time points throughout their ECT treatment; within 72-hours pre-ECT, within 72-hours post-ECT, and approximately one-month post-ECT. During the first visit, participants completed clinical, cognitive, and TMS assessments (if eligible). Participants then completed their ECT treatment as prescribed by their physician, for which the modality and duration varied among
participants. Within 72-hours after their last acute ECT treatment, the clinical, cognitive, and TMS assessments (if eligible) were repeated. Finally, one-month after their last acute ECT treatment, participants completed only the clinical and cognitive assessments. The study timeline is outlined in Figure 3.

Figure 3. Study Timeline. TMS = transcranial magnetic stimulation. ECT = electroconvulsive therapy.

2.3 Study Modifications

Due to in-person study restrictions brought on by COVID-19, participation started remotely. As such, at the beginning of our study, the TMS component could not be conducted and all screening, consent, clinical, and cognitive portions of the study were completed over the phone by a trained research personnel. When the MoCA was administered remotely, two subscales could not be completed as they required the participant to draw and see images which cannot be done over the phone. In some instances, the participant completed the first two study visits in-person and was unable to complete the final assessment in-person, therefore final assessments were completed over the phone. Although the ECCA did not have to be modified to be administered remotely,
the questions in the autobiographical memory section were modified to better suit an in-patient population. The questions such as "recall what they had for dinner the night before," and "recall what psychiatric medication they are taking" were removed and replaced with five additional autobiographical memory questions we believed were better suited for an in-patient population and that had a higher likelihood of their informant being able to answer them. Those questions were "what was the name of the company or organization where you last worked?", "what is the month and day of your close friend or family member's [their informant's] birthday?", "where did you meet your close friend or family member you suggested we contact for this study?", "what is the name of the city where you were born?", and "what was the name of the last pet you owned?" The first two questions were taken from the AMI-Short Form (McElhiney et al., 1995) and the following three were developed by the research team. More than the original number of questions were asked to the participant to ensure their informant would be able to verify the required number of questions for scoring on the ECCA, as there can often be little communication between a participant and their informant when they are in-patients. As not all participants had a close family member or friend to be their informant, or not all informants were able to be reached, some informant sections and autobiographical memory sections could not be completed or verified.

To account for missing sections on both the MoCA and ECCA, the total scores for all participants were computed as a percent, rather than a raw score. In addition, not all informants were able to verify all autobiographical memory questions or answer all informant questions, therefore, these two ECCA subscales were also computed as a percent. Due to the very quick changing nature of ECT a few study visits were outside the approved study window (i.e., more than 72-hours before or after ECT). These changes were noted in the participant's study file and kept track of in a study deviation log for the REB. Some participants had an interruption in their ECT treatments due to sickness, medical outbreaks on their units, ECT clinic repairs, contraindications to ECT the day of their treatment, or were not able to receive 2 to 3 treatments every week due to scheduling conflicts. These were also noted in the deviation log for the REB.
2.4 ECT Treatment

As this is a naturalistic study, ECT treatment followed the ROMHC ECT clinic's standard procedure and ECT parameters were determined by the clinical team; the research team was not involved. Participants received ECT treatment two or three times a week, referred to as the acute phase. Some participants received additional maintenance treatments, at decreasing frequencies (i.e., once per week or once every two weeks) after their acute phase was completed. For the purposes of this study, "post-ECT" refers to after the acute phase of treatment. Treatment was brief pulse bifrontal, brief pulse bitemporal, brief pulse right unilateral, or ultrabrief pulse right unilateral, administered using a square-wave, constant current, brief pulse device (MECTA Corporation, Lake Oswego, OR). Seizure threshold was determined at the first session according to the standard stimulus dose titration procedure. Anaesthetic medications (typically propofol and succinylcholine, but sometimes with the addition of ketamine and/or remifentanil) were administered prior to each treatment according to standard dosing guidelines. Treatment duration was determined by the treating physician, taking into consideration response, occurring side-effects, and the patient's expressed wish to discontinue treatment.

2.5 Assessments

2.5.1 Clinical Assessments

Clinical assessments were conducted 72-hours pre- and post-ECT, and one-month post-ECT. Assessments were either self-report or clinical interviews administered by a trained research team member. Self-report assessments included the 16-item Quick Inventory of Depressive Symptoms-self report (QIDS-SR-16), the Beck Scale for Suicidal Ideation (BSS) and the General Anxiety Disorder-7 scale (GAD-7). If the participant had a primary or sub-diagnosis of bipolar disorder, they completed the self-report Altman Self-Rating Mania Scale (ASRM) and if the participant had a primary diagnosis of schizophrenia, a schizophrenia spectrum disorder, or depression with psychotic features, the 8-item Positive and Negative Syndrome Scale for Schizophrenia (PANSS-8) interview was conducted.

The QIDS-SR-16 is a structured self-report measure to assess severity of depressive symptoms during the past week. There are 16 questions which assess nine
domains of symptoms; sad mood, concentration, self-criticism, suicidal ideation, interest, energy/fatigue, sleep disturbances, decrease/increase in appetite/weight, and psychomotor agitation/retardation. The score ranges from 0-27, with a score of 0-5 indicating no depression, a score of 6 to 10 indicating mild depression, a score of 11 to 15 indicating moderate depression, a score of 16 to 20 indicating severe depression, and a score greater than 21 indicating very severe depression (Rush et al., 2003). The BSS is a structured 21-item self-report questionnaire to quantify and assess suicidal ideation during the past week. The BSS is rated on a Likert scale of 0-2, with a possible total score of 0-38, higher scores indicating more severe suicidal ideation (Beck et al., 1988). The GAD-7 is a structured 7-item Likert-scale self-report questionnaire to assess the severity of anxiety over the past two weeks, including symptoms such as restlessness, worry, and irritability. The score ranges from 0-21, with a score of 5-9 indicating mild anxiety, a score of 10-14 indicating moderate anxiety, and a score of 15-21 indicating severe anxiety (Spitzer et al., 2006). The ASRM is a 5-item self-report measure used to assess the presence and severity of manic or hypomanic symptoms during the past week. Items are scored from 0-4, for a total score between 0-20, higher scores indicating more severe manic or hypomanic symptoms (E. G. Altman et al., 1997). The PANSS-8 is a semi-structured interview to assess remission status of schizophrenia over the past week. The PANSS-8 assesses eight domains including delusions, conceptual disorganization, hallucinatory behaviour, blunted affect, passive or apathetic social withdrawal, lack of spontaneity and flow of conversation, mannerisms and posturing, and unusual thought content. Each domain is scored from 1 (absent) to 7 (extreme), for a total score between 8-56, higher scores indicating more severe psychotic symptoms (Kay et al., 1987). Clinical assessments are detailed in Table 1.
Table 1

**Clinical Assessments**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Description of Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>QIDS-SR-16</td>
<td>Structured 16 item self-report questionnaire to assess severity of depressive symptoms</td>
</tr>
<tr>
<td>BSS</td>
<td>Structured 21-item self-report questionnaire to quantify and assess suicidal ideation</td>
</tr>
<tr>
<td>GAD-7</td>
<td>Structured 7-item self-report questionnaire to assess severity of anxiety</td>
</tr>
<tr>
<td>ASRM*</td>
<td>Structured 5-item self-report questionnaire to assess presence and severity of manic or hypomanic symptoms</td>
</tr>
<tr>
<td>PANSS-8**</td>
<td>Semi-structured interview to assess schizophrenia remission status</td>
</tr>
</tbody>
</table>

*Note.* QIDS-SR-16 = 16-item Quick Inventory of Depressive Symptoms-Self-report; BSS = Beck Scale for Suicidal Ideation; GAD-7 = General Anxiety Disorder-7; ASRM = Altman Self-Rating Mania Scale; PANSS-8 = Positive and Negative Syndrome Scale for Schizophrenia, 8-items

*Only administered to participants with a diagnosis or sub-diagnosis of bipolar disorder.

**Only administered to participants with a primary diagnosis of schizophrenia, a schizophrenia spectrum disorder, or depression with psychotic features.

### 2.5.2 Main Clinical Outcome

The QIDS-SR-16 was the main clinical outcome measure for depression and was used to determine response to treatment and remission of depressive symptoms. Response to treatment was defined as a ≥ 50% reduction in pre-treatment QIDS-SR-16 score post-ECT. Remission was defined as a QIDS-SR-16 score of ≤ 5 post-ECT (Parker Schwab et al., 2021). The QIDS-SR-16 is considered an acceptable and reliable measure as the total scores were shown to be highly correlated with the 30 item Inventory of Depressive Symptomatology self-report (IDS-SR$_{30}$; Rush et al., 1996) and the 24 item Hamilton Rating Scale for Depression (HAM-D$_{24}$), which are often used as outcome measures (Hamilton, 1960; Rush et al., 2003). The QIDS-SR-16 has also been shown to be an adequate measure for in-patient populations with diagnoses of depression (Feng et al., 2016), geriatric populations (Doraiswamy et al., 2010), and outpatient populations with diagnoses of MDD and bipolar disorder (TRIVEDI et al., 2004). The QIDS-SR-16 is also commonly used in ECT studies to assess mood disorders with a variety of populations (Luccarelli et al., 2022; Oka et al., 2022; Parker Schwab et al., 2021).
The PANSS-8 was the main clinical outcome measure for schizoaffective disorder and was used to determine response to treatment and remission. Response to treatment was defined as a $\geq 20\%$ reduction in pre-treatment symptom severity post-ECT measured by the mean PANSS-8 score. Remission was defined as a score of $\leq 3$ on each item of the PANSS-8 measured post-ECT. The PANSS-8 is a shorter version of the 30-item PANSS (Kay et al., 1987), developed to assess the positive and negative symptoms in schizophrenia, which has shown to have strong psychometric properties (Kay et al., 1988). The PANSS-8 was also shown to be a reliable and valid instrument that is sensitive to change in individuals with schizophrenia (Lin et al., 2018). The PANSS is commonly used in ECT studies to assess symptoms of schizophrenia (Danenberg et al., 2021; Kim et al., 2017).

The ASRM was the main clinical outcome measure for bipolar disorder and was used to determine response to treatment and remission. Response to treatment was defined as a $\geq 50\%$ reduction in pre-treatment ASRM score. Remission was defined as a score $\leq 5$ post-ECT measured by the ASRM (E. G. Altman et al., 1997). The ASRM has shown to be a highly valid, reliable, and sensitive instrument for in-patient populations (E. Altman et al., 2001; E. G. Altman et al., 1997).

2.5.3 Cognitive Assessments

Cognitive assessments were administered by a trained research personnel 72-hours pre- and post-ECT, and one-month post-ECT. These assessments included the MoCA and the ECCA. To minimize practice effects, a different version of the MoCA and ECCA were administered at each assessment timepoint.

The MoCA was used to screen individuals for possible dementia or cognitive dysfunction and to monitor cognition throughout treatment. It assesses different cognitive domains including attention and concentration, executive function, memory, language, visuoconstructual skills, conceptual thinking, calculations, and orientation. The MoCA score ranges from 0-30, with a lower score indicating worse cognitive functioning; a score of 26 or above is considered normal cognitive functioning (Nasreddine et al., 2005). The MoCA and it’s subscales have been shown to be a reliable and valid measure to assess global cognitive function and specific cognitive domains in patients with a diagnosis of depression (Srisurapanont et al., 2017).
The ECCA was specifically designed to measure cognitive domains most affected by ECT. These five domains are temporal orientation, attention, verbal delayed recall, factual knowledge, and autobiographical memory. The ECCA also includes an assessment of self-reported cognitive difficulties (subjective subscale) and a section to be completed by a close friend or family member to assess the participant's cognitive function (informant subscale), as it is most often the person closest to the individual who notices the first sign of cognitive impairment. The responses to the autobiographical memory section were confirmed by the close friend or family member. Like the MoCA, the ECCA is scored from 0-30, a lower score indicating worse cognitive functioning. The authors of the ECCA determined it to be a reliable and potentially useful tool to monitor cognition throughout ECT in a population with diagnoses of depression (Hermida et al., 2020).

2.5.4 TMS Assessments

TMS was applied to the left primary motor cortex using a Magpro X100 device with a 70mm figure-of-eight coil with a monophasic pulse (Magventure, Denmark). The coil was held at a 45° angle with the handle pointing away from the midline for all TMS procedures. During TMS procedures, a BrainSight neuronavigation system (Rogue Research Inc., Montreal) was used to ensure the coil was properly positioned. Electrodes were placed on the skin overlying the right first dorsal interosseous muscle, the proximal interphalangeal joint of the right index finger, and the right elbow. These electrodes recorded EMG signals throughout the TMS procedures, reflecting corticospinal excitability. Prior to placing the electrodes, the skin in these areas were exfoliated with Nuprep skin prep gel then cleaned with 70% Isopropyl Alcohol Health Care Plus alcohol swabs to reduce electrical impedance and improve signal to noise ratio (Chaves et al., 2021). EMG signals were recorded using the BrainSight EMG module (Rogue Research Inc., Montreal). To determine the resting motor threshold (RMT), the motor "hot spot" was found. To do this, multiple areas on the left primary motor cortex were stimulated using a suprathreshold single pulse TMS (sp-TMS) delivered every 5-7 seconds until the location that produced the highest, most consistent MEPs was found. The "hot spot" was targeted in BrainSight and was stimulated for the rest of the TMS procedures. Next, again using sp-TMS, the RMT (i.e., the proper stimulation intensity) was determined by
gradually decreasing the intensity until the lowest intensity that produced an EMG amplitude of 50µV or higher was recorded in 5 out of 10 trials.

Five blocks of TMS recordings were conducted to assess cortical inhibition and excitation in the motor cortex. First, a block of sp-TMS pulses were sent at 130% RMT to record baseline cortical activity. For CSP, again sp-TMS was sent at 130% RMT, although during this measurement participants maintained a slight muscle contraction for the duration of the measure. Specifically, participants were asked to maintain 10% of their maximum contraction throughout the CSP measurement which was monitored using EMG signals or a Baseline Hydraulic Pinch Gauge. Next, paired pulse TMS measures (i.e., SICI, LICI, and ICF) were conducted. For SICI and ICF measures, a conditioned stimulus of 80% RMT was sent prior to the test stimulus of 130% RMT, at an interval of 2ms and 12ms, respectively. For LICI both the conditioned and test stimulus were sent at 130% RMT at an interval of 100ms. For each of the five measures, 20 pulses were sent every 5-7 seconds while EMG activity was recorded.

EMG data was collected from a minimum of 50ms pre-TMS stimulus to a maximum of 800ms post-TMS stimulus. To quantify TMS outcome measures of cortical activity, the magnitude of cortical inhibition was measured with SICI, LICI, and CSP and the magnitude of cortical excitation was measured with ICF. TMS measurements were conducted 72-hours pre- and post-ECT.

2.6 Data Analysis
2.6.1 TMS Data Preprocessing

Peak to peak MEP amplitudes (µV) from Brainsight were manually inputted into Excel for all five measures (sp-TMS, CSP, SICI, LICI, and ICF) for each participant, pre- and post-ECT. These MEP amplitudes were averaged for each TMS measure (sp-TMS, CSP, SICI, LICI, and ICF). To quantify cortical inhibition and excitation with SICI and ICF, a ratio of the mean conditioned MEP amplitude (i.e., SICI or ICF) to the mean unconditioned MEP amplitude (i.e., sp-TMS) was computed (i.e., SICI or ICF divided by sp-TMS). To quantify cortical inhibition with LICI, a ratio of the mean conditioned to the mean unconditioned MEP amplitude between the two LICI pulses was computed (i.e., LICI pulse 2/LICI pulse 1). Ratios greater than one represented facilitation/excitability and ratios less than one represented inhibition (Daskalakis et al., 2002; Fatih et al., 2021).
The duration of the silent period recorded in the EMG signal during CSP was used to quantify CSP cortical inhibition. The CSP onset began when the MEP amplitude consistently surpassed +/- 2SD from the mean pre-stimulus EMG background activity and the CSP offset was the point at which the EMG background activity post-MEP returned to within +/- 2SD from the mean post-stimulus EMG background activity. We calculated CSP duration as CSP offset - CSP onset in milliseconds (Chaves et al., 2021). This analysis was completed visually in Excel using graphs of the CSP recording.

All TMS data was visually inspected on BrainSight for noise, abnormal responses/TMS artifacts, and to ensure proper stimulation location. MEP amplitudes were excluded if any of the previously mentioned errors were present. For each measure, MEP amplitudes that were +/- 3SD from the mean were excluded (the measure’s mean was individually calculated for each participant). Using Excel, a prior contraction background check was performed for each TMS pulse sent, in which pulses were excluded if a muscle contraction of more than 3SD from the participant’s mean was present prior to the TMS pulse being sent. This is conducted as contracting prior to a TMS pulse will increase neural excitability at the cortical or spinal level promoting cortico-motor excitability and will increase the MEP amplitude, even without increasing stimulation intensity (Rossini et al., 2015). An average of 4 pulses were removed per participant (range 0-10 pulses) due to abnormal responses, MEP outliers, or prior background EMG contraction.

2.6.2 Statistical Analysis

All statistical analyses were computed using the open-source R statistical software Version 4.2.2 (R core Team, Vienna, Austria and the R Studio package rstatix; Kassambara, 2022). TMS, clinical, and cognitive data was carefully inspected for extreme outliers. As this is a small sample, only clear outliers who had a value that could not be within normal range of values were excluded. No outliers were excluded.

Change scores were computed for all TMS, clinical and cognitive total scores and cognitive subscales measures to reflect the difference in scores between pre- and both post-ECT measures. Seventy-two-hour change scores refer to the difference in scores between pre- and 72-hours post-ECT. One-month change scores refer to the difference in scores between pre- and one-month post-ECT. For TMS measures, clinical, and cognitive total scores, the difference was calculated in the form of a ratio (post/pre). For cognitive
subscales, the difference was calculated by subtraction (post-pre). These calculations were decided to best accommodate our statistical tests.

Normality was assessed for each TMS, total clinical and cognitive scores, and cognitive subscales while computing repeated-measures ANOVA (RM-ANOVA) and pairwise t-tests using the Shapiro-Wilk test.

2.6.3 Objective One: Examine the Short and Long-term Effects of ECT on Cognition

RM-ANOVAs were computed to examine the short- and long-term effects of ECT on cognition. The ECCA and MoCA total scores and subscales were examined over the three study timepoints: 72-hours pre- and post-ECT, and one-month post-ECT. Post-hoc pairwise t-tests (two-tailed) were computed for significant or trending significant RM-ANOVA results. Bonferroni correction was used for post-hoc tests.

2.6.4 Objective Two: Determine the Short- and Long-term Effects of ECT on Clinical Symptoms

RM-ANOVAs were computed to examine the short- and long-term effects of ECT on clinical symptoms. The QIDS-SR-16, BSS, and GAD-7 total scores were examined over the three study timepoints: 72-hours pre- and post-ECT, and one-month post-ECT. Post-hoc pairwise t-tests (two-tailed) were computed for significant or trending significant RM-ANOVA results. Bonferroni correction was used for post-hoc tests.

2.6.5 Objective Three: Monitor the Short-term effect of ECT on Cortical Excitability

Pairwise t-tests (two-tailed) were computed to examine the short-term effects of ECT on cortical inhibition and excitation. TMS measures (CSP, SICI, ICF, and LICI) were examined over the two study timepoints when TMS was administered: 72-hours pre- and post-ECT. Bonferroni correction was used.

2.6.6 Objective Four: Investigate if Baseline Levels or Change in Cortical Inhibition or Excitation is Related to Change in Cognitive or Clinical Symptoms Post-ECT

Pearson's correlations were conducted between each baseline TMS measure (CSP, SICI, LIC, ICF) and each change in total scores 72-hours and one-month post-ECT for each clinical and cognitive measure (ECCA, MoCA, QIDS-SR-16, BSS, and GAD-7).
Further Pearson’s correlations were conducted between each change in TMS measure that showed a significant difference between pre- and post-ECT measures (determined in objective 3), and each change in total clinical and cognitive measure 72-hours and one-month post-ECT. The same correlations were conducted for cognitive subscales that showed a significant difference between study timepoints, determined in objective 1.

3. Results

3.1 Demographics

The sample consisted of 10 females and 6 males, with a mean age of 55. MDD was the most common primary diagnosis, bipolar disorder (depressive episode) was the second most common, and persistent depressive disorder, AUD, and schizoaffective disorder (bipolar type) were the least common. Average time between pre-ECT assessments and the start of ECT was 2.15 days, average time between end of ECT and second assessments was 3.23 days and average time between end of ECT and one-month assessments was 31.75 days. This closely follows our study protocol of completing assessments within 72-hours pre- and post-ECT and one-month post-ECT. There were 6 responders and 10 non-responders within 72-hours post-ECT, with response defined as $\geq 50\%$ reduction in pre-treatment QIDS-SR-16 score. Of the 6 responders, three remitted with a score of $\leq 5$ on the QIDS-SR-16 within 72-hours post-ECT. At one-month post-treatment there were 6 responders and 8 non-responders (two individuals did not complete one-month assessments). Interestingly two individuals who did not respond 72-hours post-ECT were responders one-month post-ECT. Only one individual who was a responder 72-hours post-ECT did not meet response criteria one-month post-ECT. Of those 6 responders, two met remission criteria one-month post-ECT. All participants were assessed for response and remission using the QIDS-SR-16, regardless of primary diagnosis. This is because the two individuals with a primary diagnosis of bipolar disorder were in a depressive episode at the time of ECT as confirmed by medical records, a high score on the QIDS-SR-16, and a very low score on the ASRM. The individual with a primary diagnosis of schizoaffective disorder was also assessed using the QIDS-SR-16 due to a low PANSS-8 score and a high QIDS-SR-16 score. The individual with a primary diagnosis of AUD was also assessed using the QIDS-SR-16. This was done as the participant had a high score on the QIDS-SR-16 and they had a co-
morbid diagnosis of persistent depressive disorder. Eight out of our 16 participants had an additional diagnosis of an anxiety disorder, or an anxiety component to their primary diagnosis (i.e., MDD with anxious distress). Demographic and medical information can be found in Table 3.

Table 2

Demographic and Medical Information for Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (62.5%)</td>
</tr>
<tr>
<td>Male</td>
<td>6 (37.5%)</td>
</tr>
<tr>
<td>Mean Age (range in years)</td>
<td>54.94 (30-78)</td>
</tr>
<tr>
<td>Primary Diagnosis</td>
<td></td>
</tr>
<tr>
<td>MDD</td>
<td>11 (68.75%)</td>
</tr>
<tr>
<td>BP</td>
<td>2 (12.50%)</td>
</tr>
<tr>
<td>PDD</td>
<td>1 (6.25%)</td>
</tr>
<tr>
<td>AUD</td>
<td>1 (6.25%)</td>
</tr>
<tr>
<td>Schizoaffective Disorder</td>
<td>1 (6.25%)</td>
</tr>
<tr>
<td>Number of Participants Taking Medication at First ECT</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>14 (88%)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>12 (75%)</td>
</tr>
<tr>
<td>Antianxiety</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Mood Stabilizer</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>7 (44%)</td>
</tr>
</tbody>
</table>

Note. Total sample (N = 16). MDD = major depressive disorder. BP = bipolar disorder. PDD = persistent depressive disorder. AUD = alcohol use disorder. ECT = electroconvulsive therapy.

All 16 participants were in-patients at the ROMHC while completing ECT treatment as this is a requirement at the ROMHC for an acute course of ECT. The mean number of acute ECT treatments was 11.94, with the number of treatments ranging from 3 to 24. The most common electrode placement was bitemporal and the least common was a combination of bitemporal and right unilateral. ECT treatment information is displayed in Table 4.
Table 3

ECT Treatment Information

<table>
<thead>
<tr>
<th>ECT Treatment Characteristics</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous ECT Treatment</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (68.75%)</td>
</tr>
<tr>
<td>No</td>
<td>5 (31.25%)</td>
</tr>
<tr>
<td>Electrode Placement</td>
<td></td>
</tr>
<tr>
<td>RUL</td>
<td>6 (37.50%)</td>
</tr>
<tr>
<td>BT</td>
<td>7 (43.75%)</td>
</tr>
<tr>
<td>Combination</td>
<td>3 (18.75%)</td>
</tr>
<tr>
<td>Number of Acute Treatments (range)</td>
<td>11.94 (3-24)</td>
</tr>
<tr>
<td>Maintenance Treatment</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (25.00%)</td>
</tr>
<tr>
<td>No</td>
<td>11 (68.75%)</td>
</tr>
<tr>
<td>Restarted Acute ECT</td>
<td>1 (0.06%)</td>
</tr>
</tbody>
</table>

Note. N=16. ECT = electroconvulsive therapy. RUL = right unilateral. BT = bitemporal. Combination = combination of RUL and BT.

3.2 Objective One: Monitoring the Short and Long-term Effects of ECT on Cognition

The mean MoCA percent score was 84.12% ($SD = 0.98\%$) at baseline, 74.32% ($SD = 14.27\%$) 72-hours post-ECT, and 77.27% ($SD = 12.91\%$) one-month post-ECT. The mean ECCA percent score was 67.64% ($SD = 12.18\%$) at baseline, 66.74% ($SD = 12.90\%$) 72-hours post-ECT, and 67.14% ($SD = 21.80\%$) one-month post-ECT.

RM-ANOVA revealed a significant difference in MoCA total scores throughout the three study time points, $F(2,24) = 4.43, p = .023$. Further post-hoc pairwise t-tests determined a significant decrease between MoCA total scores at 72-hours pre- and 72-hours post-ECT, $t(14) = 3.61, p.adj = .008, d = 0.80$. RM-ANOVA revealed there was no significant difference in ECCA total scores throughout the three study time points, $F(2,26) = 0.02, p = .977$. See Figure 4 for MoCA and ECCA total score boxplots.
Figure 4. Boxplots of MoCA and ECCA Total Scores. ECT = electroconvulsive therapy. MoCA = Montreal Cognitive Assessment. ECCA = ElectroConvulsive therapy Cognitive Assessment. **p < .01. Note. Significant differences are adjusted p values with Bonferroni correction.

RM-ANOVA revealed a significant difference in the MoCA abstraction subscale throughout study time points, $F(2,24) = 6.63, p = .005$. Although there were no significant differences in any other MoCA subscales, RM-ANOVA revealed trending significant differences ($p < .100$) for the naming, attention, language, and delayed recall subscales ($F(2,16) = 2.8, p = .091, F(2,24) = 2.97, p = .071, F(2,24) = 3.17, p = .06$, and $F(1.37, 16.46) = 3.12, p = .085$, respectively). Further post-hoc pairwise t-tests
determined a significant increase in abstraction subscale scores between 72-hours pre-and one-month post-ECT, $t(12) = -2.94$, $p_{adj} = .037$, $d = -0.76$, and a significant decrease in delayed recall subscale scores between 72-hours pre- and 72-hours post-ECT, 
$t(14) = 3.02$, $p_{adj} = .028$, $d = 0.72$. There were also trending significant decreases in both attention and language subscale scores between 72-hours pre- and one-month post-ECT, 
$t(12) = 2.64$, $p_{adj} = 0.065$, $d = 0.91$ and $t(12) = 2.54$, $p_{adj} = .078$, $d = 0.79$, respectively.

RM-ANOVA revealed no significant or trending significant differences in any ECCA subscales throughout the study timepoints. See Table 5 for all mean and standard deviation values for ECCA and MoCA subscales and Table 6 for post-hoc pairwise t-test results for significant and trending significant subscales determined by RM-ANOVA.

Table 4

*Mean and Standard Deviation Values for MoCA and ECCA Subscales for the Three Study Visits*

<table>
<thead>
<tr>
<th>Subscales</th>
<th>72-Hours Pre-ECT Mean (SD)</th>
<th>72-Hours Post-ECT Mean (SD)</th>
<th>One-Month Post-ECT Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Executive</td>
<td>4.23 (1.01)</td>
<td>4.00 (0.71)</td>
<td>4.78 (0.44)</td>
</tr>
<tr>
<td>Naming</td>
<td>2.85 (0.38)</td>
<td>2.62 (0.65)</td>
<td>2.89 (0.33)</td>
</tr>
<tr>
<td>Attention</td>
<td>5.53 (0.74)</td>
<td>5.00 (1.25)</td>
<td>4.77 (0.93)</td>
</tr>
<tr>
<td>Language</td>
<td>2.40 (0.74)</td>
<td>2.07 (0.70)</td>
<td>1.62 (1.19)</td>
</tr>
<tr>
<td>Abstraction</td>
<td>1.40 (0.74)</td>
<td>1.53 (0.64)</td>
<td>1.85 (0.38)</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>2.80 (0.57)</td>
<td>1.53 (1.92)</td>
<td>2.00 (1.96)</td>
</tr>
<tr>
<td>Orientation</td>
<td>5.87 (0.35)</td>
<td>5.40 (0.83)</td>
<td>5.62 (0.77)</td>
</tr>
<tr>
<td>ECCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orientation</td>
<td>3.88 (0.34)</td>
<td>3.56 (0.63)</td>
<td>3.50 (0.76)</td>
</tr>
<tr>
<td>Subjective</td>
<td>1.81 (0.98)</td>
<td>2.25 (1.29)</td>
<td>2.00 (1.52)</td>
</tr>
<tr>
<td>Informant</td>
<td>44.23% (35.58%)</td>
<td>57.69% (46.08%)</td>
<td>59.09% (43.69%)</td>
</tr>
<tr>
<td>Attention</td>
<td>1.88 (0.96)</td>
<td>1.81 (0.98)</td>
<td>1.50 (1.02)</td>
</tr>
<tr>
<td>Autobiographical Memory</td>
<td>90.77% (11.23%)</td>
<td>82.05% (20.93%)</td>
<td>87.88% (21.20%)</td>
</tr>
<tr>
<td>Factual Knowledge</td>
<td>3.50 (1.21)</td>
<td>3.63 (1.31)</td>
<td>3.57 (1.28)</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>2.13 (1.41)</td>
<td>1.63 (1.67)</td>
<td>2.21 (1.72)</td>
</tr>
</tbody>
</table>

Table 5

*Post-hoc Paired t-test t and p-values for Significant and Trending Significant MoCA Subscales According to Repeated-measures ANOVA*

<table>
<thead>
<tr>
<th>MoCA Subscales</th>
<th>t</th>
<th>p</th>
<th>p.adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naming</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T₁ vs T₂</td>
<td>1.90</td>
<td>0.082</td>
<td>0.246</td>
</tr>
<tr>
<td>T₁ vs T₃</td>
<td>-1.00</td>
<td>0.347</td>
<td>1.000</td>
</tr>
<tr>
<td>T₂ vs T₃</td>
<td>-2.00</td>
<td>0.080</td>
<td>0.242</td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T₁ vs T₂</td>
<td>2.09</td>
<td>0.056</td>
<td>0.167</td>
</tr>
<tr>
<td>T₁ vs T₃</td>
<td>2.64</td>
<td>0.022</td>
<td>0.065</td>
</tr>
<tr>
<td>T₂ vs T₃</td>
<td>0.46</td>
<td>0.656</td>
<td>1.000</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T₁ vs T₂</td>
<td>1.44</td>
<td>0.173</td>
<td>0.519</td>
</tr>
<tr>
<td>T₁ vs T₃</td>
<td>2.54</td>
<td>0.026</td>
<td>0.078</td>
</tr>
<tr>
<td>T₂ vs T₃</td>
<td>1.14</td>
<td>0.213</td>
<td>0.639</td>
</tr>
<tr>
<td>Abstraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T₁ vs T₂</td>
<td>-1.00</td>
<td>0.334</td>
<td>1.000</td>
</tr>
<tr>
<td>T₁ vs T₃</td>
<td>-2.94</td>
<td>0.012</td>
<td>0.037</td>
</tr>
<tr>
<td>T₂ vs T₃</td>
<td>-2.31</td>
<td>0.040</td>
<td>0.118</td>
</tr>
</tbody>
</table>

*Note. MoCA = Montreal Cognitive Assessment. T₁ = 72-hours pre-ECT. T₂ = 72-hours post-ECT. T₃ = one-month post-ECT. p = uncorrected p-value. p.adjusted = adjusted p-value with Bonferroni correction. *p < .05. ^ = trending significant (p = 0.06 - 0.100).*

3.3 Objective Two: Monitoring the Short- and Long-term Effects of ECT on Clinical Symptoms

At baseline, the mean QIDS-SR-16 score was 19.88 (SD = 3.01), 11.00 (SD = 5.85) 72-hours post-ECT, and 13.23 (SD = 6.10) one-month post-ECT. RM-ANOVA revealed a significant difference between QIDS-SR-16 total scores throughout the three study time points, $F(2,24) = 13.44, p < .001$. Further post-hoc pairwise t-tests indicated a significant decrease in QIDS-SR-16 total scores between 72-hours pre- and 72-hours post-ECT, and between 72-hours pre- and one-month post-ECT, $t(15) = 6.09, p.adj < .0001, d = 1.91$ and $t(12) = 3.98, p.adj = .005, d = 1.38$, respectively.

At baseline, the mean BSS score was 15.07 (SD = 9.11), 7.55 (SD = 6.62) 72-hours post-ECT, and 8.63 (SD = 8.33) one-month post-ECT. RM-ANOVA revealed a significant difference between BSS total scores throughout the three study time points, $F(2,24) = 14.43, p < .001$. Further post-hoc pairwise t-tests indicated a significant decrease in BSS total scores between 72-hours pre- and 72-hours post-ECT, and between
72-hours pre- and one-month post-ECT, \(t(14) = 4.63, p.adj = .001, d = 0.95,\) and \(t(12) = 3.96, p.adj = .006, d = 0.74,\) respectively.

At baseline, the mean GAD-7 score was 12.13 (SD = 5.19), 7.82 (SD = 4.69) 72-hours post-ECT, and 8.78 (SD = 6.32) one-month post-ECT. RM-ANOVA revealed a trending significant difference between GAD-7 total scores throughout the three study time points, \(F(1.3, 15.63) = 2.90, p = 0.101.\) Further post-hoc pairwise t-tests indicated a significant decrease in GAD-7 total scores between 72-hours pre- and 72-hours post-ECT, \(t(15) = 3.02, p.adj = .026, d = 0.87.\) QIDS-SR-16, BSS, and GAD-7 total score boxplots can be seen in Figure 5.
Figure 5. Boxplots of QIDS-SR-16, BSS, and GAD-7 Clinical Scales. QIDS-SR-16 = Quick Inventory of Depressive Symptoms, Short Form. BSS = Beck Scale for Suicide Ideation. GAD-7 = General Anxiety Disorder-7 Scale. *p < .05. **p < .01. ****p < .0001. Note: Significant differences are adjusted p-values with Bonferroni correction.
3.4 Objective Three: Investigate the Short-term Effects of ECT on Cortical Excitability

Pairwise t-tests revealed a significant increase in LICI-related inhibition between 72-hours pre- and post-ECT, \( t(7) = 2.41, \ p(adj) = .047, \ d = 0.33 \). There were no significant differences between 72-hours pre- and post-ECT measures for CSP, SICI, or ICF (\( t(5) = 0.71, \ p(adj) = 0.513 \), \( t(8) = 0.66, \ p(adj) = 0.527 \), and \( t(8) = 0.83, \ p(adj) = 0.431 \), respectively). See Figure 6 for boxplots of TMS measures 72-hours pre- and post-ECT. See Figure 7 for MEP responses of TMS measures 72-hours pre- and post-ECT.

Figure 6. Boxplots of CSP, SICI, ICF, and LICI Measures. ECT = electroconvulsive therapy. CSP = cortical silent period. SICI = short interval intracortical inhibition. ICF = intracortical facilitation. LICI = long interval intracortical inhibition. sp-TMS = single pulse transcranial magnetic stimulation. *\( p \leq .05 \). Note. Significant differences are adjusted \( p \)-values with Bonferroni correction.
A

SINGLE PULSE TMS 72-HOURS PRE-ECT

![Graph showing MEP amplitude (microvolts) over time (seconds) for 72-hours pre-ECT.]

SINGLE PULSE TMS 72-HOURS POST-ECT

![Graph showing MEP amplitude (microvolts) over time (seconds) for 72-hours post-ECT.]

B

CORTICAL SILENT PERIOD 72-HOURS PRE-ECT

![Graph showing EMG background activity, return of EMG background activity post-TMS pulse, and silent period for 72-hours pre-ECT.]

CORTICAL SILENT PERIOD 72-HOURS POST-ECT

![Graph showing EMG background activity, return of EMG background activity post-TMS pulse, and silent period for 72-hours post-ECT.]

Legend:
- P1, P2, P3, P4, P5, P6, P7, P8, P9
- Average

Legend for graphs:
- MEP AMPLITUDE (MICROVOLTS)
- TIME (SECONDS)
- Time ranges: 0.1 to 0.18 seconds pre-ECT and post-ECT.
Figure 7. Individual and Averaged MEP Responses for Each TMS Measure 72-hours Pre- and Post-ECT. Average signal is denoted by a black line. Individual responses are denoted by colours.Px = participant ID. ECT = electroconvulsive therapy. MEP = motor evoked potentials. TMS = transcranial magnetic stimulation. LICI = long interval intracortical inhibition. A: Baseline single pulse-TMS 72-hours pre-and post-ECT. B: Cortical silent period 72-hours pre- and post-ECT. C: Short interval intracortical inhibition 72-hours pre- and post-ECT. D: Long interval intracortical inhibition 72-hours pre-and post-ECT. E: Intracortical facilitation 72-hours pre- and post-ECT.

3.5 Objective Four: Investigate if Cortical Inhibition or Excitation is Related to Change in Cognitive or Clinical Symptoms

Pearson correlations were conducted between all baseline levels of TMS measures and LICI change scores and cognitive and clinical total scores. Correlations with TMS change scores were only conducted for LICI because it was the only TMS measure that showed a significant difference between 72-hours pre- and post-ECT (determined in objective 3). For cognitive total scores, Pearson correlations revealed a negative relationship between baseline LICI measures and ECCA total change score one-month post-ECT ($r = -.093, p < .001$). There were no other correlations between TMS measures and ECCA or MoCA total scores.
Pearson correlations were conducted between cognitive subscales that showed a significant or trending significant difference throughout study time points (determined in objective 1) with baseline levels of TMS measures and change in LICI scores. These Pearson correlations revealed a significant negative correlation between change in LICI scores and MoCA attention change scores one-month post-ECT ($r = -.880, p = .020$).

Pearson correlations also revealed a trending significant positive relationship between baseline levels of SICI and MoCA abstraction change scores one-month post-ECT ($r = .710, p = .073$). There was also a trending significant negative relationship between baseline levels of CSP and abstraction change scores one-month post-ECT ($r = -.83, p = .081$). There were no other significant or trending significant relationships between TMS measures and cognitive subscales that showed significant or trending significant differences between timepoints in objective one. See Figure 8 for significant and trending significant correlation graphs.
Figure 8. Significant and Trending Significant Correlations Between TMS Measures and Total and Subscale Scores of Cognitive Measures. ECT = electroconvulsive Therapy. 

For clinical scales, Pearson correlations revealed a positive relationship between baseline levels of SICI and BSS total change score one-month post-ECT ($r = .76, p = .046$). There was a trending significant positive relationship between LICI change scores and BSS total change score 72-hours post-ECT ($r = .67, p = .098$). There were no other significant or trending significant correlations between TMS measures and clinical total scores. See Figure 9 for the correlation graphs.
Figure 9. Significant and Trending Significant Correlations Between TMS Measures and Change in Total BSS Scores. BSS = Beck Scale for Suicide Ideation. SICI = short interval intracortical inhibition. sp-TMS = single pulse transcranial magnetic stimulation. LICI = long interval intracortical inhibition. ECT = electroconvulsive therapy.

4. Discussion

The current study monitored the short- and long-term cognitive effects of ECT using the ECCA and the MoCA in an in-patient population receiving ECT treatment. This study also monitored the short- and long-term effects of clinical symptoms using the QIDS-SR-16, BSS, and GAD-7. Our third objective was to investigate the short-term effects of ECT on cortical inhibition and excitation using CSP, SICI, LICI, and ICF TMS measures. Finally, our last objective was to determine if baseline levels and change in levels of cortical inhibition and excitation were related to change in cognition and clinical symptoms following ECT.

This study revealed ECT had a temporary negative effect on cognition according to the MoCA. Analysis of change of specific subscales of the MoCA revealed that ECT had a short-term negative impact on delayed recall and a long-term improvement of abstraction skills. Second, ECT significantly improved symptoms of depression and suicidal ideation 72-hours and one-month post-ECT, and improved anxiety symptoms 72-hours post-ECT. Third, there was a short-term increase of GABA_B related cortical inhibition, indexed by LICI, post-ECT. Further, some correlations were obtained between cortical inhibition levels and cognitive outcomes, such as the ECCA total score, and MoCA abstraction and attention subscale scores. However, the direction of the
relationship differed from one measure to the other. Finally, levels of cortical inhibition, measured with SICI and LICI, correlated with change in symptoms of suicidal ideation.

4.1 Cognitive Findings

Our study revealed a significant decline of cognition, measured with MoCA total scores, in the acute phase post-ECT. This decrease resolved one-month post treatment, suggesting that ECT might have a short-lasting detrimental effect on cognition. This is contrary to Hebbrecht and colleagues (2020) who did not find a short-term decline in MoCA scores at the group level, but instead found a significant improvement in MoCA scores three months post-ECT in comparison with the first three sessions of treatment and compared to one-week post-ECT (Hebbrecht et al., 2020). Of note, they reported a decline in MoCA total scores one week after ECT at the individual level for 26% of patients (compared to 69% of participants in our study). In another study, a decline in MoCA total scores was also found in 25% of individuals with depression 1 to 5 days post-ECT (Moirand et al., 2018).

Interestingly, some studies reported improvements in cognition post-ECT. Hermida and colleagues (2020) found MoCA total scores significantly increased one-week post-ECT (Hermida et al., 2020). However, the average score of the MoCA from baseline to one-week post-ECT only increased by one point in that study (from 25.7 to 26.9), which suggests that it may be marginally significant on a clinical point of view. In our study, the average MoCA score 72-hours post-ECT decreased by 10% (from 84.12% to 74.32%), which translates to a 2-3 point decrease (depending on how many sections the participant completed). This suggests a slightly more clinically relevant decrease in cognition. Seow and colleagues (2019) also found an increase in MoCA total score after six sessions of ECT (Seow et al., 2019). The latter study had a much lower pre-ECT MoCA total score compared to our study (63% compared to 84%, when converted to percentages). These lower baseline scores could be linked to cognitive impairments associated with depression (Perini et al., 2019), which may have improved as depressive symptoms improved throughout treatment. In a diverse mental health population no changes in MoCA total scores were found after six sessions of ECT on a group level, although the authors did report a trend of worsening cognitive symptoms specifically in individuals with a diagnosis of depression (P. C. Tor et al., 2021).
Tor and colleagues (2021) also found a trend for improvement in MoCA scores in individuals with a diagnosis of mania, psychotic depression, and catatonia, and a significant improvement in individuals with positive psychotic symptoms (P. C. Tor et al., 2021). These findings highlight the heterogeneity of cognitive outcomes following ECT. Supporting this, Hebbrecht and colleagues (2020) divided their sample into cognitively impaired (MoCA score below 23 at baseline) and non-cognitively impaired individuals. They found non-cognitively impaired individuals had a significant decline of MoCA scores from baseline to one-week post-ECT, and then a significant increase three-months post-ECT. This is compared to the cognitively impaired group who showed no significant differences between the time points. They also found individuals with psychosis significantly improved from the first three sessions of ECT to three- and six-months post-ECT, and individuals without psychosis showed no significant differences between timepoints (Hebbrecht et al., 2020). This highlights the need to study cognitive impairments at the individual level rather than group level, as any cognitive impairment following ECT is clinically important.

In addition to total scores, we investigated the impact of ECT on cognitive subscales. The MoCA abstraction and delayed recall subscales were the only subscales that showed any significant difference throughout the time points. Specifically, the abstraction score significantly improved from 72-hours pre-ECT to one-month post-ECT. This is like other studies that found a significant improvement in the abstraction subscale after a full session of ECT (Moirand et al., 2018; Seow et al., 2019). It is unclear why abstraction may change throughout ECT, however it may be due to the higher level thinking needed to answer these questions correctly, which may be limited at baseline when cognition is impaired by depression (Perini et al., 2019). Delayed recall subscale scores had a significant short-term decline post-ECT. This is contrary to Hebbrecht and colleagues (2020) who found a significant improvement in delayed recall scores three-months post-ECT compared to before the third-ECT session and one-week post-ECT (Hebbrecht et al., 2020). There was no significant difference in delayed recall subscale found by Moirand and colleagues (2018) for the full sample, however for patients who experienced cognitive deficits post-ECT, delayed recall was one of the subscales most affected (Moirand et al., 2018).
Regarding the ECCA, our findings revealed no acute or long-term changes in total or subscale scores. This is contrary to our hypothesis and to the results from the initial study from Hermida and colleagues (2020) who showed a significant decrease one-week post-ECT on the ECCA total score, and a decrease in all subscales one week post-ECT, except for orientation and factual knowledge (Hermida et al., 2020). Although, in a sample of elderly patients with bipolar depression, Parker Schwab and colleagues (2021) found either no change or improvement in ECCA total scores post-ECT in most individuals (85.7%). The mean ECCA change for the whole group increased almost significantly ($p = 0.054$), contrary to our study in which change in ECCA scores over time was not close to significance (Parker Schwab et al., 2021). One key difference between this study and ours is that all participants in Parker Schwab and colleagues' (2021) study received right unilateral electrode placement, which has been shown to cause less cognitive impairment (C. Loo, 2013; C. K. Loo et al., 2008, 2014), whereas bitemporal placement was the most common in our study. Overall, there are many factors which may account for the variability in cognitive outcomes post-ECT seen in our study and others. The lack of significant change in ECCA total and subscale scores may indicate the ECCA is not sensitive enough to assess cognition throughout ECT, especially since the MoCA total and subscale scores revealed significant changes. The MoCA has previously been shown to be a more sensitive measure compared to other cognitive measures, such as the Mini Mental Status Exam (Moirand et al., 2018), adding support for this cognitive measure being used in research and potentially clinical settings.

4.2 Clinical Findings

The significant short- and long-term improvement in depressive symptoms post-ECT supports previous research on the antidepressant effects of ECT (Grunhaus et al., 2002; Health Quality Ontario, 2016; Hermida et al., 2020; Kellner et al., 2005; Kennedy et al., 2009; Nucifora et al., 2019; Schoeyen et al., 2015). Specifically, this reduction in depression symptoms has been seen post-ECT using the same measure of depression, the QIDS-SR-16 (Hermida et al., 2020; Parker Schwab et al., 2021). Although, our study had a much lower response rate than is typically reported (Health Quality Ontario, 2016; Hebbrecht et al., 2020; Parker Schwab et al., 2021). Using the same response and remission criteria, Parker Schwab and colleagues (2021) had a much higher response and
remission rate than our study (80% and 65% compared to 38% and 19%, respectively; (Parker Schwab et al., 2021). One key difference between this study and our study are the patient populations. Our study incorporated mostly individuals with a diagnosis of depression 30 years or older, whereas Parker Schwab and colleagues only included participants with a diagnosis of late-life bipolar depression (Parker Schwab et al., 2021). Although it has been shown there are no differences in responder rates between individuals with a diagnosis of depression compared to bipolar disorder (Nordenskjöld et al., 2012), it has been shown that older age has a significant effect on response. Specifically, ECT has shown to have a stronger positive effect on quality of life in older patients compared to younger patients (Brus et al., 2017; Güney et al., 2020; Nordenskjöld et al., 2012). It is important to note as well, even though few participants met the response or remission criteria in our study, there was a significant decrease in depression scores post-ECT, which is clinically significant, and supports previous research on the efficacy of ECT for depression. The higher response and remission rates found in other studies may be due to using more sensitive measures such as clinical interviews like the HAM-D24. Clinical interviews might be more sensitive as they are administered by a trained research personnel who can probe for deeper and more detailed responses, compared to self-report questionnaires which have restrictive multiple-choice questions.

The significant short- and long-term improvement in suicidal ideation also supports previous research on the clinical effects of ECT (Kennedy et al., 2009). In a study using the BSS with patients with a diagnosis of major depressive episodes, it was found both responders and non-responders had a significant improvement in suicidal ideation post-acute-right unilateral ECT treatment (Youssef et al., 2021).

The significant short-term improvement in anxiety symptoms post-ECT observed in our study is not well documented in the literature. Although, one study by Huang and colleagues (2019) found that anxiety largely decreased post-ECT. An important result from this study is that a bidirectional relationship between anxiety and depression was found, meaning higher levels of anxiety did not necessarily mean higher levels of depression and vice versa. This finding indicates a reduction in depression may not be the cause of a reduction in anxiety symptoms, therefore ECT may directly impact anxiety
symptoms (Huang et al., 2019). Overall, our study adds to the abundance of research showing the therapeutic effect of ECT on depression, suicidal ideation, and anxiety.

4.3 Cortical Inhibition and Excitation

This study revealed a significant increase in cortical inhibition measured by LICI 72-hours after ECT. This finding supports previous research that ECT increases cortical inhibition (Bajbouj et al., 2005, 2006; Sommer et al., 2002). As LICI is thought to measure GABA<sub>B</sub> receptor activity, this finding aligns with research showing GABA<sub>B</sub> activity increases post-ECT. For example, animal models of ECT show increased GABA<sub>B</sub> activity in mouse frontal cortices, while increases in hypothalamic GABA<sub>B</sub> receptor activity was found in humans [through a baclofen challenge blood test (see Esel et al., 2008); Esel et al., 2008; Green & Grey, 1987]. The increase of GABA<sub>B</sub> activity post-ECT provides insight into the therapeutic effect of ECT as GABA<sub>B</sub> receptors may be involved in the pathophysiology of depression. GABA<sub>B</sub> receptors affect the release of other neurotransmitters such as norepinephrine and serotonin because norepinephrinergic and serotonergic neurons are under the inhibitory control of GABA (Shiah & Yatham, 1998). Therefore, one possibility to how ECT might exert its therapeutic effects is by upregulating GABA<sub>B</sub> receptors and in turn upregulating norepinephrinergic and serotonergic neurotransmission (Gray & Green, 1987).

This study did not find any other significant changes in cortical inhibition or excitation measured by CSP, SICI, or ICF post-ECT. A lack of significant change in CSP, SICI, and ICF supports the finding from Voineskos and colleagues who also found no change in these measures (Voineskos et al., 2016). Notably, Voineskos and colleagues did not measure LICI. As CSP is thought to measure GABA<sub>B</sub> activity like LICI, a lack of significant change in CSP levels in our study may be due to the small sample size, resulting in lower statistical power. The finding that ECT did not have a significant effect on SICI in our study, may be due to the differences in GABA measurements. As mentioned, SICI is linked to GABA<sub>A</sub> receptor activity, therefore suggests that ECT may specifically act on GABA<sub>B</sub> activity.

In terms of glutamate activity, our study supports the lack of change in ICF levels that has been previously reported (Voineskos et al., 2016). In our study, this finding may also be due to the large sample of non-responders as it has been shown that excitability
remains unchanged after a course of unsuccessful ECT treatments (Bajbouj et al., 2005). Lack of change in ICF, a measure of glutamate, is an interesting finding since seizures are thought to increase glutamate levels (Barker-Haliski & White, 2015), although results are conflicting (see Sarlo & Holton, 2021 for a review). Additionally, one study found that glutamate levels return to normal within six minutes post-seizure (Elisabeth Ronne-Engström et al., 1992). Our results align with this, suggesting that glutamate levels were back to normal when post-ECT ICF measures were taken. These findings provide insight into the distinct mechanisms of ECT on GABAergic and glutamatergic mechanisms, although more research with a larger human sample is needed.

4.4 Relationship Between Cortical Inhibition and Excitation and Clinical and Cognitive Symptoms

Levels of cortical inhibition at baseline, assessed with LICI, CSP, and SICI, were correlated with ECCA total scores and MoCA abstraction subscale scores. Specifically, individuals with higher levels of baseline inhibition, measured with LICI, were more likely to see long-term cognitive improvement. In addition, individuals with a stronger increase in LICI inhibition post-ECT had a stronger improvement in the MoCA attention subscale one-month post-ECT. These findings may lead to baseline levels and changes in cortical inhibition, measured with LICI, providing insight regarding long-term cognitive changes post-ECT.

A trending significant relationship was seen between both baseline SICI and CSP values and change in MoCA abstraction subscale scores one-month post-ECT, such that individuals with lower baseline inhibition showed a stronger long-term improvement on the MoCA abstraction subscale. The relationships between different TMS measures and cognitive total scores and subscales are interesting as they may provide a better understanding of the mechanisms involved in specific cognitive functions. Most importantly, they may help better understand the neurophysiological underpinnings of the cognitive impact of ECT. Although, as this sample is small (especially for CSP), these relationships should be interpreted with caution.

For clinical symptoms, there was a relationship between cortical inhibition and change in suicidality symptoms. Specifically, there was a trending significant relationship between LICI change scores and BSS change score 72-hours post-ECT, such that
individuals with a larger increase in LICI inhibition post-ECT had a larger short-term improvement in BSS scores. This finding shows that the level of change in inhibition may underlie the change in suicidal ideation symptoms. This supports Sun and colleagues (2018) who also found a relationship between LICI and suicidal ideation symptoms after a course of magnetic seizure therapy (MST). Although, LICI was measured in the DLPFC with interleaved TMS and electroencephalography (TMS-EEG), instead of the motor cortex like in our study (Sun et al., 2018). This study was a follow up to their previous study which found that baseline levels of LICI in the DLPFC correlated with change in suicidal ideation symptoms after MST (Sun et al., 2016). Both studies also explored the relationship between suicidal ideation symptoms and LICI measured in the motor cortex, however no significant relationships were found. In their 2018 study, Sun and colleagues were also able to use LICI, measured in the DLPFC, to identify patients who achieved resolution of suicidal ideation (having a pre-MST suicidality score of 1 or above and a post-MST suicidality score of 0) with a 90% sensitivity and 88% specificity. As the DLPFC has been implicated as an important brain region in the pathophysiology and treatment of depression (Koenigs & Grafman, 2009), these previous findings, along with ours, support the need for further research into the relationship between cortical inhibition and clinical symptoms, especially predicting reduction of suicidal ideation symptoms.

Similar to the relationship of LICI and BSS, it was also found that higher levels of baseline inhibition, measured with SICI, was related to a stronger improvement in BSS scores one-month post-ECT. This finding is less clinically significant as levels of SICI did not change between 72-hours pre- and post-ECT, however it is still worth noting.

Altogether these relationships provide very useful information regarding the association of inhibition and clinical and cognitive symptoms. Importantly, these findings suggest clinical symptoms and cognitive outcomes following ECT may have similar mechanisms and must be further researched.

The lack of relationship between depression scores measured with the QIDS-SR-16 and any baseline level of TMS measure or change in LICI score supports the lack of relationship between depression symptoms and CSP and SICI seen in the study by Voineskos and colleagues (Voineskos et al., 2016). To our knowledge there are no
studies looking at the relationship of LICI or ICF and depression. As previously mentioned it is worth investigating cortical inhibition and excitation in brain regions implicated in depression, rather than just the motor cortex, as these regions have shown different results (Sun et al., 2016, 2018).

4.4 Future Directions

The next steps for this research would be to recruit a larger sample size to increase statistical power and allow covariates (e.g., electrode placement, diagnosis, sex, age) into the analyses. Recruitment for this study is currently on-going as we aim to recruit a sample size of 60. Including electrode placement as a covariate may also be important as it has been shown to influence cognitive and clinical symptoms during ECT in previous research (Hermida et al., 2020; Kellner, Knapp, et al., 2010; Kellner, Tobias, et al., 2010; Prudic, 2008; Sackeim et al., 2007). Research should also group samples by diagnosis, as it has been shown that ECT may affect cognition differently depending on diagnosis (P. C. Tor et al., 2021). Cortical inhibition and excitation levels should also be investigated by diagnosis, to better understand the mechanisms of the disorders and how ECT impacts brain activity in specific diagnoses. Further research should also investigate the impact of ECT on clinical and cognitive outcomes at the individual level, as group and individual statistics can widely differ for the same sample (Hebbrecht et al., 2020; Parker Schwab et al., 2021). Finally, with a larger sample size, baseline levels of cortical inhibition and excitation should be used to investigate predictors of response to ECT using receiver operating characteristic to plot baseline levels of TMS measures of cortical inhibition and excitation with clinical response, as Voineskos and colleagues did in 2016.

4.5 Strengths and Limitations

This study has many strengths. First, it was one of the first studies to validate the ECCA developed by Hermida and colleagues (2020) and to study its use in a diverse psychiatric population. This study also has important clinical applications. It is the first study to investigate the neural mechanisms of action in a diverse psychiatric population using TMS. Using a transdiagnostic approach is a great advantage as it will help understand mechanisms relating to specific symptoms and disorders with a larger sample size. Finally, this study protocol was suitable and easily administered to a severely ill population receiving ECT treatment, therefore can be used in the future as a template to
further explore clinical and cognitive symptoms and cortical inhibition and excitation throughout the course of ECT.

Limitations of this study include a small sample size, limiting the ability to analyze group differences in sex, responders vs. non-responders, diagnosis, and electrode placement. Also, this study did not include the full population that receives ECT since it was missing individuals who were unable to participate in this study (e.g., incapable of consenting to research, non-verbal). This is important because there is evidence suggesting people with and without capacity to consent may experience different cognitive effects after ECT (P.-C. Tor et al., 2020). Cortical inhibition and excitation could not be collected from people who had contraindications to TMS, such as individuals with a history of epilepsy, who may provide additional insight into cortical inhibitory and excitability findings specific to that patient population.

As previously mentioned, there were limitations due to the COVID-19 pandemic. The main limitation was in relation to the small sample size. This was due in part by the ECT clinic being shut down for a period of time and in-person study restrictions due to COVID-19. These in-person study restrictions particularly limited the amount of data collected for the TMS measures of inhibition and excitation. These restrictions did not prevent us from collecting clinical and cognitive data remotely, however two sections on the MoCA could not be completed this way, also limiting the amount of data collected.

There were also limitations specifically with the ECCA. First, although in theory having an informant to complete and verify the informant and autobiographical memory section would be helpful and has been previously suggested in the literature (Kellner, Knapp, et al., 2010; Weiner et al., 1986), these sections were not always accurate because informants and participants (who were all in-patients at the ROMHC) did not live together for the first two assessments, and in some cases, for the full study. This became a challenge as informants were not always aware of cognitive functioning or able to correctly answer autobiographical memory questions (e.g., recall which restaurant the participant visited last). This may have led to the lack of change in autobiographical memory post-ECT, as informants might agree with the participant’s answer by default. In addition, some of the autobiographical memory questions chosen for the ECCA by Hermida and colleagues (2020) are not suitable for an in-patient population (i.e., what
psychiatric medication are they taking?). These questions are challenging for the participant but also the informant to answer as their list of medication is often very long and often changing. Also, the five factual knowledge questions on the assessment were the same for the three versions, therefore there were likely practice effects. More detailed instructions, like the MoCA has, would also be beneficial to ensure reliability between researchers when administering the assessment. Altogether, this highlights the need to refine the ECCA for a diverse population of out-patients and in-patients.

Finally, although this study can provide additional evidence regarding the mechanisms of ECT, clinical, and cognitive outcomes, we are unable to infer causation from these findings.

5.0 Conclusion

In summary, this study revealed ECT increases cortical inhibition, which provides additional information to understand the mechanisms of ECT. The findings from this study added evidence that ECT effectively improves depression, suicidal ideation, and anxiety. This study also revealed that the MoCA appears to be a more sensitive cognitive measure than the ECCA to assess cognition following ECT with a diverse in-patient population. This is important so clinicians and patients are aware of possible cognitive deficits following ECT. Finally, this study revealed cortical inhibition is potentially related to suicidal ideation and cognitive outcome post-ECT. Overall, these findings can be used to further understand the clinical and cognitive outcomes and mechanisms of ECT. The important finding that cortical inhibition is related to clinical outcome following ECT may be used to identify patients who are most likely to respond to ECT, leading to improved treatment selection for individuals with mental health disorders.
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