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Demographic And Clinical Variables Associated With Transcranial Magnetic Stimulation Response In Depression: A Growth Mixture Modeling Study

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DEMOGRAPHIC AND CLINICAL VARIABLES ASSOCIATED WITH TRANSCRANIAL MAGNETIC STIMULATION RESPONSE IN DEPRESSION: A GROWTH MIXTURE MODELING STUDY

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Dedication

Dedicated to my wonderful wife and sons,

Veronica, you have been my rock and my driving force throughout this entire process. Your untiring love and inspiration have carried me through the challenges of completing this doctoral dissertation amidst many challenges.

Juan Se and Santi you both are the foundation of my strength and the motivation for my perseverance. I hope you have learned that with hard work you can do anything you set your mind to!

Thank you for your patience, understanding, and continuous encouragement during the long hours of research and writing. Your support and encouragement kept me moving and fueled my drive to achieve my goals.

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by

JOHN WILLIAM CAPPS IV, MA

DISSERTATION

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Abstract

Depression is a growing public health crisis impacting millions around the world. Transcranial Magnetic Stimulation (TMS) is a non-invasive treatment for depression which has been FDA approved but the factors related to how well patients respond are still under investigation. The current study aimed to identify different treatment response patterns based on Patient Health Questionnaire (PHQ-9) scores over the course of transcranial magnetic stimulation (TMS) treatment for depression and to identify the differences between these response classes on demographic and clinical variables. A total of 285 patients from a psychiatric clinic were included with a sizable number of Hispanics and Military Families. Growth mixture modeling (GMM) was used to classify participants according to their response during TMS treatment. Three classes were identified: Responsive (56.5%), Excellent Response (56.6%), and Non-Response (13.3%). Various demographic and clinical variables were compared across these classes using chi-square tests of independence and analysis of variance (ANOVA) revealing 12 significant differences/associates ($p<.01$). Notably, higher depression severity at treatment initiation and comorbid chronic pain diagnosis was associated with poorer response. The results contribute to the literature confirming factors associated with TMS treatment response in a sample with underrepresented populations. Future research should include a follow-up at various timepoints to better understand the longevity of TMS treatment for depression. Likewise, brain biomarkers such as EEG could aid in better quantifying depression subtypes to further enhance treatment outcomes.

Table of Contents

List of Tables

List of Figures

Introduction

Globally, depression is one of the most prevalent mental health disorders and is considered the 4th leading cause of disability by the World Health Organization (Herrman et al., 2022; World Health Organization, 2017). The 2017 Global Burden of Disease study shows that approximately 264 million people can be considered as having depression and has increased from 1990 to 2017 in higher sociodemographic status areas, especially in North America (Liu et al., 2020). Importantly, the prevalence of depression is estimated to have tripled due to the COVID-19 pandemic (Ettman et al., 2020). Depression negatively impacts overall health and quality of life, which also increases the risk of death by suicide (Herrman et al., 2022). An estimated 15% of those with depression will die from suicide. (Blair-West, Mellsop, & Eyeson-Annan, 1997; Harris, Barraclough, Harris, & Barraclough, n.d.; Hedegaard, Curtin, & Warner, 2018).

Depression is a mood disorder characterized by low mood, anhedonia, significant weight loss/gain, insomnia/hypersomnia, psychomotor agitation/ retardation, fatigue, feelings of worthlessness / inappropriate guilt, decreased cognitive functioning, or recurrent thoughts of death, suicidal ideation. For a clinical diagnosis of major depressive disorder (MDD), the diagnosis and the Statistical Manual of Mental Disorders 5th edition text revision (DSM-V-TR) states that at least five of the previous symptoms must be present for at minimal a two-week period (American Psychiatric Association, 2013).

The causes of depression are not completely understood; however, many do agree that there is an interplay between biological, psychological, and societal factors (Remes, Francisco, & Templeton, 2021). Biological factors such as genetics, brain structural and functional connectivity, neurotransmitter levels, hormone imbalances, gut microbiome imbalances, and

chronic medical conditions have been implicated as important factors (Faravelli, Alessandra Scarpato, Castellini, & Lo Sauro, 2013; Gadzinowska et al., 2022; Godfrey, Gardner, Kwon, Chea, & Muthukumaraswamy, 2018; Katon, 2022; Kirkegaard & Faber, 1998; Mullins & Lewis, 2017; Steiger, Dresler, Kluge, & Schüssler, 2013; K. Wang et al., 2015; Zhao et al., 2012).

Numerous studies have identified certain risk factors and groups which may be at risk for developing depression. For example, depression is more common in those who experience trauma, stressful life events, or who come from lower socioeconomic backgrounds may be at higher risk for depression (Mandelli, Petrelli, & Serretti, 2015; Muntaner, Eaton, Miech, & O'Campo, 2004; Tang, Liu, Liu, Xue, & Zhang, 2014). Various populations, including women, members of the LGBTQ community, people with chronic health conditions, and certain racial/ethnic minority groups are also at an increased risk for depression (Bailey, Mokonogho, & Kumar, 2019; Birk et al., 2019; Kaniuka et al., 2019; Kessler, Mcgonagle, Swartz , Blazer ', & Nelson, 1993). Likewise, military members and their families are also at a higher risk of depression due to trauma, stressors, and military culture (Bonde et al., 2016; Donoho et al., 2018; McFarlane, 2009).

Since the 1960s, the prominent etiology of depression attributes the symptom profile to the lack or imbalance of monoamine neurotransmitters in the brain, dubbed the monoamine hypothesis (Heninger, Delgado, & Charney, 1996; Hirschfeld, 2000; Pryor & Sulser, 1991). Evidence demonstrates that pharmaceuticals that modulate synaptic concentrations of norepinephrine, serotonin, and/or dopamine can improve depressive symptoms (Delgado, 2000). Therefore, initial treatment of depression consists of four to eight weeks of antidepressant drugs such as selective serotonin reuptake inhibitors (SSRI) or selective norepinephrine reuptake inhibitors (SNRI) (Gelenberg, 2010).

Despite the development of over 50 different antidepressants, remission of depressive symptoms using medications has not significantly increased over the past 30 years (Lacerda, 2020; Papakostas & Fava, 2009). Approximately two-thirds of individuals with MDD do not respond to initial antidepressant treatment and require changes in medications, additional medications, and psychotherapy (Fava, 2003; Gaynes et al., 2020). If a person still fails to respond after this increased level of care, the diagnosis is labeled as treatment resistant depression (TRD) (Papakostas, Jackson, Rafeyan, & Trivedi, 2020; Philip, Carpenter, Tyrka, & Price, 2010). TRD is further treated with combinations of pharmaceuticals, or if available, brain stimulation therapies, such as electroconvulsive therapy or transcranial magnetic stimulation (TMS) (Benadhira et al., 2017a; Conelea et al., 2017; Griffiths, O'neill-Kerr, Millward, Ksenija Da Silva, & Da Silva, 2019).

Even though the monoamine hypothesis of depression is the most prominent, two main observations conflict with its basis. First, healthy individuals who have depleted dietary tryptophan, which leads to decreased levels of serotonin, show little to no mood fluctuations (Booij, Van Der Does, & Riedel, 2003). The second observation is the delayed effect in which monoamine antidepressants medications have on improvement of mood symptoms. Researchers who focus on the biology of depression observe that changes within the cells produce changes in monoamine receptors and intracellular signal transduction, which evolved the monoamine hypothesis into the molecular hypothesis of depression. (Coyle & Duman, 2003; Manji, Drevets, & Charney, 2001; Wong & Licinio, 2004). Yet evidence from basic and applied neuroscience has changed core ideas about how antidepressants are and are not resulting in efficacious treatment.

Animal models demonstrate that monoamines are critical in brain development as they impact organization and cortical circuity, known as neural plasticity (Berardi, Pizzorusso, & Maffei, 2000; Gaspar, Cases, & Maroteaux, 2003). When genes that impact monoamine production are altered or pharmaceutical agents are administered, widespread changes in neural plasticity and behavior result (Doboszewska et al., 2017; Marathe, D'almeida, Virmani, Bathini, & Alberi, 2018). Equally, neuroimaging studies demonstrate that depression is associated with reduced grey matter volume and connectivity in both the prefrontal cortex and the hippocampus (Belleau, Treadway, & Pizzagalli, 2019; W. Liu et al., 2017; Price & Duman, 2020; Wise et al., 2017). Grey matter is made up of synaptic connections and reduced volume is thought to be indicative of reduced neuronal complexity and connectivity, hence, demonstrating concerns with neuronal organization and neuroplasticity (Castrén, 2005). These findings have led to the network hypothesis of depression.

The network hypothesis of depression proposes that dysfunctional information processing in specific brain networks is the primary cause of depressive symptoms. This idea is supported by one critical foundation of neuroscience: That the principal role of the nervous system is to store and process information, which is accomplished by complex interaction of neurons in networks (Buzsáki, 2004; Hua & Smith, 2004; Nakajima & Schmitt, 2020; Skilling, 2020). The nervous system is a highly adaptive structure which develops through interaction with the external and internal environment that constantly refines structure and function via neuroplasticity to process, store, and recall relevant information (Katz & Shatz, 1996). These networks are ones in which monoamines are critical, however, the augmentation of neurotransmitters alone is not believed to cause the clinical benefits. Many of the clinical benefits of antidepressants are thought to be the result of the augmentation of neurotransmitters

have on neural circuits via activating plasticity mechanisms, remodeling of synaptic connectivity, and changes on functional properties of the elements in specific circuits (Leistedt & Linkowski, 2013). Thus, the network hypothesis proposes that psychiatric disorders such as depression result from disturbances in information processing in core circuit nodes, which for depression, is the prefrontal cortex.

The prefrontal cortex is the most significantly connected brain area and controls behavior, interprets the importance of sensory information, and controls internal states of arousal (George, Ketter, & Post, 1994). The prefrontal cortex has connections to almost all other brain areas with some of the most significant being connected with cortical sensory areas, the limbic system, and the brainstem (Li et al., 2018). Neuroimaging studies demonstrate that the pathophysiology of depression involves significant dysfunction within fronto-limbic networks which includes the dorsal lateral prefrontal cortex (dlPFC) (Liao et al., 2013; Sexton et., 2009;). More specifically, it is thought that depressive symptoms arise from disrupted connections within neural networks involved in cognitive control (central executive), reward processing (salience network), and emotional processing (default mode network) (Anderson et al., 2016; Menon, 2011; Seeley et al., 2007; Fan et al., 2019) (See Figure 1). Decreased activity within the central executive network is associated with increased activity in the default mode and decreased activity in the salience network (Kaiser et al., 2015; Liao et al., 2018; Hamilton et al., 2013; Menon, 2011; Seeley et al., 2007). Studies involving the activation of dlPFC via transcranial magnetic stimulation has shown direct effects on these connected areas and on depressive symptomology (Chen et al., 2013; Kozel et al., 2011; Zheng et al., 2020).

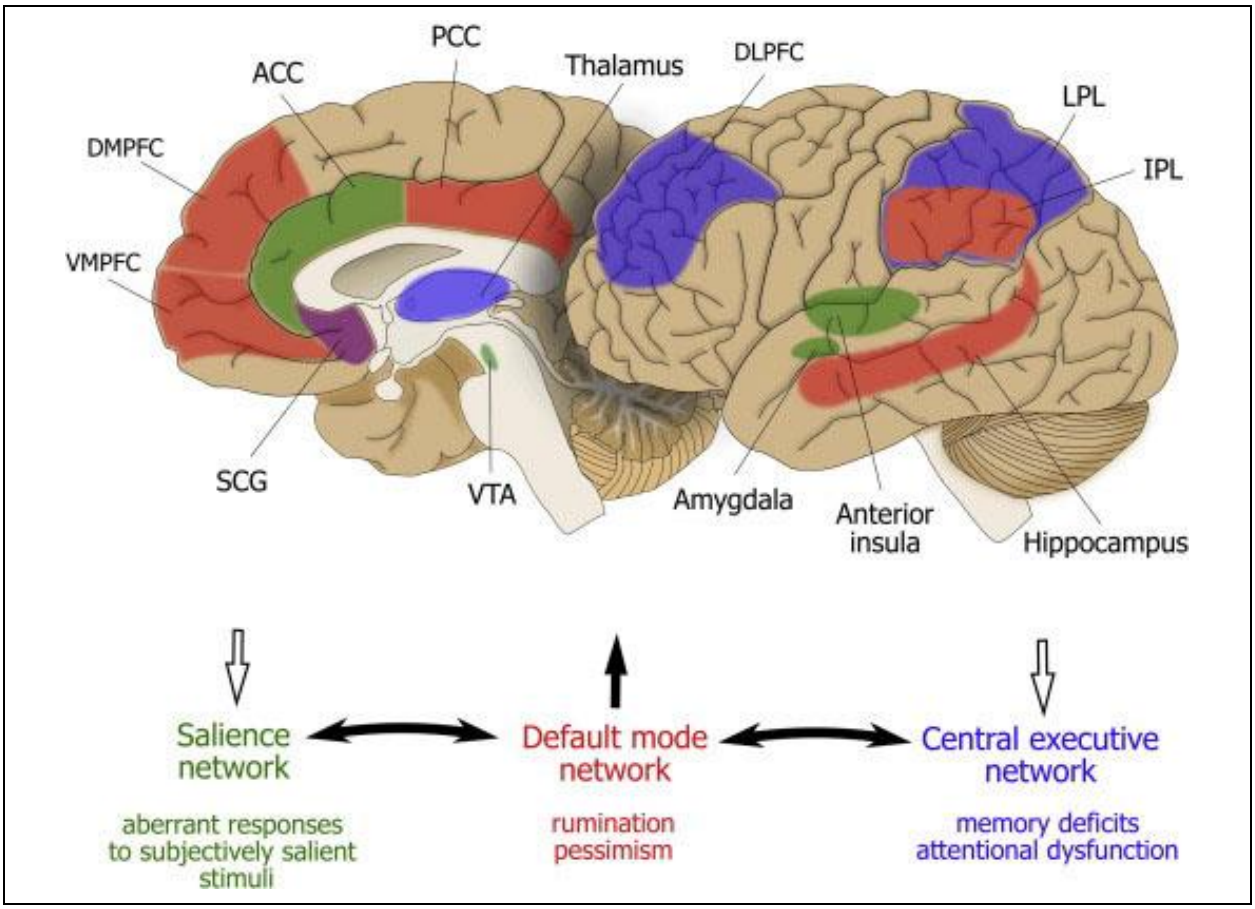

Figure 1: Areas and networks involved in Depression

Note. Blue = Central executive associated areas; Red = Default Mode Network associated areas; Green = Salience network involved areas; ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; IPL = inferior parietal lobe; LPL = lateral parietal lobe; PCC = posterior cingulate cortex; SCG = subgenual cingulate gyrus; VMPFC = ventromedial prefrontal cortex; VTA = ventral tegmental area. Adapted from "Repetitive Transcranial Magnetic Stimulation for Treatment Resistant Depression: Re-establishing Connections" by R. J. Anderson, K. E. Hoy, Z. J. Daskalakis, and P. B. Fitzgerald, 2016, Clinical Neurophysiology, 127(11), p. 3394-3405. Copyright 2016 by Elsevier.

Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation (TMS) is a non-invasive procedure which involves delivery of magnetic stimulation using short duration, alternating, pulsed, magnetic waves to stimulate to the cerebral cortex. TMS was first introduced by Anthony Barker and colleagues in 1985 as a means to stimulate the human motor cortex (Barker, Jalinous, & Freeston, 1985).

Barker, now retired, had a long career which was mainly focused on medical physics and clinical engineering including the effects of electromagnetic fields on the human body (Hamad Medical Corporation, 2023).

Most commonly, pulses of TMS are delivered repetitively, known as repetitive TMS, or rTMS. These pulses can be delivered at either high (10–20 Hz | HF-TMS) or low frequency (≤ 1 Hz | LF-TMS). These pulses generate electrical currents which modulate cortical excitability, and it is principally believed that HF-TMS produces excitatory processes and LF-TMS causes inhibitory processes (P. B. Fitzgerald, Brown, & Daskalakis, 2002; Fregni & Pascual-Leone, 2007; Marangell, Martinez, Jurdi, & Zboyan, 2007). These focal pulses are generated and delivered to the cerebral cortex using an electromagnetic coil with the strength of each pulse being approximately 1.5 tesla equivalent to what is generated by magnetic resonance imaging (MRI) device (Deng, Lisanby, & Peterchev, 2013; Roth, Amir, Levkovitz, & Zangen, 2007).

HF-TMS has been approved since 2008 by the FDA as a treatment for MDD (George et al., 1995; Rosedale, Lisanby, & Malaspina, 2009). The recommended procedure for treatment of depression involves high frequency, left prefrontal TMS occurring five times per week over a 4–6 week period (Lefaucheur et al., 2014; Perera et al., 2016). The selection of cortical sites of stimulation in the treatment of depression is based on pathophysiological changes considered to underlie these disorders, as mentioned prior. Since cortical activity is asymmetric in the dlPFC with depression, various directions of TMS treatments have been explored. Primarily these treatments include HF-TMS on the left dlPFC to address hypoactivity, LF-TMS on the right dlPFC to address hyperactivity, or a combination of these procedures (Berlim, Eynde, & Daskalakis, 2013; Berlim, Eynde, Tovar-Perdomo, & Daskalakis, 2014a). Even though the exact effect on the cortical tissues, neuron activation, glial activity is not completely understood, the

important antidepressant therapeutic effect is considered to be from the long-term changes beyond the time of stimulation (Lefaucheur et al., 2014; Perera et al., 2016).

The antidepressant effects of TMS are associated with changes in modulating network connectivity (Dichter, Gibbs, & Smoski, 2015). Via neuroplasticity, TMS can modulate connections within and between networks by changing the effectiveness of synapses between neurons (i.e. long-term potentiation or long-term depression; LTP/LTD) (Ridding & Rothwell, 2007). Neuroimaging demonstrates that after HF-TMS to the left dlPFC, healthy individuals have increased connectivity between anterior cingulate cortex (ACC) and the fronto-parietal network, which includes dorsal cingulate cortex, posterior dorsal media PFC (dmPFC), dlPFC, inferior parietal lobule, inferior frontal cortex and posterior temporal lobes (Tik et al., 2017). Other studies demonstrate that depression symptom reduction was associated with greater modulation in connectivity in these networks (Fox et al., 2014; Fox, Buckner, White, Greicius, & Pascual-Leone, 2012; PB Mitchell, 2006; Salomons et al., 2014). All together these demonstrate that dlPFC TMS enacts long-term adjustments of abnormal connectivity within the networks involved in depression. However, the exact mechanisms which TMS produces its long-term therapeutic response are not completely understood and many details are still debated (Goldsworthy, Hordacre, Rothwell, & Ridding, 2021).

There is an agreement on treatment factors related to outcomes which have aided in creation of TMS treatment guidelines. These factors include stimulation intensity, frequency, number of pulses administered, and duration of the treatment course (Gershon, Dannon, & Grunhaus, 2003; Padberg et al., 2002; Sachdev et al., 2002). These primary studies informed practices which have resulted in guidelines to follow in clinical applications of TMS for depression (Perera et al., 2016). Better response to TMS has been seen in individuals who

received treatment at a stimulation intensity closer to the individual's maximum threshold (P. Fitzgerald, Hoy, Anderson, & Daskalakis, 2016). This common finding is also demonstrated in neuroimaging paradigms as the TMS magnetic field is able to effect more of the target brain area.

There is also extensive evidence of an TMS antidepressant effect (Benadhira et al., 2017a, 2017b; Berlim, Berlim, Eynde, & Daskalakis, 2012; Berlim, Eynde, Tovar-Perdomo, & Daskalakis, 2014b; Berlim et al., 2014a; Berlim, Eynde, & Daskalakis, 2013; Fitzgerald et al., 2009). Recent meta-analysis comparing the efficacy and tolerability of treatment resistant depression (TRD) interventions demonstrated that TMS was one of the most efficacious treatments (Papadimitropoulou, Vossen, Karabis, Donatti, & Kubitz, 2017). This meta-analysis looked at change from baseline, response rates, and remission rates at different time points. Only TMS demonstrated statistically significant mean difference in symptom severity change from baseline at 4 weeks post-intervention. Furthermore, at 6 weeks post-intervention, TMS demonstrated higher response rates when compared to 17 other depression treatments included in the meta-analysis. TMS also demonstrated robust remission rates at 2, 4, and 6-weeks post-intervention. At 6 weeks post-intervention, TMS also showed the highest remission rates and ranked first among all interventions. Even though there is a consensus that TMS is effective for depression, many review studies include a wide variety of treatment factors, such as TMS protocol used, brain area targeted, the number of TMS sessions, and the settings for which the treatment took place (M. Berlim et al., 2012; M. T. Berlim et al., 2014a, 2014b; Marcelo T. Berlim, Van Den Eynde, & Daskalakis, 2013; Marcelo T. Berlim, Van Den Eynde, & Jeff Daskalakis, 2013; Cao, Deng, Su, & Guo, 2018; De Santis, Azorina, & Reitz, 2014; Razza et al.,

2021). This inconsistency in the literature has produced variable findings on response rate in major depressive disorder and treatment resistant depression.

A meta-analysis of 34 randomized controlled trials containing 1371 subjects with major depressive disorder demonstrate that after 13 dlPFC HF-TMS sessions, 29.3% of the participants had significant reduction in depression and 18.6% of the participants showed remission. For those participants who received sham, TMS showed a 10.4% reduction and also showed 5% remission (Berlim et al., 2014b). Some argue that the evidence is not yet conclusive and the treatment too experimental to be included as a first line treatment for MDD (Malhi et al., 2021). While it is true that studies have shown varying response and remission rates for TMS, consideration of different subgroups of TMS response is important for advancing the literature on TMS. Exploring these latent subgroups and the predictive factors of TMS response can aid in making important clinical decisions concerning treatment of TRD.

A variety of demographic, clinical, and neuroimaging aspects have also been explored as important variables associated with response to TMS. With respect to demographic variables, older age has been found to be related to poorer TMS response (Fregni et al., 2005; Manes et al., 2001; Pallanti et al., 2012; Rostami, Kazemi, Nitsche, Gholipour, & Salehinejad, 2017; Su, Huang, & Wei, 2005). The reasoning behind age as an important factor is the increased cortical atrophy and the increased the space between the coil and the target brain area and other neurodevelopmental factors that are present in older individuals (Sabesan et al., 2015). Another potentially interactive factor may be the length of the treatment, as other studies with longer TMS treatments (> 2-3 weeks) have found no effect of age (Kaster et al., 2019; Lisanby et al., 2009). Finally, a meta-analysis of 54 studies has also found that being female is also associated with better TMS response (De Santis et al., 2014; Huang, Wei, Chou, & Su, 2008).

A wide variety of clinical features can predict the antidepressant response to TMS. The most common included factors relate to treatment resistance, depressive characteristics, comorbidities, medication use/history, and treatment course. In general, individuals who have failed to respond to fewer treatments (decreased treatment resistance) have better response to TMS (Brakemeier, Luborzewski, Danker-Hopfe, Kathmann, & Bajbouj, 2007a; Fregni et al., 2005, 2006; Lisanby et al., 2009).

Factors related to depression are also predictive of TMS response. Individuals who have less severe depression, a shorter duration of their current episode, and a history of recurrent episodes have a greater antidepressant response (Brakemeier, Luborzewski, Danker-Hopfe, Kathmann, & Bajbouj, 2007b; Fitzgerald, Hoy, Anderson, & Daskalakis, 2016; Holtzheimer, Russo, Claypoole, Roy-Byrne, & Avery, 2004; O'Reardon et al., 2007). Poorer response to TMS has been found in those who have psychotic symptoms of MDD (Mitchell & Loo, 2006).

Furthermore, Rostami and colleagues (2017) explored which symptom profile of depression was the most predictive of positive response to TMS. They found that individuals with more cognitive-affective symptoms (i.e., sadness, pessimism, feelings of guilt, feeling punished, self-dislike, suicidal ideation, crying, agitation, worthlessness) when compared to individuals with somatic symptoms (i.e., fatigue, sleep problems, irritability, appetite problems, concentration difficulties) were more likely to have a positive response to TMS.

One of the most common TMS targets is the dlPFC and the impact on depression involves increased cognitive functioning. However, somatic symptomology is thought to reflect depression that involves a greater deal of autonomic nervous system dysfunction (Rostami et al., 2017). This finding complements findings from Drysdale et al., (2017) which demonstrated that different neurophysiological profiles predicted TMS response. Within these profiles, the

common clinical symptoms always included depressed mood, anhedonia, and fatigue. When considering anhedonia there was abnormal connectivity in fronto-striatial network which is especially important in cognitive-affective functioning. Notably, these authors also found that the profiles associated greater anxiety and sleep symptoms of depression had better response to dmPFC TMS (Drysdale et al., 2017).

There are also similar findings concerning comorbidity with other mental health and physical health conditions. Fitzgerald et al. (2016) found that response rates to TMS were higher for individuals who had no comorbid mental health disorders (54.1%) than in those with panic disorder (35%), post-traumatic stress disorder (47%), or generalized anxiety disorder (47%). This finding is in line with previous findings showing enhanced response to TMS is more likely if there is no comorbid anxiety disorder (Fitzgerald et al., 2016; Lisanby et al., 2009).

Anxiety medication was also found to have a similar result. According to research by Kaster and colleagues (2019), people who use benzodiazepines are more likely to respond slowly than they are to respond quickly. Others have not found antipsychotic medications to have an impact on TMS, but few studies have taken this into account when predicting TMS response. (Fitzgerald et al., 2016). The overall variables that are related to the TMS response from the previous research reviewed are listed in Table 1.

Table 1: Summary of Variables Associated with TMS Response

Better Response	**Poorer Response**
• Younger Age • Female • Decreased Treatment Resistance • Less severe depression • Short depressive episode • History of Recurrent episodes • Cognitive Symptoms of MDD • No Comorbid Psychiatric Disorders	• Older Age • Psychotic Symptoms of MDD • Somatic Symptoms of MDD • Diagnosis of Panic Disorder • Diagnosis of PTSD • Diagnosis of General Anxiety Disorder • Increased use of Benzodiazepines

Even though studies have shown that the above variables are linked to TMS response, the results vary on which variables are the most accurate predictors of TMS's anti-depressant effect. Additionally, many of these results come from experimental TMS paradigms that don't reflect how TMS is used to treat depression in the real-world clinical settings. The current knowledge does indicate that each person's response to TMS variers and that this response is likely to be influenced by demographic and clinical factors. Therefore, there is a need for studies that look at differences in TMS response.

Method

The current study used a retrospective methodology and utilized data from a psychiatric clinic to examine the response to TMS for individuals experiencing depression. By implementing growth mixture modeling (GMM), the current study examines TMS response patterns during TMS depression treatment, while considering the unique patterns across participants and the response within each individual. The two main aims were to; 1) determine specific TMS response groups within real-world clinical data and 2) characterize and compare these groups on demographic and clinical variables. All study procedures were submitted to the University of Texas at El Paso internal review board (IRB) alongside a letter of collaboration from the clinic providing the data.

Research Context and Timeframe

The data for this investigation was obtained from a psychiatric clinic located in El Paso, Texas. El Paso is a city in southwest Texas that borders both Mexico and New Mexico. According to the U.S. Census of 2021, there were 839,238 people living in El Paso County, and about 83% of those living there indicated they were Hispanic. (U.S. Census Bureau, 2021). Fort Bliss is a renowned US Army post and one of the largest military installations in the world. Part of it is within the city limits of El Paso. As of 2022, the installation has approximately 31,400 active-duty military members, more than 11,500 civilian employees, and approximately 33,800 family members (Military OneSource, n.d.).

Furthermore, the data examined in this study comes from patients who received TMS treatments between May 2021 and February 2023. This period was significantly affected by the COVID-19 pandemic. The pandemic had serious effects on mental health around the world through contributing to increased stress, anxiety, and depression (Ettman et al., 2020).

Clinic Setting

A local Board Certified Psychiatric-Mental Health Clinical Nurse Specialist owns and runs the psychiatric clinic that provided the data. (PMHCNS). It has two locations in El Paso, one of which is about 5 miles from Fort Bliss. The clinic has approximately fifteen staff members, including a Board Certified Psychiatric-Mental Health Clinical Nurse Specialist, a Board Certified Psychiatric-Mental Health Nurse Practitioner (PMHNP), a Licensed Vocational Nurse, a Registered Nurse, a Medical Assistant, and a Certified Medical Assistant. It has two supervising psychiatrists and one advising psychiatrist.

The clinic offers a wide range of mental health services, such as psychiatric evaluation, psychological testing, neurophysiological testing, medication management, Spravato (esketamine) treatment, and transcranial magnetic stimulation. The clinic has used multiple forms of media, including traditional and social media, to promote its services. In February 2020, transcranial magnetic stimulation (TMS) was added as a service. Since starting this service the number of TeleEMG Neurosoft TMS (K160309 "CloudTMS") has increased from 1 to 4.

Individuals seen at the clinic come from diverse referral sources. The majority of patients are referred from local primary care doctors, psychiatrists, and other mental health experts. Furthermore, some individuals may self-refer to the clinic. The clinic accommodates a variety of insurance providers including commercial insurance policies, Tricare, and Veterans Affairs. For those experiencing financial difficulties, the clinic offers the option to apply for reduced rates by submitting a hardship letter.

Patients who are referred to the clinic, will first complete a psychiatric evaluation, unless they are directly referred only for a specific treatment regimen (i.e., Veteran Affairs may refer with a diagnosis for Medication Management, Spravato®, or Transcranial Magnetic

Stimulation). After an initial psychiatric evaluation and any necessary psychological testing have been completed, the provider recommends a treatment plan based on their psychiatric and medical history, symptom profile, medication history, and preference for continued care.

Their provider would offer TMS treatment as an option if; 1) failed to respond to 2 or more antidepressants (in different classes) or had unwanted side effects from taking antidepressants at a clinically beneficial dose, 2) had no history of seizures, 3) had no metal implants or objects in the head or body, such as cochlear implants, pacemakers, or aneurysm clips. Alongside this suggestion, the provider would explain the treatment and the necessary time requirements and commitment. They would also provide other recommendations, their benefits, and commitment and let the patient decide which option would work best for their situation.

Participants

As of February 2023, there were 611 people who had started TMS treatment at the clinic. All of the patients signed an informed consent form before getting treatment. However, the informed consent did not specify that the clinic could use their unidentified data for research until May 2021. A total of 285 patients diagnosed with Depression (ICD-10 codes F32.2, F33.0, F33.1) were included in the study. Exclusion criteria included patients with Major Depression with Psychotic Features- recurrent- severe with psychotic features (ICD-10: 32.3), those who were not between the ages of 18 and 60, and those who had not completed at least 30 TMS treatment sessions. (See Figure 2).

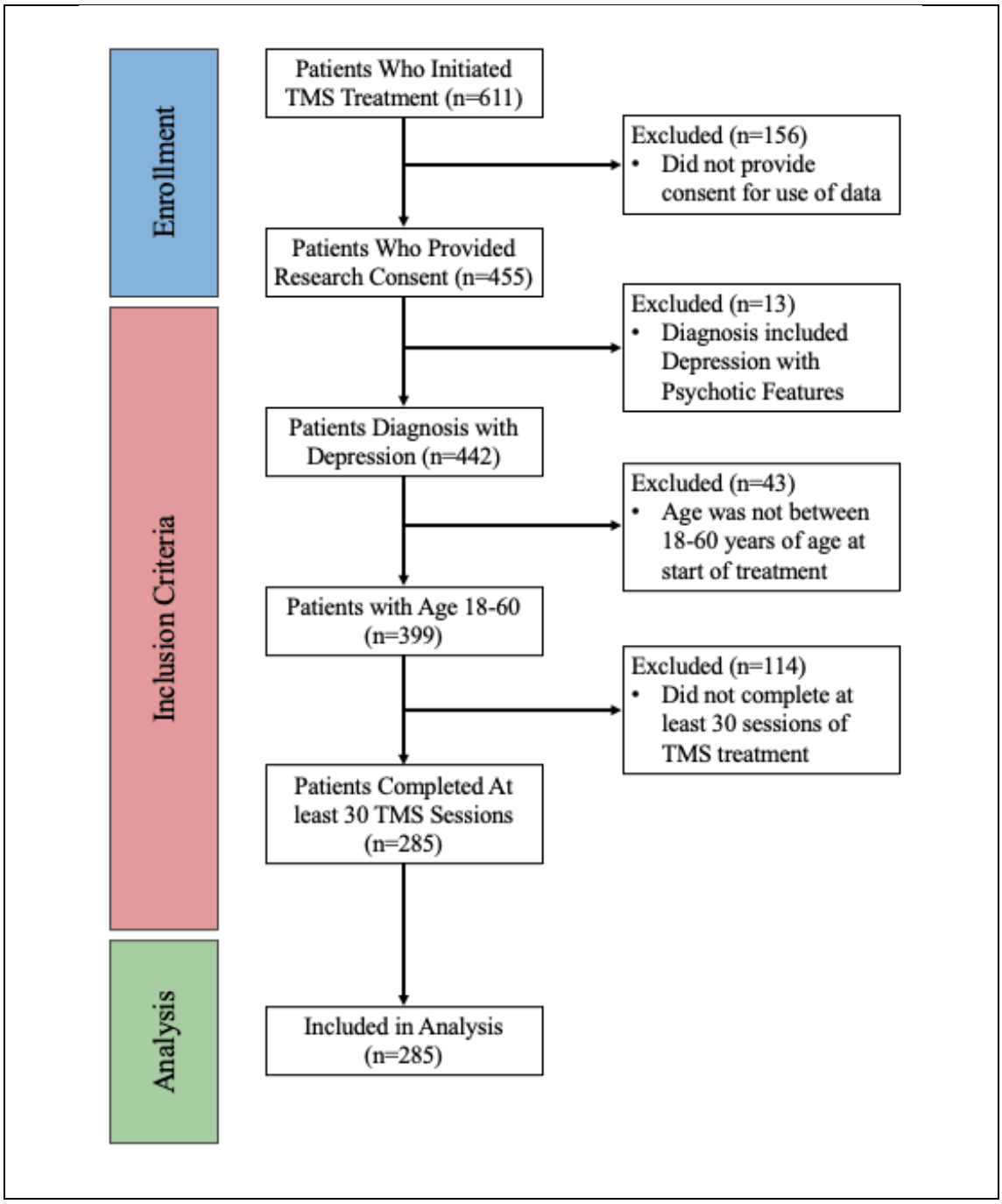

Figure 2: Diagram for Inclusion in the Study Dataset

An attrition analysis was conducted comparing the excluded 114 patients which did not complete 30 sessions to the 285 included in the dataset. An independent samples T-test indicated no significant difference between the those included in the dataset and those excluded on Age, $t(397) = -0.164$, $p = .87$. Chi-squared tests of independence indicated there were no significant

associations between exclusion/inclusion membership and Gender, Ethnicity/Race, Education Level, or Employment Status, Insurance Coverage, Sexual Orientation/Identity, or Relationship Status, $p > .05$. The chi-square tests did indicate there was an association between exclusion/inclusion membership and Military Involvement, χ^2 (1, N = 399) = 9.33, $p = .002$. and Military Dependent, χ^2 (1, N = 399) = 4.694, $p = .03$. Inspection of the contingency table for Military Involvement revealed that there were less individuals with military involvement than expected in the excluded group. Inspection of the contingency table for Military Dependent revealed that there were less individuals who were not military dependents than expected in the excluded group.

The participants included in the study (N=285) were mostly women (69.83%). The two most prevalent ethnicities/races were Hispanic (47.02%) and White (43.86%). The participants' average age was 37.25 (SD = 10.49). The sample included people with education levels ranging from less than a fifth-grade education to a graduate degree. Most of the people in the group had at least a high school education (43.51%). Most participants reported not working (39.65%) or working full time (37.90%). Employment for those reporting current employment varied greatly, with Healthcare (15.2%), Education (9.6%), and Law Enforcement (8%) sectors being the most frequent. Insurance/Payment used by the patient for treatment cost was categorized into four segments: Tricare (47.02%), Commercial insurances (i.e. Blue Cross Blue Shield, Cigna, United Healthcare, Aetna) (32.98%), Veteran Affairs (11.23%), and self-pay (8.77%) (See Table 2).

Table 2: Basic Sample Demographics

Gender	**Frequency**	**Percentage**
Female	199	69.83%
Male	86	31.18%
Ethnicity/Race		
African American	19	6.67%
Asian	4	1.40%
Caucasian	125	43.86%
Hispanic	134	47.02%
Native American (Navajo)	1	0.35%
Native Hawaiian / Pacific Islander	2	0.70%
Education		
< 5th Grade	1	0.35%
< High School	7	2.46%
Associate	39	13.68%
Bachelor	45	15.79%
GED	12	4.21%
Graduate	35	12.28%
High School	124	43.51%
Missing	22	7.72%
Employment Status		
Disability/Medically Retired	24	8.42%
Not Working	113	39.65%
Full Time	108	37.90%
Part-Time	17	5.97%
Retired	6	2.11%
Missing	17	5.97%
Employment Sector		
Education	12	9.60%
Finance	7	5.60%
Food and Beverage	8	6.4%
Healthcare	19	15.2%
Law Enforcement	10	8%
Transportation/Delivery	5	4%
Active-Duty Military	4	3.2%
Other Categories *	60	48%
Insurance		
Commercial Insurance	94	32.98%
Self-Pay	25	8.77%
Tricare	134	47.02%
VA	32	11.23%

*Note: *Other categories of Employment Sector have 3.2% or less in percent of frequency*

There was a sizable proportion of participants who have served/serve in the United States armed forces (23.86%). All five major branches of the military were represented in this proportion of the sample, with the Army being the most frequent (55.88%). Notably, there were also a very large proportion of the entire sample who were dependents of Military members (36.49%). (See Table 3).

Table 3: Sample Descriptive Table: Military Service and Military Dependent

Military Service	**Frequency**	**Percentage**
Served/Serving	72	25.26%
No Service	217	74.74%
Military Branch		
Airforce	2	2.8%
Army	38	52.8%
Army National Guard	1	1.4%
Army Reserves	2	2.8%
Coast Guard	1	1.4%
Multiple Branches	2	2.8%
National Guard	1	1.4%
Navy	8	11.1%
Unknown Branch	18	25.0%
Military Dependent		
Yes	104	36.49%

The majority of the sample reported their sexual orientation/identity as heterosexual (84.21%). The relationship status varied across the sample, however most reported being married (65.26%). For the majority, they had only been married once (67.02%), however, some reported multiple marriages (23.51%). The number of previous marriages ranged from 1 to 4 with a mean of 1.41 (*SD* = .71). The number of children that participants had ranged from 1 to 7 with over half reported having at least 1 child (60.35%). Most participants reported being sexually active (60.70%) (See Table 4).

Table 4: Sample Descriptive Table: Sexual and Relationship Characteristics

Sexual Orientation/Identity	Frequency	Percentage
Bisexual	7	2.46%
Heterosexual	240	84.21%
Homosexual	5	1.75%
Transgender	1	0.35%
Missing	32	11.23%
Relationship Status		
Committed	13	4.56%
Divorced	15	5.26%
Married	186	65.26%
Separated	4	1.40%
Single	42	14.74%
Widowed	3	1.05%
Missing	22	7.72%
Previous Married		
Yes	67	23.51%
No	191	67.02%
Missing	27	9.47%
Parental Status		
Children	172	60.35%
No Children	89	31.23%
Missing	24	8.42%

Apparatus and Materials

TeleEMG Neurosoft TMS (K160309 "CloudTMS")

TeleEMG Neurosoft TMS (K160309 "CloudTMS") devices were used by the clinic for delivery of TMS treatments. The Neurosoft CloudTMS delivers magnetic waves via the discharge of high voltage capacitor (1.8 kV) through a stimulation coil (U.S. Food and Drug Administration, 2016). The pulsed magnetic field, which is generated by the discharge current (up to 10 kA), penetrates through tissues to induce electrical currents in cortical neurons. The Neurosoft TMS consists of the following components: Cooled figure-of-eight coil FEC-02-100-C (A. Figure 2), K8 coil holder and flexible arm for coil positioning (B. Figure 2), Laptop with

Neurosoft CloudNeuro software (D. Figure 2), Main unit of the magnetic stimulator (C. Figure 2), Cooling unit (E. Figure 2), Extra power supply unit (F Figure 2), Trolley with casters (G. Figure 2), and Patient Chair (H. Figure 2).

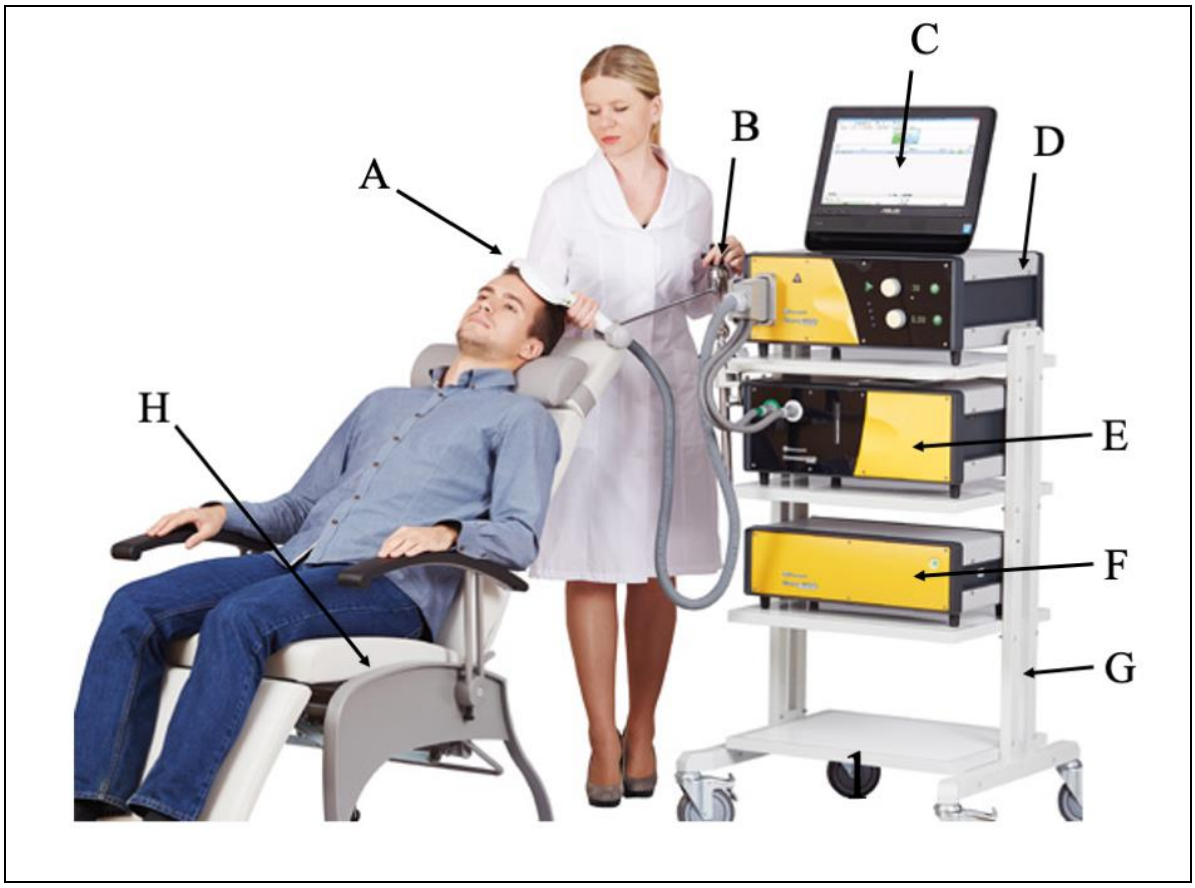

Figure 3: TeleEMG Neurosoft TMS "CloudTMS"

Note. Adapted from "Transcranial Magnetic Stimulation" [Image].(n.d.). *Retrieved December 12, 2022 from https://www.hightechinstruments.com/product/transcranial-magnetic-stimulation/*

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a commonly used questionnaire for the screening, diagnosing, and monitoring of depressive symptomatology. This self-report questionnaire was specifically designed for use in primary care and in respect to DSM-IV criteria (Kroenke, Spitzer, & Williams, 2001; Spitzer, Kroenke, & Williams, 1999). The PHQ-9 continues to be the standard as DSM-V core criteria of MDD have not changed (Nemeroff et al., 2013). The PHQ-9 consists

of 9 symptom questions and asks responders to indicate how often you have been bothered by the symptom in the previous two weeks. Responders can indicate not at all (0), several days (1), more than half the days (2), and nearly every day (3) The final question asks how much these symptoms have made it difficult to perform activities of daily living (See Appendix E). The 9 symptoms items are summed, and scores can range from 0-27. The PHQ-9 is extensively used as a monitoring tool in clinical research and practice and shows good reliability (Cronbach's α ranging from 0.84-0.89) (Beard, Hsu, Rifkin, Busch, & Björgvinsson, 2016; Korsen & Gerrish, 2022; K Kroenke et al., 2001; Kurt Kroenke, Spitzer, & Williams, 2001a; Mcmillan, Gilbody, & Richards, 2010). The PHQ-9 also has excellent validity, and correlations with measures such as the Hamilton Depression Scale (r = 0.61), the Short Form General Health Survey (r = 0.73), and is negatively related to mental/emotional well-being scales (r =-0.406 to 0.531) (Beard, Hsu, Rifkin, Busch, & Björgvinsson, 2016; Keum, Miller, & Inkelas, 2018; Kroenke, Spitzer, & Williams, 2001; Sun et al., 2020).

Patients completed the PHQ-9, before their initial TMS mapping session. To track their progress during treatment, at the beginning of each week, patients were sent a secure and encrypted link via SMS to the phone number which they provided. This link contained the PHQ-9 questionnaire administered by the TMS CloudNeuro software. When given instructions for the PHQ-9, patients were reminded to think about symptoms since the last time they completed the questionnaire. The TMS technician overseeing their daily session would then check the CloudNeuro software and add the data to the TMS session note. If the patient had not completed the questionnaire, the technician would remind the patient to complete it or have them complete during their visit. If the patient did not complete it on their own, the technician may have administered the questionnaire verbal, recording their responses in the CloudNeuro questionnaire

system. The majority of the time, patients had already completed their PHQ-9 from their mobile phone by their first session of the week.

Demographic and Clinical Variables

A semi-structured interview was conducted by the provider to learn more about the patient during the psychiatric evaluation. The information gathered during the appointment was recorded in the electronic health record (EHR) system at the clinic. The majority of these appointments lasted approximately one hour. The collected information included both demographic data, such as age and gender, as well as clinical data related to the patient's mental health. Psychiatric medications, diagnoses, and COVID-19 were extracted using the EHR system to filter by the time in which they underwent the TMS treatment. COVID-19 was extracted from cancellation notes, which the clinic didn't implement until early 2022. Treatment-related variables such as motor threshold (MT) and the number of different TMS technicians seen over their treatment were extracted from the TMS session note completed during each patient's TMS session.

Following the literature regarding treatment response and depression remission, participants' change in PHQ-9 scores over the treatment was classified as Treatment Response and Depression Remission (Mcmillan, Gilbody, & Richards, 2010; Yeung et al., 2012). Treatment response was determined by calculating the difference between the Initial PHQ-9 score and the last PHQ-9 score and multiplying it by 100 to convert it to a percent; If that percent change was 50% or greater, participants were classified as having Treatment Response. Depression Remission was defined using their last submitted PHQ-9 score, if this score was less than 5, they were classified as Depression Remission.

TMS Treatment Procedures

All TMS treatment procedures followed the clinical guidelines and standards of practice (Perera et al., 2016). The general treatment procedure was an initial mapping session with initial treatment, and 35 subsequent TMS sessions. During the TMS mapping and initial session, and 35 subsequent TMS sessions. During the initial mapping session, the remaining sessions were scheduled by the attending TMS technician. The first 30 sessions were scheduled 5 times per week, Monday through Friday. The remaining sessions were scheduled to occur in a step-down fashion; the following week would consist of 3 sessions, the next week would consist of 2 sessions, and the final session would happen the following week.

The first TMS appointment consisted of TMS mapping and initial session. The PMHCNS and the supervising psychiatrist would first fit the patient with a TMS cap provided by CloudNeuro. During fitting, the PMHCNS and supervising psychiatrist used the beam method (see Beam et al., 2006 for a full description) to locate the dorsal lateral prefrontal cortex, verifying all measurements twice and marking the TMS cap to indicate treatment site. A TeleEMG Neurosoft TMS was used to measure motor threshold and deliver treatment. Participants' motor threshold (MT) was measured by placing the TMS coil over the left motor cortex area, M1. Incremental changes to TMS intensity were made until at least three movements in the right hand were observed during five stimulations, and the motor threshold was recorded. Then the coil was placed over the left dlPFC. The initial treatment intensity was dialed in according to the participant's tolerance while trying to be as close as possible to their motor threshold. Following this initial preparation of the TMS session, an initial 20-minute TMS session was conducted (See Appendix C).

The same FDA approved treatment protocol was performed during the remaining sessions, where sessions lasted approximately 20 minutes with 3000 pulses of stimulation being delivered over the entire session. Pulses were biphasic at an amplitude of 120% of MT. Each treatment consisted of 75 trains of pulses and pauses. Each train delivered 40 pulses with an 11-second pause between trains of pulses. Pulses in each train were delivered at 10Hz, that is, 10 pulses over 1 second. Every three sessions of TMS, the intensity was increased to the participant's preference until their maximum MT was reached, if not already reached.

In some cases, patients would receive additional or change in protocol from the standard HF L-dfPFC 10hz FDA approved protocol, if response was not notable by the 18 session or if other symptoms warranted it. This additional protocol was at the discretion of the overseeing provider, the overseeing psychiatrists, and based on the symptoms of the patient. The additional protocols included the bilateral procedure; 1. Bilateral Procedure - iTBS left dlPFC: triplet bursts with a pulse frequency of 50Hz, a burst frequency of 5Hz and 85% of motor threshold for ~4 minutes followed by inhibition right dlPFC: continuous pulses with a burst frequency of 1Hz and 120% MT, ~26 minutes; 2) OCD – inhibition over the supplementary motor area (SMA) continuous pulses with a burst frequency of 1Hz and 50% MT, ~20 minutes); 3) PTSD/Anxiety – right DLPFC, PTSD, continuous pulses with a burst frequency of 1Hz and 110% MT, ~7 minutes.

During each session, the attending TMS technician would attend to the patient in an office dedicated to TMS treatments. Then they have the patient fit the cap. Patients were sat in a reclining position in a fully adjustable chair purchased from CloudNeuro. The CloudNeuro software was used to locate the patient’s file. This recorded session data and synced it with their

online service and all TMS machines at the practice. The technician would then place the coil as indicated by the marks on the TMS cap and began their TMS protocol. The technician would monitor the participant to ensure that the coil placement was correct and made any adjustments mid-session due to patient movements. During treatment, the patient was allowed to have their music of choice. The attending TMS technician would monitor daily patient status, speaking with patients about their treatment, current mood, and general conversation. All information was noted in the electronic health records of the clinic during this time (See Appendix D). Providers would stop in approximately once a week to check on patient status and treatment response.

Data Extraction

A database was constructed from the electronic health record (EHR) system and CloudNeuro TMS software for patients who gave consent. The EHR system data contained demographic information, medical history, and clinical data. To create the database, the data was extracted from the EHR system using the software's Patient Reporting and Assignment utility. This utility allows for variables to be extracted from patient notes into a excel file. Coding for variables were done to conduct chi-squared tests of independence and ANOVA analysis (See Appendix E).

PHQ-9 and session information were also extracted from the CloudNeuro software, data was downloaded for those who gave research consent. Names in the TMS software sometimes differed in format from the EHR system. These names were manually inspected and then coded into the same format of the EHR system by matching of the patient age, their appointment dates, and TMS session data. Patient session data and PHQ-9 data was inspected in EHR data manually to look for potential errors in clinical note taking. When an error was found, the original online

questionnaire data or session data tracked by the TMS device and software was inspected and the research database updated.

In the database, PHQ-9 scores represent each time they completed the measure during treatment. The aim of the clinic was to have the PHQ-9 completed every Monday, some patients may have not completed it that day and may have not completed that entire week. Likewise, since patient start dates and the beginning of the next week varied, the PHQ-9 data used to model longitudinal response needed to be defined. To understand participants' response over their TMS treatment, nine PHQ-9 measure variables were extracted. The first PHQ-9 measure variable represented the initial PHQ-9 score before participants began treatment, PHQ-9 measure variables 2 – 6 represent PHQ-9 data submitted within TMS sessions 1-6, 7-12, 13-18, 19-24, and 25-30, respectfully. The final two PHQ-9 measurement variables represented PHQ-9 scores submitted within TMS sessions 34-35, and session 36. Any missing PHQ-9 scores during these time periods were marked a Missing (999) in the data base. If a patient had summitted multiple during these time periods due to schedule – session match, the highest value was extracted.

Statistical Analysis

Growth Mixture Modeling was conducted using Mplus Version 8.5 (Muthén and Muthén, 1997-2023). GMM allows for a parsimonious alternative representation of change trajectories with complex shapes (Ram and Grimm, 2009). Growth mixture modeling is an extension of Latent Growth Curve Modeling, however, GMM assumes that different classes exist within the population. GMM can determine mean growth trajectory and variation among the individuals in different latent classes, where class membership is presumed to not change over time (Muthén et al., 2002).

This analysis allows the study to examine different growth trajectories based on differences of intercept, slope, and acceleration/growth for the different classes (Asparouhov & Muthén, 2014; Nylund, Asparouhov, & Muthén, 2007). As Ram and Grimm (2009) describe, this model can be written as:

$$Y[t]_n = \sum_{C=1}^{C} \left(\pi_{nc}(g_{0nc} * A_{0c}[t] + g_{1nc} * A_{1c}[t] + e[t]_{nc})\right)$$

Given $0 \leq \pi_{nc} \leq 1$ and $\sum_{c=1}^{c} \pi_{nc} = 1$

In this equation, the portion within the inner parentheses represents a multiple group growth curve, where *c* represents to which group (or latent class) individual *n* belongs. Groups can differ in specific basis vectors, which describe the general pattern of change (e.g. linear, quadratic, etc.), means of latent variables, and variances of latent variables. Observed longitudinal data is represented on the left side of the equation by variable *Y* which is repeated measure at times *t* = 0 to T. On the right hand side of the equation, two latent variables g_{0n} and g_{1n} , two basis vectors A_0 and A_1, and a residual considering time, respectively describe the pattern, mean change, and individual variance in change. A_0 and A_1 help describe the pattern of change, as A_0 represents a fixed vector of 1s which represent the intercept for each class while A_1 is estimated growth pattern for each class (Ram & Grimm, 2009). Change is also described by the means, variance and covariance of the latent variables g_{0n} and g_{1n}, where the mean of g_{0n} represent the mean starting point and g_{1n} represents the amount of change from *t* = 0 to T. Finally, the variance and covariance of g_{0n} and $g_{1n.}$ represents the amount to which individuals differ from one another based on initial level, amount of change, and how initial level and amount of change are related (Ram & Grimm, 2009).

GMM allows for the probability that an individual n belongs to class *c* to be determined represented by π_{nc} (Ram & Grimm, 2009). This variable can range between 0 and 1 and determines the likelihood that the individual belongs to the latent class. This parameter allows for the latent classes *c* to be derived empirically from the analysis. Since these classes are unknown a-priori, previous research studies should guide the selection of how many subgroups are expected to exist(Nylund-Gibson, Grimm, & Masyn, 2019; Ram & Grimm, 2009; Wang & Bodner, 2007).

Statistical Procedure

Following the general literature, analysis was implemented using a step-by-step procedure (Grimm, Ram, & Estabrook, 2017; Nylund-Gibson et al., 2019; Ram & Grimm, 2009; Wikcrama, Lee, O'Neal, & Lorenz, 2017). First, the primary research hypothesis was generated: Patients' antidepressant response while undergoing TMS treatment does not represent a homogenous pattern. The specific hypothesis is that growth mixture modeling (GMM) will identify mulitple classes, likely three, based upon findings from Kaster et al. (2019). Kaster and colleagues (2019) used a sample of individuals with depression receiving six weeks of 37.5 minute 10hz TMS found three types of response in a sample of 388 individuals. Even though the depression measurement tool is different and several other aspects of the study, it is expected that GMM will be able to reveal latent classes of TMS treatment response (Blumberger et al., 2018).

As part of this first step, a latent growth curve model (LGCM) was conducted. The model includes 9 timepoints, Y_1-Y_9. Where Y_1 represents patient's initial PHQ-9 score and Y_9 represents their last PHQ-9 score. It was critical to include the number of TMS sessions which had been completed when the PHQ-9 was submitted. Since clinical procedures were not designed in a way that equally spaced-out collection of the PHQ-9 from patients, the model includes the regression

of PHQ-9 scores on the number of sessions which had been completed at time of submission (X_2 – X_8). Since initial PHQ-9 acted as the intercept and the last PHQ-9 always coincided on the 36th session, there was no need to control for number of sessions. This allows for the model to control for the amount of sessions up to the completion of the PHQ-9.

This "single-group" LGCM model served to determine the first the type of growth present in our data (Linear vs Quadratic) and presence of heterogeneity in the sample. LGCM assumes homogeneous population with a common growth trajectory when there were subgroups of individuals with different patterns of change over time. Next, we conducted a growth mixture model (GMM) to identify the subgroups within the sample and determine their unique growth trajectories.

First, a series of models were defined to determine if and how the groups differ in respect to the mean amount of change, the individual differences in change, and the pattern of changes. These models included 1-class, 2-class, 3-class, 4-class, and 5-class models. Following model definition, the final step was selection and interpretation of the model which has best fit. In the process outlined by Ram and Grimm (2009), this process initially involves an examination of the numeric values of the estimated parameters to find parameter estimates which are problematic. No problematic parameters were identified so the models were compared to the baseline model on the following statistics: The Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and adjusted Bayesian Information Criterion (aBIC) fit indices. Models with lower AIC, BIC, or aBIC fit indices indicate better model fit (Ram & Grimm, 2009; M. Wang & Bodner, 2007). Figure 4 depicts the latent growth mixture model for this study.

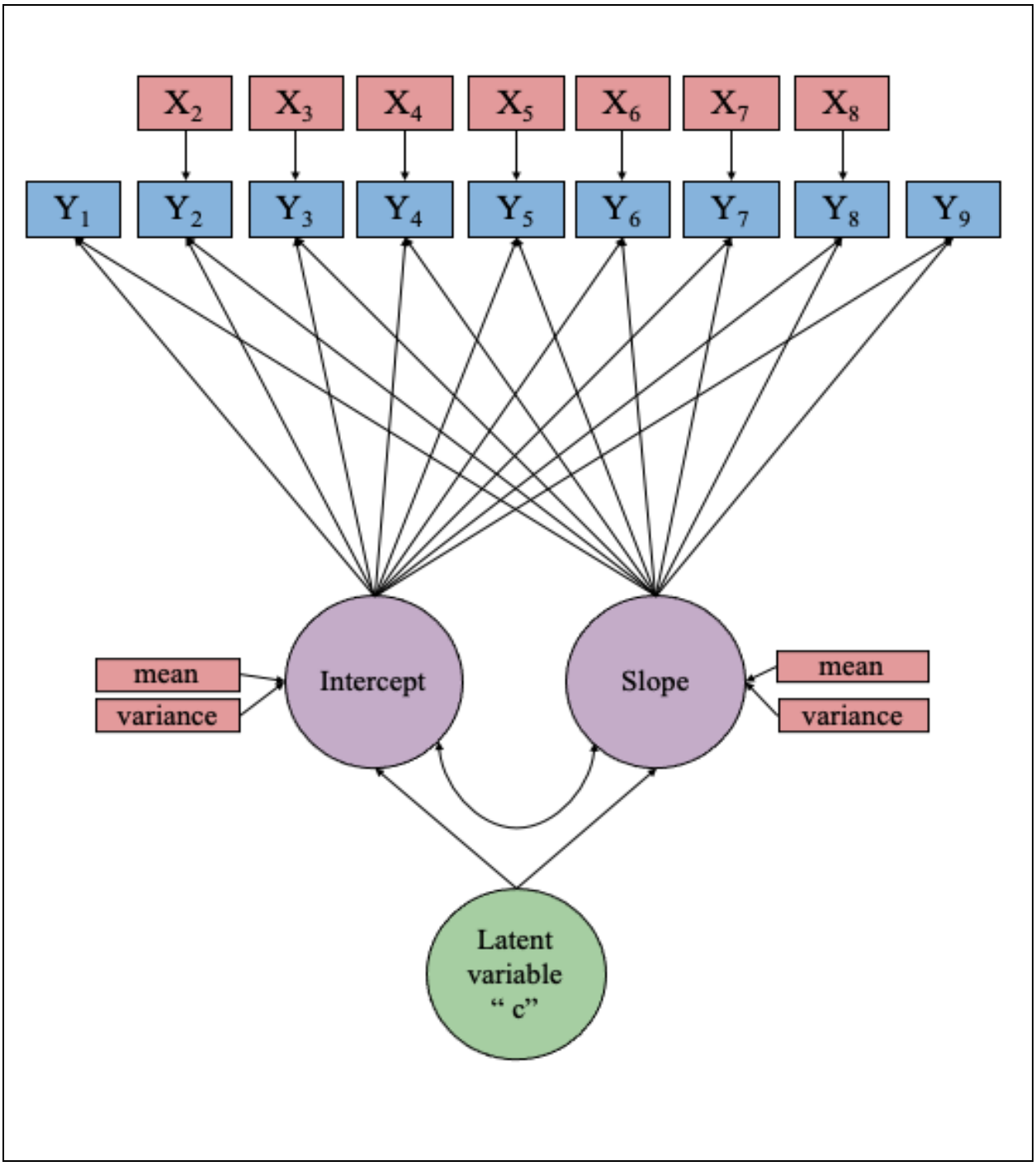

Figure 4: Growth Mixture Model Diagram for TMS Response

When fit indices are lower than the baseline model's fit indices, then entropy was examined (Ram & Grimm, 2009). Entropy is the amount of information explained by class separation and can be thought of a measure of how accurately one could assign cases to classes.

Classification in GMM is not as a fixed division, but rather, entropy represents the probability that each person belongs to each class. Entropy was compared among the competing models. Entropy values approaching 1 indicate better model fit, but they may vary depending on the context of the research. After entropy was assessed, then likelihood ratio tests were also evaluated. Vuong–Lo–Mendell–Rubin likelihood ratio (VLMR-LRT) and Adjusted likelihood ratio (Adjusted LRT) tests were examined to indicate that the model with C – 1 classes should be rejected in favor of the model with C classes. These measures statistically determined differences in model fit among competing models at $p = .05$ level of statistical significance. Data was examined exploring the expected and logical group differences, then a model of best fit was chosen.

Once the number of classes was determined, characterization and comparison of clinical, demographic, and treatment associated variables were performed (See Table 5). For some variables, like categories were collapsed to increase group sizes in each category. For example, having a GED and have at most high school were combined into one. When examining the associations between categorical variables and the classes of TMS treatment response, a chi-square test of independence was used. This test determines if there is an association between categorical variables and the TMS response classes. Cramer's-V was also obtained to determine the strength of the association. Cramer's V can also be employed to compare the association strengths between categorical variables, regardless of any differences in the sizes of the contingency tables, making it critical for comparing across different demographic and clinical variables. In general, with Cramer's V, a value of .1 or less indicates a weak association, a value between .1 and .3 indicates a moderate association, and a value of .3 or greater indicate a strong association (Kelley & Preacher, 2012; Tomczak & Tomczak, 2014)

Table 5: Variables to Be Compared Across the Three TMS Response Classes

Category	Variables	
PHQ-9	○ Initial PHQ-9 Score ○ Last PHQ-9 Score ○ Percentage Change in PHQ-9	○ Treatment Response Classification ○ Depression Remission Classification
Demographic	○ Gender ○ Age ○ Ethnicity/Race ○ Education Level ○ Employment Status/Sector	○ Military Service ○ Military Dependent ○ Sexual Orientation/Identity ○ Relationship Status ○ Parental Status
Clinical	○ Psychiatric Diagnoses	○ Prescribed Medications
Symptoms	○ Anxiety ○ Increased Appetite ○ Decreased Appetite ○ Depressive Mood ○ Excess Energy ○ Excess Worry ○ Fatigue ○ Feelings of Hopelessness ○ Feelings of Abandonment ○ Feelings of Emptiness ○ Feelings of Guilt	○ Feelings of Worthlessness ○ Impulsivity ○ Anhedonia ○ Increased Need for Sleep ○ Unable to Sleep / Stay Asleep ○ Paranoia ○ Racing Thoughts ○ Duration of Depression ○ Depression Onset ○ Presence of Suicidal Ideations ○ Impact of Symptoms on Life Areas
Psychiatric History	○ History of Abuse ○ History of Inpatient	○ History of Outpatient Treatment History of Suicide Attempt
Health	○ Tobacco Use ○ Alcohol Use ○ Drug Use	○ Regular Exercise ○ Medical Diagnoses ○ COVID-19
Treatment	○ Treatment Start Date ○ TMS Treatment Type ○ TMS Sessions Completed ○ Number of Technicians	○ Motor Threshold at Session 18 ○ # of Weeks to Complete 30 sessions ○ # of TMS Protocols Used ○ Type of Additional Protocol Used

For continuous variables, an analysis of variance (ANOVA) was used to determine significant variations in means across the classes of TMS treatment response. Before conducting the ANOVAs, variables were examined for violations of the analysis of variance model. When model assumptions concerning homogeneity of variance were violated, the Welch test was used to accommodate unequal variances. Results from ANOVA also have their effect sizes reported in omega-squared (ω^2) to better account for bias which may arise from sample variances and violations of the assumptions of analysis of variance (Albers & Lakens, 2018).

In cases where the overall ANOVA revealed a significant difference among the groups, post-hoc analyses were used to examine differences between the classes of TMS treatment response. Based on the homogeneity of variances, the Games-Howell test for unequal variances which also controls for family-wise error rate, decreasing the probability of making a type I error. When conducting the comparisons across the three classes it is important to consider the results in considering the number of comparisons made and our sample size. Since the current studied compared many variables across the three TMS response classes, one must consider type I error rates at the .05 level. As more comparisons are made, the chances of finding spurious significant results inadvertently increase, leading to potentially inaccurate conclusions. Taking this into account, even though we report significant findings which met the common error rate ($p<.05$), we act conservatively and only consider the results at the $p<.01$ level as sound when making conclusions from the study.

Results

In accordance with the outlined process, latent growth curve modeling (LGCM) was conducted to examine the longitudinal change of PHQ-9 scores during TMS treatment. The first step in this process was to determine the best-fitting growth model, which in this case was found to be a linear growth model rather than a quadratic growth model (See Table 6).

Table 6: Fit indices for the Latent Growth Curve Model Defining Growth

Fit Indices	**Linear**	**Quadratic**
AIC	11578.2	11596.5
BIC	11654.9	11673.2
RMSEA	0.094	0.098
CFI	0.877	0.868
TLI	0.873	0.864
Chi-Square	338.49	356.79
DF	96	96
p-value	<.001	<.001

Note. Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Root Mean Square Error of Approximation (RMSEA), Comparative Fit Indices (CFI), Tucker-Lewis Index (TLI), Degrees of Freedom (DF)

Despite using the best-fitting growth function, the results of the LGCM indicated a poor model fit. This poor fit can be attributed to the presence of heterogeneity in the sample, as discussed by Wikcrama, Lee, O'Neal, and Lorenz (2017). The LGCM assumes a homogeneous population with a common growth curve when there were classes of individuals with different patterns of change over time, therefore leading to poor model fit.

Next, growth mixture modeling was conducted to examine the presence of latent classes The fit of models with 2, 3, 4, and 5 latent classes was evaluated using multiple fit indices, including the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Sample-size Adjusted BIC (SABIC), entropy, and two statistical tests, Vuong-Lo-Mendell-Rubin test, and Lo-Mendell-Rubin Adjusted Likelihood Ratio Test (See Table 7).

Table 7: Fit Indices for Growth Mixture Modeling: PHQ-9 scores During TMS Treatment

Model	AIC	BIC	SABIC	Entropy	LMR-LRT (*p*-value)	VLMR-LRT (*p*-value)	Sample size by class
1-Class	11582	11659	11592	--	--	--	285
2-Class	11513	11600	11524	0.88	70.67 (.55)	-5769.76 (.53)	51/234
3-Class	11498	11597	11511	0.80	19.44 (.04)*	-5732.33 (.04)*	86/161/38
4-Class	11490	11599	11504	0.84	13.56 (.58)	-5722.04 (.57)	140/91/28/26
5-Class	11488	11608	11504	0.80	7.47 (.65)	-5714.86 (.65)	81/28/22/127/27

*Note. AIC = Akaike information criterion; BIC = Bayesian information criterion; LMR-LRT = Lo-Mendel-Rubin Adjusted LRT test; VLMR= Vuong-Lo-Mendell-Rubin LRT test; * = p<.05.*

The AIC, BIC, and SABIC values all indicated that the more complex models (with more classes) fit the data better. However, the differences in these values between the models were small, making it difficult to assess which model was best based on only the fit statistics. The entropy values were high for all models (>.80), indicating good accuracy in classification. The 2-class model yielded the best entropy values overall. However, the likelihood ratio tests all suggested that additional classes improved the fit of the model, with the 3-class model yielding the only significant result over the 2-class model. The 4-class model did not provider better statistical fit than the 3-class model.

Furthermore, group sizes for the additional classes in the 4-class and 5-class models were relatively small and did not contribute substantively nor practically to the overall classification of participants. By use of multiple fit indices, the likelihood ratio tests, and practical and meaningful review of the classes and their statistical changes the 3-class model and 2-class and 3-class model, the 3-class model was selected to be the most appropriate choice for the data. According to their TMS responses these classes were designated Responsive (Class 1), Excellent Response (Class 2), and Non-Response (Class 3) (See Figure 5). When inspecting model parameters for the 3-class solution, it was found that all model parameters were

statistically significant (p <.01), except for the slope factor of the Non-Response class, due to the growth over time being flat.

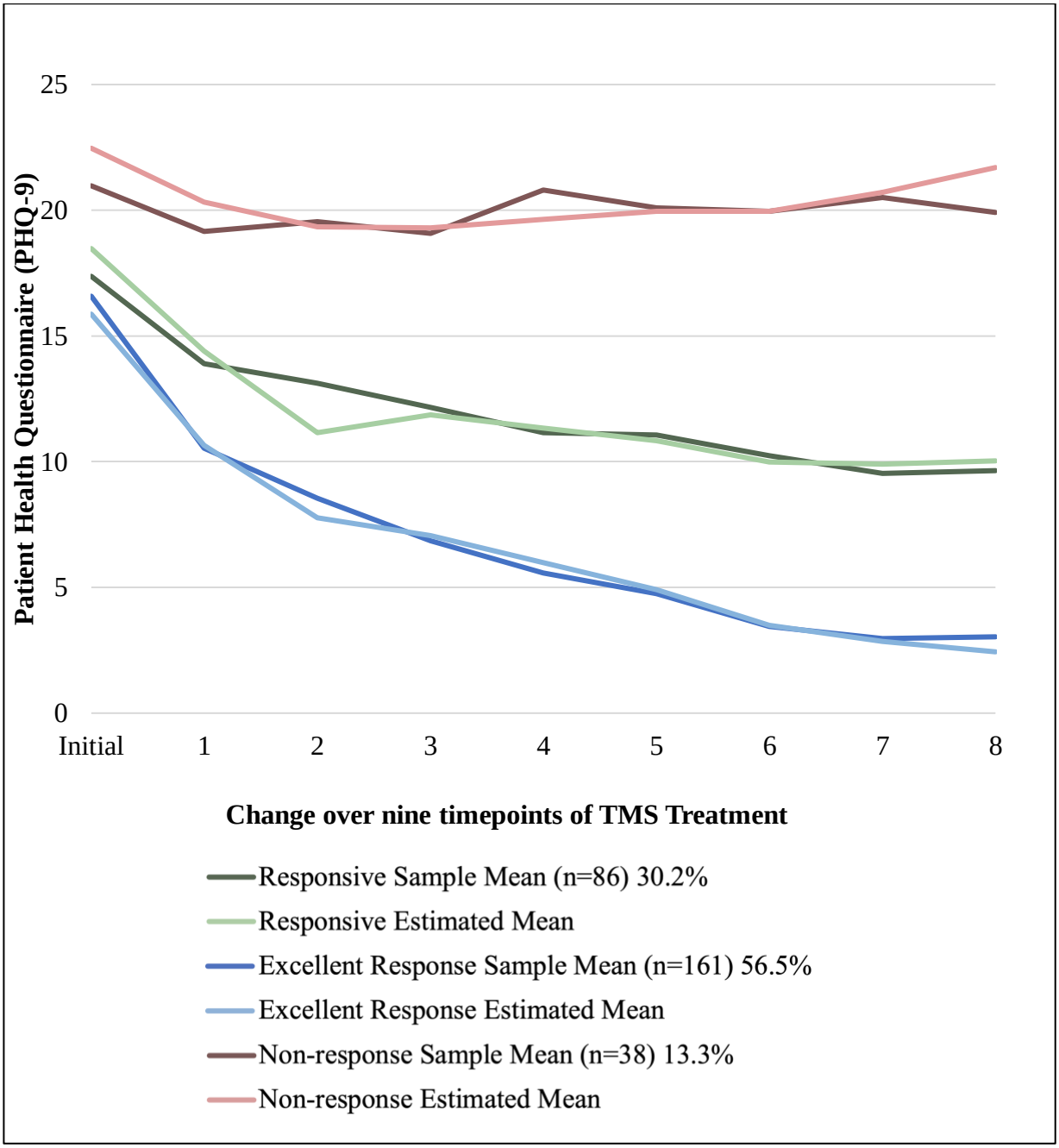

Figure 5: Three Class Growth Mixture Model: PHQ-9 Scores During TMS (n=285)

After identifying the number of latent classes and class membership, the descriptive statistics and frequencies for the PHQ-9 scores and categories were extracted (See Table 8). An

analysis of variance (ANOVA) was conducted implementing the Welch test to examine differences among the three classes. Significant differences were found for Initial PHQ-9 Score $F(2,108.594) = 12.630$, $p < .001$, $\omega^2 = .057$ Last PHQ-9 Score, $F(2, 98.054) = 377.734$, $p < .001$, $\omega^2 = .723$.

Games-Howell post-hoc tests were conducted to determine the directionality of significant differences. For Initial PHQ-9 Score, the mean for the Non-Response class ($M = 21.0$, $SD = 4.568$) was significantly higher than mean the Responsive class ($M = 17.337$, $SD = 4.803$), $t(74.273) = -4.051$, $p < .001$ and significantly higher than the Excellent Response class ($M = 16.621$, $SD = 6.067$) and $t(71.369) = -4.965$, $p < .001$.

For Last PHQ-9 Score, there were significant differences in mean scores between all pairs of response classes. The Non-response class ($M = 21.789$, $SD = 3.542$) had significantly higher mean Last PHQ-9 scores than the Responsive class ($M = 12.279$, $SD = 3.655$), $t(170.046) = -14.988$, $p < .001$. The Non-response class also had significantly higher mean Last PHQ-9 scores than the Excellent Response class ($M = 5.025$, $SD = 3.565$), $t(56.066) = 26.208$, $p < .001$. The Responsive had significantly higher mean Last PHQ-9 scores than Excellent Response ($M = 5.025$, $SD = 3.565$), $t(170.046) = 14.988$, $p < .001$.

As can be seen in Table 9, there is a significant relationship between class membership and initial PHQ-9 classification, $\chi 2$ (8, N= 285) = 21.373, $p = 0.006$. Cramer's V indicates a moderate effect size for the association (V = 0.194). Likewise, the frequencies across the three class indicated a significant association between response class membership and Last PHQ-9 classification, $\chi 2(8, N = 285) = 305.601$, $p < 0.001$. Cramer's V indicates a strong effect size for the association (V = 0.86).

Table 8: PHQ-9 Descriptive Statistics and Frequencies by Response Class

	M (*SD*)		
PHQ-9 Scores	**Responsive**	**Excellent Response**	**Non-Response**
Initial Score**	17.34 (4.8)	16.62 (6.1)	21 (4.6)
Last Score**	12.28 (3.7)	5.0 (3.6)	21.8 (3.5)
	Frequency (%)		
Initial PHQ-9 Category**	**Responsive**	**Excellent Response**	**Non-Response**
Minimal Depression	-	4 (2.5%)	-
Mild Depression	8 (9.3%)	23 (14.3%)	-
Moderate Depression	17 (19.8%)	30 (18.6%)	5 (13.2%)
Moderately Severe Depression	31 (36.0%)	38 (23.6%)	7 (18.4%)
Severe Depression	30 (34.9%)	55 (41.0%)	26 (68.4%)
Last PHQ-9 Category**			
Minimal Depression	6 (7.0%)	128 (79.5%)	-
Mild Depression	46 (53.5%)	33 (20.5%)	-
Moderate Depression	28 (32.6%)	-	2 (5.3%)
Moderately Severe Depression	6 (7.0%)	-	22 (57.9%)
Severe Depression	-	-	14 (36.8%)
Response and Remission			
Response**	39 (45.3%)	159 (98.8%)	-
Depression Remission**	6 (7.0%)	128 (79.5%)	-

*Note. ** A significant association with class membership, p<.01 – See text for analysis and test statistics.*

Demographic Variables Comparison Across Classes

The descriptive statistics and frequencies for the basic demographic variables were extracted (See Table 9). Next, ANOVA and chi-squared test of independence were conducted. There were no association found between class membership and age, $F(2,98.701) = .24$, $p = .781$. Using chi-squared tests of independence, the remaining variables were compared across the three classes of TMS response. The chi-squared tests of independence indicated an association between the TMS treatment response class and employment status, χ^2 (8, N = 268) = 22.334, p = .004. Cramer's V indicated a moderate association between the two variables (V = 0.204). In the Excellent Response class, fewer participants (3.9%) were Disability/Medically Retired, while most participants (46.1%) were not working. In contrast, the Non-Response class, had a higher

percentage (19.3%) of reporting working part-time and a lower percentage (32.3%) reporting working full-time.

The chi-squared tests of independence also indicated a significant association between response class membership and insurance, $\chi 2$ (6, N = 285) = 20.848, p = 0.002. Cramer's V indicates a moderate effect size for the association (V = 0.191). Notably, the Non-Response class, is underrepresented in the commercial insurance and self-pay categories, whereas it is overrepresented in the VA category, with most (34.4%) participants in this group having VA insurance. Additionally, the Excellent Response group, is overrepresented in the commercial insurance (61.7%) and self-pay (64%) categories, but underrepresented in the VA category, with fewer (33.6%) participants in this group having VA insurance. No other demographic variables resulted in statistically significant differences.

Additionally, the chi-squared tests of independence also indicated a significant association between response class membership and military service, $\chi 2$ (2, N = 285) = 7.49, p = 0.024. Cramer's V indicates a moderate effect size for the association (V = 0.162). Notably, the Non-Response and Responsive classes, were slightly overrepresented in the military service category.

Table 9: Sample Demographics by TMS Response Class

	M (*SD*)		
Demographic Variables	**Responsive**	**Excellent Response**	**Non-Response**
Age	37.37 (9.62)	36.94 (10.90)	38.29 (10.79)
	Frequency (%)		
Gender	**Responsive**	**Excellent Response**	**Non-Response**
Female	57 (66.3%)	120 (74.5%)	22 (57.9%)
Male	29 (33.7%)	41 (25.5%)	16 (42.1%)
Ethnicity/Race			
African American	6 (7%)	11 (6.8%)	2 (5.3%)
Asian	-	2 (1.2%)	2 (5.3%)
Caucasian	36 (41.9%)	72 (44.7%)	17 (44.7%)
Hispanic	42 (48.8%)	75 (46.6%)	17 (44.7%)
N.A./N.H./P.I.	2 (2.3%)	1 (0.6%)	-
Education			
Less than High School	3 (3.5%)	4 (2.5%)	1 (2.6%)
High School / GED	43 (50%)	78 (48.4%)	15 (39.5%)
Associate/Bachelor	29 (33.7%)	46 (28.6%)	9 (23.7%)
Graduate	8 (9.3%)	22 (13.7%)	5 (13.2%)
Employment Status**			
Disability/Medically Retired	13 (15.1%)	6 (3.7%)	5 (13.2%)
Not Working	34 (39.5%)	70 (43.5%)	9 (23.7%)
Full Time	33 (38.4%)	65 (40.4%)	10 (26.3%)
Part-Time	3 (3.5%)	8 (5%)	9 (23.7%)
Retired	2 (2.3%)	3 (1.9%)	1 (2.6%)
Employment Sector			
Education	4 (4.7%)	5 (3.1%)	3 (7.9%)
Healthcare	4 (4.7%)	12 (7.5%)	3 (7.9%)
Law Enforcement	4 (4.7%)	6 (3.7%)	-
Active-Duty Military	2 (2.3%)	-	2 (5.3%)
Insurance **			
Commercial Insurance	22 (25.6%)	58 (36%)	14 (36.8%)
Self-Pay	8 (9.3%)	16 (9.9%)	1 (2.6%)
Tricare	45 (52.3%)	77 (47.8%)	12 (31.6%)
Veterans Affairs	11 (12.8%)	10 (6.2%)	11 (28.9%)
Military Service*			
Served/Serving	27 (31.4%)	28 (17.4%)	13 (34.2%)
Military Dependent			
Spouse/Child	31 (36%)	63 (39.1%)	10 (26.3%)

*Note. N.A. = Native American; N.H. = Native Hawaiian; P.I. = Pacific Islander; * A significant association with class membership, p<.05; ** A significant association with class membership, p<.01 – See text for analysis and test statistics.*

Table 9: Sample Demographics by TMS Response Class Continued

	Frequency (%)		
Sexual Orientation/Identity	**Responsive**	**Excellent Response**	**Non-Response**
Bisexual	2 (2.3%)	3 (1.9%)	2 (5.3%)
Heterosexual	78 (90.7%)	148 (91.9%)	31 (81.6%)
Homosexual	4 (4.7%)	-	1 (2.6%)
Relationship Status			
Divorced	7 (8.1%)	8 (5%)	-
Married	57 (66.3%)	105 (65.2%)	24 (63.2%)
Separated	2 (2.3%)	2 (1.2%)	-
Single	15 (17.4%)	22 (13.7%)	5 (13.2%)
Widowed	-	3 (1.9%)	-
Married / Parental Status			
Married	20 (23.3%)	40 (24.8%)	7 (18.4%)
Has Children	53 (61.6%)	99 (61.5%)	20 (52.6%)

Psychiatric Diagnosis and Medication Comparisons Across Classes

Next, frequencies of psychiatric diagnoses across class membership were obtained (See Table 10). Results from the chi-squared tests of independence indicated an association between the TMS treatment response class and Reaction to Severe Stress / Adjustment and Attention/Cognitive diagnoses. As the frequencies in table 10 indicate, there was a significant relation between class membership and PTSD diagnosis, $\chi 2$ (2, N = 285) = 6.146, p = 0.046. Cramer's V indicates a moderate size of effect (V = 0.147). In particular, the Excellent Response class is overrepresented among participants without PTSD diagnosis (70.19%), while the Non-Response class is overrepresented among participants with PTSD diagnosis (39.47%).

Results from the chi-squared test of independence also indicated a significant association between class membership and Mild Cognitive Impairment, $\chi 2$ (2, N=285) = 10.093, p = 0.006. Cramer's V also indicates a moderate effect size for the association (V = 0.188). Notably, the Non-Response class appears to be overrepresented in the Mild Cognitive Impairment (7.90%)

followed by the Excellent Response class (1.24%), while no participants with mild cognitive impairment were in the responsive class.

Results from the chi-squared test of independence also indicated a significant association between class membership and the number of psychiatric diagnoses, $\chi 2$ (6, N = 285) =13.235, p = 0.039. Cramer's V also indicates a moderate effect size for the association (V = 0.152). Notably, the Non-Response class appears to be overrepresented in the 4 or more Diagnoses category (10.53%) and underrepresented in the Excellent Response class (0.60%). All other comparisons results failed to reach statical significance.

Table 10: Frequency of Psychiatric Diagnosis by TMS Response Class

	Frequency (%)		
Depression Diagnosis	**Responsive**	**Excellent Response**	**Non-Response**
F33.2 – Recurrent, severe	86 (100%)	157 (97.5%)	38 (100%)
Anxiety Diagnosis			
F40.1 – Social phobia	3 (3.5%)	-	2 (5.3%)
F41.0 – Panic disorder	25 (29.1%)	49 (30.4%)	11 (28.9%)
F41.1 – Generalized anxiety disorder	26 (30.2%)	63 (39.1%)	14 (36.8%)
F41.9 – Anxiety disorder, unspecified	3 (3.5%)	6 (3.7%)	-
Obsessive-compulsive Disorder			
F42.2 – Mixed obsessional thoughts/acts	-	2 (1.2%)	-
F42.9 – OCD, unspecified	1 (1.2%)	7 (4.3%)	1 (2.6%)
Reaction to Severe Stress / Adjustment			
F43.0 – Acute Stress Reaction	-	1 (0.6%)	-
F43.1 – Post Traumatic Stress Disorder*	39 (45.3%)	48 (29.8%)	15 (39.5%)
F43.2 – Adjustment Disorder	1 (1.2%)	-	-
Attention / Cognitive Disorders			
F90.0 – ADHD, inattentive	1 (1.2%)	1 (0.6%)	1 (2.6%)
F90.9 – ADHD, unspecified	1 (1.2%)	1 (0.6%)	1 (2.6%)
G31.84 – Mild Cognitive Impairment**	0 (0%)	2 (1.2%)	3 (7.9%)
Number of Psychiatric Diagnoses*			
1 - Diagnosis	19 (22.1%)	37 (23%)	8 (21.1%)
2 - Diagnoses	34 (39.5%)	66 (41%)	16 (42.1%)
3 - Diagnoses	31 (36%)	57 (35.4%)	10 (26.3%)
4 or more - Diagnoses	2 (2.3%)	1 (0.6%)	4 (10.5%)

*Note. * A significant association with class membership, p<.05; ** A significant association with class membership, p<.01 – See text for analysis and exact values.*

Frequencies of psychiatric medications across the three classes were obtained (See Table 11). Results from the chi-squared tests of independence indicated an association between the class membership and Antipsychotics, $\chi 2$ (2, N=184) = 12.232, p = 0.002. Cramer's V indicates a moderate size of effect (V = 0.208). Notably, the Non-Response class has the highest percentage of participants with antipsychotic prescription (35.1%), followed by the Responsive class (20.9%) and the Excellent Response class (11.8%). All other comparisons results failed to reach statistical significance.

Table 11: Frequency of Psychiatric Medications by TMS Response Class

	Frequency (%)		
Medication Variables	**Responsive**	**Excellent Response**	**Non-Response**
Antipsychotic**	18 (20.9%)	19 (11.8%)	13 (35.1%)
Anxiolytic	33 (38.4%)	77 (47.8%)	17 (44.7%)
Antidepressant	48 (55.8%)	79 (49.1%)	18 (47.4%)
Mood Stabilizer	15 (17.4%)	16 (9.9%)	7 (18.4%)
Benzodiazepines	50 (58.1%)	86 (53.4%)	26 (68.4%)
ADHD Medications	7 (8.1%)	7 (4.3%)	3 (7.9%)
Anti-epileptics	7 (8.1%)	7 (4.3%)	4 (10.5%)
Hypnotics	31 (36%)	58 (36%)	11 (28.9%)

*Note. Medications extracted from clinic's EHR system and may not include medications from other healthcare providers; ** A significant association with class membership, p<.01 – See text for analysis and test statistics.*

Symptom Variables Comparisons Across Classes

Next, descriptive statistics for the symptom variables were extracted (See Table 12). An analysis of variance (ANOVA) was conducted to examine differences among the three classes. Significant differences were found for Depressed Mood, F(2, 84.466) = 3.363, p = 0.016, ω^2 =0.016, Excessive Worry, F(2, 105.031) = 7.167, p = .001, ω^2 = 0.016, Anhedonia, F(2, 77.030) = 7.149, p = .001, ω^2 = 0.045, Sleep Problems, F(2, 84.772) = 4.390, p = .015, ω^2 = 0.020, and Feelings of Worthlessness, F(2, 74.010) = 4.253, p = .018, ω^2 =0.027. However, no significant

differences were found for any of the other symptom variables, nor Symptom Severity or Duration of Depression.

Games-Howell post-hoc tests were conducted to determine the significant difference between the three response classes. For Depressed Mood, none of the pairwise comparisons reached statically significant using the Games-Howell procedure. For the Excessive Worry, the mean for the Non-Response class (M = 2.83, SD = 0.531) was significantly higher than mean the Responsive class (M = 2.45, SD = 0.953), $t(92.134) = -2.661$, $p = .025$ and significantly higher than the mean for the Excellent Response class (M = 2.362, SD = 1.015) and $t(79.037) = -3.689$, $p = .001$. For Anhedonia, the mean for the Non-Response class (M = 2.138, SD = 1.026) was significantly higher than the mean for the Responsive class (M = 1.50, SD = 1.054), $t(51.415) = -2.839$, $p = 0.017$, and significantly higher than the mean for the Excellent Response class (M = 1.336, SD = 1.084), $t(41.997) = -3.796$, $p = .001$. For Sleep Problems, the mean for the Non-Response class (M = 2.367, SD = .999) was significantly higher means for the Excellent Response class (M =1.753, SD = 1.246), $t(49.473) = -2.926$, p=0.014. For Feeling of Worthlessness, the mean for the Non-Response class (M = 1.793, SD = 1.082) was significantly higher means for the Excellent Response class (M =1.162, SD = 1.010), $t(38.327) = -2.890$, p=0.017. All other comparisons did not reach statistical significance.

Table 12: Descriptive Statistics Reported Symptoms by TMS Response Class

	M (*SD*)		
Symptom Variables	**Responsive**	**Excellent Response**	**Non-Response**
Anxiety	1.19 (0.96)	1.19 (0.93)	1.5 (1.14)
Increased Appetite	1.09 (1.15)	0.97 (1.12)	1.1 (1.18)
Decreased Appetite	1.09 (1.15)	0.97 (1.12)	1.1 (1.18)
Depressive Mood *	2.66 (0.67)	2.42 (0.91)	2.7 (0.7)
Easily Distracted	2.2 (1.11)	1.9 (1.22)	2 (1.11)
Risky Behaviors	0.06 (0.24)	0.13 (0.46)	0.07 (0.25)
Excess Energy	0.18 (0.57)	0.07 (0.26)	0 (0)
Excess Worry**	2.45 (0.95)	2.36 (1.01)	2.83 (0.53)
Fatigue	2.52 (0.89)	2.44 (0.92)	2.7 (0.65)
Hopelessness	1.41 (1.12)	1.11 (0.93)	1.47 (1.11)
Abandonment	0.86 (1.09)	0.66 (0.94)	1 (1.08)
Emptiness	1.6 (1.14)	1.31 (1.09)	1.48 (1.21)
Impulsivity	1.6 (1.11)	1.28 (1.11)	1.6 (1.19)
Feelings of Guilt	0.84 (0.97)	0.68 (0.92)	0.66 (0.86)
Worthlessness*	1.5 (1.05)	1.34 (1.08)	2.14 (1.03)
Anhedonia**	2.02 (1.08)	1.95 (1.16)	2.43 (0.86)
Increased Need for Sleep	1.99 (1.19)	1.75 (1.25)	2.37 (1)
Sleep Problems*	0.17 (0.38)	0.09 (0.41)	0.17 (0.38)
Paranoia	0.23 (0.64)	0.13 (0.5)	0.19 (0.69)
Racing Thoughts	1.33 (1.05)	1.16 (1.01)	1.79 (1.08)
Symptom Severity	2.7 (.62)	2.6 (.62)	2.6 (.77)
Symptoms Duration	5.5 (5.1)	5.2 (6.3)	5.1 (4.7)

*Note. Symptoms were based on the scale: 0 = None, 1 = Sometimes, 2 =Frequent, 3= Constant; Symptom Duration measured in Years; * A significant association with class membership, p<.05 – See text for analysis and exact test statistics.*

Next, the frequencies of Suicidal Ideations & Symptom Impact on Life Areas across class membership were obtained (See Table 13). Chi-square tests of independence indicated an association between the TMS treatment response class and reported symptom impact on sex life, $\chi 2$ (2, N=256) = 8.186, p = 0.017. There was a moderate effect size for the association (V = 0.179). Notably, the Non-Response class has the highest percentage of participants with who

reported an impact on sex life (70%), followed by the Responsive class (68.35%) and the Excellent Response class (51.02%). Neither the presence of suicidal ideations nor other variables comparisons reached statistical significance.

Table 13: Frequencies of Suicidal Ideations & Symptom Impact on Life by Response Class

	Frequency (%)		
Symptom Variables	**Responsive**	**Excellent Response**	**Non-Response**
Suicidal Ideations	1 (1.2%)	15 (9.3%)	6 (15.8%)
ADL	75 (87.2%)	143 (88.8%)	28 (73.7%)
Finance	24 (27.9%)	44 (27.3%)	7 (18.4%)
Housing	26 (30.2%)	44 (27.3%)	8 (21.1%)
Recreation	78 (90.7%)	138 (85.7%)	30 (78.9%)
Relationships	80 (93%)	148 (91.9%)	28 (73.7%)
School	8 (9.3%)	29 (18%)	3 (7.9%)
Self-Esteem	78 (90.7%)	142 (88.2%)	30 (78.9%)
Sex Life*	54 (62.8%)	75 (46.6%)	21 (55.3%)

*Note. ADL = Activities of Daily Living, Percentages are reported within Response Class; * A significant association with class membership, p<.05 – See text for analysis and exact values.*

Psychiatric History Variables Comparisons Across Classes

Next, frequencies of Psychiatric History across class membership were obtained (See Table 14). Results from the chi-square tests of independence indicated no statistically significant results from any of the psychiatric history variables.

Table 14: Frequencies of Psychiatric History by Response Class

	Frequency (%)		
Psychiatric History Variables	**Responsive**	**Excellent Response**	**Non-Response**
Emotional Abuse	38 (14.6%)	69 (26.4%)	18 (6.9%)
Physical Abuse	23 (8.8%)	41 (15.7%)	6 (2.3%)
Sexual Abuse	34 (13%)	62 (23.8%)	11 (4.2%)
Previous Outpatient Treatment	74 (28.6%)	133 (51.4%)	26 (10%)
Previous Inpatient Treatment	22 (8.4%)	39 (14.9%)	8 (3.1%)
Suicide Attempt	1 (0.4%)	4 (1.5%)	1 (0.4%)

Health Variables Comparisons Across Classes

Next, frequencies for the health variables were extracted by class membership (See Table 15). Using Chi-squared tests of independence, the variables were compared across the classes TMS response. Results from the Chi-squared tests of independence indicated an association between the TMS treatment response class and Arthritis and Chronic Pain self-report diagnoses. There was a significant association between class membership and Arthritis, $\chi 2(2, N=261) = 8.006$, $p = 0.018$. Cramer's V indicates a moderate effect size of effect (V = 0.175). There was also a significant association between class membership and Chronic Pains, $\chi 2(2, N=261) = 12.787$, $p = 0.002$. Cramer's V also indicates a moderate effect size for the association (V = 0.179). All other comparisons results failed to reach statical significance.

Table 15: Frequencies of Health Variables by TMS Response Class

	Frequency (%)		
Health Variables	**Responsive**	**Excellent Response**	**Non-Response**
Tobacco Use	12 (14%)	23 (14.3%)	2 (5.3%)
Alcohol Use	23 (26.7%)	31 (19.3%)	3 (7.9%)
Drug Use	2 (2.4%)	2 (1.3%)	2 (6.7%)
Regular Exercise	49 (57%)	84 (52.2%)	20 (52.6%)
Anemia	2 (2.3%)	1 (0.1%)	2 (5.2%)
Arthritis*	2 (2.4%)	-	2 (5.7%)
Diabetes	3 (1.1%)	9 (3.4%)	1 (0.4%)
Chronic Pain **	16 (19.5%)	9 (6.0%)	7 (23.3%)
COVID-19	7 (8.1%)	14 (8.7%)	4 (10.5%)

*Note. * A significant association with class membership, p<.05; ** A significant association with class membership, p<.01 – See text for analysis and test statistics.*

Treatment Related Variables Comparison Across Classes

Next, descriptive statistics for the treatment variables were extracted by TMS response class (See Table 16). Results from the ANOVA and chi-square tests indicated no statistically significant results from any of the treatment related variables.

Table 16: Descriptive Statistics and Frequencies for Treatment Variables by Response Class

	M (*SD*)		
Treatment Variables	**Responsive**	**Excellent Response**	**Non-Response**
Number of Technicians	6.1 (1.2)	5.8 (1.3)	6 (1.2)
Number of Sessions Completed	35.7 (0.9)	35.6 (1)	35.1 (1.6)
Weeks to Session 30	10.8 (2.6)	10.3 (2.7)	10.8 (4.1)
Percentage of Max MT at Session 18	84.1 (20.8)	89.4 (11.6)	86.4 (19.5)
Percentage of Max MT at Session 30	92.9 (10.8)	94.1 (9.3)	91.3 (19)
Number of TMS protocols	1.2 (.40)	1.08 (.27)	1.18 (.39)
	Frequency (%)		
Treatment Start Date	**Responsive**	**Excellent Response**	**Non-Response**
Mid-2021	20 (23.3%)	28 (17.4%)	5 (13.2%)
Late-2021	14 (16.3%)	39 (24.2%)	5 (13.2%)
Early-2022	22 (25.6%)	31 (19.3%)	12 (31.6%)
Mid-2022	12 (14%)	24 (14.9%)	7 (18.4%)
Late-2022	10 (11.6%)	25 (15.5%)	5 (13.2%)
TMS Protocols Used			
Bilateral Protocol	11 (12.8%)	7 (4.3%)	3 (7.4%)
PTSD/Anxiety	6 (7.0%)	4 (2.5%)	3 (8.0%)
OCD	-	2 (1.2%)	1 (2.6%)

Military and Military Dependents

As a result of the solid representation of veterans and military dependents, analysis were conducted comparing Non-military, Military, and Military Dependents. First, descriptive statistics and frequencies for the PHQ-9 variables were extracted (See Table 17). An analysis of variance (ANOVA) was conducted to examine differences among the three groups. Significant differences were found for Last PHQ-9 Score, $F(2, 179.221) = 4.710$, $p = 0.01$, $\omega^2 = 0.022$. Games-Howell post-hoc tests were conducted to determine the significant difference between the three groups. The mean Last PHQ-9 score for the Military group ($M = 8.85$, SD = 6.0) was significantly lower than mean the Non-military group ($M = 11.55$, SD = 6.989), $t(166.982) = 2.775$, $p = .017$ and significantly lower than the mean for the Military Dependent group ($M = 11.356$, $SD = 6.686$), $t(162.584) = 2.464$, $p = .027$.

Chi-square tests of independence indicated an association between the Non-military, Military, and Military Dependents and Last PHQ-9 Depression Classification, $\chi 2$ (8, N=285) = 20.410, p = 0.009. An association in frequencies for these groups were also found for Response, $\chi 2$ (2, N=285) = 10.656, p = 0.005, and Remission, $\chi 2$ (8, N=285) = 14.450, $p < 0.001$.

Table 17: PHQ-9 Descriptive Statistics: Non-Military, Military, vs Dependents

	***M* (*SD*)**		
PHQ-9 Scores	**Non-Military (N=109)**	**Military (N=72)**	**Military Dependent (N=104)**
Initial Score	17.5 (5.6)	17.7 (5.9)	17.2 (5.6)
Last Score**	11.6 (6.9)	8.8 (6.0)	11.4 (6.7)
		Frequency (%)	
Initial PHQ-9 Category**	**Non-Military**	**Military**	**Military Dependent**
Minimal Depression	10 (9.2%)	8 (11.1%)	13 (12.5%)
Mild Depression	2 (1.8%)	1 (1.4%)	1 (1%)
Moderate Depression	22 (20.2%)	12 (16.7%)	18 (17.3%)
Moderately Severe Depression	23 (21.1%)	24 (33.3%)	29 (27.9%)
Severe Depression	52 (47.7%)	27 (37.5%)	43 (41.3%)
Last PHQ-9 Category**			
Minimal Depression	29 (26.6%)	26 (36.1%)	24 (23.1%)
Mild Depression	57 (52.3%)	20 (27.8%)	57 (54.8%)
Moderate Depression	8 (7.3%)	10 (13.9%)	12 (11.5%)
Moderately Severe Depression	11 (10.1%)	8 (11.1%)	9 (8.7%)
Severe Depression	4 (3.7%)	8 (11.1%)	2 (1.9%)
Response and Remission			
Response**	53 (48.6%)	18 (25%)	37 (35.6%)
Remission**	57 (52.3%)	20 (27.8%)	57 (54.8%)
Response Class Membership			
Responsive	28 (25.7%)	27 (37.5%)	31 (29.8%)
Excellent Response	67 (61.5%)	31 (43%)	63 (60.6%)
Non-Response	14 (12.8%)	14 (19.4%)	10 (9.6%)

*Note. ** A significant association with class membership, p<.01 – See text for analysis and test statistics.*

Summary of Findings

In short, the overall sample demonstrated three different response classes. Growth mixture modeling was able to identify these classes through their PHQ-9 scores over their TMS treatment. These classes differed on several demographic and clinical variables (See Table 18).

A conservative approach was taken since many comparisons were made between the three response classes, therefore only results at the $p < .01$ level were considered as sound when making conclusions from the study.

Table 18: Summary of Variables Associated with TMS Response In the Current Study

Better Response	Poorer Response
• Lower PHQ-9 Score at Treatment Initiation • Employment Status as Not Working / Full Time • No Comorbid Diagnosis • Reporting Lower Levels of Excess Worry at Intake • Reporting Lower Levels of Anhedonia at Intake	• Higher PHQ-9 Score at Treatment Initiation • Employment Status as Disability/Medically Retired • VA Insurance Coverage • Diagnosis of Mild Cognitive Impairment • Antipsychotic Prescription During Treatment • Reporting Greater Levels of Excess Worry at Intake • Reporting Greater Levels of Anhedonia • Reporting a Chronic Pain Diagnosis

Discussion

Depression is a pervasive and growing public health crisis which impacts millions around the world. The importance of understanding depression interventions has only grown considering the rise in prevalence during the COVID-19 pandemic. Most people with major depressive disorder still struggle to overcome their symptoms despite the advancements in psychopharmacology and the numerous variations of antidepressant medications which are available.

In light of modern findings from neuroimaging and neural network research, the traditional monoamine hypotheses have given way to the network hypothesis. The network hypothesis of depression proposes that depressive symptoms arise from disrupted connections within neural networks involved in emotional processing, cognitive control, and reward processing. Transcranial magnetic stimulation (TMS) has been shown to aid with depression by modulating neural network activity, which is consistent with the network hypothesis of depression.

Even though TMS has been widely studied and shown to be effective, few studies examine the variability of TMS response and factors which may attribute to this variability in the real-world application of TMS. Likewise, many of the studies of TMS and depression lack inclusion of underserved groups such as Hispanic individuals, veterans, and military families. Given the limitations in existing literature, it is crucial to expand our knowledge of TMS response and the factors which contribute to TMS response variability, particularly in real-world settings and among underrepresented populations.

Our studied aimed to investigate the change of PHQ-9 scores during TMS treatment for individuals with depression and to identify potential subgroups (classes) of participants with

distinct treatment responses, focusing on changes in PHQ-9 scores and identifying potential subgroups of participants with distinct treatment outcomes. By examining a diverse sample from a real-world clinic which included underrepresented populations such as Hispanic individuals, Veterans, and military families, this study builds on the understanding of TMS response variability in small clinical practice settings.

To achieve the aims, the study employed growth mixture modeling to determine the optimal number of latent classes representing different treatment response patterns. Furthermore, the study explored demographic and clinical variables across these identified classes to better understand their nature and association with TMS response variability. By investigating these factors, the study aimed to provide insights that could inform clinical decision-making and help tailor TMS treatment strategies to improve outcomes for a wider range of individuals suffering from depression.

The results of our analysis showed that the 3-class model (Responsive, Excellent Response, and Non-Response classes) was the most appropriate and interpretable explanation for the PHQ-9 scores during TMS treatment. While inspecting the model, we considered the practical implications, as models with too many classes may decrease interpretability and not be useful in the wider context. Our study took into consideration prior research by Kaster et al. (2019), who identified four types of response to TMS treatment in a sample of patients with depression receiving 10hz TMS treatments or iTBS, and only three types of response when considering only those who received 10hz TMS treatment. Since some of our participants did receive multiple TMS protocols we expected anywhere from three to four classes, apriori.

Our results are in line with those from Kaster et al. (2019) who found three types of response in their sample. However, there was some difference between the two studies, such as

the different TMS protocols used, the sample characteristics, depression measure used, and the underlying framework of the study. Additionally, the sample in the current study were those with treatment-resistant depression, while the Kaster et al. (2019) included patients with major depressive disorder. Kaster et al. (2019) used the Hamilton depression inventory (HAM-D) while the current study used the PHQ-9. The HAM-D has 21 questions with 4 levels of response making it more precise in its measurement of depression severity (Carrozzino, Patierno, Fava, & Guidi, 2020).

TMS Treatment Response

Overall, our study demonstrated that 198 participants (69.5%) had a 50% or greater change in PHQ-9 scores (Treatment Response) while 134 (47%) had scores on the PHQ-9 below 5 (Remission). This is somewhat higher than Berlim and colleagues (2014c) found in their meta-analysis of RCT trials of HF-TMS where 29.3% were classified as responders and 18.6% were classified as having achieved remission. However, their meta-analysis only looked at 13 sessions of TMS from clinical trials and included mixed unipolar and bipolar depression types. Likewise, Cao, Deng, Su, & Guo 2018 found that responses rates were approximately 44.6% and remission rates were approximately 21.9%. Again, their meta-analysis included RCTs with 10 or more sessions. As the field of TMS evolves, the outcomes and overall efficacy become more complex as new treatment targets are found, tested, published on, and used in clinical studies and practice. In our study, participants always began treatment with the standard HF 19-minute left dlPFC, 10hz treatment. In some cases, additional protocols were used, however, this was in very little cases (Total sample mean number of protocols = 1.13, *SD* = .34).

Likewise, differences in the delivery of TMS sessions have not been widely explored. In the clinic included in the study, patients are monitored by a trained TMS technician. During each

session, the technician will speak to the patient about their current state and treatment response. This may include many details about their current life situation, stressors, past, and symptoms. The technicians are trained to listen, provide support, and be empathetic to bolster the therapeutic environment and patient-technician repour. A study from Donse et al. (2018) demonstrated that psychotherapy can augment the effects of TMS for those with treatment resistant depression. They found that responses rates of 66% and remission rates of 56%. Even though the clinic in the current study does not employ concurrent psychotherapy, general conversation during session about current life situation, stressors, past, and symptoms may augment the effects of TMS via mechanisms underlying Hebb's law and talk therapy (Donse, Padberg, Sack, Rush, & Arns, 2018; Rossouw BA Hons, Hons, Psych, & Master, 2013)

Nonetheless, we found that the majority (56.5%) of participants receiving TMS at this clinic were in the Excellent Response class. Our results demonstrate 98.8% of these had a 50% or greater change in PHQ-9 scores (Treatment Response) and that 79.5% achieved remission (a PHQ-9 score less than 5). While less participants were in the Responsive class (30.2%), over 45% had a 50% or greater change in their PHQ-9 scores from initial to last PHQ-9. However, only 7% of participants in the Responsive class achieved remission. The Non-Response class have neither participants whose change in PHQ-9 scores could be categorized as response nor remission.

Our findings support the wealth of research showing that TMS is an effective treatment for depression and treatment-resistant depression (TRD) (Fitzgerald, George, & Pridmore, 2021; Paul B. Fitzgerald et al., 2021; Fregni et al., 2005; Hyde et al., 2022; O'Reardon et al., 2007; Razza et al., 2021). Since commercial, Tricare, and VA insurance coverage only approves TMS for treatment resistant depression, we can be sure that at least 86.5% can be considered as having

treatment resistant depression (TRD) as individuals who self-paid for treatment may not include the perquisites for treatment coverage.

When discussing the findings from the chi-square tests of independence and analysis of variance (ANOVAs) it is important to note that each of these statistical tests is conducted in separation from other variables. Thus, when discussing comparisons and differences between groups, it is imperative to consider that other characteristics related to variables could account for differences between our three TMS response classes. Evidence from several of the variables compared across the 3 TMS response classes reflect that depression severity is an influence factor in TMS response. We found significant differences between response classes in four comparisons, the initial PHQ-9 scores, employment status, and antipsychotic prescription. The last two variables may reflect a proxy for symptom severity in our study.

Initial PHQ-9 scores and PHQ-9 classification data demonstrated that our Non-Response class had the highest mean PHQ-9 scores (M = 21.0, SD = 4.6) at initial, followed by Responsive class (M = 17.34, SD = 4.8), and then Excellent Response class (M = 16.62, SD = 6.1). The Non-Response class had no participants who were classified as minimal or mild depression at the start of TMS treatment, with the largest percentage of the class being classified as severe depression (68.4%). However, it is notable that 41% of Excellent Response class and 34.9% in the Responsive class fell into the severe depression classification.

In our study, the Non-Response group was overrepresented by those who reported disabled/medically retired but not those who are retired. Systematic reviews demonstrate that depression severity is highly associated with employment status (Lerner & Henke, 2008; Linder, Gerdtham, Trygg, Fritzell, & Saha, 2020). Those who have depression, especially treatment resistant depression (TRD) have much higher rates of employment status change and work loss-

related costs than participants with non-TRD major depressive disorder (MDD) and non-MDD participants (Amos et al., 2018; Rizvi et al., 2015). However, employment status also can be thought of as a representation of a social determinate of health. Those with better income may be able to maintain better health, have more access to diverse health and mental health resources, and therefore have better response during treatment (Crowe & Butterworth, 2016; Kessler, House, & Turner, 1987; Weich & Lewis, 1998).

Additionally, we found that an antipsychotic prescription during treatment was associated with TMS treatment response class. The Non-Response class was overrepresented by participants who were prescribed an antipsychotic medication. Antipsychotic medications are used in cases of severe depression when common antidepressants have failed or as an adjunctive medication (Cantù et al., 2021; Jha & Mathew, 2023; Mulder et al., 2018; P. Wang & Si, 2013). Antipsychotics can produce very serious side effects (i.e. metabolic syndrome, extrapyramidal symptoms, high prolactin, sedation, abnormal liver function, and cardiac irregularities) therefore the case for use in depression is almost exclusive to severe TRD (Cantù et al., 2021; Hynes et al., 2020; Jha & Mathew, 2023; Kaar, Natesan, McCutcheon, & Howes, 2020). Likewise, Abo Aoun and colleagues (2023) report that antipsychotic use as a negative predictor of TMS response. However, as they report antipsychotics which block D2 receptors, decrease the effectivity of TMS via decreased GABA and altering mechanism underlying neuroplasticity. Therefore, another explanation of our finding could reflect the attenuating properties of antipsychotics on TMS response(Abo Aoun et al., 2023).

While our findings suggest associations between class membership and initial PHQ-9 scores, employment status, and insurance provider, our study did not find a significant difference between the TMS response classes on the reported severity of symptoms. Upon inspection of the

means, all means were high (Responsive *M* = 2.7, Excellent Response *M* = 2.6, Non-Response *M* = 2.6) with little variation (.62, .62, .77). These similarly high means could be due to several factors. First, many patients who were referred to the clinic come from primary care physicians and mental healthcare workers, which may represent a time of crisis or intense mental health problems for the patient to seek additional help. Furthermore, within the semi-structured interview the symptom severity question was located after questions concerning all other symptoms, thus, patient responses may have not been specific to depression related symptoms. Lastly, during semi-structured interviews provider discretion allowed them to use clinical judgement to complete fields without the need to directly ask the question basing it on the patient's account of symptoms and impact on their life.

Nevertheless, there is an agreement across TMS research that symptom severity is highly related to TMS response. The literature clearly demonstrates that those with severe baseline depressive symptoms are less likely to respond to various TMS protocols (Carpenter et al., 2012; Gill, De Felice, Gill, Page, & Hooke, 2023; Gonterman, 2023; Grammer et al., 2015; Sackeim et al., 2020; Trevizol et al., 2020). For example, Sakeim et al. (2020) demonstrated that even in routine clinical practice this is still true. Their study explored data from 103 practice sites with 5010 participants included and showed that initial symptom severity had higher scores on the PHQ-9 and Clinical Global Impression – Severity scale following TMS treatment, these participants were also much less likely to have remission of depression symptomology.

Depression Symptoms

Our study also found two symptom related variables to be associated with TMS response class, Excessive Worry and Anhedonia. Participants in the Non-Response class rated their excess worry significantly higher than the other response classes. Generally excessive worry represents

a persistent, uncontrollable, and unrealistic worry about everyday events or activities and can be contrasted with anxiety, as anxiety is more of a natural response to stress or threat (Davey, Hampton, Farrell, & Davidson, 1992; Gana, Martin, & Canouet, 2001; Zebb & Beck, 1998). Nevertheless, excessive worry is the primary feature of general anxiety disorder (American Psychiatric Association, 2013; Crocq, 2022). There is mixed evidence for the impact of general anxiety comorbidly in respect to TMS response. Fitzgerald et al. (2016) found that response rates to TMS were higher for individuals who had no comorbid mental health disorders (54.1%) than in those with generalized anxiety disorder (47%). Lisanby et al., (2009) also saw that the absence of anxiety disorder was positively related to treatment outcomes. However, Drysdale et al. (2017) and found that the profiles associated greater anxiety had better response to TMS. In our study, both anxiety and excess worry were assessed, therefore, there could be issues of the conceptualization of these constructs in patient's reports of their symptoms.

Our results are in line with several other studies which found that lower anhedonia at baseline was related to better TMS response (Downar et al., 2014; Krepel, Rush, Iseger, Sack, & Arns, 2020; Rostami et al., 2017). However, more recent studies using direct measures of anhedonia (in contrast to questions from depression measures from the previously mentioned studies) found that those with high baseline anhedonia had equal chance of depression response or remission at conclusion of TMS treatment (Fukuda et al., 2021).

Comorbid Chronic Pain

When comparing the three TMS response classes on health variables, we found that those in the Non-Response class had more frequency of reported chronic pain disorder as compared to the excellent response and responsive classes. However, the number of those reporting chronic pain in the sample were very low (N=32). Nevertheless, this parallels chronic pain research from

Corlier and colleagues (2023) who found that even though patients with comorbid chronic pain benefited from TMS, those with greater pain symptoms were 27% less likely to respond to TMS treatment for their depression.

Covid-19

Since this data was collected during the 2021 and 2022, as part of our study, we did include a variable which looked at self-reported COVID-19 and included the date of treatment initiation. Class membership was not significantly associated with neither variable. However, self-reported COVID diagnosis was only able to be extracted from cancellation notes, which the clinic did not start using until early 2022 which resulted in few participants with this classification. With this said, this study has little to no ability to determine if COVID diagnosis or increased stress from the pandemic influenced their treatment outcomes.

Military Service and Military Dependents

Our naturistic sample contained a solid representation of military and military dependents who belong to a unique population at risk of depression due to trauma, stressors, and military culture (Bonde et al., 2016; Donoho et al., 2018; McFarlane, 2009). Our initial findings demonstrated that even though the number of participants in the Non-Response class was small (n = 32), there were higher proportion of participants with Veterans Affairs (VA) coverage (n=10). It was also found that veterans were underrepresented in the Excellent response class (17.4%) verses Responsive (31.4%) and Non-Response (34.2%) classes.

Our analysis comparing non-military, military, and military dependents indicate that the military group had statistically significantly lower Last PHQ-9 scores, however, had much more variability. Military dependents did not significantly differ from non-military proportion of the sample on Last PHQ-9 score. Findings on Last PHQ-9 depression classification showed that all

groups had similar frequencies of participants within the various levels of depression severity, expect for severe classification. The military group was overrepresented in severe category. Additionally, the military group had lower frequencies of participants who achieved Response (25%) and Remission (27.8%) compared to Military dependents (35.6% & 54.8%) and non-military (48.6% & 52.3%). The military proportion of our sample contained the highest number of those with PHQ-9 scores that did not change over treatment.

Our findings are somewhat different from a recent study which used a sample of 770 veterans receiving TMS for depression and PTSD (Madore et al., 2022). Madore and colleagues (2022) saw that veterans who received at least 30 treatments of various frontal TMS procedures had clinically meaningful and statistically significant reductions in depression and found that response and remission rates to be 41.4% and 20% respectively. They indicated that more treatment sessions yielded more robust decreases in depression symptomology and that a comorbid diagnosis of PTSD did not hinder TMS response (Madore et al., 2022).

This difference may reflect complex factors with military culture and Veterans Affairs. Issues such as stigma may delay veterans from seeking services until crisis or high severity of depression, which may lead to more treatment resistance. Equally, bureaugenic effects may lead to an increase in symptoms, more resistance in treatment, and less motivation to demonstrate improvement in mental health symptoms (Hooyer, 2022). Notably, Hooyer (2022) argues that military cultural values are challenged through the objectification of sacrifices via screening tools and quantification of their experience to calculate percentages of disability. Veterans view this compensation as a validation of their losses, sacrifices, and experiences which may influence their responses on measures such as the PHQ-9 (Hooyer, 2022). Likewise, this difference could be a result of other various which our study did not account for in a multivariable analysis.

Studies demonstrate that the prevalence of mental health disorders within the Veterans Health Administration are higher than the general population and that it is very common for veterans to have multiple psychiatric diagnoses such as depression, anxiety, PTSD, and substance use disorder which were related to military service (Trivedi et al., 2015). Veterans represent a population with a unique culture, complex history, and increased risk factors for depression, anxiety, and PTSD via exposure to combat and trauma. Even though our findings somewhat differ, TMS has been found to be an effective tool in the treatment of depression in veterans, however, as indicated by the general literature, treatment for veterans requires extensive evaluation, close monitoring, and personalization of treatment using multiple modalities to best improve treatment outcomes. Veterans may require more TMS especially those with more treatment resistance and more complex psychiatric histories. On the other hand, it seems that military dependents in our study did not significantly differ from the general population. With military dependents, it does not seem that the increased stress, military culture, nor increased risk factors for depression hindered their response to TMS.

Limitations

The retrospective methodology of the current study and its use of clinical data from a single psychiatric lead to several limitations. First, the sample is limited to patients at one clinic that doesn't accept Medicaid or Medicare and may not reflect the greater population of those with depression or specific other groups which were not included in this study. Therefore, this lack of representation limits our generalizability to this population, which may represent a population with more severe depression and worse response to TMS. Likewise, TMS requires that individuals have the resources to integrate their work or home schedule with the daily session 5 times per week thus this may be another treatment barrier influencing our sample and findings.

Also, the clinical data used in our study lacks a control group. In the absence of a control group, it is difficult to determine if differences in TMS response is from the treatment or other external factors.

Additionally, the study's dependence on self-reported demographic and clinical variable may not completely account for other confounding variables that could influence TMS treatment response. This limitation makes it more challenging to establish connections between TMS response and the variable included in this study. The use of self-reported data has another limitation. Participants might withhold certain information from their clinician. Patients might be hesitant to reveal various aspects of their mental health or may not be aware of certain symptoms. This reluctance to disclose particular information could compromise the validity of self-report measures and prevent a thorough understanding of the participant's symptoms and experiences. Additionally, patients receiving TMS therapy might be more likely to report that their symptoms have improved, which could skew the study's results. Furthermore, the use of electronic health record (EHR) data and coding limited the variables which were able to be accessed. Since the data comes from a clinic, the data collected was designed more for clinical practice than research, therefore some variables of interest were not included which limits the inclusion of variables which also may influence TMS response.

Lastly, latent growth mixture modeling has several potential drawbacks, despite being a useful statistical technique for modeling longitudinal change and inter- and intra-individual variations. The model can be susceptible to outliers and assumptions regarding the distribution of the data. Furthermore, growth mixture modeling needs a sizable sample size to achieve sufficient statistical power. Even though the study falls within suggested sample size needs, modeling latent growth mixture models highly depends on research context and questions.

Future Directions

Future studies which address the limitations can build on the findings to improve our understanding of the TMS response for those with depression. Expanding the number of participants and diversity could be one direction for future research to improve the generalizability of the results. Data from various clinical settings and populations may need to be gathered to establish whether the results of the current study apply in other contexts. Future research may also examine the potential long-term effects of TMS treatment by measuring participants' depression for additional time to see if the changes in symptoms continue or if participants' depression scores indicate that treatment was very successful. These additions would help us better understand the longevity of TMS for depression and develop strategies for preventing individuals from regressing from their prior gains.

Incorporating other measures of TMS response, such as functional imaging or brain biomarkers (EEG), could also improve validity and expand our understanding of how the depression subtypes may react to TMS (Hackett, 2018). With the addition of these objective measures, a better understanding of patients' response to TMS can shed light on the underlying mechanism of depression. Furthermore, there is research where EEG is used to personalize TMS treatments for depression. Depending on the data of the EEG, such as peak alpha frequency and hemispheric differences in activation, customization of TMS protocols can be based upon an individual's neurophysiological data in order to improve treatment outcomes (Hackett, 2018; Heller, Nitschke, Etienne, & Miller, 1997; Schiena, Maggioni, Pozzoli, & Brambilla, 2020). This may be especially important to those who fail to respond to the traditional HF left-dlPFC 10hz treatment. Furthermore, specialized treatment plans should be further explored in non-responders which the ultimate goal of standardized treatment guidelines for TMS for clinical practice.

Furthermore, matched control patients could be added to better identify environmental factors and pressures which may be influencing TMS response. Future studies might also investigate other possibilities, such as the impact of clinical environment, concurrent talk therapy or other types of counseling/psychotherapy, a person's understanding / belief in TMS, or their compliance to following the advised course of treatment. By examining these variables, researchers could help develop customized treatment strategies for depressive disorders by identifying subpopulations that might be more or less responsive to TMS-based interventions.

Furthermore, as healthcare moves toward a preventative paradigm, mental health professionals should follow suit. Future studies could investigate the use of TMS for the prevention of depression in vulnerable populations such as military, veterans, healthcare workers, or survivors of trauma. Prevention of depression may be a much easier task than treatment, especially if caught early.

Clinical Implications

While keeping in mind the limitations of the study, implications for clinical practice can be mentioned. First, TMS is an effective treatment for reducing depression symptoms in patients with different severity levels of depression and that have failed other treatments. However, clinicians should conduct extensive psychiatric evaluations on patients in order to determine if the symptom profile, psychiatric history, psychiatric medications, or comorbid conditions which may hinder a traditional approach to TMS treatment. The field of TMS research is quickly growing and evolving, it is critical that clinicians stay informed and attentive to patients progress while integrating evidence-based methods for personalization of TMS protocols. Personalization of TMS treatment based on EEG biomarkers, depression symptoms, and specific treatment response allow for targeting of specific areas and brain activation patterns or additional treatment

sessions to better reduce the particular symptomology of that patient, therefore improving outcomes and overall functioning. While our study only included TMS up to 36 sessions, other findings demonstrate that longer course of treatment may be beneficial even when no improvement is seen by session 30 (Avery et al., 2008).

Personalization of treatment also may require that TMS resistant patients engage in various other treatments, such as changes in medication regiments and/or engagement in counseling or psychotherapy. Additionally, clinics should design their TMS treatment programs from a data driven point of view. Progress notes and depression monitoring should be conducted considering that close monitoring of depression symptomology and TMS response can be useful in adjusting treatment protocols or the additional treatment modalities to best serve the patient's goal of achieving treatment response and depression remission.

Conclusion

Overall, our findings provide findings on the factors that influence the response to transcranial magnetic stimulation (TMS) treatment for depression. Most participants in our sample demonstrated a good response to TMS treatment for depression. However, our findings suggest that participants with more severe depression symptoms, with comorbid chronic pain, and higher levels of excess worry and anhedonia may need to have more specialized treatments to improve treatment outcomes. On the other hand, participants with less serve depression at intake, who present with lower levels of anhedonia, no comorbid medical conditions were more likely to have a better response to TMS for depression symptoms. Our results are in line with previous research indicating that depression severity, comorbid medical conditions are an important factor in TMS response and clinical outcomes.

The current study's reliance on self-reported data, data collected from one clinic, and lack of a control group suggest a need for further research to validate and extend these findings. Future research should consider incorporating objective measures of TMS response, such as EEG or fMRI, continue to follow patients after completing, and examining additional potential factors, such as concurrent psychotherapy. Likewise, TMS as a preventive measure for mental health disorders should be explored. As we improve our understanding of the neurobiological basis of depression and the nuisances of TMS response, we are closer to developing more targeted, effective, and personalized treatments for the millions of individuals affected by this rapidly growing public health crisis.

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Appendix A: TMS Informed Consent Form

CloudTMS Informed Consent Form for Transcranial Magnetic Stimulation (TMS)

This is a patient consent for a medical procedure called Transcranial Magnetic Stimulation (TMS). This consent outlines the treatment that the psychiatric provider has prescribed, the risks of this treatment, the potential benefits of this treatment and any alternative treatments that are available if I decide not to be treated with TMS. The term "psychiatric provider" includes both psychiatrists, and nurse practitioners. For the purposes of this form, the word "I" refers to either the patient receiving treatment and/or the adult caregiver who is a legal guardian of the patient.

TMS is FDA cleared to treat refractory Major Depressive Disorder (depression that has not responded adequately to medications and therapy) in adults only, any other use would be considered off label. Off label meaning that the *FDA* has not approved TMS for any other use. The FDA advises that two different antidepressants be used at a high enough dose for a long enough period of time and not be successful prior to trying TMS. Therapy may be beneficial as well in treating depression. There are alternatives to TMS, including no TMS, therapy, alternative medications, and ECT. I also know that I can obtain a second opinion regarding diagnosis and treatment options.

I understand that:

1. A TMS treatment session is performed with an FDA cleared system that delivers pulsed magnetic stimulations over the scalp and into the brain. The magnetic fields are of a similar in strength as those used In magnetic resonance imaging (MRI) machines.

2. TMS has been shown to be a relatively safe and effective treatment for patients with depression.

3. TMS was shown to reduce depressive symptoms in adults who had been treated with antidepressants and medicine but did not get adequately better.

4. I understand that the TMS treatment that I undergo may include off-label use of TMS. Off-label device use (OLDU) means using an FDA cleared device for a different condition, or using a device settings, that have not been specifically cleared by the FDA. OLDU is common, it occurs in every specialty of medicine. After a device has been cleared for one condition, clinicians are not limited to the FDA-approved indications and are allowed to use it for any condition if, in their professional judgement, is reasonably safe and effective, and potential risks outweigh potential benefits in the clinician's determination. Commonly used off-label uses for TMS include use for many other psychiatric diagnoses (obsessive compulsive disorder, ADHD, Anxiety Disorders, Autism, Addiction, etc.), varying frequencies and amplitude of stimulation, varying positions on the *head* to stimulate different parts of the brain, shorter or extended protocols, more or less time between stimulation sessions, and/or bilateral treatments.

5. During a TMS treatment session, the psychiatric provider or a qualified member of the clinic staff will place the magnetic coil against the scalp over the treatment area. The magnetic field produced by the device is targeted over areas of the brain that the psychiatric provider believes may be affected in the patient's condition.

6. We will then position the patient's head and TMS device and introduce a series of single magnetic pulses over the motor cortex of the brain to find the right stimulation dose. There will be a clicking sound and the patient may feel a tapping like sensation on the scalp. The psychiatric provider will adjust the device to give enough energy into the are of the brain that controls the right hand so that the right hand makes a twitching movement The amount of energy needed for this stimulation is called the "motor threshold." (MT). MT's differ between patients, and the treatments are individualized.

7. TMS risks: Long term side effects are unknown at this time. The changes made to the brain are expected to *be* permanent and beneficial but may be permanent and harmful. There is a risk that measurements taken are not accurate and that the wrong area of the brain is treated. There is risk that the magnetic energy coil is not placed correctly and is not delivered to the expected treatment area in the brain. t understand that t should inform my psychiatric provider or a member of the TMS Therapeutic staff of any side effects. There may be discomfort and headaches over time. TMS is not effective for all patients. My signs or symptoms of a worsening condition should be reported Immediately to your psychiatric provider. It may be beneficial to ask a family member or caregiver to monitor your symptoms to help you spot any signs of worsening problems. Please understand that many but not all patients benefit from TMS treatment and that it may take up to the fourth week of treatment for it to work or it may never work at all Some patients may experience results in less time while others may take longer.

8.Then the magnetic coil will be moved, and the patient will receive the treatment as a series of "pulses" for 4 seconds every 28 seconds, but other patterns may be used off label. Treatment is to the left front side of the patient's head and will take between 6 and 40 minutes. The patient will receive these treatments 5 times a week for approximately 4-6 weeks (20-30 treatments). My psychiatric provider will evaluate the patient as necessary during this treatment course and may be scheduled when requested. The psychiatric provider may make off label changes to the treatment settings, add additional treatments, stimulate a different place on the head in order to get a more effective outcome.

9. During the treatment the patient may experience headaches, tooth pain, muscle contractions, tapping or uncomfortable sensations at the treatment site when the stimulator Is on. These were felt by about 1/3 of patients in the research studies. The patient (if able) should inform the psychiatric provider or staff if the sensation is uncomfortable or painful. My psychiatric provider or staff may then adjust the dose or change the location of the coil to make the procedure more comfortable.

10. TMS should not be administered to anyone who has magnetic metal in their head or within 12 inches of the TMS coil that cannot be removed. Failure to follow this restriction could result in serious injury or death.

11. Objects that may have this kind of metal include the below, **please initial to attest that I do not,** and/or the patient does not have any of the following:

- No aneurysm dips or coils
- No pellets, bullets, or metallic fragments
- No implanted stimulator or pacemaker
- No other metal devices or objects implanted in the head
- No electrodes to monitor brain activity
- No magnetic implants in the patient's ears or eyes
- No bullet or shrapnel fragments
- No magnetically active dental implants

Initial to attest that I do not (and/or the patient does not) have the previous listed

12. My psychiatric provider and the staff will do their best to move the coil carefully over the patient's head, although rare, the patient stands a chance of getting hit in the head by the magnet during positioning (this occurs very rarely).

13. There is no guarantee that this treatment will improve the condition, TMS is not effective for every patient. I will tell the psychiatric provider right away if I have any worsening depression or unusual behavior.

14. Seizures (sometimes called convulsions or fits) have been reported with TMS. There were no seizures in the clinical trials, which involved over 10,000 patient treatment sessions. In a 300 patient clinical trial, no seizures were observed. But, seizures have occurred during other research and clinical use of TM& The risk of having a seizure is very, very low, but I will give the psychiatric provider complete medical information so that the level of risk can be assessed and discussed with me. The current estimated risk of seizure is 1 In 30,000 treatments (0.003%) or 1 in 1,000 patients (0.1%)

15. I understand that I can stop the treatment at any time.

16. l understand that I may be responsible for out of pocket costs for this procedure.

17. I have read the information contained in this consent form about This and its potential risks. I have discussed it with the psychiatric provider who has answered all questions. I understand there are other treatment options including medications, psychotherapy, and other kinds of brain stimulation like electroconvulsive therapy (ECT). These alternative treatment options may be discussed with me but I have chosen TMS.
18. I consent for Alfredo H. Alfredo, PMHCNS-BC,PA to use my unidentified clinical data for research. Any personal health information (PHI) that could identify you will be removed and all data anonymous. That is, it will not include name or any personal identifiers. Any health data will be held in strict confidentiality and will be used only for the purposes of aggregate research results. Any results will be reported or published in aggregate form.

19. I promise to inform the psychiatric provider or assistant if I experience anything uncomfortable, during or after the stimulation even if I think that it is not caused by the stimulation. Remember, TMS is optional and it Is not an obligation. I request and allow my psychiatric provider or staff to administer this treatment to me.

By signing below I confirm that I am either the adult patient or the legal guardian of the patient and that I consent to treatment with TMS.

Patient Name: John Doe
Patient Signature:

_____

Responsible Party Name: John Doe
Responsible Party Signature:

_____

Signature of Provider: _____

Appendix B: Clinical Psychiatric Evaluation

CLINICAL PSYCHIATRIC EVALUATION TEMPLATE

Presenting Problem

What are the problem(s) for which you are seeking help?

Current Symptoms

Review each symptom and if experiencing it, select the checkbox and how often the symptom occurs during the day.

Symptom & How Often Symptom Occurs During the Day

Anxiety Attacks	Guilt
Appetite, Increased	Impulsive
Appetite, Decreased	Unable to Feel Pleasure
Depressed Mood	Increased Activity
Easily Distracted	Increased Need for Sleep
Engage in Risky Behaviors	Unable to Fall Sleep
Excessive Energy	Paranoia
Excessive Worry	Preoccupied with Sex
Fatigue	Racing Thoughts
Feeling Hopeless	Talkativeness
Feelings of Abandonment	Worthlessness
Feelings of Emptiness	Other (Specify)

When did the symptom(s) start? (onset)

Use the scale to indicate the overall severity of symptoms.

Are these symptoms affecting any of the following?

Activities of Daily Living, Finances, Housing, Legal Matters, Recreational Activities, Relationships, School, Self-Esteem, Sexual Activity, Work

Using the scale below what is the impact of these symptoms on the areas of your life selected from the previous question?

Psychiatric ROS, MSE, Musculoskeletal, and Constitutional Exams

History of Present Illness: Descriptive Account

PSYCHIATRIC ROS SYMPTOMS

Aggressive	Loss of Interests
Akathisia	Nervous or Suspicious of Others
Apathy	Paranoia
Assaultive	Mood Changes
Difficulty Staying Asleep	Peculiar or Uncharacteristic Behavior
Drop in Functioning	Problems with Thinking/ Concentrating
Frequent Crying	Restless
Feeling Disconnected	Withdrawal
Irritability	Other Psychiatric ROS (specify)

Psychiatric Exam

Speech

- *Appropriate with Normal Tone, Rate, and Volume*
- *Accent*
- *Fast Rate*
- *Intonations, Monotone*
- *Latency, Decreased*
- *Latency, Increased*
- *Lisp*
- *Stuttering*
- *Slow Rate*
- *Volume, Soft*
- *Volume, Loud*
- *Other Speech (specify)*

Thought Process

- *Coherent, Logical, Appropriate*
- *Blocked*
- *Circumstantial*
- *Clang Associations*
- *Egocentric*
- *Evasive*
- *Flight of Ideas*
- *Incoherent*
- *Loose Associations*
- *Magical Thinking*
- *Neologisms*
- *Racing*
- *Tangential*
- *Word Salad*
- *Other (specify)*

Thought Content

- *Intact*
- *Depersonalization*
- *Derealization*
- *Phobias*
- *Obsessions/Compulsions*
- *Suicide Ideation (Plan/Intent/Means)*
- *Homicide Ideation (Plan/Intent/Means)*

Abnormal or Psychotic Thoughts

- *Patient Denies*
- *Hallucinations – Auditory*
- *Hallucinations – Gustatory*
- *Hallucinations – Olfactory*
- *Hallucinations – Visual*
- *Delusions – Bizarre*
- *Delusions – Grandiose*
- *Delusions – Jealously*
- *Delusions – Nihilistic*
- *Delusions – Persecutory*
- *Delusions – Reference*
- *Delusions – Somatic*
- *Other (Specify)*

Judgement / Insight

- *Appropriate Judgment and Insight*
- *Impulsive Behavior*
- *Unrealistic Decisions*
- *Insight, Fair*
- *Insight, Poor*
- *Other(Specify)*

Orientation

- *Oriented to Person, Place, Date, and Time*
- *Disoriented to Date and Time*
- *Disoriented to Place*
- *Disoriented to Person*

Recent Memory

- *Short-term Memory Test Used*
- *Good Recall*
- *Poor Recall*

Remote Memory

- *Long-term Memory Test Used*
- *Good Recall*
- *Poor Recall*

Attention and Concentration

- *Immediate Recall, Adequate Concentration*
- *Impaired*
- *Easily Distracted*
- *Poor Concentration*
- *Preoccupation*
- *Other Attention/Concentration (specify)*

Language

Articulate, Fluent
Articulation Difficulties
Incoherent
No Verbal Response
Other Language (specify)

Fund of Knowledge

Aware of Past and Current Events
Unaware of Current Events
Unaware of Past History
Other (specify)

Mood

Appropriate Mood and Affect
Patient's Description of their Emotional State
Patient's Self-Reported Scale of their Mood
Anxiety Level

Affect

Blunted
Anxious
Broad
Fatigued
Flat
Irritable
Labile
Suspicious
Tearful
Withdrawn
Restricted
Other Mood/Affect (specify)

Eye Contact

Direct
Avoidant
Intense
Intermittent
No Contact

Constitutional

Appropriate Appearance and Grooming
Body Odor
Disheveled
Poorly Groomed
Prominent Scars
Tattoos
Weight Gain
Weight Loss
Other Constitutional (specify)

Gait/Station

Gait Smooth with No Abnormal Movement.
Ataxic
Diplegic
Myopathic
Neuropathic
Parkinsonian
Sensory
Shuffling
Other Gait/Station (specify)

Psychomotor Behavior

Muscles Symmetric without Abnormalities.
Agitation
Atrophy
Hand Wringing
Retardation
Tics
Tremors
Other Psychomotor Behavior (specify)

Vitals

Weight (lbs.)
Height (in.)
BMI
Previous Weight (lbs.)
Weight Change (lbs.)
Pulse Respiration
Blood Pressure
Previous Blood Pressure

Objective Measures

PHQ-9 / HAMILTON/ ANXIETY MOCA

HISTORY

Medical History

Do you have any concerns about your physical health that you would like to discuss?

Select the checkbox if you have been diagnosed with any of the following problems.

Anemia	*Seizures*
Diabetes	*Chronic Fatigue*
Arthritis	*Chronic Pain*
Head Trauma	*Other Problems (specify)*
Asthma	

Past Psychiatric History

Have you ever had Outpatient Treatment?

Yes/No

If yes, list the reason and dates treated.

Have you ever had Inpatient Psychiatric Hospitalization?

Yes/No

If yes, list the reason and dates treated.

Family Psychiatric History

Select the family member who has been diagnosed or treated for any of the following diagnosis.

Alcohol Abuse	Child	Parent	Sibling	Grandparent
Anger	Child	Parent	Sibling	Grandparent
Anxiety	Child	Parent	Sibling	Grandparent
Bipolar Disorder	Child	Parent	Sibling	Grandparent
Depression	Child	Parent	Sibling	Grandparent
Post-Traumatic Stress Disorder	Child	Parent	Sibling	Grandparent
Schizophrenia	Child	Parent	Sibling	Grandparent
Substance Use Disorder	Child	Parent	Sibling	Grandparent

Past/Current Psychiatric Medications

If you have ever taken any of the following medications, document the dosage, indicate if the medication was effective by selecting Yes or No; and select the check box if side effects were experienced.

MEDICATION (ANTIDEPRESSANT)	DOSE (mg, QD)	Effective Yes/No	Side Effects Present
Zoloft (Sertratline)			
Celexa (Citalopram)			
Cymbalta (Duloxetine)			
Effexor (Venlafaxine)			
Elavil (Amitriptyline)			
Lexapro (Escitalopram)			
Luvox (Fluvoxamine)			
Vibryd (vilazodone)			
Paxil (Paroxetine)			
Prozac (Fluoxetine)			
Remeron (Mirtazapine)			
Serzone (Nefazodone)			
Trazodone			
Wellbutrin (Bupropion)			

MEDICATION (MOOD STABILIZER"STB")	DOSE (mg, QD)	Effective Yes/No	Side Effects Present
Depakote (Valproate)			
Lamictal (Lamotrigine)			
Lithium			
Tegretol (Carbamazepine)			
Topomax (Topiramate)			

MEDICATION (ANTIPSYCHOTIC/MOOD STB)	DOSE (mg, QD)	Effective Yes/No	Side Effects Present
Clozaril (Elozapine)			
Haldol (Haloperidol)			
Latuda (Lurasidone)			
Risperdal (Risperidone)			
Seroquel (Quetiapine)			
Zyprexa (Olanzepine)			

MEDICATION (ADHD)	DOSE (mg, QD)	Effective Yes/No	Side Effects Present
Adderall (Amphetamine)			

MEDICATION (ANTI-ANXIETY)	DOSE (mg, QD)	Effective Yes/No	Side Effects Present
Adderall (Amphetamine)			
Ativan (Lorazepam)			
Buspar (Buspirone)			
Klonopin (Clonazepam)			
Tranxene (Clorazepate)			
Valium (Diazepam)			

SOCIAL HISTORY
Born
Sibling
Family
Highest Educational Level Completed
Developmental Tasks Met

RELATIONSHIP STATUS
Have you been married previously?
If you are female, what is your pregnancy status?
Do you have children?
Living Arrangements
Are you sexually active?

How would you identify your sexual orientation/identity?
Heterosexual/Straight, Bisexual, Unsure
Homosexual/Gay, Transgender, Prefer Not to Answer

Do you work outside the home?

Have you served in the military?

Do you exercise regularly?

Do you have a history of abuse? If yes, select the type(s).
No History of Sexual, Emotional, Physical or Neglect
Sexual
Emotional
Physical
Neglect

Smoking Status
Do you use tobacco products? What kind? (cigarettes, pipes, vape)
If a smoker, how many times during the day do you use tobacco products?

Alcohol Use Status
Do drink alcohol?
If yes, how many times in a week, do you drink alcohol? per week
Have you felt bad or guilty about your drinking?

Legal History
Have you ever been arrested?
Do you have any pending legal problems?

Spiritual Life
Do you belong to a religion or spiritual group?
Is this involvement helpful or stressful?

Risk Assessment
Suicide Risk Assessment
1. Been so distressed you seriously wished to end your life?
2. Has anything happened recently to make you feel you don't want to live? If yes, describe the incident / event.

Have you had or do you have:
3. A specific plan how you would kill yourself?
4. Access to weapons or means of hurting self?
5. Made a serious suicide attempt?
6. Purposely done something to hurt yourself?
7. Heard voices telling you to hurt yourself?
8. Had relatives who attempted or committed suicide?
9. Had thoughts of killing or seriously hurting someone?
10. Heard voices telling you to hurt others?
11. Hurt someone or destroyed property on purpose?
12. Slapped, kicked, punched someone with intent to harm?
13. Been arrested or detained for violent behavior?
14. Been to jail for any reason?
15. Been on probation for any reason?
16. Do you have access to guns?

Substance Use Assessment
1. Do you think you may have a problem with alcohol or drug use?
2. Have you ever been treated for alcohol or drug abuse?
3. Have you used any street drugs in the past 3 months?
4. Have you ever abused prescription medications?

Select the substances you have tried and the date you last used them.

SUBSTANCE	YES/NO USED	DATE LAST USED
Benzodiazepines/Tranquilizers		
Cocaine		
Ecstasy / MDMA		
Heroin		
Inhalants		
LSD / Hallucinogens		
Marijuana		
Methadone		
Methamphetamine		
Opioids		
Pain Killers not prescribed to you		
Stimulant Pills		
OTHER (Specify)		

Treatment Recommendations
Treatment Goals
Diagnosis
Treatment Plan & Medication Regimen

Appendix C: Initial TMS Mapping / Session Note

TMS MAPPING / INITIAL SESSION NOTE

TMS Mapping Completed by:

Psychiatric History Review:

Response and Recommendations:

Measurements:

Tragus to Tragus: **Nasion to Inion:**

Head Circumference:

Motor Threshold M1:

Initial Treatment MT:

Dosage Level:

Baseline Objective Measures:

PHQ-9:

GAD-7:

TMS Session #

Additional Session # Information:

TMS Protocol(s) Used:

Current MT: **Increased MT:**

MT MAX: **Dosage Level:**

Subjective: Mood: Energy: Anxiety: Sleep: Concentration/Focus: Interactions with Friends and Family: Overall Level of Functioning: Overall Quality of Life: Impressions of TMS:

Objective: Restless, Reports isolation, Reports difficulty sleeping, Apathy, Problems concentrating, Low energy, Dressed casually & appropriately, Good hygiene, Poor hygiene, Responded well to questions, Did not initiate conversation, Cooperative and talkative during treatment, Cooperative and relaxing with eyes closed during treatment, Cooperative and playing with phone during treatment, Smiling and Joking, Positive Affect, Neutral Affect, Blunted Affect

Evaluation of Treatment and Recommendations:

TMS Treatment Completed by:

Treatment Reviewed & Evaluated by:

Diagnosis & CPT Code:

Appendix D: Daily TMS Session Note

TRANSCRANIAL MAGNETIC STIMULATION TREATMENT NOTE

TMS Session #

Additional Session # Information:

TMS Protocol(s) Used:

Current MT: **Increased MT:**

MT MAX: **Dosage Level:**

Subjective: Mood: Energy: Anxiety: Sleep: Concentration/Focus: Interactions with Friends and Family: Overall Level of Functioning: Overall Quality of Life: Impressions of TMS:

Objective: Restless, Reports isolation, Reports difficulty sleeping, Apathy, Problems concentrating, Low energy, Dressed casually & appropriately, Good hygiene, Poor hygiene, Responded well to questions, Did not initiate conversation, Cooperative and talkative during treatment, Cooperative and relaxing with eyes closed during treatment, Cooperative and playing with phone during treatment, Smiling and Joking, Positive Affect, Neutral Affect, Blunted Affect

Weekly Objective Indicators:
PHQ-9: **GAD-7:** **Y-BOCS:**

Evaluation of Treatment and Recommendations: Patient tolerated rTMS very well with no concerns voiced or discomfort noted., I have reviewed the interval events since the last visit in order to formulate my clinical decisions, impressions and recommendations., Treatment progress, rTMS treatments, MT%, PHQ-9"s and response to treatment reviewed with patient and staff., Medication history reviewed and discussed with patient., Discussed with patient continuing with current treatment plan, rTMS schedule and evaluate daily response to treatment. No side effects noted or reported., Supportive therapy and education provided to patient regarding depression, treatment and personal changes needed to assist with recovery., Talk, supportive therapy provided to facilitate expression of thoughts, feelings, conflicts and patient behaviors., Talk, supportive therapy provided to facilitate expression of thoughts, feelings, conflicts and patient behaviors., Talk, supportive therapy provided to facilitate expression of thoughts, feelings, conflicts and patient behaviors., Talk, supportive therapy provided to facilitate expression of thoughts, feelings, conflicts and patient behaviors., Education provided regarding rTMS and effects on brain and emotions. All questions answered.

TMS Treatment Completed by:

Treatment Reviewed & Evaluated by:

Diagnosis & CPT Code:

Appendix E: Patient Health Questionnaire (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ DATE:_____

Over the last 2 *weeks*, how often have you been bothered by any of the following problems? *(use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
		add columns	+	+

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	_____
	Somewhat difficult	_____
	Very difficult	_____
	Extremely difficult	_____

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Vita

John William Capps IV is a father of two who was born and raised in North Carolina and now lives in Cuidad Juarez, Mexico. He earned his M.A. in Experimental Psychology from the University of Texas at El Paso in 2020. John also holds a B.A. in Psychology with Honors and minors in Chemistry, Biology, and Neuroscience from the University of North Carolina Wilmington, as well as an A.A. in Psychology from Cape Fear Community College. John's primary focus is on health psychology with an emphasis on neuropsychological assessment, cognitive neuroscience, and the application of technology in psychological and clinical research. His master's thesis titled "*Adiposity and Arterial Stiffness: Associations with Prefrontal Cortex Hemodynamic Response and Response Inhibition*" integrated his concentrations in health psychology and cognitive neuroscience.

His experience is multifaceted, as he has served in a teaching role at UTEP from 2015-2022 and worked as a web developer/project manager for medical clinics and a telemedicine startup. John has been involved in interdisciplinary research projects and works together with his wife, Veronica Portillo Reyes, PhD, focusing on integrative health science research and neuropsychological testing. Some of their most recent publication titles include "*Psychometric properties of the ASEBA older adult self-report in a Mexican sample"*, "*Daily stress and coping strategies: Relationships with anxiety and resilience in preadolescents from Ciudad Juarez, Mexico"*, and "*Omega-3 and Cognition in Children with Malnutrition*". He has clinical experience working as a TMS, EEG, and psychological testing technician under the supervision of Alfredo H. Arellano, PMHCNS-BC, and as a mental health volunteer and intern at Cape Fear Clinic under the supervision of Antonio E. Puente, PhD.

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