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SAN DIEGO STATE UNIVERSITY

Predictors and Neurophysiological Biomarkers of Response to Neuromodulatory Interventions in
Treatment-Resistant Depression

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of
Philosophy

in

Clinical Psychology

by

Lindsay Benster

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Professor Cory Weissman

San Diego State University

Professor Nader Amir
Professor Linda Gallo

2026

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Chair

University of California San Diego

San Diego State University

2026

DEDICATION

This dissertation is dedicated to my family, whose unwavering support in my dreams and aspirations have been a constant source of strength and inspiration throughout my life.

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LIST OF ABBREVIATIONS

Acronym	Definition
ACC	Anterior Cingulate Cortex
APB	Abductor Pollicis Brevis
AUC	Area Under the Curve
BDNF	Brain-Derived Neurotrophic Factor
BiTBS	Bilateral Theta Burst Stimulation
BMI	Body Mass Index
CI	Confidence Interval
CSP	Cortical Silent Period
DCA	Decision Curve Analysis
DDD	Daily Defined Dose
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive Therapy
EEG	Electroencephalography
EMR	Electronic Medical Records
ENet	Elastic Net Regression
ERP	Event-Related Potential
FDA	Food and Drug Administration

Acronym	Definition
FDR	False Discovery Rate
fMRI	Functional Magnetic Resonance Imaging
GBM	Gradient Boosting Machine
HFL	High-Frequency Left (rTMS protocol)
HL	Hosmer-Lemeshow Test
iTBS	Intermittent Theta Burst Stimulation
KM	Kaplan-Meier
LFR	Low-Frequency Right (rTMS protocol)
LICI	Long-Interval Intracortical Inhibition
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MEP	Motor-Evoked Potential
ML	Machine Learning
mTOR	Mammalian Target of Rapamycin
NMDA	N-methyl-D-aspartate (receptor)
NNT	Number Needed to Treat
NSSI	Non-Suicidal Self-Injury
OCD	Obsessive-Compulsive Disorder
PFC	Prefrontal Cortex
PHQ-9	Patient Health Questionnaire–9

Acronym	Definition
rMT	Resting Motor Threshold
RMSE	Root Mean Square Error
ROC	Receiver Operating Characteristic
rsEEG	Resting-State Electroencephalography
rTMS	Repetitive Transcranial Magnetic Stimulation
SHAP	SHapley Additive exPlanations
SI	Suicidal Ideation
SMOTE	Synthetic Minority Over-sampling Technique
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
SVM	Support Vector Machine
TEP	TMS-Evoked Potential
TMS	Transcranial Magnetic Stimulation
TMS-EEG	TMS with EEG recording
TMS-EMG	TMS with Electromyography
TRD	Treatment-Resistant Depression
UCSD-IPP	University of California San Diego – Interventional Psychiatry Program

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RESEARCH INTERESTS

Interventions and predictors of response for severe and treatment-resistant mental illness.

PEER-REVIEWED PUBLICATIONS

1. Stapper, N., **Benster, L.**, Menon, S., Boyd, E., Poorganji, M., Hadas, I., Sun, Y., Appelbaum, L., Daskalakis, Z., & Weissman, C. (2025). Neurophysiological biomarkers of treatment response in suicidal ideation: A systematic review. *Translational Psychiatry*, **15**, 473.

2. Gabard-Durnam, L., McCormick, S., Underwood, E., Tao, A., Kim, I., Coffman, S., **Benster, L.**, Nelson, C., Berde, C., Cornelissen, L., Graziano Maloney, M., & Hensch, T. (2025) General anesthesia in early infancy accelerates visual cortical development. *Proc. Natl. Acad. Sci.* 122 (31).
3. **Benster, L.**, Weissman, C., Suprani, F., Toney, K., Afshar, H., Stapper, N., Tello, V., Stolz, L., Poorganji, M., Daskalakis, Z., Appelbaum, L., & Kohn, J. (2025). Predictive modeling of response to repetitive transcranial magnetic stimulation in treatment-resistant depression. *Translational Psychiatry*.
4. Stapper, N., Kohn, J., **Benster, L.**, Daniels, H., Tello, V., et al. (2025). Repetitive transcranial magnetic stimulation for the treatment of suicidal ideation in a naturalistic setting. *Brain Stimulation*.
5. **Benster L.L.**, Stapper N, Rodriguez K, Daniels H, Villodas M, Weissman CR, Daskalakis ZJ, Appelbaum LG (2024). Developmental Predictors of Suicidality in Schizophrenia: A Systematic Review. *Brain Sciences*, 14(10):995.
6. Noback, M., Bhakta, S.G., Talledo J.A., Kotz, J.E., **Benster, L.L.**, et al. (2024). Amphetamine increases motivation of humans and mice as measured by breakpoint, but does not affect an EEG biomarker. *Cog, Affective, and Behavioral Neuroscience*.
7. **Benster, L.L.**, Weissman, C.R., Stolz, L.A. et al. (2023). Pre-clinical indications of brain stimulation treatments for non-affective psychiatric disorders, a status update. *Translational Psychiatry* **13**, 390.
8. Stolz, L. Kohn, J., Smith, S., **Benster, L.**, Appelbaum, L. (2023). Predictive biomarkers of treatment response in Major Depressive Disorder. *Brain Sci*, 13(11):1570.
9. Lochhead, L.D., Stolz, L.A., **Benster, L.L.** (2023). "Transcranial magnetic stimulation." In: Kirby ED, Glenn MJ, Sandstrom NJ, Williams CL, eds. *Introduction to Behavioral Neuroscience*, 1e. Houston, TX: OpenStax.
10. **Benster, L.L.**, Weissman, C.R., Daskalakis, Z.J. (2022). Suicidal Ideation and Obsessive-Compulsive Disorder: Links and Knowledge. *Psychology Research and Behavior Management*, 15:3793-3807.
11. Bhakta, S., Cavanagh, J., Talledo, J., Kotz, J., **Benster, L.**, et al. (2022). EEG reveals that dextroamphetamine improves cognitive control through multiple processes in healthy participants. *Neuropsychopharmacology*, 47:1029-1036.
12. Swerdlow, N.R., Bhakta, S., Talledo, J., **Benster, L.**, et al. (2021). Auditory discrimination and frequency modulation learning in schizophrenia patients: Amphetamine dose response and time course. *Psychological Medicine*, 1-9.

13. **Benster, L.L.**, Swerdlow, N.R. (2020). Pathways to empathy in mental health care providers. *Advances in Health and Behavior* 3(1):125-136.
14. Swerdlow, N.R., Bhakta, S.G., Talledo, J., **Benster, L.L.**, Kotz, J., Lavadia, M.L. (2019). Lessons learned by giving amphetamine to antipsychotic-medicated schizophrenia patients. *Neuropsychopharmacology* 44(13):2277-2284.

ABSTRACT AND PROFESSIONAL PRESENTATIONS

1. Appelbaum, L.G., Kohn, J., Stolz, L., **Benster, L.**, Poorganji, M., et al. (2025). “Predicting treatment response to repetitive transcranial magnetic stimulation from medical records and electroencephalography.” Society for Biological Psychiatry, Toronto, CA. (Conference)
2. Cui, B., Kohn, J., **Benster, L.**, Stapper, N., et al. (2025). “Longitudinal trajectories of symptom improvement with rTMS treatment for treatment-resistant depression.” UC San Diego Medical School Student Conference. (Local Conference)
3. Wade, B., Kohn, J., **Benster, L.**, Weissman, C., et al. (2025). “Multisite external validation of a machine learning model to predict individual treatment selection between electroconvulsive therapy and ketamine.” International Brain Stimulation Conference. (Conference)
4. Appelbaum, L.G., Poorganji, M., Stolz, L., **Benster, L.**, Daskalakis, Z., et al. (2025). “Clinical, demographic, and neurophysiological predictors of treatment response to repetitive transcranial magnetic stimulation.” Symposium at the 6th International Brain Stimulation Conference. (Conference)
5. Wade, B., Kohn, J., **Benster, L.**, Weissman, C., et al. (2024). “Multisite prediction of optimal treatment allocation between electroconvulsive therapy and ketamine.” ACNP 63rd Annual Meeting. (Conference)
6. **Benster, L.** (2024). “Clinical neuroscience research.” Neur 372, Clinical Neuroscience. University of San Diego, CA. (Invited lecture)
7. **Benster, L.** (2024). “Pre-clinical indications of brain stimulation treatments for non-affective psychiatric disorders.” Department of Psychiatry Grand Rounds, UCSD, San Diego, CA. (Invited lecture)
8. **Benster, L.**, Suprani, F., Weissman, C., Toney, K., Afshar, H., Daskalakis, Z., Appelbaum, L., Kohn, J. (2024) “Predictors of treatment response to rTMS in treatment-resistant depression: a retrospective clinical cohort study.” NYC Neuromodulation, New York, NY. (Conference & oral highlight)

9. Stolz, L. Kohn, J., Smith, S., **Benster, L.**, Appelbaum, L. (2024). “Machine learning predicts response to rTMS in treatment-resistant depression.” NYC Neuromodulation, New York, NY. (Conference)
10. **Benster, L.**, Punsalan, A. (2024). “Imposter Phenomenon: Strategies for Graduate and Professional Studies.” Physician Assistant Program, UCSD, San Diego, CA. (Community outreach talk)
11. Stapper, N., Kohn, J., **Benster, L.**, Tello, V., Appelbaum, L., Weissman, C. (2024). “Predictors of Decreases in Suicidal Ideation in Patients with Treatment-Resistant Depression Receiving Repetitive Transcranial Magnetic Stimulation Treatment: A Retrospective Clinical Cohort Analysis.” Society for Biological Psychiatry, Austin, TX. (Conference)
12. **Benster, L.**, Suprani, F., Weissman, C., Toney, K., Afshar, H., Daskalakis, Z., Appelbaum, L., Kohn, J. (2024). “Predictors of treatment response to repetitive transcranial magnetic stimulation in treatment-resistant depression: a retrospective clinical cohort study.” Society for Biological Psychiatry, Austin, TX. (Conference)
13. **Benster, L.**, Arrigoni, L. (2024). “Fostering Professional Relationships.” Chemistry PhD Program, UCSD, San Diego, CA. (Community outreach talk)
14. Rogers, J., Fitzgerald, R., Iudicello, J., Grant, I., **Benster, L.**, Marcotte, T. (2024). “Pattern of recent cannabis use differentiates pharmacokinetic responses to ad-lib cannabis smoking among regular users.” 19th Annual Lewis L. Judd Young Investigators Research Symposium, San Diego, CA. (Conference)
15. Dexter, T., Bhakta, S., Talledo, J., Kotz, J., **Benster, L.**, Nungaray, J., Light, G., Swerdlow, N., Brigman, J., Cavanagh J., Young, J. (2024). “Modafinil increases motivation and modulates an EEG biomarker of progressive ratio breakpoint in humans.” 19th Annual Lewis L. Judd Young Investigators Research Symposium, San Diego, CA. (Conference)
16. Stapper, N., Kohn, J., **Benster, L.**, Tello, V., Daskalakis, Z., Appelbaum, L., Weissman, C. (2024). “Transcranial magnetic stimulation for the treatment of suicidal ideation.” 19th Annual Lewis L. Judd Young Investigators Research Symposium, San Diego, CA. (Conference)
17. **Benster, L.**, Punsalan, A. (2024). “Overcoming Burnout.” HDH, UCSD, San Diego, CA. (Community outreach talk)
18. **Benster, L.**, Punsalan, A. (2024). “16 Personalities.” HDH, UCSD, San Diego, CA. (Community outreach talk)

19. **Benster, L.**, Punsalan, A. (2024). “Imposter Syndrome/Phenomena: Strategies for Graduate and Professional Studies.” Biomedical Sciences, UCSD, San Diego, CA. (Community outreach talk)
20. **Benster, L.** (2023). “Clinical neuroscience research: Pathways and examples.” Neur 372, Clinical Neuroscience. University of San Diego, CA. (Invited lecture)
21. **Benster, L.**, Arrigoni, L. (2023). “Managing Professional Relationships.” BioSci Program, UCSD, San Diego, CA. (Community outreach talk)
22. **Benster, L.**, Arrigoni, L. (2023). “Write to Heal: Journaling Through Grad School.” HDH, UCSD, San Diego, CA. (Community outreach talk)
23. **Benster, L.**, Arrigoni, L. (2023). “Managing Stress in Grad School.” School of Engineering, UCSD, San Diego, CA. (Community outreach talk)
24. **Benster, L.**, Sandoval, R., Punsalan, A. (2023). “Mindful Self-Compassion: Building Inner Strength for Grad School.” HDH, UCSD, San Diego, CA. (Community outreach talk)
25. **Benster, L.**, Sandoval, R. (2023). “Mindfulness Workshop.” Grad Life, UCSD, San Diego, CA. (Community outreach talk)
26. **Benster, L.**, Zhu, S. (2023). “Imposter Syndrome/Phenomena: Strategies for Graduate and Professional Studies.” Competitive Edge, UCSD, San Diego, CA. (Community outreach talk)
27. **Benster, L.**, Stolz, L., Smith, S., Hill, A., Zomorodi, B., Voytek, B., Blumberger, D., Daskalakis, Z., Hadas, I. (2023). “Repetitive transcranial magnetic stimulation (rTMS) induces decreases in aperiodic activity in resting-state EEG.” Society for Biological Psychiatry, San Diego, CA. (Conference)
28. Suprani, F., **Benster, L.**, Jiang, T., Appelbaum, L., Daskalakis, Z., Weissman, C. (2023). “The role of concurrent antidepressant medications on repetitive transcranial magnetic stimulation (rTMS) effectiveness in treatment-resistant depression (TRD).” Society for Biological Psychiatry, San Diego, CA. (Conference)
29. Roberts, B., Bhatka, S., Talledo, J., Kotz, J., **Benster, L.**, et al. (2023). “Elevated delta power in people choosing to expend less effort in a cognitive effort task.” Society for Biological Psychiatry, San Diego, CA. (Conference)
30. Roberts, B., Bhatka, S., Talledo, J., Kotz, J., **Benster, L.**, et al. (2023). “Elevated delta power in people choosing to expend less effort in a cognitive effort task.” 17th Annual Lewis L. Judd Young Investigators Research Symposium, San Diego, CA. (Conference)

31. Stolz, L., Kohn, J., Smith, S., **Benster, L.**, Appelbaum, G. (2023). “Deriving biomarkers of treatment response from resting-state EEG in major depressive disorder.” 17th Annual Lewis L. Judd Young Investigators Research Symposium, San Diego, CA. (Conference)
32. **Benster, L.**, Askew, A., Ozturk, E. (2023). “Mindfulness Skills for Your Self Care Toolbox.” OLP Women’s Symposium, Academy of Our Lady of Peace, San Diego, CA. (Community outreach talk)
33. **Benster, L.** (2023). “Neuromodulation for treatment-resistant mental illness.” The Michael Haney Distinguished Lecture Series, University of San Diego, CA. (Invited Lecture)
34. **Benster, L.** (2023). “Career Paths: Clinical Psychology PhD.” Psychology Club PhD Career Panel, University of San Diego, CA. (Talk)
35. **Benster, L.**, Kennedy, L., Chlebowski, C., Arredondo, E. (2023). “Addressing mental health concerns in your community.” Catholic Diocese of San Diego, CA. (Community outreach talk)
36. **Benster, L.** (2022). “Clinical neuroscience research: Pathways and examples.” Neur 372, Clinical Neuroscience. University of San Diego, CA. (Invited lecture)
37. **Benster, L.**, Daskalakis, Z., Appelbaum, L. G., Hadas, I. (2022). “A comprehensive model for matching rTMS treatments to individual patient biology in anhedonic depression.” 17th Annual Lewis L. Judd Young Investigators Research Symposium, San Diego, CA. (Conference)
38. Noback, M., Cavanagh, J., Bhatka, S., Talledo, J., Kotz, J., **Benster, L.**, et al. (2022). “Amphetamine increases motivation in humans and mice although did not affect the parietal alpha biomarker.” 17th Annual Lewis L. Judd Young Investigators Research Symposium, San Diego, CA. (Conference)
39. Bhatka, S., Cavanagh, J., Talledo, J., Kotz, J., **Benster, L.**, et al. (2022). “Dextroamphetamine-Enhanced 5C-CPT Performance and Neural Correlates of Healthy Subjects: A Proof of Concept Study.” 59th Annual American College of Neuropsychopharmacology Conference, Virtual. (Conference)
40. Swerdlow, N.R., Bhatka, S.G., Clifford, R., Talledo, J., Kotz, J., **Benster, L.**, et al. (2019). “Memantine enhances measures of auditory fidelity and learning in schizophrenia.” 58th Annual American College of Neuropsychopharmacology Conference, Orlando, FL. (Conference)
41. Swerdlow, N., Franz, D., **Benster, L.**, et al. (2018). “Early auditory information processing in schizophrenia as a therapeutic target: Preliminary dose-response findings with amphetamine.” 57th Annual American College of Neuropsychopharmacology Conference. (Conference)

42. Fisher, T., Morse, A., **Benster, L.**, Hales, J. (2017). "The role of the medial entorhinal cortex in temporal aspects of memory processing in rats." 27th Annual Creative Collaborations Conference, College of Arts and Sciences, USD. (Conference)
43. Hales, J.B., **Benster, L.L.**, Breslin, P.J, *et al.* (2016). "Role of the medial entorhinal cortex in odor sequence learning in rats." 46th Annual Society for Neuroscience, San Diego, CA. (Conference)
44. **Benster, L.**, Fisher, E., Morse, A., Hales, J. (2016). "Role of the medial entorhinal cortex in odor sequence learning in rats." 26th Annual Creative Collaborations Conference, College of Arts and Sciences, USD. (Conference)

ABSTRACT OF THE DISSERTATION

Predictors and neurophysiological biomarkers of response to neuromodulatory interventions in treatment-resistant depression

by

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Doctor of Philosophy in Clinical Psychology

University of California San Diego, 2026
San Diego State University, 2026

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Rationale: Treatment-resistant depression (TRD) poses a significant challenge in psychiatry, characterized by the persistence of symptoms despite multiple treatment attempts. Approximately 30-50% of patients with major depressive disorder (MDD) do not achieve adequate response from first-line interventions, leading to TRD. This underscores the urgent need for novel interventions and personalized treatment strategies. Neuromodulatory treatments

such as repetitive transcranial magnetic stimulation (rTMS) and esketamine have emerged as promising options, yet considerable heterogeneity in treatment outcomes underscores the urgent need for robust, individualized predictive frameworks. This dissertation aimed to enhance understanding of response in TRD by integrating clinical, demographic, and neurophysiological predictors across three complementary studies.

Study 1 (published) aimed to identify clinical and demographic predictors of rTMS treatment response in TRD. This retrospective study utilized electronic medical records from UC San Diego and included 232 TRD patients who received rTMS. Machine learning models were trained to predict treatment response and remission. Key predictors included comorbid anxiety disorder, former tobacco use, obesity, comorbid trauma disorder, antipsychotic use, benzodiazepine use, protocol type, and number of rTMS sessions.

Study 2 employed survival analyses to compare temporal response trajectories between rTMS and esketamine, revealing distinct profiles: esketamine was associated with more rapid response and remission, while rTMS demonstrated a slower but steady trajectory that was significantly influenced by patient-specific factors, such as comorbidity burden, treatment protocol type, and number of sessions.

Study 3 explored the cortical silent period (CSP) as an exploratory neurophysiological marker of response, revealing preliminary and inconsistent associations with symptom change. These findings suggest CSP warrants further study within broader multimodal predictive frameworks.

Conclusions and Clinical Implications: These studies converge to support the value of a multimodal, data-driven approach to treatment prediction in TRD. The integration of machine learning, survival analysis, and neurophysiological data contributes to a more nuanced

understanding of patient-specific treatment pathways. Findings underscore the limitations of single-domain predictors and reinforce the promise of personalized treatment selection grounded in real-world, ecologically valid data. This work advances the precision psychiatry paradigm and lays a foundation for future prospective validation of predictive models capable of informing clinical decision-making in TRD.

INTRODUCTION

Major depressive disorder (MDD) is a prevalent and debilitating mental health condition characterized by persistent feelings of sadness, loss of interest in activities, and a range of cognitive and physical symptoms (American Psychiatric Association & American Psychiatric Association, 2013). Affecting millions globally, MDD is a leading cause of disability and is associated with significant morbidity and mortality (Ferrari et al., 2013). Despite the availability of various pharmacological and psychotherapeutic treatments, approximately 30% to 50% of patients do not achieve full remission, underscoring the complexity and heterogeneity of the disorder (Fava, 2003; Rush et al., 2006). Treatment-resistant depression (TRD) is operationalized as the failure to respond to at least two trials of antidepressant therapies of adequate dosage and duration (Rush et al., 2006). TRD patients often experience chronic and severe symptoms that lead to substantial impairments in daily functioning, increased risk of comorbid medical conditions, and higher suicide rates compared to those with treatment-responsive depression (Mrazek et al., 2014). Economically, TRD is associated with increased healthcare utilization, frequent hospitalizations, and higher medical costs (Shah et al., 2021). Additionally, the indirect costs, including lost productivity and absenteeism, contribute to the significant financial strain on society. The total annual cost of depression in the United States, including both direct and indirect costs, is estimated to be over \$210 billion, with TRD accounting for a considerable portion of this burden (Greenberg et al., 2015). This profound impact highlights the urgent need for effective treatment strategies to alleviate the burden of TRD on both individuals and the healthcare system.

Neuromodulatory interventions, such as repetitive transcranial magnetic stimulation (rTMS) and esketamine, have emerged as promising interventions specifically targeting TRD.

These therapies purportedly modulate neural circuits implicated in depression, offering new avenues for patients who have exhausted other options (Daly et al., 2018; O'Reardon et al., 2007). rTMS has shown particular efficacy in TRD by stimulating the dorsolateral prefrontal cortex (DLPFC), a region critical to emotion regulation (Caparelli et al., 2022; George et al., 2010a). Similarly, esketamine, an N-methyl D-aspartate (NMDA) receptor antagonist often administered intranasally, has demonstrated rapid antidepressant effects, addressing the need for quicker symptom relief in severe cases (Nikolin et al., 2023). Despite these advances, an estimated 30-40% of TRD patients still do not achieve adequate symptom relief with neuromodulation, highlighting the necessity for identifying predictors of treatment response (Trifu et al., 2021).

Understanding the predictors of response to these interventions is crucial for optimizing treatment strategies and personalizing patient care. Previous research has suggested that factors such as fewer psychiatric comorbidities and baseline symptom severity may influence treatment outcomes (Chou et al., 2021; Fitzgerald et al., 2016). Furthermore, neurophysiological markers, including motor-evoked potentials (MEPs), TMS-evoked potentials (TEPs), and resting-state EEG have shown potential in predicting response to neuromodulation therapies (Farzan, 2024; Ziemann, Rothwell, et al., 1996). Biomarkers, objective quantifiable indicators with a biological basis, may play a valuable role in intervention studies within psychiatry. They offer a means to uncover objective indicators that provide insight into the dynamic changes occurring in the brain during and after administration of rTMS and esketamine, informing treatment strategies and enhancing our understanding of therapeutic mechanisms. However, evidence supporting their clinical utility in screening and determining treatment outcomes is still limited, creating a need for comprehensive studies that can bridge this gap.

1.1 Treatment-Resistant Depression

TRD represents a significant subset of the depressive population, necessitating more focused research and innovative therapeutic approaches (Mrazek et al., 2014). Patients with TRD experience more severe and chronic symptoms compared to those who respond to initial treatments, leading to a greater impact on overall quality of life (Jamieson et al., 2023). The chronicity of TRD often results in higher levels of functional impairment, greater comorbidity with anxiety and other psychiatric disorders, and increased suicide risk (Corral et al., 2022). These patients frequently require more intensive and costly healthcare services, contributing to a substantial economic burden on healthcare systems. For instance, TRD patients incur approximately double the healthcare costs compared to non-TRD patients, largely due to increased hospitalizations, emergency visits, and long-term disability (Greenberg et al., 2015). This economic impact underscores the necessity for developing more effective and targeted interventions.

As previously mentioned, TRD is commonly defined as the failure to respond to at least two adequate trials of antidepressants from different pharmacologic classes (Fava, 2003). While this two-trial threshold offers a pragmatic and widely adopted operational definition in research and clinical settings, it is not without controversy. The cutoff, though useful for standardization, may conflate patients with differing degrees of treatment resistance, potentially obscuring important clinical distinctions (Fornaro & Giosuè, 2010). However, individuals who fail only one adequate antidepressant trial may still achieve remission with subsequent treatments, whereas those who fail two or more trials are significantly less likely to respond to additional monotherapy approaches and may require alternative strategies such as neuromodulation (Rush et al., 2006). Thus, the two-failure criterion reflects both a practical benchmark and a meaningful

clinical shift toward more refractory illness. Findings from the STAR*D trial underscore the progressive nature of treatment resistance. In this large, multicenter, real-world effectiveness study, remission rates declined steeply with each successive treatment level: 36.8% after the first step, 30.6% after the second, 13.7% after the third, and just 13% after the fourth (Rush et al., 2006; J. K. Trivedi, 2006). These results suggest that while a subset of patients may recover with second- or third-line treatments, the likelihood of remission diminishes considerably beyond the second failed trial. Furthermore, patients who fail multiple treatment steps are more likely to present with a distinct clinical phenotype characterized by longer illness duration, greater chronicity, comorbid anxiety or personality disorders, and higher functional impairment (Ionescu et al., 2013; Nierenberg et al., 2007). Compared to those with treatment-responsive depression, individuals with TRD also demonstrate increased cognitive dysfunction, greater suicidality, and poorer long-term prognoses, even when subsequent treatments are pursued (Bergfeld et al., 2018; McIntyre et al., 2023; Vancappel et al., 2023).

Despite its utility, the two-treatment definition of TRD remains an imperfect proxy for true treatment refractoriness. Some individuals may meet criteria despite poor adherence or subtherapeutic dosing in past trials, while others may experience significant impairment after failing a single, high-quality antidepressant course. As such, experts have advocated for a more dimensional or staging-based approach to characterizing TRD, incorporating not only number of treatment failures but also illness duration, symptom burden, comorbidity, and functional impact (Fekadu et al., 2009; McAllister-Williams et al., 2020). This nuanced understanding of TRD is critical for optimizing treatment selection and for guiding the application of neuromodulatory interventions, which may be more appropriate for patients with verified, multidimensional resistance to conventional treatments.

The marked heterogeneity of TRD presents a critical challenge to effective clinical management and underscores the necessity for individualized treatment selection strategies. TRD is not a unitary disorder but rather a multifactorial condition with diverse biological, psychological, and environmental contributors that shape its course and treatment responsiveness. Etiological variability (including early-life adversity, genetic predispositions, and neuroinflammatory processes) has been increasingly recognized as contributing to differential illness trajectories and treatment resistance (Felitti et al., 1998; Miller & Raison, 2016; Mössner et al., 2007). Subtyping within TRD has also revealed clinically meaningful distinctions. For example, melancholic depression is often associated with greater HPA-axis dysregulation and may respond more robustly to certain therapies such as ECT or rTMS, whereas atypical depression, marked by mood reactivity and hypersomnia, has been linked to different neurobiological and pharmacological response profiles (Kraus, Kadriu, et al., 2019; Kunugi et al., 2010; Pozuelo Moyano et al., 2024). Similarly, TRD with anxious or psychotic features has demonstrated poorer outcomes and may require fundamentally different approaches, including earlier consideration of neuromodulation (Fava et al., 2008; Ionescu et al., 2013). This diagnostic and phenomenological variability reinforces the inadequacy of one-size-fits-all treatment approaches.

Further compounding this complexity is the considerable inter-individual variability in treatment response, even among patients who meet similar diagnostic criteria or share comparable clinical histories. Such variation highlights a core rationale for this dissertation: the need for robust predictive models capable of integrating multiple domains of patient data to guide treatment selection. The literature largely has emphasized that the future of psychiatry must pivot toward precision medicine frameworks, where predictive tools—not diagnostic

categories alone—inform the most appropriate interventions for a given individual (Appelbaum et al., 2022; T. Insel et al., 2010; McGrath et al., 2013). In the context of TRD, this paradigm shift is particularly urgent, given the disorder’s profound clinical and economic toll.

1.1.1 Neurobiological Underpinnings and Mechanisms of TRD

Recent investigations into the neurobiology of TRD suggest that distinct neurophysiological profiles may underlie variability in treatment response, offering further justification for the development of predictive models tailored to specific interventions. rTMS exerts its therapeutic effects through modulation of cortical excitability, particularly targeting the DLPFC and its connectivity with subcortical limbic structures (Fox et al., 2012). Evidence indicates that patients exhibiting baseline hypofrontality, manifesting as reduced prefrontal activity or disrupted fronto-limbic connectivity, are more likely to respond favorably to rTMS (Liston et al., 2014). Moreover, neurophysiological markers such as the cortical silent period (CSP) and other measures of cortical inhibition may index individual differences in GABAergic tone and neuroplastic potential, both of which are mechanistically relevant to rTMS efficacy (Radhu et al., 2013; Ziemann et al., 2015). Thus, identifying patients with a neurobiological profile characterized by deficient top-down regulation or impaired inhibitory control may allow for more targeted application of rTMS.

In contrast, esketamine primarily engages glutamatergic signaling pathways through NMDA receptor antagonism, leading to rapid increases in synaptic plasticity via downstream activation of the mTOR pathway and release of brain-derived neurotrophic factor (BDNF) (Abdallah et al., 2015; Duman et al., 2016). Neuroimaging studies suggest that esketamine induces widespread functional reorganization, particularly in the anterior cingulate cortex (ACC), thalamus, and default mode network (DMN), regions implicated in self-referential

processing and emotional salience (J. H. Krystal et al., 2013; Nugent et al., 2019). Accordingly, individuals with preserved or hyperactive glutamatergic signaling, heightened ACC activation, or DMN hyperconnectivity may demonstrate enhanced responsiveness to esketamine's rapid-acting effects (Demchenko et al., 2022). Conversely, excessive neuroinflammation or dysregulated stress responses may attenuate these effects, reinforcing the importance of individualized neurobiological assessment in guiding treatment decisions (Miller & Raison, 2016).

In the context of TRD, the limitations of traditional and evidence-based pharmacological and psychotherapeutic interventions become even more pronounced. Antidepressant medications, particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), often exhibit delayed therapeutic onset, with 4–6 weeks typically required before meaningful symptom reduction occurs (Trivedi et al., 2006). This delay is clinically significant, especially in cases of severe or suicidal depression where rapid intervention is critical. Moreover, common side effects such as weight gain, sexual dysfunction, emotional blunting, and gastrointestinal disturbances contribute to poor adherence and high dropout rates (Papakostas et al., 2008).

In addition to diminished response rates, placebo responsiveness (a significant confounding factor in early treatment trials) appears to plateau or diminish substantially after one or two failed antidepressant trials (Fava, 2003). This attenuated placebo effect further complicates the management of TRD, as the likelihood of spontaneous remission or nonspecific improvement diminishes with treatment refractoriness. Consequently, repeated trials of pharmacotherapy in individuals with established TRD may yield limited clinical benefit while exposing patients to cumulative side effect burdens and psychological demoralization.

Psychotherapy, while highly effective for many individuals with moderate depression, also presents notable challenges in the TRD population. Cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), and other evidence-based modalities require active cognitive engagement, emotional insight, and sustained motivation--capacities often compromised in those with severe, chronic, or melancholic depression (Holtzheimer & Mayberg, 2011). Furthermore, access to high-quality psychotherapy remains inconsistent, particularly in low-resource settings, and dropout rates remain high among individuals with comorbidities, low functioning, or past non-response (Warden et al., 2007). For patients experiencing significant cognitive impairment, psychomotor retardation, or anhedonia, hallmarks of chronic TRD, psychotherapy may not be sufficient as a standalone intervention. These limitations underscore the urgent need for mechanistically distinct, biologically targeted interventions capable of producing therapeutic effects in individuals who have not benefited from conventional treatments. Neuromodulation offers promising alternatives precisely because they circumvent traditional monoaminergic pathways and are thought to operate through modulation of neural circuitry and synaptic plasticity (George & Aston-Jones, 2010; A. D. Krystal et al., 2020). Their ability to induce relatively rapid symptom improvements, coupled with distinct side effect profiles and novel mechanisms of action, make them particularly well-suited for individuals with refractory depression.

rTMS is believed to exert its antidepressant effects by restoring top-down regulation from the DLPFC to hyperactive subcortical structures involved in affective processing, such as the amygdala and ventral striatum (Fox et al., 2012). In TRD, functional MRI studies consistently reveal hypoactivity in the left DLPFC and disrupted fronto-limbic connectivity, impairing emotion regulation and cognitive control (Koenigs & Grafman, 2009; Mayberg, 2003). High-

frequency rTMS (typically 10 Hz) applied to the left DLPFC is thought to increase cortical excitability and enhance neuroplasticity, while low-frequency stimulation of the right DLPFC exerts inhibitory effects on hyperactive circuits (George et al., 2010a). The therapeutic efficacy of rTMS is therefore contingent, in part, on the capacity of prefrontal regions to engage and recalibrate downstream limbic networks. Measures of cortical inhibition, such as the CSP, may reflect underlying GABA_B-mediated inhibitory tone and offer a window into the individual neurophysiological landscape that modulates rTMS responsiveness (Tremblay et al., 2013; Ziemann, Rothwell, et al., 1996). TRD patients with greater baseline CSP durations may possess enhanced cortical integrity or neuroplastic potential, which could account for differential treatment outcomes observed in neuromodulation studies (Radhu et al., 2013).

In contrast and as previously mentioned, esketamine targets glutamatergic systems through antagonism of the NMDA receptor, producing a cascade of downstream effects that enhance synaptic plasticity and functional connectivity. Specifically, esketamine increases presynaptic glutamate release, activates AMPA receptors, and stimulates intracellular signaling pathways such as mTOR, which promotes dendritic spine growth and synaptogenesis (Abdallah et al., 2015; Duman et al., 2016). These neuroplastic changes are thought to reverse the synaptic atrophy and reduced connectivity observed in TRD, particularly in key regions such as the ACC, thalamus, and DMN (A. D. Krystal et al., 2020; Nugent et al., 2019). Moreover, esketamine's rapid antidepressant effects are hypothesized to emerge from a shift in excitation/inhibition (E/I) balance, favoring transient cortical excitation and resetting dysfunctional neural circuits (Fagerholm et al., 2021). This mechanism is complementary to, but distinct from, that of rTMS, emphasizing the relevance of identifying neurophysiological profiles, such as disrupted E/I

homeostasis or blunted neuroplasticity, that may selectively predict responsiveness to one treatment over another.

The differing neurobiological pathways targeted by rTMS and esketamine underscore the importance of selecting interventions based on individualized circuit dysfunction rather than diagnostic category alone. A deeper understanding of cortical inhibition and glutamatergic activity may enhance predictive accuracy and help determine which neuromodulatory intervention is most appropriate for a given patient. Chapter 3 of the current dissertation contributes to this emerging precision psychiatry framework by linking neurophysiological measures, particularly CSP, with clinical outcomes in TRD, laying the groundwork for future multimodal models that can optimize treatment selection.

1.2 Neuromodulation

Neuromodulation has emerged as a pivotal approach in the management of TRD, offering alternative therapeutic strategies for patients unresponsive to traditional pharmacological and psychotherapeutic interventions. Among the neuromodulation techniques, rTMS and esketamine have shown substantial promise, each with distinct protocols and mechanisms of action. Notably, both modalities are FDA-approved for the treatment of depression in the United States (Commissioner, 2019, 2020b, 2020a). rTMS is a non-invasive technique that modulates cortical activity through the application of magnetic pulses (Ding et al., 2014). rTMS primarily targets the DLPFC, a brain region implicated in mood regulation and implicated in the pathophysiology of depression (George et al., 2010a). The typical rTMS protocol involves daily sessions over several weeks, with high-frequency stimulation (10 Hz) generally applied to the left DLPFC (O'Reardon et al., 2007). Clinical trials have demonstrated that rTMS can significantly reduce depressive symptoms in TRD patients, with response rates around 50% and remission rates up to

30% (O'Reardon et al., 2007). In addition to the standard high-frequency protocol, other rTMS protocols have been developed to enhance treatment efficacy. Intermittent theta-burst stimulation (iTBS) is a newer protocol that delivers bursts of high-frequency stimulation patterned at theta frequencies, which has been shown to produce similar antidepressant effects as traditional high-frequency rTMS but in a shorter treatment time (Blumberger et al., 2018). Low-frequency rTMS (LFR), typically applied to the right DLPFC, is used to reduce cortical excitability and has been shown to be effective in some TRD patients (Fitzgerald et al., 2008). High-frequency left rTMS (HFL) is another common protocol that aims to increase cortical excitability (George et al., 2010a). Accelerated rTMS protocols, which involve multiple sessions per day over a shorter period, are also being explored to expedite therapeutic outcomes with early promise (Baeken et al., 2014).

The mechanisms of rTMS are thought to involve modulation of cortical excitability and plasticity. High-frequency stimulation (such as 10 Hz and iTBS) generally increases cortical excitability, promoting neuroplasticity and enhancing mood regulation, whereas low-frequency stimulation (such as 1 Hz) decreases cortical excitability, potentially reducing hyperactivity in certain brain regions (Huang et al., 2005). The intensity of stimulation is typically set relative to the individual's motor threshold, which ensures that the magnetic pulses are strong enough to induce cortical changes without causing discomfort or adverse effects (Rossi et al., 2009). The non-invasive nature and favorable side effect profile of rTMS make it an attractive option for many patients. However, the variability in individual response and optimal protocols remains unclear, underscoring the need for further research into predictors of treatment outcome.

Esketamine represents a groundbreaking development in the treatment of TRD. Unlike conventional antidepressants, which typically take weeks to achieve efficacy, esketamine can

produce rapid antidepressant effects, often within hours of administration (Daly et al., 2018). Esketamine is administered in a clinical setting due to its dissociative effects, with a protocol typically involving twice-weekly dosing during the induction phase, followed by maintenance doses (Swainson et al., 2019). Clinical studies have reported that esketamine, in conjunction with an oral antidepressant, significantly improves depressive symptoms and reduces suicidal ideation (SI) in TRD patients (Popova et al., 2019). The rapid antidepressant effects of esketamine are primarily attributed to its antagonism of NMDA receptors, which leads to a cascade of neurobiological events enhancing synaptic plasticity and connectivity (Zorumski et al., 2016). This mechanism is thought to involve the modulation of glutamate, a key neurotransmitter in brain regions implicated in mood regulation. By blocking NMDA receptors, esketamine increases the release of BDNF and activates the mTOR pathway, promoting synaptogenesis and strengthening neural connections (Duman et al., 2016). Esketamine's efficacy in TRD has been demonstrated in several randomized controlled trials, with antidepressant effects observed within 24 hours of administration (Daly et al., 2018; Popova et al., 2019). However, esketamine's long-term safety and efficacy remain areas of ongoing investigation. Despite its promise, not all patients respond to esketamine, and the predictors of response are not well-established.

1.3 Predictors of Response

Understanding predictors of response to antidepressant interventions is crucial for personalizing therapeutic strategies and improving outcomes for patients with TRD. Various non-neurophysiological factors have been identified that may predict differential responses to antidepressants, rTMS and esketamine. For conventional antidepressants, several clinical and demographic variables have been linked to treatment outcomes. Studies suggest that younger age, shorter duration of the current depressive episode, and higher baseline functioning are

associated with better responses to antidepressant medications (Fournier et al., 2010; Rush et al., 2006). Additionally, patients with fewer psychiatric comorbidities, such as anxiety disorders, and lower baseline severity of depressive symptoms tend to show more significant improvements (Papakostas et al., 2004). These predictors are consistent across various classes of antidepressants, including SSRIs and SNRIs, highlighting their potential utility in clinical decision-making.

In the context of rTMS, similar non-neurophysiological predictors have been identified. Research indicates that younger age and a shorter duration of the current depressive episode are associated with better treatment outcomes (O'Reardon et al., 2007). Additionally, patients with a lower number of prior antidepressant treatment failures and higher baseline cognitive function tend to respond more favorably to rTMS (Fitzgerald, Benitez, et al., 2006). The presence of fewer comorbid psychiatric conditions also predicts better outcomes, suggesting that rTMS may be particularly beneficial for patients with a less complicated clinical profile (Kozel et al., 2004).

Predictors of response to esketamine are still being elucidated, but early studies suggest that demographic factors such as younger age and female gender may be associated with better outcomes (Fedgchin et al., 2019). Furthermore, patients with lower baseline severity of depressive symptoms and fewer prior treatment failures tend to respond more favorably to esketamine (Canuso et al., 2019). The presence of fewer psychiatric comorbidities, particularly anxiety disorders, also appears to predict a better response to esketamine treatment (Daly et al., 2018).

Across both rTMS and esketamine modalities, several common predictors of treatment response have emerged. Younger age is consistently associated with better outcomes, likely due to greater neuroplasticity and fewer cumulative life stressors (Fedgchin et al., 2019; O'Reardon

et al., 2007; Rush et al., 2006). A shorter duration of the current depressive episode also predicts better responses, suggesting that early intervention may prevent the entrenchment of maladaptive neural circuits and depressive behaviors (Rush et al., 2006; UK ECT Review Group, 2003). Higher baseline functioning and lower baseline severity of depressive symptoms are associated with improved outcomes across treatments, indicating that patients with less severe and less chronic illness may have a greater capacity for recovery (Fitzgerald, Benitez, et al., 2006; Papakostas et al., 2008). Lastly, the presence of fewer psychiatric comorbidities consistently predicts better treatment responses, underscoring the complexity added by co-occurring mental health disorders and the potential benefits of targeted, multimodal interventions (Kozel et al., 2004; Papakostas et al., 2008).

1.3.1 Neurophysiological Biomarkers of Response

In the context of TRD, neurophysiological markers have emerged as potentially critical tools for predicting and understanding treatment responses across various modalities, including antidepressants, rTMS and esketamine (Klooster et al., 2024; Stolz et al., 2023). Among the wide range of potential indicators, biomarkers derived from TMS, including motor-evoked potentials (MEPs), short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and the CSP, have received increasing attention. While several of these markers have shown potential in identifying individual differences in cortical excitability and inhibitory tone, findings remain mixed, and their clinical applicability has not yet been fully established. Within this dissertation, the CSP is emphasized as the primary neurophysiological measure of interest due to its theoretical relevance to both rTMS and esketamine mechanisms and its emerging role in treatment prediction.

1.3.2 Cortical Silent Period

CSP is a measure of cortical inhibition, typically assessed using TMS (E. Wassermann et al., 2008)(Daskalakis et al., 2006). During a CSP assessment, a suprathreshold TMS pulse is delivered to the motor cortex while the subject maintains a voluntary muscle contraction, and the subsequent interruption of electromyographic (EMG) activity in the target muscle is measured. CSP duration is believed to reflect the inhibitory processes in the motor cortex, influenced by both GABAergic and glutamatergic neurotransmission (E. Wassermann et al., 2008). Research has shown that CSP duration may predict antidepressant treatment response (Fitzgerald et al., 2004). For instance, patients with longer CSP durations have been found to respond better to SSRIs, suggesting that increased cortical inhibition may be associated with greater therapeutic benefit (E. M. Wassermann, 1998). In the context of rTMS, longer CSP durations have also been linked to better clinical outcomes, indicating that baseline levels of cortical inhibition might influence the efficacy of neuromodulatory interventions (Fitzgerald et al., 2004; Kobayashi & Pascual-Leone, 2003). Additionally, preliminary studies suggest that CSP duration may change following esketamine administration, potentially serving as a biomarker for treatment response (Höffken et al., 2013). Similarly, in ECT, differences in CSP at baseline have successfully distinguished responders from non-responders (Voineskos et al., 2016).

1.4 Gaps in Current Knowledge

Despite significant advancements in neuromodulatory interventions for TRD, substantial limitations persist in our ability to predict individual responses to treatments such as rTMS and esketamine. Current literature highlights a considerable variability in patient outcomes, with response rates for rTMS typically ranging from 40% to 60% (Brunoni et al., 2017; Carpenter et al., 2012), and for esketamine from approximately 50% to 70% (Daly et al., 2018; Popova et al.,

2019). However, identifying reliable predictors of who will respond to these treatments remains challenging. Studies examining demographic, clinical, and treatment-specific factors have yielded inconsistent results, emphasizing the complexity and heterogeneity of TRD (Fava, 2003; Fitzgerald et al., 2016).

In addition to these inconsistencies, most existing studies focus on binary outcomes, such as response or remission, at fixed time points, offering limited insight into the temporal dynamics of treatment response. This lack of temporal resolution obscures important clinical differences between interventions like rTMS and esketamine, which differ markedly in their speed and pattern of therapeutic effect. For instance, esketamine is known for its rapid onset of action, while rTMS often yields more gradual improvement over multiple weeks. However, few studies have directly compared these response trajectories in naturalistic settings using time-sensitive analytical approaches. As a result, clinicians lack empirically grounded guidance on the expected timeline of symptom change, which is critical for monitoring, patient counseling, and treatment planning. Addressing this gap requires the application of survival analysis techniques to real-world data to clarify how treatment response evolves over time across neuromodulatory modalities.

Further compounding prediction issues is the limited integration of diverse predictors—including clinical, demographic, and neurophysiological markers—within existing predictive frameworks. Although each of these domains has individually demonstrated some predictive utility, their combined potential remains underexplored (Cash et al., 2019; McClintock et al., 2018). For example, neurophysiological biomarkers, such as the CSP, have shown promise in preliminary studies, yet their integration with clinical characteristics and demographic factors in robust predictive models has not been sufficiently addressed (Fitzgerald et al., 2004; Lefaucheur

et al., 2014; Radhu et al., 2013). Additionally, most predictive models developed to date have relied on highly controlled clinical trial data, limiting their generalizability and real-world clinical utility. The applicability of these models to typical clinical settings is constrained by differences in patient populations, treatment adherence, and variability in clinical practice, resulting in limited translation of findings into practical treatment selection tools (Chekroud et al., 2016).

These significant gaps underscore the pressing need for robust, integrated predictive models capable of guiding personalized treatment selection. Addressing this gap requires leveraging large-scale, real-world datasets and advanced analytical techniques, such as machine learning, to improve predictive accuracy and clinical applicability. Such personalized predictive approaches are essential to enhance clinical outcomes, reduce the burden of ineffective treatments, and optimize healthcare resources for individuals living with TRD.

1.5 Rationale for Selected Methodological Approaches

Addressing the complex and multifactorial nature of TRD necessitates advanced analytical methodologies capable of handling intricate predictor relationships and temporal patterns in treatment outcomes. Machine learning (ML) approaches offer distinct advantages over traditional statistical methods by efficiently modeling complex, nonlinear interactions among numerous clinical, demographic, and neurophysiological predictors (Chekroud et al., 2016; Iniesta et al., 2016). ML algorithms, including support vector machines, gradient boosting machines, and random forests, can manage high-dimensional datasets and identify subtle predictor-outcome relationships often overlooked by conventional statistical approaches, enhancing predictive accuracy and clinical utility (Dinga et al., 2018; Kessler et al., 2016). Despite growing enthusiasm around ML applications in psychiatry, the integration of such

models into routine clinical decision-making remains limited. One major barrier is the lack of reliable, generalizable biomarkers with consistent predictive validity across diverse populations and treatment modalities (Arbabshirani et al., 2017; T. R. Insel, 2014). Although neuroimaging, electrophysiological, and behavioral data have shown promise in small studies, real-world implementation is hindered by methodological heterogeneity, inconsistent replication, and challenges in data harmonization (Woo et al., 2017). Moreover, many ML models in psychiatry are developed using highly curated research samples that do not reflect the clinical complexity encountered in real-world practice, limiting their translational utility. Another critical hurdle is the interpretability of complex ML models—a prerequisite for clinical adoption—where “black box” algorithms may yield accurate predictions but offer little transparency regarding underlying mechanisms or actionable clinical insights (Rudin, 2019). As a result, there is a growing call for models that not only predict outcomes but also provide explanatory frameworks grounded in biological plausibility. Advancing the field will require large, multimodal datasets, rigorous external validation, and cross-disciplinary efforts that bridge computational modeling, neuroscience, and clinical psychiatry.

Furthermore, employing survival analysis to evaluate treatment trajectories over time provides critical insights into not just whether, but how rapidly, clinical responses occur following neuromodulatory interventions such as rTMS and esketamine (Carpenter et al., 2012; Popova et al., 2019). Survival analysis techniques, including Kaplan-Meier (KM) curves and Cox proportional hazards modeling, can elucidate critical temporal dynamics, offering clinicians valuable information for treatment planning, prognosis estimation, and patient counseling (Austin, 2011; Singh & Mukhopadhyay, 2011). Utilizing real-world EMR data further enhances the clinical relevance and practical applicability of predictive models. Real-world data more

accurately reflect the heterogeneity and complexities of clinical populations compared to highly controlled clinical trials, thereby increasing the generalizability and translational value of findings (Corrigan-Curay et al., 2018; Schneeweiss et al., 2016). EMR datasets provide rich clinical information, including demographics, medical and psychiatric comorbidities, medication use, and treatment adherence, allowing for the development of models that are directly relevant to routine clinical practice and patient management (Rumsfeld et al., 2016) (Berner et al., 2020). Incorporating these methodological approaches thus supports the development of robust, clinically-actionable predictive models essential for personalized treatment selection and improved patient outcomes in TRD.

1.6 Dissertation Objectives and Completed Studies Overview

The overarching objective of this dissertation was to enhance clinical decision-making in the treatment of TRD by characterizing individual differences in response to neuromodulatory interventions. To this end, the research aimed to: (1) identify clinical and demographic predictors of treatment response to rTMS using real-world EMR data and ML methods; (2) examine and compare the temporal trajectories of treatment response to rTMS and esketamine using survival analysis techniques; and (3) evaluate the CSP as a neurophysiological biomarker of treatment response in patients undergoing neuromodulation. Collectively, these studies were designed to inform the development of more personalized, mechanism-informed treatment approaches for individuals with TRD.

Study 1 (published) utilized a retrospective, real-world clinical dataset from EMR to identify clinical, demographic, and treatment-related predictors of response and remission following rTMS treatment. Leveraging advanced ML techniques, this study highlighted key patient-specific factors—including psychiatric comorbidities, medication use, and specific rTMS

protocols—that significantly influenced treatment outcomes. This investigation underscored the utility of machine learning methodologies in capturing complex interactions among predictive variables, enhancing the precision and applicability of predictive models in clinical settings.

Study 2 performed a comparative analysis of clinical trajectories between patients undergoing rTMS and esketamine therapy using survival analysis methods. By evaluating temporal patterns of treatment response and remission, this study elucidated critical differences in how patients respond over the course of treatment, providing valuable insights into the timing and sustainability of therapeutic effects. Additionally, this study examined predictors contributing to response trajectories. The survival analysis approach allowed for a nuanced understanding of treatment dynamics, emphasizing the importance of temporal factors in clinical decision-making for TRD.

Study 3 explored the CSP as an exploratory neurophysiological correlate of treatment response in TRD patients receiving neuromodulatory interventions. This study aimed to clarify whether baseline CSP was associated with subsequent clinical improvement; however, findings were preliminary and somewhat inconsistent. Accordingly, CSP should be interpreted cautiously, not as a definitive standalone biomarker, but as an early neurophysiological signal that may warrant further study as part of broader multimodal predictive frameworks.

Collectively, these studies provide comprehensive insights into the complex interplay of clinical, demographic, and neurophysiological factors influencing treatment outcomes in TRD, ultimately aiming to enhance the personalization of therapeutic strategies and improve patient prognosis and care quality.

Chapter 1: Predictive modeling of response to repetitive transcranial magnetic stimulation in
treatment-resistant depression

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ABSTRACT

Identifying predictors of treatment response to repetitive transcranial magnetic stimulation (rTMS) remain elusive in treatment-resistant depression (TRD). Leveraging electronic medical records (EMR), this retrospective cohort study applied supervised machine learning (ML) to sociodemographic, clinical, and treatment-related data to predict depressive symptom response ($>50\%$ reduction on PHQ-9) and remission ($\text{PHQ-9} < 5$) following rTMS in 232 patients with TRD (mean age: 54.5, 63.4% women) treated at the University of California, San Diego Interventional Psychiatry Program between 2017 and 2023. ML models were internally validated using nested cross-validation and Shapley values were calculated to quantify contributions of each feature to response prediction. The best-fit models proved reasonably accurate at discriminating treatment responders (Area under the curve (AUC): 0.689 [0.638, 0.740], $p < 0.01$) and remitters (AUC 0.745 [0.692, 0.797], $p < 0.01$), though only the response model was well-calibrated. Both models were associated with significant net benefits, indicating their potential utility for clinical decision-making. Shapley values revealed that patients with comorbid anxiety, obesity, concurrent benzodiazepine or antipsychotic use, and more chronic TRD were less likely to respond or remit following rTMS. Patients with trauma and former tobacco users were more likely to respond. Furthermore, delivery of intermittent theta burst stimulation and more rTMS sessions were associated with superior outcomes. These findings highlight the potential of ML-guided techniques to guide clinical decision-making for rTMS treatment in patients with TRD to optimize therapeutic outcomes.

INTRODUCTION

Major depressive disorder (MDD) is a prevalent and debilitating condition characterized by persistent feelings of sadness, hopelessness, and loss of interest or pleasure in daily activities (American Psychiatric Association & American Psychiatric Association, 2013). An estimated 322 million individuals worldwide meet criteria for MDD, representing a substantial public health challenge impacting quality-of-life, productivity, and overall well-being ((WHO), n.d.). While various pharmacological, psychotherapeutic, and neuromodulatory treatments are available, 30-40% of individuals with MDD experience treatment-resistant depression (TRD), defined as non-response to two or more trials of first-line interventions (Zhdanova et al., 2021). Because MDD is a highly heterogeneous disorder, with 277 possible symptom combinations meeting DSM-5 criteria (Zimmerman et al., 2015), it is possible that different subtypes or symptom clusters of MDD may respond differentially to various treatments (Lynch et al., 2020). Therefore, aligning optimal treatment strategies to symptom presentations may be valuable for addressing TRD. This first requires understanding the mechanisms and predictors of treatment response in MDD, as this knowledge can inform the development of more personalized treatments that are optimal for different individuals based on their unique symptom profiles.

Repetitive transcranial magnetic stimulation (rTMS) is an established clinical intervention for the treatment of TRD, with response rates of approximately 40-60%, providing a valuable treatment option for patients not responding to first line psychotherapy and pharmacotherapy (Aaronson, 2021; Benster et al., 2023). rTMS involves the application of repetitive magnetic pulses to the cortex, with the dorsolateral prefrontal cortex (DLPFC) a common target for MDD due to its role in mood regulation, cognitive control, executive functioning, and emotion processing (Fitzgerald, Oxley, et al., 2006). The DLPFC is also

implicated in the pathophysiology of depression due to its connections with the limbic system, while acute elevations in mood following rTMS provide further evidence of DLPFC dysfunction in MDD (Chung et al., 2015; Cole et al., 2020; George et al., 2010a; Mayberg, 1997). Ultimately, rTMS is thought to exert its therapeutic effects through modulation of cortical excitability, neurotransmitter systems, and neuroplastic mechanisms (Peng et al., 2018), but understanding the predictors of treatment response is crucial for tailoring treatment strategies and enhancing clinical outcomes in individuals with TRD.

In recent years, advances in machine learning (ML) have provided new opportunities for leveraging large-scale datasets, such as electronic medical records (EMR), to improve healthcare delivery and inform clinical decision-making (A. L. Beam & Kohane, 2018). For instance, ML prediction models can be used as structured tools to more accurately stratify patients into subgroups or individualized treatment pathways (Rajkomar et al., 2019). In psychiatry, particularly in TRD and rTMS, ML can reveal latent multifactorial relationships that conventional methods might overlook. Recent studies utilizing large clinical registries have demonstrated the effectiveness of predictive and inferential models of treatment response and remission, highlighting factors such as the influence of treatment protocols, patient demographics, and psychiatric comorbidities on outcomes (Blumberger et al., 2022; Sackeim et al., 2020). Despite the rapid growth of ML in psychiatric research, the generalizability and clinical utility of many ML models published to date remain poor (Meehan et al., 2022). Motivated by the potential of ML to enhance understanding of rTMS treatment for patients with TRD, this study performed a comprehensive retrospective analysis to investigate demographic, clinical, and treatment-related factors associated with treatment response and remission.

This retrospective approach offers several strengths, including a moderately sized sample, the ability to capture real-world clinical practices, and identify long-term treatment outcomes (Rassen et al., 2018) without the resource demands of a clinical trial. Specifically, this study explores 1) demographic and clinical characteristics of TRD patients receiving rTMS treatment, 2) various protocols and parameters utilized in rTMS administration, and 3) pre-treatment and treatment-related factors predictive of treatment response or remission. This paper aims to address the following questions: whether ML can predict response or remission following rTMS based on pre-treatment patient features and treatment-related factors better than chance; which features distinguish individuals responding favorably to rTMS from those who do not; and whether the ML models may offer clinical benefit. In generating ML models to predict rTMS treatment response and identifying the features that drive both positive and negative outcomes, this study aims to advance understanding of TRD, optimize treatment strategies, and ultimately improve patient outcomes.

MATERIALS AND METHODS

Design.

A retrospective study was conducted, including EMR (Epic, Verona, WI, USA) of TRD patients, collected from the clinical database of the UC San Diego Interventional Psychiatry Program (UCSD-IPP). All contributing procedures comply with the ethical standards of the relevant national and international committees on human subjects' research and the Helsinki Declaration and were approved by the UCSD Human Research Protections Program.

Patients.

Included patients were prescribed rTMS treatment from UCSD psychiatrists credentialed in delivering rTMS. rTMS was initiated in outpatients who met criteria for TRD, did not present with any treatment contraindications, had adequate insurance coverage, and provided consent. As illustrated in **Figure 1**, EMR records for 419 patients seeking rTMS in 2017-2023 at UCSD were screened for the following inclusion criteria: (i) primary diagnosis of MDD; (ii) aged 18 years and older; (iii) completion of at least 15 sessions by the date of final PHQ-9; (iv) clinically meaningful depressive symptoms, as indicated by PHQ-9 total score > 4 ; (v) failure to respond to at least 2 antidepressant pharmacotherapy trials; and (vi) completion of clinical evaluations prior to and following the acute treatment phase.

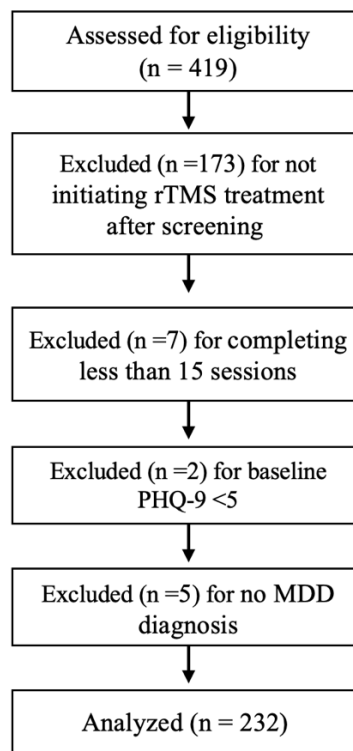


Figure 1: Flowchart of patient inclusion.

A total of 246 patients began a rTMS treatment course and 239 completed at least 15 sessions before their final PHQ-9 assessment. Two participants had baseline PHQ-9 scores < 5 ,

indicating no clinically significant depressive symptoms, and were excluded from analyses. Five patients were excluded for not having received an MDD diagnosis, yielding a final analytical sample of 232 MDD patients. All patients had previously failed to respond to at least two antidepressant treatments and 90% reported having an MDD diagnosis >10 years.

Treatment procedure.

All rTMS treatment was performed in the UCSD-IPP clinic by technicians trained in protocol administration with oversight by an attending psychiatrist. Overseeing psychiatrists reviewed the treatment plans after each session. rTMS was delivered using either a Magventure MagPro with a B70 coil or a BrainsWay H1-coil system. For all patients, the resting motor threshold (rMT) was identified by finding the motor hotspot and utilizing the lowest level of stimulation intensity to elicit movement in the opposite abductor pollicis brevis (APB) muscle on 50% of stimulation attempts. Once rMT was obtained, treatment session parameters were determined. For Magventure treatments, the coil position was localized using the Beam F3 method, and treatment was delivered per standard practice (W. Beam et al., 2009). Patients who were initiated on the iTBS protocol (at 120% rMT), involving 600 total pulses in bursts of 3 with 8-second inter-train-intervals, were transitioned to either BiTBS (90% rMT; 3600 total pulses, 1800 delivered via 3-iTBS and 1800 delivered cTBS 120% rMT protocol to the left and right hemispheres, respectively) or 3-iTBS (iTBS delivered three times consecutively, per Li et al 2014 (Li et al., 2014) if there was deemed poor efficacy or issues with tolerability). High-frequency left (HFL; 19 minutes) and low-frequency right (LFR; 10 minutes) protocols were used less commonly, both at 120% rMT. The obsessive-compulsive disorder (OCD) protocol uses a B70 coil and delivers 2000 pulses per session via 50, 2-second trains to dorsomedial prefrontal cortex (DMPFC), at 100% rMT of the foot with the Magventure B70 coil. For the

BrainsWay H1-coil system either iTBS or the standard FDA-approved 18 Hz protocol was used at 120% rMT. The end of each patient's acute treatment period was clinician-determined and coincided with reduced frequency of rTMS treatment to <2 sessions per week. Sequencing of TMS protocols across all patients included in the analysis is depicted in **Supplemental Fig. 1**.

Clinical assessment.

The PHQ-9 is a nine-item self-report scale used to assess the presence and severity of depressive symptoms based on the Diagnostic and Statistical Manual (DSM) criteria for a Major Depressive Episode (MDE). Questions are on a four-point scale related to the frequency of symptoms presented on each item, including “not at all,” “several days,” “more than half the days,” and “nearly every day.” Total scores are calculated by adding scores to all nine items (total range: 0–27), and previously established cutoff scores for severity are: 0–4 (no symptoms), 5–9 (mild symptoms), 10–14 (moderate symptoms), 15 – 19 (moderately severe symptoms), and 20–27 (severe symptoms). The PHQ-9 was administered pre-treatment and at rTMS visits throughout the acute treatment phase to monitor changes in depressive symptoms. Only pre-treatment and post-acute treatment phase scores were used in the present analyses.

Predictive features.

Pre-treatment features. A total of 32 EMR-derived features were extracted from patient records, including: age, gender, ethnicity, religious affiliation, educational attainment, employment status, relationship status, body mass index (BMI) category (obesity: $\geq 30 \text{ kg/m}^2$; overweight: $25 \leq \text{kg/m}^2 < 30$; normal $18.5 < \text{kg/m}^2 < 25$), alcohol, tobacco, and cannabis use (each operationalized as 3-level factor: current, former, or never), family history of mood disorders, 1st degree relatives with mood or psychiatric disorder diagnoses, prior ECT treatment, prior rTMS treatment, history of psychological trauma, non-suicidal self-injury (NSSI), history

of suicidal ideation (SI) or suicide attempts, psychiatric hospitalizations, and duration of current MDE. Psychiatric comorbidities were also recorded, including anxiety disorders, trauma-related disorders, substance use disorders, OCD, somatic symptom and related disorders, personality disorders, autism spectrum disorders, eating disorders, and neurocognitive disorders. Comorbid diagnoses were extracted from physician notes. Psychiatric medication use, including benzodiazepines, non-benzodiazepine sedatives, anxiolytics, antipsychotics, and psychostimulants, was recorded, and antidepressant medication burden was translated into daily defined dose (DDD) equivalents. A detailed description of the coding for each drug category can be found in the **Supplement**. Certain continuous variables were categorized to align with clinically relevant thresholds, enhancing interpretability in the context of TRD treatment. Age was grouped into age brackets (<45, 45–64, ≥65 years), PHQ-9 scores were categorized by established severity levels, BMI was grouped by WHO classifications (normal, overweight, obese), and MDE duration was categorized as <6 months, 6–12 months, and >12 months to capture differences in chronicity. While this approach may reduce statistical power, it provides a meaningful, clinically interpretable framework for evaluating treatment outcomes. Features were extracted by manual search through individual patient’s EMR. Variables were primarily collected via initial treatment consultation note completed by the prescribing psychiatrist. In the case where specific data points were not immediately available in the consultation note, searches were conducted to identify the nearest timepoint in which that information was available.

Treatment-related features. To determine the role of treatment-related factors in depression outcomes, the following five parameters were recorded: protocol type (deep TMS, iTBS, bilateral TBS, or others that included HFL, LFR, 3-iTBS, or OCD protocols); number of total

rTMS sessions; cumulative number of pulses received throughout the treatment course; and, whether patients switched rTMS protocols during treatment.

Statistical analysis.

R statistical software (v.4.3.1) was used for data analysis. Independent sample *t*-tests and chi-square tests were used to compare demographic and clinical characteristics between rTMS non-responders and responders, defined as patients with $\geq 50\%$ decrease in post-treatment PHQ-9 scores from pre-treatment scores. Pairwise post-hoc tests for factors with more than two levels were false discovery rate (FDR)-corrected. To mitigate low variance within categorical variables, variables were combined and/or operationalized as follows: rTMS protocols: 18 Hz deep TMS (dTMS), BiTBS, or iTBS, made up the majority (86.6%) of rTMS protocols in the sample; therefore, other protocols, including 3-iTBS, 3-iTBS/OCD, OCD, and HFL were combined into a single factor level (“Other”). Race/ethnicity: patients were coded as non-Hispanic, white, or “Other”. Psychiatric comorbidities: patients were coded with 1 if they had at least one comorbid diagnosis for each individual comorbidity of interest. Duration of current MDE: patients were coded as <6 months, 6–12 months, or >12 months in duration. Patients were binarized indicating completion of a 4-year degree or not. Relationship status was coded as: currently single/unpartnered, partnered/married, or separated/divorced/widowed. Non- antidepressant psychiatric medication use was coded 1 or 0 for each drug category.

To identify pre-treatment patient characteristics and treatment-associated features that best discriminate response and remission groups, a series of classification models were trained using the *caret* package: (i) regularized logistic regression (elastic net regression; ENet); (ii) support vector machine (SVM) with radial basis function; (iii) random forest (RF); and (iv) stochastic gradient boosting machines (GBM). All features were filtered for near-zero-variance

(<5%) and linear combinations. Nested cross-validation was used for hyperparameter tuning and model performance evaluation using *nestedcv* with 10 inner folds and 20 outer folds. RF parameters optimized in the nested grid search included *mtry* (number of variables to split), *splitrule* (quality of each node split), and *min.node.size* (minimum number of samples in a node), and GBM parameters included *interaction.depth* (highest interaction per tree), *n.minobsinnode* (minimum number of samples in a node to split), *n.trees* (total number of trees), and *shrinkage* (learning rate), whereas the default tuning grids in *caret* were applied for ENet and SVM. To mitigate class imbalance in the dataset, Synthetic Minority Over-sampling TEchnique (SMOTE) was applied to equalize the class ratio (1:1)(Chawla et al., 2002). Tree-based classification models, such as gradient boosted trees and random forest, detect interactions by optimizing decision tree paths in which the influence of a given variable is conditioned on the values of preceding variables in the path. It is possible to visualize these relationships from the global model via SHAP interaction values.

Feature selection via a univariate filter was performed on each outer fold prior to hyperparameter tuning, and a Relief-based algorithm (ReliefFbestK in *CORElearn* package; k=10) was applied in parallel for comparison with the univariate filter. Generally, performance was superior for models trained after univariate filtering (**Supplemental Fig. 3**), with 10 features selected on average (range: 7–13) for all models. Optimization criteria for each model's hyperparameter tuning procedure were receiver operating characteristic area under the curve (ROC AUC). Continuous features were standardized, and categorical features were one-hot encoded, with the first level dropped as reference. Missing variables were treated as missing completely at random and nonparametric random forest-based imputation was performed using *missForest*.

Generalization performance and 95% confidence intervals were generated by averaging AUC across the best tune of all outer folds. Predicted probabilities across all outer folds were merged to generate additional performance metrics (*F*-score, sensitivity, specificity) and models with the best performance for an outcome were selected for downstream analysis. Significance of AUC values were determined by permutation testing (B=99) of class labels, re-running the procedure for each model, and calculating the proportion of permuted models with AUC values greater than the observed data. Alpha level was set at 0.05. The contributions of predictive features were determined using SHapley Additive exPlanations (SHAP) analysis in the *fastshap* R package, and directionality of associations between features and outcome variables was ascertained by visualizing individual SHAP values and their dependencies with the *shapviz* package in R. SHAP values explain the output of machine learning models by quantifying the contribution of each feature to a specific prediction, helping to identify which factors positively or negatively influence the model's outcome.

Using the best performing models, the predicted probabilities of treatment response and remission were derived. Model calibration was assessed with the Hosmer-Lemeshow (HL) goodness-of-fit test by binning predicted probabilities into deciles. Probability estimates were updated using beta regression, which has been shown to outperform other calibration methods (Ojeda et al., 2023), and recalibrated probabilities were reassessed using HL test. Decision curve analysis (DCA) was applied using *dcurves* to assess the clinical utility of prediction models through estimation of net benefit across thresholds of predicted risks using recalibrated probabilities from both “response” and “remission” classification models. Net benefit is equivalent to the percentage of individuals appropriately treated (“true positives”, responders and remitters) minus a weighted percentage of those inappropriately treated (“false positives”).

Results

Patient and treatment-related characteristics

Sociodemographic and clinical characteristics of patients, and treatment-related characteristics included in the analysis are outlined in **Table 1**. Across all patients, post-treatment PHQ-9 scores were significantly reduced compared to pre-treatment values (mean difference = -7.56, $t_{231} = -17.6$, $d=1.16$, 95% CI=0.99–1.32). Eighteen patients had baseline PHQ-9 scores < 10, indicative of minimal depressive symptoms, and response rates within this subgroup were lower than patients with PHQ-9 ≥ 10 at baseline (38.9% vs. 43.9%) but did not significantly differ ($X^2 = 0.17$, $p = 0.68$). In total, 101 patients (44%) responded to rTMS, (mean difference = -13.0, $t_{100} = -29.4$, $d=2.94$, 95% CI=2.48–3.39; **Fig. 2**) and 53 patients (23%) remitted. The average patient age was 55.1 ± 16.9 and 54.1 ± 17.0 years in the responder and non-responder groups, respectively. Patient sex and ethnicity did not differ between groups; however, responders were more likely to have been former smokers than non-responders, and less likely to have never used alcohol. Most patients were naïve to rTMS (88.4%) and ECT (83.3%) treatment, and the majority (60%) had MDEs lasting longer than 12 months at treatment outset. Response and remission rates for patients in this study with a history of rTMS were 48.1% and 18.5%, respectively. Relative to patients without a history of rTMS, there were no differences with response to response ($X^2=0.09$, $df=1$, $p=0.76$) or remission ($X^2=0.11$, $df=1$, $p=0.74$). Baseline PHQ-9 scores did not differ between responders (17.9 ± 5.4) and non-responders (17.6 ± 5.3). Responders were more likely to have a history of trauma and to be diagnosed with trauma disorder compared to non-responders, but were less likely to have an anxiety disorder or be prescribed benzodiazepines or antipsychotic medications. The ratio of patients receiving sequential iTBS-BiTBS to iTBS-only treatment was higher among non-responders than

responders ($p_{adj} = 0.04$), and non-responders received fewer rTMS sessions on average compared to responders.

Table 1: Sociodemographic and clinical characteristics of patient sample.

	All patients (n=232)	Responders (n=101; 43.5%)	Non-Responders (n=131; 56.5%)	Test Statistic
<i>Sociodemographic characteristics</i>				
Age (yrs)	54.5 (16.9)	55.1 (16.9)	54.1 (17.0)	$t_{198} = 1.13, p = 0.26$
Sex (%F)	63.4%	62.4%	64.1%	$\chi^2_1 = 0.02, p = 0.89$
Ethnicity (%NHW/B/H/A/P/MO)	76/1/6/4/1/12	75/1/4/5/2/13	76/2/7/3/0/12	$\chi^2_6 = 5.43, p = 0.49$
Religiously affiliated (%)	23.9%	18.2%	28.3%	$\chi^2_1 = 3.16, p = 0.08$
Relationship status (S/P/SW)	35 / 48 / 17	39 / 46 / 15	31 / 50 / 19	$\chi^2_1 = 1.59, p = 0.45$
College graduate (%)	81.6%	79.8%	82.9%	$\chi^2_1 = 0.37, p = 0.54$
BMI category (%Nm / Ow / Ob)	40 / 30 / 30	48 / 29 / 23	34 / 31 / 35	$\chi^2_2 = 5.79, p = 0.06$
1 st -degree relative w/ psych dx (%)	77.4%	81.9%	74.0%	$\chi^2_1 = 1.92, p = 0.17$
Tobacco use (% N/C/F)	75 / 7 / 18	63 / 9 / 28	85 / 5 / 10	$\chi^2_2 = 14.7, p < 0.01$
Cannabis use (% N/C/F)	67 / 22 / 11	63 / 25 / 12	69 / 20 / 11	$\chi^2_1 = 1.01, p = 0.60$
Alcohol use (% N/C/F)	37 / 46 / 17	26 / 52 / 22	45 / 41 / 14	$\chi^2_1 = 10.1, p < 0.01$
<i>Clinical characteristics</i>				
Psychiatric comorbidities (n)	0.23 (0.4)	0.23 (0.4)	0.24 (0.4)	$t_{216} = 0.16, p = 0.87$
Antidepressant drug use (DDD)	1.75 (1.7)	1.65 (1.5)	1.83 (1.8)	$t_{229} = 0.79, p = 0.43$
Prior rTMS treatment	11.6%	15.8%	8.4%	$\chi^2_1 = 3.07, p = 0.08$
Baseline PHQ-9 score	17.8 (5.3)	17.9 (5.4)	17.6 (5.3)	$t_{213} = 0.42, p = 0.67$
MDE duration (<6/6-12/12+mo)	21%/18%/60%	28%/19%/53%	16%/18%/66%	$\chi^2_2 = 4.76, p = 0.09$
Prior ECT	17.7%	13.9%	20.6%	$\chi^2_1 = 1.79, p = 0.18$
History of trauma	45.3%	54.5%	38.2%	$\chi^2_1 = 6.11, p = 0.01$
Prior psych hospitalization	35.8%	41.6%	31.3%	$\chi^2_1 = 2.63, p = 0.11$
Suicidal ideation history	65.1%	66.3%	64.1%	$\chi^2_1 = 0.12, p = 0.73$
Non-suicidal self-injury history	11.2%	9.9%	12.2%	$\chi^2_1 = 0.31, p = 0.58$
Anxiety disorder	72.8%	65.3%	78.6%	$\chi^2_1 = 5.08, p = 0.02$
Prior suicide attempt	25.9%	29.7%	22.9%	$\chi^2_1 = 1.38, p = 0.24$
Substance use disorder	14.2%	14.9%	13.7%	$\chi^2_1 = 0.06, p = 0.81$
ADHD diagnosis	15.5%	19.8%	12.2%	$\chi^2_1 = 2.51, p = 0.11$
Trauma disorder diagnosis	22.4%	31.7%	15.3%	$\chi^2_1 = 8.84, p < 0.01$
Benzodiazepine use	29.0%	21.8%	34.4%	$\chi^2_1 = 4.20, p = 0.04$
Antipsychotic medication use	24.2%	17.0%	29.8%	$\chi^2_1 = 5.04, p = 0.02$
Psychostimulant medication use	19.5%	20.0%	19.1%	$\chi^2_1 = 0.03, p = 0.86$
Non-benzodiazepine sedative use	25.5%	27.0%	24.4%	$\chi^2_1 = 0.20, p = 0.66$
Mood stabilizer use	18.2%	14.0%	21.4%	$\chi^2_1 = 2.07, p = 0.15$
<i>Treatment-related characteristics</i>				
TMS protocol (% BiTBS/dTMS /iTBS/iTBS-BiTBS/Other)	16/36/10/25/13	13/41/16/18/13	18/33/5/31/14	$\chi^2_4 = 11.8, p = 0.02$
Total number of rTMS sessions	37.4 (10.6)	39.1 (10.8)	36.2 (10.2)	$t_{209} = 2.08, p = 0.04$
Cumulative rTMS pulses	88,804(44,862)	88,832(48,831)	88,782(41,738)	$t_{196} = 0.01, p = 0.99$
rTMS protocol switch (%)	58.2%	53.5%	61.8%	$\chi^2_1 = 1.64, p = 0.20$
Weeks from final patient in DB	136 (81)	146 (85)	128 (78)	$t_{204} = 1.62, p = 0.11$
Resting motor threshold (%)	46.0%	46.3%	45.7%	$t_{200} = 0.44, p = 0.66$
Length of treatment (days)	66.3 (19.9)	69.0 (19.5)	64.2 (19.9)	$t_{217} = 1.85, p = 0.07$

Other rTMS protocols include 3-iTBS, 3-iTBS/OCD, HFL, and OCD. Ethnicities reported include Non-Hispanic White (NHW), Black (B), Hispanic (H), Asian (A), Persian (P), and Mixed or Other (MO). Substance use reported as never (N), current (C), or former (F). Relationship status reported as Single (S), Partnered/Married (P), or Widowed/Divorced (W). Psychiatric comorbidities included OCD, somatic symptom disorders, personality disorders, autism spectrum disorders, eating disorders, and neurocognitive disorders. BMI categories corresponded to $\text{kg/m}^2 \geq 30$ (Ob), $25 \leq \text{Ow} < 30$, and $18.5 < \text{Nm} < 25$.

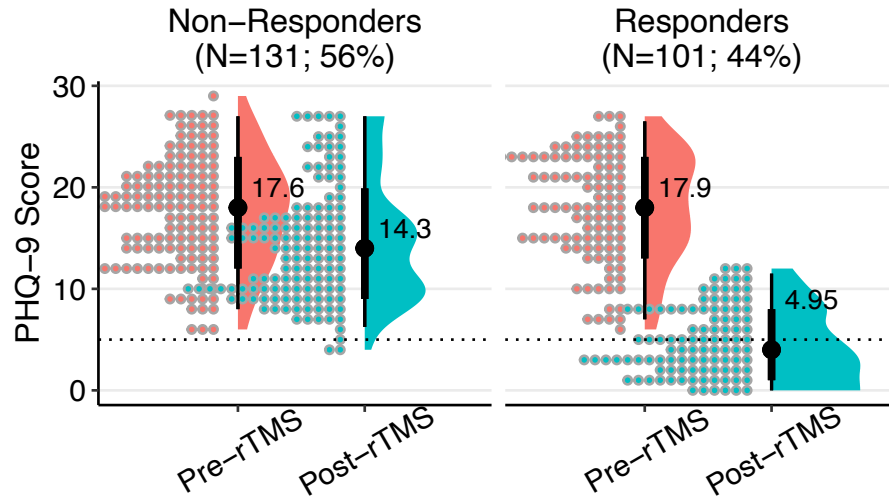


Figure 2: Depression scores pre- and post-rTMS treatment course. Each point represents an individual patient’s PHQ-9 score at baseline and the conclusion of their acute treatment phase, grouped by response status. Horizontal dashed line at PHQ-9 = 5 indicates the threshold for depression remission.

Classification results

Treatment Response. Across the four models tested, the SVM model predicted treatment response significantly above chance ($p < 0.01$; **Supplemental Fig. 2**) with modest discrimination performance (mean AUC=0.689, 95% CI=0.638–0.740), outperforming RF (0.654, 0.594–0.715), ENet (0.668, 0.616–0.719), and GBM (0.617, 0.563–0.671) models (**Supplemental Fig. 3**). Thus, the SVM model was evaluated further. The sensitivity and specificity of the model to discriminate treatment responders from non-responders were 72.3% and 53.4%, respectively, with an F-score of 0.64. Misclassification rates varied across rTMS protocols: BiTBS had a misclassification rate of 27.8%, iTBS 47.8%, dTMS 41.7%, and Other protocols 41.9%. Following recalibration, observed and predicted probabilities of treatment response were similar (HL test: $\chi^2_8=5.51$, $p=0.70$, RMSE=1.73; **Supplemental Fig. 4**). In descending order, the most important variables in prediction of treatment response were anxiety disorder, former tobacco

use, obesity, trauma disorder, antipsychotic use, benzodiazepine use, iTBS-BiTBS protocol, >12-month duration of current MDE, history of trauma, number of rTMS sessions, and iTBS protocol (**Fig. 3A**). Partial dependence plots illustrating the relationship between the top-3 features, the total number of rTMS sessions, and treatment response are shown in **Fig. 3B**, and the expected response probability for a representative patient is shown in **Supplemental Fig. 5**). DCA indicated that for threshold probabilities between 25% and 55%, corresponding to a number needed-to-treat (NNT) between 4 and 2 respectively, the net benefit of applying the model to aid in determining whether a patient should undergo rTMS is higher than either a “treat all” or “treat none” approach (**Fig. 5A**).

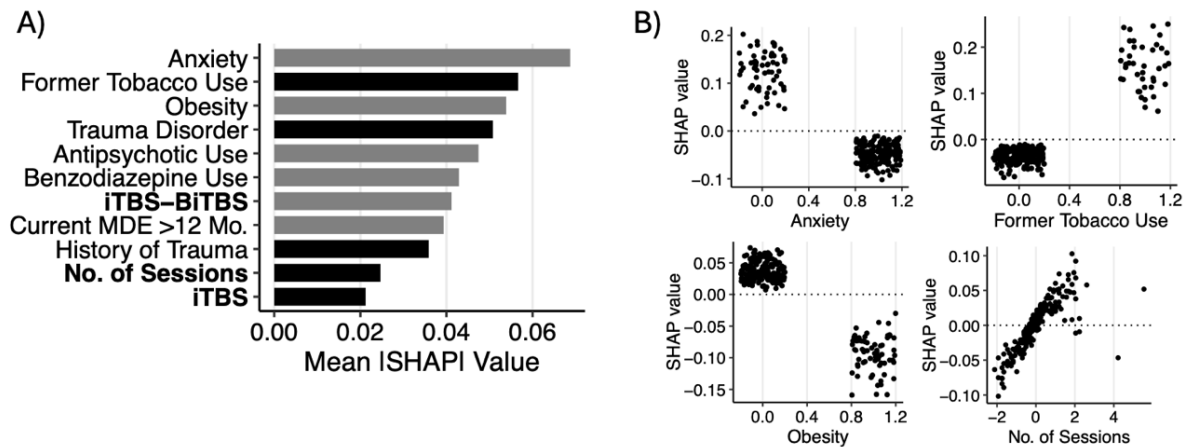


Figure 3: Treatment response predictors and associations. Fig 3A) Ranked feature importance for treatment response classification model. Grey bars indicate negative association with treatment response (worse outcome), and black bars indicate positive association (better outcome). Fig 3B) Partial dependence plots illustrating directional associations between selected features and treatment response. Larger positive SHAP values indicate greater probabilities of treatment response, whereas more negative values indicate lower probabilities of response.

Depression remission. Across the four models tested, the GBM model predicted remission following rTMS treatment significantly above chance ($p<0.01$; **Supplemental Fig. 2**) with good discrimination performance (mean AUC=0.745, 95% CI=0.692–0.797), outperforming

RF (0.735, 0.680–0.791), ENet (0.740, 0.668–0.813), and SVM (0.683, 0.627–0.738) models (**Supplemental Fig. 3**). Thus, the GBM model was evaluated further. The sensitivity and specificity of the model to discriminate remitters from non-remitters were 58.5% and 77.7%, respectively, with an F-score of 0.50. Misclassification rates for remission also differed by rTMS protocol: BiTBS had a rate of 33.3%, iTBS 30.4%, dTMS 23.8%, and Other protocols 29.0%. Following recalibration, the observed and predicted probabilities of treatment response remained dissimilar (HL test: $\chi^2_8=19.1$, $p=0.01$, RMSE=2.73; **Supplemental Fig. 4**). In descending order, the most important variables in the prediction of depression remission were pre-treatment PHQ-9 score, obesity, antipsychotic use, current MDE greater than 12 months, benzodiazepine use, anxiety, prior ECT, and iTBS-BiTBS protocol (**Fig. 4A**). Partial dependence plots illustrating the relationship between the top-four features and treatment response are shown in **Fig. 4B**. DCA indicated that for threshold probabilities between 15% and 40%, corresponding to a NNT between approximately 7 and 3, respectively, using the model to determine whether a patient should undergo rTMS yielded greater net benefit than employing either a “treat all” or “treat none” strategy (**Fig. 5**).

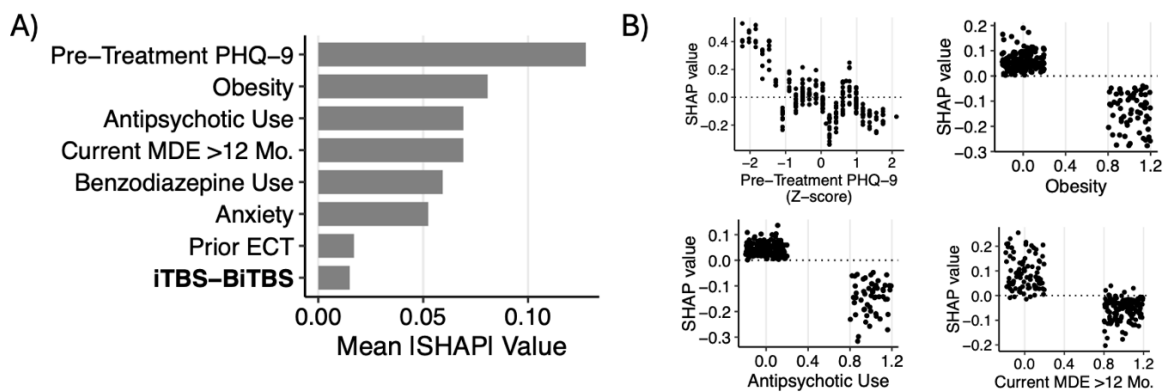


Figure 4: Treatment remission predictors and associations. Fig 4A) Ranked feature importance for depression remission classification model. Grey bars indicate negative association with remission (worse outcome). Fig 4B) Partial dependence plots illustrating directional associations between selected features and depression remission, indicated by SHAP values.

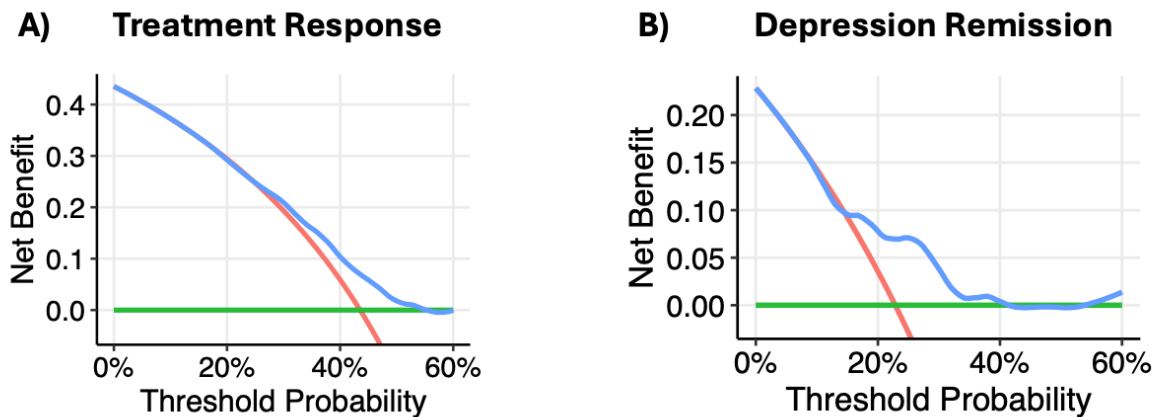


Figure 5: Decision curve analysis for recalibrated A) treatment response and B) depression remission models. Threshold probability represents the point at which a positive response is equally valued to avoiding unnecessary treatment. Decision curves for each model are shown in blue, compared to a “treat all” approach shown in red and a “treat none” approach shown in green.

DISCUSSION

Findings presented in this study underscore the substantial variability in depression responses and remission, despite rTMS efficacy, and the promise of ML to predict treatment outcomes using EMR data alone. Importantly, both ML models for response and remission identified psychiatric comorbidities, depressive episode duration, and specific rTMS protocols as predictive features, with trauma history also associated with response outcomes.

Predictive features of treatment outcomes

Past research investigating the relationship between psychiatric comorbidities and treatment response has yielded valuable insights into the complex interplay between mental health conditions and their respective treatments (Krishnan, 2003). This literature presents mixed results regarding impact of trauma history on rTMS. Experiences of childhood trauma and PTSD diagnosis have been reported to negatively affect rTMS outcomes in MDD patients (Hu et al.,

2021; Yesavage et al., 2018) or to have no significant impact (Ng et al., 2023). Positive findings, as presented here, may point to a consequence of trauma-induced neuroplastic changes that sensitize the brain to neurostimulation (Karsen et al., 2014). For example, the therapeutic impact of rTMS could be modulated by individual differences in neural circuitry affected by trauma, which are not always uniformly engaged by standard rTMS protocols, such as 10 Hz rTMS to the left DLPFC as done in Hu et al. (2021) and Yesavage et al. (2018).

Former tobacco use was identified as a positive predictor of treatment response. Past literature on tobacco use in rTMS outcomes is mixed (Abdelrahman et al., 2021; Poulet et al., 2016), but nicotine's complex neurobiological effects may enhance efficacy. However, the lack of association with current tobacco use suggests that other unaccounted factors may be influencing this finding, or it may be a statistical anomaly. Further investigation is needed to determine whether former tobacco use truly enhances rTMS response, if it serves as a proxy for another predictor, or if it is not directly related to treatment outcomes. Given the current findings, and coupled with trauma history, these associations suggest past experiences and lifestyle modifications may prime the brain's receptivity to rTMS.

Features including comorbid anxiety disorder, concomitant benzodiazepine or antipsychotic medications, and a longer duration of current MDE were linked to lower probabilities of treatment response and remission. Anxiety is highly comorbid with depression, and this specific comorbidity may reflect distinct neurobiological underpinnings, affecting the response to rTMS (Shin & Liberzon, 2010). For instance, hyperactivity in the amygdala and its connectivity with the PFC, can be more pronounced in individuals with comorbid anxiety (Shin & Liberzon, 2010). An extensive body of research supports that comorbid anxiety can

complicate the course of depression, often leading to a more chronic and treatment-resistant condition.

Concurrent use of benzodiazepines or antipsychotics was associated with less favorable responses. These medications exert sedative effects and reduce cortical excitability, potentially impeding operating mechanisms of rTMS. Benzodiazepines, for instance, enhance GABAergic inhibition, which may diminish excitatory processes (Wilson et al., 2021). Antipsychotics, particularly those blocking dopamine receptors, have been shown to attenuate rTMS outcomes (Hebel et al., 2020), potentially disrupting the dopaminergic modulation crucial for rTMS-induced neuroplasticity. These findings suggest patients prescribed benzodiazepines or antipsychotics may require adjusted protocols, perhaps with increased intensity or frequency to overcome medication-induced reductions in cortical excitability, or timing treatment sessions relative to medication dosing.

The observation that longer depressive episodes correlated with poorer outcomes is consistent research indicating depression chronicity can negatively impact the efficacy of various treatments. Chronic depression is associated with more severe neurobiological changes, including alterations in the hippocampus and PFC (Sheline et al., 2003). Earlier intervention might enhance response by addressing such changes before they become entrenched. Fava (2003) highlighted the predictive role of untreated depression duration in treatment resistance and underscoring the possibility that adjusting standard protocols, or combining with other interventions, may increase efficacy for these patients.

The observed absence of sociodemographic variables, such as age, sex, and ethnicity, impacting outcomes aligns with past studies, yet diverges from others (Hanlon & McCalley, 2022; M. K. Leuchter et al., 2024). For example, Hanlon and colleagues (2022) found younger

age and female sex were associated with better rTMS response rates, suggesting demographic characteristics may influence treatment success (Yu et al., 2024). Slan and colleagues (2024) recently found iTBS was more effective for males, while 10 Hz favored females, and rTMS overall being most effective in patients over 50, particularly females. The contrasting evidence indicates a complex relationship between sociodemographic and rTMS efficacy, warranting further investigation to clarify their roles in treatment personalization and optimization.

Accrued effects from patient history, such as trauma and anxiety, and concurrent benzodiazepine use may influence rTMS outcomes. The potential cumulative effect of these factors on response could be linked to their disparate impact on brain neuroplasticity and neurotransmission. For instance, a history of trauma and relatively lower anxiety might enhance receptivity to rTMS via induced neuroplastic changes, whereas the suppressive effect of benzodiazepines on cortical excitability could counteract these benefits, requiring adjustments in treatment protocols to optimize efficacy. Recent studies demonstrate that while rTMS produces generalized improvement across depressive symptoms, anxiety-related symptoms are less responsive, with outcomes influenced more by baseline symptom profiles than protocol variations ((Hutton et al., 2024; Kaster et al., 2023). Further investigation into the interaction of these factors may provide deeper insights into personalized rTMS strategies for patients with complex clinical profiles.

Regarding treatment-related factors, the number of rTMS sessions was a positive predictor, with SHAP values indicating a positive linear dose-response relationship. This relationship aligns with notions that additional sessions sustain antidepressant effects, possibly through cumulative neuroplastic changes. However, this is not consistently upheld, as a meta-analysis reported higher doses of rTMS, measured by total pulses, were not always associated

with depression improvement (Hanlon & McCalley, 2022). Adherence to the iTBS protocol was also among the strongest predictors of response. Notably, iTBS demonstrated superiority over iTBS-BiTBS in our sample, challenging some of the existing literature that suggests bilateral approaches can be advantageous for certain patient populations (Elnazali et al., 2024). Despite this, the current findings likely relate to iTBS-BiTBS patients experiencing greater treatment-resistance at baseline, with providers transitioning protocols from unilateral to bilateral in cases of inadequate symptom relief.

Machine learning, electronic medical records, and clinical decision-making

Recent reviews of ML prediction models in psychiatric research have found that despite relatively ‘good’ discrimination performance (AUC ~0.65–0.80), most studies had methodological weaknesses that limited their generalizability and utility in clinical decision-making (Meehan et al., 2022; Nie et al., 2018). While AUC values below 0.7 are generally considered modest, they can still offer meaningful insights in complex psychiatric conditions like TRD. These models help identify relevant predictors and inform future strategies for refining and validating predictive approaches (Grzenda & Widge, 2024; Nie et al., 2018). The authors recommended more comprehensive reporting of ML methods and results, more robust validation methods, model calibration, and formal assessment of clinical utility, such as DCA (Benrimoh et al., 2024; Nie et al., 2018; Vickers et al., 2016). In our analyses, DCA demonstrated that the response and remission models outperformed "treat all" and "treat none" strategies within probability threshold ranges of 25–55% and 15–40%, or NNT between 2 and 4 patients, and 3 and 7 patients, respectively. In other words, the NNT results suggest that for every 2 to 4 patients treated based on the response model, or every 3 to 7 patients treated based on the remission

model, one additional patient would experience a superior outcome from rTMS compared to treating all patients or none. While immediately applying this analysis to real-world clinical decision making is not warranted at this time, we included it here to advocate for the use of DCA in precision psychiatry prediction and prognostic models, aiming to illustrate its potential future utility. Both models indicate net clinical benefit within their respective threshold ranges, though more refined models incorporating additional patient features, such as neurobiological markers, polygenic risk scores, and psychosocial determinants, may confer additional benefit. Considering the use of internal cross-validation and novel methods, this model is best positioned as a preliminary predictive tool, offering foundational insights that can inform the development of more refined predictive models with future external validation. Despite demonstrating good discrimination performance, the remission model failed recalibration, as evidenced by a significant Hosmer-Lemeshow test ($p = 0.01$), indicating a mismatch between predicted and observed probabilities. This lack of calibration reduces the model's reliability in clinical settings, as it may overestimate or underestimate remission probabilities, ultimately limiting its immediate utility for decision-making.

The implications of these findings are multi-fold. Firstly, they re-affirm the clinical utility of rTMS in managing TRD, especially when considering individual patient histories and comorbidities. Secondly, these results lend support for the predictive power of ML algorithms derived from EMR for refining treatment approaches, suggesting that these tools could become integral to psychiatric precision medicine. Future research should aim to validate these predictive models in diverse clinical settings, ensuring that findings are replicable and robust.

Limitations

The retrospective study design provides a robust dataset but holds inherent limitations. Firstly, while our tree-based models implicitly account for interaction effects, we did not explicitly analyze these due to sample size constraints, which may have limited our ability to detect and interpret nuanced interactions among predictors. Secondly, this study is susceptible to selection bias since it involves patients who initiated and completed treatment, which may exclude those with different response trajectories, possibly skewing findings towards patients more likely to complete treatment. Moreover, the sample in this study was predominantly highly educated and non-Hispanic White, limiting generalization to other demographics and pointing more towards the need to address disparities in access to TMS (Nagra et al., 2024). Third, information bias may arise from EMR data availability, accuracy, and completeness, with additional variability in the timing of data collection vis-à-vis treatment, possibly creating discrepancies between recorded and actual patient conditions. Reliance on EMR-extracted data presents challenges particularly in terms of incomplete entries, inconsistent documentation, and potential coding errors, which may affect the robustness of the model's predictions. Further, our predictive models rely on several key assumptions. Tree-based models inherently capture non-linear relationships and interactions among predictors, eliminating the need for explicit interaction terms. Missing data were addressed through single imputation, assuming that data were missing at random. Overfitting was mitigated through feature selection, with checks for highly correlated predictors during preprocessing. These assumptions and limitations underscore the preliminary nature of this model, which serves as a foundation for future refinements. Future research should address these limitations by implementing prospective designs, standardizing rTMS protocols, timely data collection, and diverse populations.

CONCLUSION

This study elucidates predictors of treatment response to rTMS in TRD patients and highlights the importance of treatment approaches tailored to individual characteristics. By leveraging EMR and ML techniques, this study identified demographic, clinical, and treatment-related factors associated with outcomes, providing valuable insights for clinical practice and research.

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Chapter 2: Comparative analysis of treatment response and trajectory in treatment-resistant depression: repetitive transcranial magnetic stimulation vs. esketamine

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ABSTRACT

Background: Transcranial Magnetic Stimulation (TMS) and esketamine have emerged as promising treatments for treatment-resistant depression (TRD), yet little is known about their comparative effectiveness, especially in real-world settings. This study aimed to evaluate response rates, treatment trajectories, and clinical predictors of response for TMS and esketamine in individuals with TRD.

Methods: We conducted a retrospective analysis using electronic health record data from UC San Diego's Interventional Psychiatry Program. Adults diagnosed with TRD and treated with either TMS ($n=279$) or esketamine ($n=93$) were included. The primary outcome was response on the PHQ-9, defined as $\geq 50\%$ reduction from baseline. Kaplan-Meier survival curves were used to compare time-to-response between treatments by sessions and days, with log-rank tests assessing group differences. Cox proportional hazards models were constructed separately for each treatment to identify clinical predictors of response, and logistic regressions were conducted to examine sustained response at treatment endpoint. Variables examined included age, trauma history, anxiety comorbidity, benzodiazepine use, former tobacco use, BMI, and baseline severity.

Results: Esketamine demonstrated a significantly faster time-to-response compared to TMS (median: 36 vs. 49 days; 10 vs. 34 sessions; $p < .001$), and notably shorter time to suicidal ideation (SI) reduction (median: 9 vs. 26 days; $p = 0.0011$). End-of-treatment response and remission rates were modestly higher for esketamine (50.5% and 41.7%) than for TMS (44.8% and 35.3%). Cox regression identified comorbid anxiety ($HR=0.69$, $p=0.039$) and benzodiazepine use ($HR=0.73$, $p=0.0459$) as significant negative predictors, and former tobacco use ($HR=1.31$, $p=0.0059$) as a significant positive predictor of TMS response. No significant

predictors emerged for esketamine, though baseline PHQ-9 severity showed a trend toward significance. Logistic regression revealed similar findings for sustained response.

Conclusion: Real-world clinical data demonstrates that esketamine yields more rapid antidepressant and anti-suicidal effects than TMS, making it a compelling option for patients in acute distress. In contrast, TMS response is modulated more by individual clinical factors, emphasizing the value of patient stratification. These results highlight the importance of aligning treatment choice with individual patient characteristics and immediacy of treatment needs, offering actionable insights for personalized care in TRD.

INTRODUCTION

Treatment-resistant depression (TRD) is a severe and debilitating condition characterized by a lack of adequate response to at least two trials of standard antidepressant therapies administered at appropriate doses and durations.(Fava, 2003)(Rush et al., 2006) Patients with TRD frequently experience persistent depressive symptoms, elevated risks of comorbid conditions, and increased healthcare utilization, underscoring the urgent need for novel therapeutic approaches.(Berlim & Turecki, 2007) Transcranial Magnetic Stimulation (TMS) and ketamine have garnered considerable attention due to their ability to effectively treat large proportions of individuals with TRD. TMS is a non-invasive neuromodulation technique that utilizes magnetic fields to stimulate neural circuits implicated in mood regulation.(Downar & Daskalakis, 2013) Multiple studies, including randomized controlled trials, have demonstrated that TMS can produce significant antidepressant effects in patients with TRD, with a favorable safety profile and minimal systemic side effects.(O'Reardon et al., 2007) (George et al., 2013) Ketamine, originally developed as an anesthetic, has emerged as a rapid-acting antidepressant, offering substantial clinical benefits within hours of administration.(Coyle & Laws, 2015) Esketamine is the S-enantiomer of ketamine administered intranasally. Unlike conventional antidepressants that typically target monoaminergic systems, esketamine acts primarily on the glutamatergic system, modulating synaptic plasticity and neuronal connectivity. Its rapid onset of action makes it particularly promising for patients with TRD, especially those at imminent risk of self-harm due to prolonged depressive episodes.(Murrough et al., 2013)(Zarate et al., 2006) Together, TMS and esketamine represent innovative therapeutic avenues that not only broaden the spectrum of available treatments for TRD but also provide new insights into the neurobiological mechanisms underlying depression.

Despite robust evidence supporting the efficacy of both TMS and esketamine in TRD, significant uncertainties remain regarding their comparative response rates and treatment dynamics in routine clinical practice. Further, evidence to suggest which treatment may be most beneficial for an individual remains unclear. Controlled trials have largely focused on evaluating each modality in isolation, demonstrating that TMS can effectively modulate neural circuits associated with mood regulation (O'Reardon et al., 2007) and that esketamine offers rapid antidepressant effects through glutamatergic modulation. (Murrough et al., 2013) (Zarate et al., 2006) However, these studies often involve tightly controlled settings that may not fully capture the heterogeneity and complexity of real-world clinical populations. As a result, clinicians are left with limited evidence to guide treatment selection and timing when balancing the benefits of a gradual versus rapid response, leaving a critical gap in our understanding of how these interventions compare in everyday practice. (Berlim & Turecki, 2007) (Fava, 2003)

The present study capitalizes on a retrospective database cultivated from the electronic medical records (EMR) of patients with TRD treated in the UC San Diego Health. By harnessing this comprehensive real-world dataset, we can evaluate treatment outcomes including response rates, time-to-response, and symptom trajectory profiles, across a heterogeneous patient population. Moreover, the use of EMR facilitates the examination of a broader range of clinical factors and comorbidities, thereby enhancing the potential relevance of our findings. (Rush et al., 2006) This approach not only addresses the current evidence gap but also lays the groundwork for developing more personalized treatment strategies in TRD. This study aims to answer the following research questions: (1) How do TMS and esketamine compare in terms of time-to-response and overall treatment outcomes in TRD, (2) What clinical factors predict treatment

response within each modality, and (3) Do TMS and esketamine differ in how those clinical predictors influence treatment response?

We hypothesize that TMS and esketamine will exhibit statistically significant differences in response rates and time-to-response when evaluated using Kaplan–Meier survival analyses. Specifically, we expect that the median time-to-response will differ between the two treatments (with esketamine recovering more rapidly than rTMS based on existing literature), reflecting distinct temporal profiles and possibly underlying differences in mechanism of action (Zarate et al., 2006). (O’Reardon et al., 2007) By identifying distinct response patterns and temporal profiles, clinicians may better predict which patients are more likely to benefit from TMS versus esketamine, thereby optimizing intervention selection and reducing the reliance on trial-and-error approaches. Such tailored treatment could lead to more rapid symptom improvement, reduce the duration of depressive episodes, and ultimately improve overall patient outcomes. (Rush et al., 2006) (O’Reardon et al., 2007)

2. METHODS

2.1 Participants

Participants ($N=372$) were adults (aged 18 years or older) diagnosed with TRD receiving either rTMS ($n=279$) or esketamine ($n=93$) treatment through the UC San Diego Health Interventional Psychiatry Program (UCSD-IPP) and identified through Epic Electronic Medical Health Records. Detailed methodology regarding dataset available in original publication. (Benster et al., 2025) Inclusion criteria consisted of a primary diagnosis of Major Depressive Disorder (MDD) meeting DSM-5 criteria and a documented history of insufficient response to at least two previous adequate antidepressant trials confirmed via EMR. Individuals

with comorbid psychiatric conditions were included unless these conditions significantly interfered with the treatment protocols or outcome assessments. Basic demographic information including age, gender, Body Mass Index (BMI), psychiatric comorbidities, trauma history, benzodiazepine use, and concurrent substance use (including alcohol, cannabis, and illicit substances) was systematically recorded.

2.2 Treatment Protocols

Participants received either rTMS or esketamine treatment based on clinical recommendations and patient preference. All rTMS treatment was performed in the UCSD-IPP clinic by technicians trained in protocol administration with oversight by an attending psychiatrist. Overseeing psychiatrists reviewed the treatment plans after each session. rTMS was delivered using either a Magventure MagPro with a B70 coil or a BrainsWay H1-coil system. For all patients, the resting motor threshold (rMT) was identified by finding the motor hotspot and utilizing the lowest level of stimulation intensity to elicit movement in the opposite abductor pollicis brevis (APB) muscle on 50% of stimulation attempts. Once rMT was obtained, treatment session parameters were determined. For Magventure treatments, the coil position was localized using the Beam F3 method, and treatment was delivered per standard practice.(W. Beam et al., 2009) Patients who were initiated on the iTBS protocol (at 120% rMT), involving 600 total pulses in bursts of 3 with 8-second inter-train-intervals, were transitioned to either BiTBS (90% rMT; 3600 total pulses, 1800 delivered via 3-iTBS and 1800 delivered cTBS 120% rMT protocol to the left and right hemispheres, respectively) or 3-iTBS (iTBS delivered three times consecutively, per Li et al 2014 (Li et al., 2014) if there was deemed poor efficacy or issues with tolerability). High-frequency left (HFL; 19 minutes) and low-frequency right (LFR; 10 minutes)

protocols were used less commonly, both at 120% rMT. The obsessive-compulsive disorder (OCD) protocol uses a B70 coil and delivers 2000 pulses per session via 50, 2-second trains to dorsomedial prefrontal cortex (DMPFC), at 100% rMT of the foot with the Magventure B70 coil. For the BrainsWay H1-coil system either iTBS or the standard FDA-approved 18 Hz protocol was used at 120% rMT. Protocol selection was based on clinician judgment, considering previous treatment history and medical background. Stimulation was applied to the left dorsolateral prefrontal cortex (DLPFC) for unilateral iTBS and to bilateral prefrontal cortices for BiTBS. Targeting was guided by standardized Montreal Neurological Institute (MNI) coordinates using the BrainSight neuronavigation system (Rogue Research, Canada). Sessions were typically conducted multiple times per week, with a standard treatment series comprising approximately 36 sessions, though this number varied (range 4–82 sessions). Esketamine was administered intranasally under clinical supervision at a typical frequency of 2 sessions per week. Dosage and session frequency adjustments were individualized based on clinician judgment, tolerability, and patient scheduling constraints. Treatment series generally included 16 sessions (range 3–44 sessions). Comparison plots of treatment frequency and interval spacing of the two interventions available in the Supplementary materials.

2.3 Clinical Outcome Measures

The primary outcome was overall depression treatment response measured by the Patient Health Questionnaire-9 (PHQ-9) total score including all nine items. The PHQ-9 is a self-administered questionnaire consisting of nine items designed to evaluate the presence and intensity of depressive symptoms as defined by the DSM criteria for a Major Depressive Episode (MDE). Respondents indicate the frequency of each symptom on a four-point scale that includes

“not at all,” “several days,” “more than half the days,” and “nearly every day.” The overall score is the sum of all nine items (with possible totals ranging from 0 to 27), with established thresholds indicating severity as follows: 0–4 signifies no symptoms, 5–9 corresponds to mild symptoms, 10–14 indicates moderate symptoms, 15–19 reflects moderately severe symptoms, and 20–27 represents severe symptoms. The PHQ-9 was administered pre-treatment and at rTMS and esketamine visits throughout the treatment series to monitor changes in depressive symptoms. Treatment response was defined as at least a 50% reduction from baseline PHQ-9 scores. Assessments were regularly administered throughout treatment at varying intervals per patient for TMS, and at each session for esketamine. A secondary outcome focused specifically on suicidal ideation (SI), using item 9 of the PHQ-9. Improvement in SI was operationalized as a 1-point or more reduction from an initial score greater than 0.(Stapper et al., 2025)

2.4 Statistical Analysis

Kaplan-Meier (KM) survival analyses were performed to estimate time-to-response separately for TMS and esketamine groups, analyzed both by the number of treatment sessions and the number of days elapsed from treatment initiation. Both number of sessions and number of days analyses were included to provide a more thorough comparison due to differences in treatment pacing and between session intervals. Survival probabilities at multiple predefined time points were calculated. Log-rank tests were employed to statistically compare survival curves between rTMS and esketamine treatment groups. Patients who did not achieve a 50% PHQ-9 reduction by their last attended session were right-censored at that session date, ensuring that discontinuations without response removed patients from the risk set without registering as events. Only true response events ($\Delta\text{PHQ-9} \geq 50\%$) produce the downward steps in the survival

curves—censoring for discontinuation never registers as an event. Because censored patients no longer contribute to the “at risk” denominator, each subsequent response is calculated against a smaller pool; this can make later drops appear steeper even though they reflect real responses, not the censored dropouts. A number-at-risk table is provided beneath each KM plot (sessions 5, 10, 15, 20, 30; days 30, 60, 90, 180) to illustrate exactly how many patients remain under observation at each time point. This analysis was repeated for the SI item of the PHQ-9, to examine the response trajectories in suicidality. Cox proportional hazards regression was conducted separately within each treatment group (rTMS and esketamine) to identify clinical predictors significantly associated with treatment response. Predictor variables included age, trauma history, current benzodiazepine usage, concurrent substance use, BMI, and the number of psychiatric comorbidities. Multicollinearity among predictor variables was assessed using Variance Inflation Factor (VIF), with VIF values less than five considered indicative of minimal multicollinearity concerns. Analyses were conducted using Python (v.3.9.12) statistical software, and significance was set at an alpha level of 0.05.

2.5 Predictive Modeling (Logistic Regression)

Logistic regression analyses were conducted to identify clinical predictors associated with sustained treatment response at the end of treatment. This analysis differs from the KM survival analysis by defining response strictly at treatment completion, rather than at any point during treatment. Predictive features included age (determined at treatment onset), history of psychological trauma, concomitant benzodiazepine use, concurrent substance use (alcohol, tobacco, cannabis, or illicit substances), body mass index (BMI), number of psychiatric comorbidities, and baseline depression severity indicated by PHQ-9 score. Selected variables

were informed by existing literature and previous findings from analyses conducted on a smaller subset of the individuals in the rTMS portion of this database.

3. RESULTS

3.1 Descriptive Statistics

A total of 279 participants receiving rTMS and 93 participants receiving esketamine treatment were included in the analysis. Baseline demographic and clinical characteristics for both groups are detailed in **Table 2** and elaborated in the **Supplementary Materials**. Analysis revealed no significant differences in Age ($t = -0.22$, $p = 0.83$), BMI ($t = -0.86$, $p = 0.39$), Anxiety Comorbidity ($\chi^2 = 0.15$, $p = 0.70$), Concurrent Substances ($\chi^2 = 0.01$, $p = 0.92$), Former Tobacco Use ($\chi^2 = 2.61$, $p = 0.11$), previously undergoing ECT ($\chi^2 = 0.40$, $p = 0.69$), or Mean Baseline PHQ-9 ($t = 0.82$, $p = 0.42$) between the rTMS and Esketamine groups. However, there was a significant difference in Trauma History ($\chi^2 = 5.50$, $p = 0.02$), with a higher proportion of individuals with a trauma history in the Esketamine group (63.8%) compared to the rTMS group (46.3%). Additionally, a significant difference was found in the proportion of individuals who had previously undergone rTMS ($\chi^2 = -7.32$, $p < 0.001$), with a higher percentage of individuals in the Esketamine group (47%) compared to the rTMS group (11.8%). For the TMS group, the number of treatment sessions completed ranged from 4 to 82, with a mean of 38.3 sessions ($SD = 12.5$) and a median of 36 sessions. In contrast, the esketamine group exhibited a range of 3 to 44 sessions, with a mean of 10.6 sessions ($SD = 6.5$) and a median of 10 sessions. Additional descriptive statistics, including detailed follow-up visit frequencies and other session-related measures, are provided in **Table 3**.

Table 2: Descriptive Statistics and Patient Characteristics.

Characteristic	TMS (n=279)	Esketamine (n=93)	Test Statistic	P-value
Mean Age (SD)	53.68 (17.21)	54.13 (17.19)	-0.218	0.827
Gender Distribution (M/F/O)	105/181/1	40/53/2	-0.859	0.390
Mean BMI (SD)	27.16 (5.89)	27.78 (6.41)	3.995	0.136
Hx of Trauma (%)	46.3%	63.8%	5.501	0.019*
Anxiety Comorbidity (%)	75.4%	78.7%	0.150	0.699
Concurrent Substances (%)	55.4%	53.7%	0.010	0.921
Former Tobacco Use (%)	15.7%	7.4%	2.608	0.106
Mean Baseline PHQ-9 (SD)	17.61 (5.39)	17.12 (4.87)	0.818	0.415
Previously Underwent ECT	16.8%	15.0%	0.404	0.686
Previously Underwent TMS	11.8%	47%	-7.315	0.001

Table 3: Number of Session and Response Characteristics.

Measure	TMS (n=279)	Esketamine (n=93)
Mean # of Sessions	38.3	10.6
Median # of Sessions	36	10
Session Range	4-82	3-44
Response (at any time) Rate	59.43%	68.82%
Remission (at any time) Rate	40.14%	45.16%

The overall response rates were 59.43% for the TMS group and 68.82% for the esketamine group, when determined at any point during treatment. Remission rates were 40.14% for TMS participants and 45.16% for esketamine participants. These response and remission rates underscore substantial clinical improvement across both treatments, with a notable higher response and remission observed in the esketamine group.

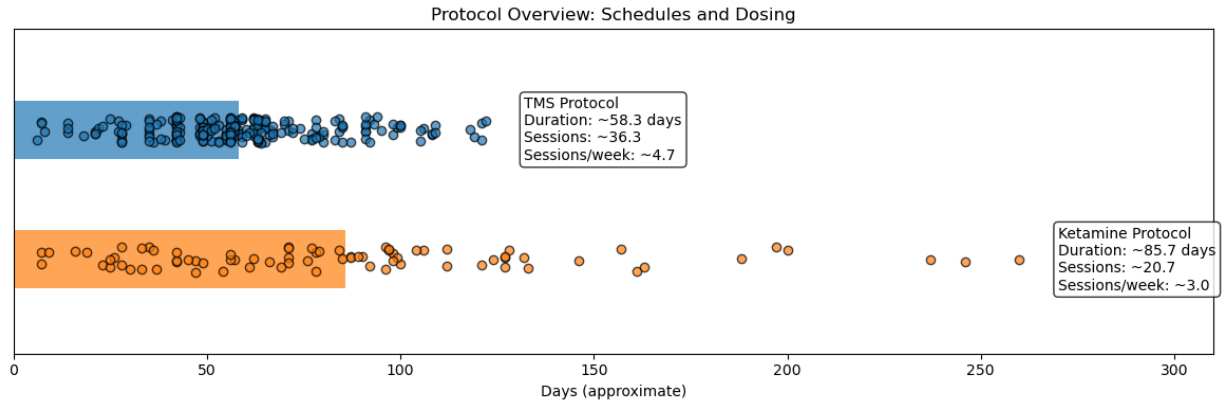


Figure 6: Protocol Overview: Schedules and Dosing. Protocol overview illustrating differences in TMS and esketamine treatment timing and duration. Each dot represents a unique individual.

3.2 Kaplan-Meier Survival Analyses for Overall Depression Response

Survival probabilities and detailed characteristics including statistics outlined in **Table 4**.

3.2.1. By Sessions: KM analyses indicated significant differences in time-to-response between treatments (Log-Rank Test Statistic = 162.55, $p < 0.001$). Median survival times to response were 32 sessions for the rTMS group and 10 sessions for the esketamine group. Survival probabilities at specified intervals were as follows: at 5 sessions, 96.8% (TMS) vs. 80.5% (esketamine); at 10 sessions, 92.2% (TMS) vs. 47.8% (esketamine); at 15 sessions, 85.0% (TMS) vs. 22.6% (esketamine); at 20 sessions, 73.3% (TMS) vs. 18.5% (esketamine); and at 30 sessions, 53.6% for TMS. **Fig. 7** illustrates KM curves by sessions. In the Esketamine cohort the maximum observed session to first response was 20 sessions—no additional first-response events occurred beyond that point, so the KM curve remains flat thereafter. In contrast, TMS first responses continued to accrue out to 50+ sessions, indicating that extending TMS beyond 20 treatments may yield further responders.

3.2.2. By Days: Analysis by days revealed significant differences in median survival times: 49 days for TMS and 36 days for esketamine (Log-Rank Test Statistic = 6.699, $p =$

0.0096). Survival probabilities at key intervals were notably distinct: at 5 days, 98.9% (TMS) vs. 91.4% (esketamine); at 10 days, 95.4% (TMS) vs. 86.0% (esketamine); at 20 days, 88.6% (TMS) vs. 77.1% (esketamine); at 30 days, 74.0% (TMS) vs. 57.4% (esketamine); at 60 days, 42.5% (TMS) vs. 30.1% (esketamine); at 90 days, 24.7% (TMS) vs. 22.2% (esketamine); and at 180 days, both treatments stabilized at 16.9% (TMS) and 16.7% (esketamine). **Fig. 8** illustrates KM curves by days.

Table 4: Survival Probabilities of Non-response.

Analysis Type	Time Interval	TMS Survival Probability (%)	Esketamine Survival Probability (%)	Median Survival (TMS)	Median Survival (Esketamine)	Log-Rank Test Statistic	p-value
Sessions	5	96.8	80.5	32	10	162.552	<0.001*
	10	92.2	47.8				
	15	85.0	22.6				
	20	73.3	18.5				
	30	53.6					
Days	5	98.9	91.4	49	36	6.699	0.0096*
	10	95.4	86.0				
	20	88.6	77.1				
	30	74.0	57.4				
	60	42.5	30.1				
	90	24.7	22.2				

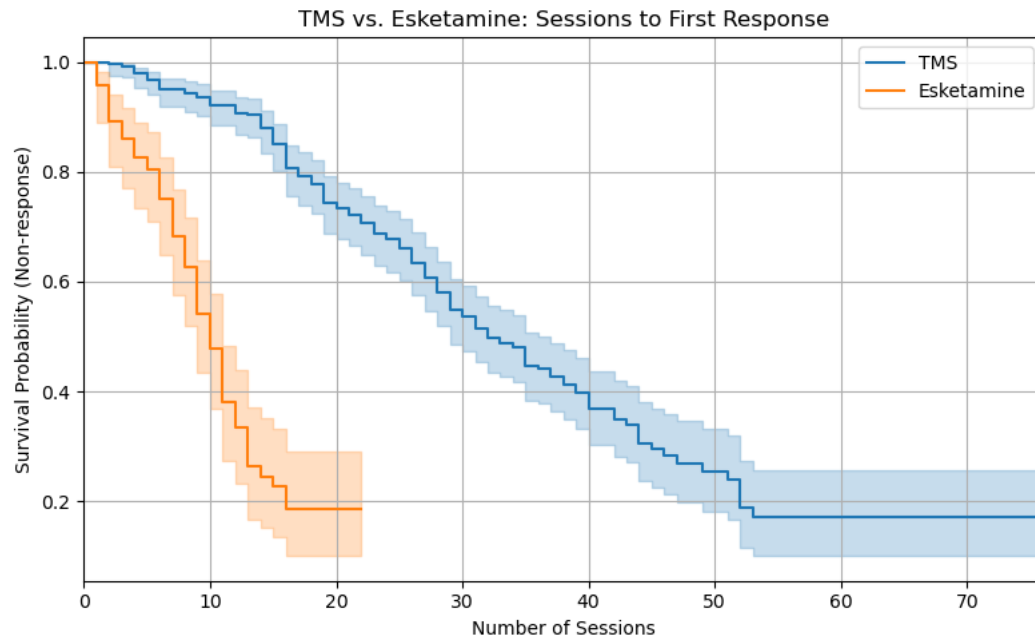


Figure 7: KM Curves Sessions to First Response. KM curve for TMS (blue) and esketamine (orange) based on number of sessions. Curve depicts probability of non-response.

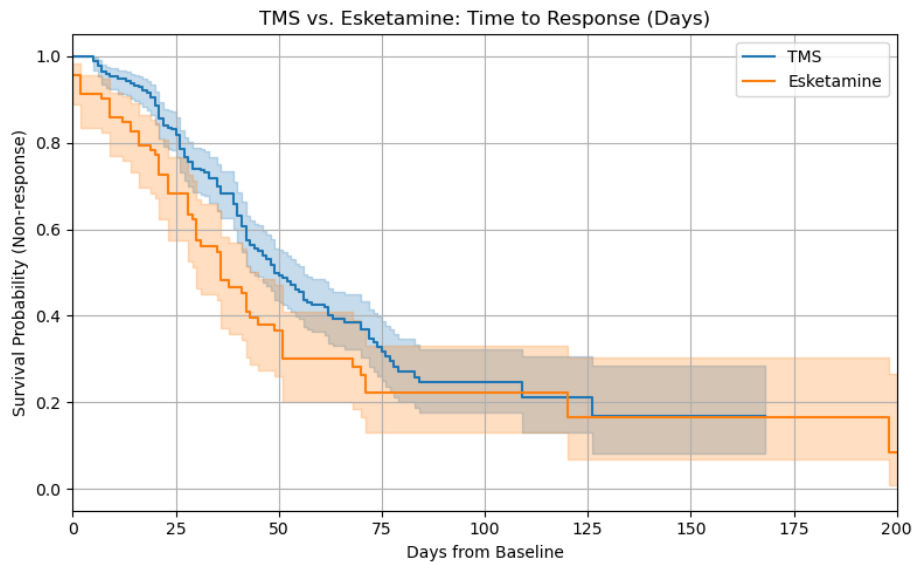


Figure 8: KM curves for days to first response. KM curve for TMS based on number of days. Curve depicts probability of non-response. TMS time to response in days represented in blue and esketamine in orange.

To better understand the temporal dynamics of treatment response, we examined the instantaneous likelihood of first-time response events by calculating the discrete derivatives of the KM survival curves for TMS and esketamine (**Fig. 9**). This was done both in terms of number of treatment sessions and days from baseline. Specifically, we computed the negative change in the survival function ($-dS/dt$) to approximate a probability density function (PDF) of response events—effectively quantifying how likely a patient is to achieve treatment response at any given time point. We then plotted the difference between these KM-derived PDFs for TMS and esketamine (i.e., TMS – Esketamine), where positive values indicate a greater instantaneous response likelihood for TMS and negative values indicate the opposite. To improve interpretability and reduce the impact of irregular censoring and sparse event occurrences, we used the KM event table method to calculate discrete differences in survival probabilities. Statistical comparison using paired t-tests confirmed that these instantaneous response profiles differed significantly across treatments. The difference in per-session response likelihood between TMS and esketamine was statistically significant ($t = -12.33$, $p < 0.000001$), as was the difference across days ($t = -20.94$, $p < 0.000001$). These findings indicate that esketamine not only produces a faster median response but does so with a substantially greater likelihood of early responders compared to TMS.

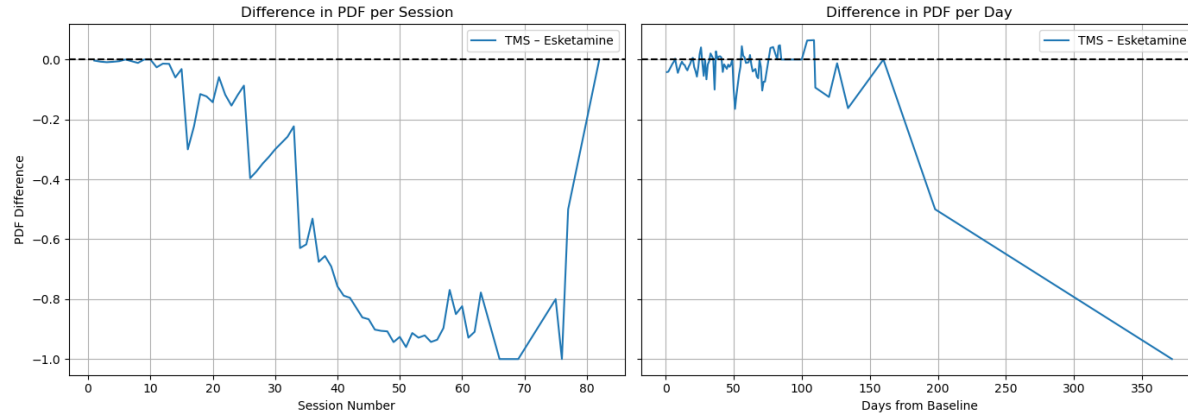


Figure 9: Difference in PDF. KM-derived differences in response likelihood between TMS and esketamine, estimated as the negative discrete derivative ($-dS/dt$) of each KM survival curve. Values above the dotted line ($y = 0$) indicate timepoints where TMS had greater likelihood of response; values below indicate greater likelihood for esketamine. Fig 9A depicts the difference in TMS and esketamine KM derivatives up to 80 sessions. Fig 9B depicts the difference in TMS and esketamine KM derivatives up to 350 days.

3.4 Cox Regression Analyses

To evaluate which baseline demographic and clinical factors are associated with faster or slower time-to-response for each treatment modality, we performed Cox proportional hazards regression analyses. Predictors for the Cox regression analyses were selected based on findings from previous analyses conducted on subsets of this dataset, indicating their potential impact on neuromodulatory treatment response. Predictors included age, trauma history, anxiety comorbidity, benzodiazepine usage, former tobacco use, and BMI (detailed rationale provided in **Table 5**).

Table 5: Cox Regression Predictor Selection and Rationale.

Category	Predictor	Rationale
Demographics	Age	Neuroplasticity tends to decline with age, which may affect both TMS and ketamine response. Older age has been associated with slower or reduced response to TMS and may influence ketamine metabolism.(Sabesan et al., 2015)
Clinical History	History of Trauma	Trauma exposure is linked to altered fronto-limbic connectivity and stress-response systems, which may interact with neuromodulatory effects of TMS and ketamine.(Feder et al., 2014)
Diagnosis	Anxiety Comorbidity	Comorbid anxiety disorders have been shown to reduce the efficacy of TMS in MDD, possibly due to differences in network responsivity or symptom interference.
Substance Use	Former Tobacco Use	Previous findings from this dataset suggested former tobacco use was associated with better TMS response, potentially due to upregulation of dopaminergic tone and altered cortical excitability.
Medication	Benzodiazepines	Benzodiazepines can suppress cortical excitability and interfere with neuroplastic mechanisms, potentially reducing response to TMS and blunting ketamine efficacy.
Physical Health	BMI	Higher BMI may alter drug pharmacokinetics and neuromodulation response, particularly for ketamine due to its lipophilic properties. TMS response has also shown mixed associations with BMI.

In the TMS group, anxiety disorder comorbidity was associated with a 31% lower hazard of achieving response (HR=0.69, $p=0.039$), indicating slower time-to-response in patients with comorbid anxiety. Former tobacco use conferred a 31% higher hazard of response (HR=1.31, $p=0.0059$), while benzodiazepine usage was linked to a 27% lower hazard (HR=0.73, $p=0.0459$), both pointing to faster response in ex-smokers but slower response in those on benzodiazepine. By contrast, age (HR=1.01, $p=0.125$), trauma history (HR=0.84, $p=0.301$), BMI (HR=0.95, $p=0.595$), and total sessions completed (HR=0.99, $p=0.154$) showed non-significant trends (each <5% change in hazard per unit) and thus were not robust predictors. In the esketamine group, none of the covariates reached significance—although point estimates suggested a 30% higher

hazard for former tobacco users (HR=1.30, $p=0.221$) and a 30% lower hazard for trauma history (HR=0.70, $p=0.217$), all confidence intervals crossed 1.0. Multicollinearity was minimal (all VIFs <5). Full coefficients, 95% CIs, and p-values are provided in **Supplementary Table 1** and illustrated in **Fig. 10**.

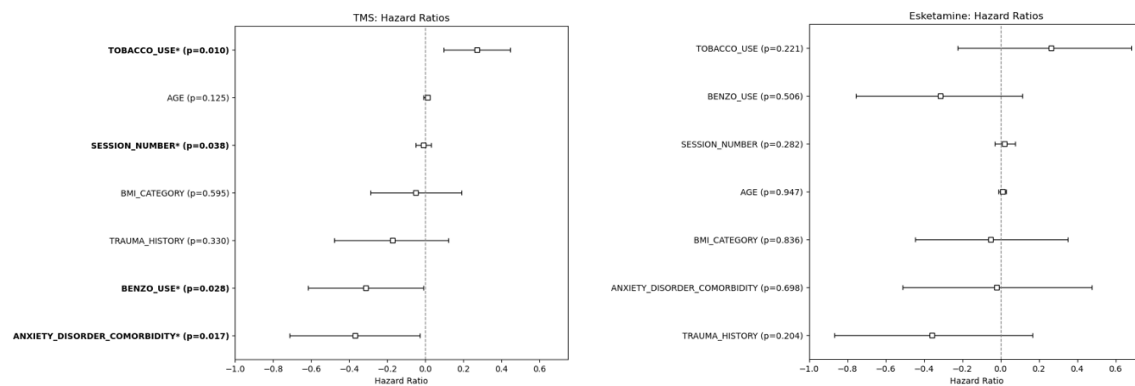


Figure 10: Hazard Ratios. Hazard ratios for TMS (left) and esketamine (right). P-values are indicated next to variables on y-axis. Significant variables in black, non-significant in gray text.

3.5 Suicidal Ideation Kaplan-Meier Survival Analysis

Survival analysis specifically focused on the reduction of SI demonstrated significant differences between groups (Log-Rank Test Statistic = 10.681, $p = 0.0011$). Median survival times for SI improvement were markedly shorter for the esketamine group (9 days) compared to the rTMS group (26 days). Survival probabilities for SI reduction at various intervals illustrated clear differences: at 5 days, survival probabilities were 90.3% (TMS) vs. 60.0% (esketamine); at 10 days, 77.0% (TMS) vs. 47.1% (esketamine); at 20 days, 60.5% (TMS) vs. 33.9% (esketamine); at 30 days, 41.6% (TMS) vs. 26.0% (esketamine); at 60 days, 32.5% (TMS) vs. 18.4% (esketamine); at 90 days and beyond, probabilities stabilized around 17.0% for TMS and 15.3% for esketamine. These results highlight the more rapid impact of esketamine on alleviating

SI compared to TMS. Survival response by timepoint is illustrated in **Fig. 11** and detailed in **Supplementary Table 2**.

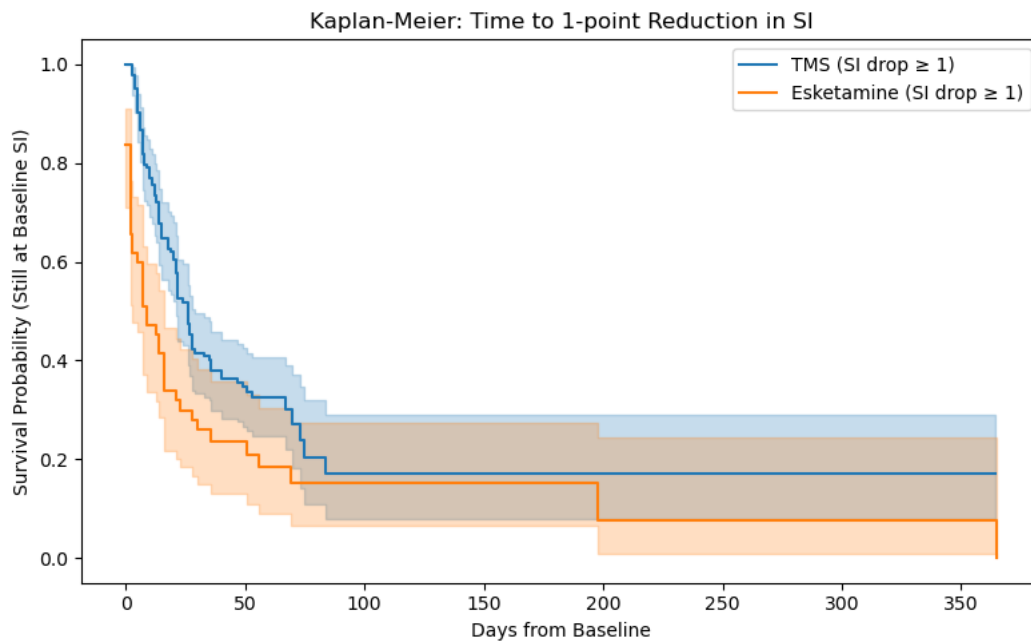


Figure 11: KM curves for suicidality response. KM curves for TMS (blue) and esketamine (orange) depicting probability of non-response for suicidality.

3.6 Logistic Regression

In the TMS model, current benzodiazepine use was associated with significantly lower odds of sustained response ($\beta = -0.7053$, $OR \approx 0.49$, $p = 0.016$), whereas concurrent substance use conferred significantly higher odds of sustained response ($\beta = 0.4135$, $OR \approx 1.51$, $p = 0.017$). Age ($\beta = 0.0095$, $OR \approx 1.01$, $p = 0.269$), trauma history ($\beta = 0.2317$, $OR \approx 1.26$, $p = 0.379$), BMI ($\beta = -0.1228$, $OR \approx 0.88$, $p = 0.344$), number of comorbidities ($\beta = -0.1121$, $OR \approx 0.89$, $p = 0.327$), and baseline PHQ-9 severity ($\beta = 0.0737$, $OR \approx 1.08$, $p = 0.470$) showed non-significant trends. In the esketamine model, no predictors reached significance; baseline PHQ-9 severity showed a trend toward higher odds of sustained response ($\beta = 0.2156$, $OR \approx 1.24$, $p = 0.071$).

Multicollinearity was minimal (all VIFs < 5). The TMS model demonstrated modest but significant explanatory power (LLR $p = 0.0397$, Pseudo $R^2 = 0.0381$), whereas the esketamine model did not (LLR $p = 0.3525$, Pseudo $R^2 = 0.0624$). Detailed coefficients, standard errors, odds ratios, and p-values are presented in **Supplementary Table 3** and visualized in **Fig. 12**.

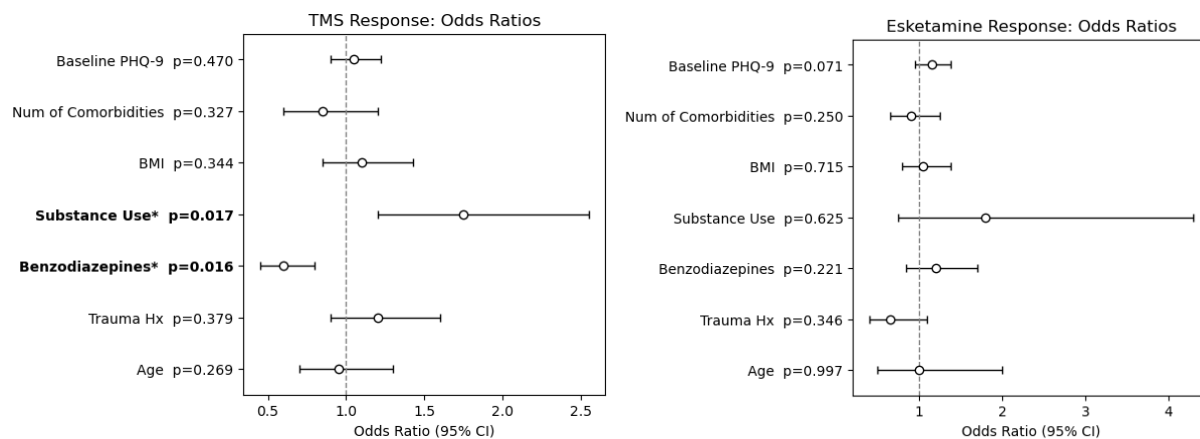


Figure 12: Response Odds Ratios. Forest plots of odds ratios (95% CI) for clinical predictors of suicidality response in TMS (left) and esketamine (right) models. Point estimates (circles) and confidence intervals (horizontal lines) illustrate the strength and direction of association for each predictor, with statistically significant effects in blue and non-significant effects black.

4. DISCUSSION

This study sought to compare the clinical trajectories and predictors of treatment response for TMS and esketamine in individuals with TRD. Through indirect comparisons within a large, real-world dataset, we observed substantial differences between the two treatment modalities in terms of response speed, trajectory, and predictability. These findings expand the current literature by offering a clinically relevant, temporally grounded understanding of how these interventions unfold across time and for different patient profiles, and by identifying unique response dynamics that can guide personalized treatment selection in TRD.

The present study's cohort (279 patients undergoing TMS and 93 receiving esketamine) is sizeable relative to many recent retrospective TRD studies. Real-world cohort analyses of

TRD often vary widely in sample size, from fewer than 20 patients up to a few thousand.(Oliveira-Maia et al., 2024) For example, a multi-center naturalistic study in France assessed 435 patients with TRD treated with rTMS(Bouaziz et al., 2023), and a recent manuscript from of our team, a single-center U.S. academic TMS program reported outcomes in 232 TRD patients.(Benster et al., 2025) Observational studies of esketamine in clinical practice have reported sample sizes on the order of 100–170 patients (e.g. 116 patients across multiple Italian centers in the REAL-ESK study)(Martinotti et al., 2022) and 171 patients in a U.S. clinic-based cohort (Brendle et al., 2022). By contrast, broader retrospective TRD cohorts leveraging large health system databases can include thousands of patients (Adekanattu et al., 2023) (Gill et al., 2025), but often rely on aggregate or single time-point analyses. In comparison, our study offers more complex analyses by examining multiple time points, capturing early, mid, and late treatment responses for patients all seen in the same clinic thereby controlling for many potential confounding factors. This allows for a better understanding of the dynamics of treatment effects and more accurately reflect the longitudinal trajectories of both rTMS and esketamine treatments in real-world settings. In light of this landscape, the current sample falls within the upper range of most retrospective TRD studies focusing on specific treatments, providing a robust real-world dataset for comparison.

Recent studies have similarly explored the differential efficacy and response trajectories of rTMS and esketamine for TRD. For instance, a retrospective naturalistic study comparing ketamine and rTMS observed that esketamine offers a notably quicker response, particularly in those with severe symptom burden or SI, which aligns with our findings (Mikellides et al., 2022). This rapid onset is consistent with esketamine's NMDA receptor antagonism, which facilitates quicker neuroplastic changes compared to the more gradual cortical stimulation seen

with rTMS. Similarly, Al-Sabbagh et al. (2022) examined esketamine following rTMS, suggesting that sequential use of these therapies may improve outcomes, particularly for patients who respond inadequately to rTMS alone (Al-Sabbagh et al., 2022). Our study supports these findings by demonstrating that esketamine has a faster time-to-response and is particularly effective in alleviating SI. This rapid effect of esketamine has significant clinical implications, especially for patients in acute distress, reinforcing its potential as a first-line intervention in such contexts. In contrast, rTMS remains a valuable treatment, particularly for patients whose response profiles may be influenced by factors such as comorbid anxiety or benzodiazepine use, which were significant predictors of treatment response in our cohort.

An important and clinically meaningful finding in the current study is the difference in time-to-response between rTMS and esketamine. The KM curves for both rTMS and esketamine depict the probability of non-response over time, with each curve reflecting how the proportion of non-responders changes as treatment progresses. As the treatment continues, the pool of patients at risk becomes smaller due to censoring, which occurs when patients discontinue treatment or fail to meet the response criteria by the last session. This leads to steeper declines in the survival curves, especially at later time points, as fewer patients remain in the analysis. The curves demonstrate that esketamine has a higher initial response rate, with fewer patients remaining non-responders over time compared to rTMS, which shows a more gradual decline in non-response probability. The censoring process ensures that patients who drop out or do not achieve the required treatment response are appropriately excluded from the analysis at later time points, reflecting the true treatment dynamics. KM survival analyses revealed a significantly shorter median time-to-response for esketamine, both by number of sessions (10 sessions vs. 34 for TMS) and by elapsed time in days (36 days vs. 49 days). This difference is not just

statistically significant, but clinically impactful, especially for patients experiencing severe symptom burden or SI. These results are consistent with prior research documenting esketamine's rapid onset, attributed to its NMDA receptor antagonism and downstream neuroplastic effects (Murrough et al., 2013)(Zarate et al., 2006) TMS, which acts via cortical stimulation and longer-term modulation of neural circuitry, naturally follows a more gradual trajectory (O'Reardon et al., 2007). Importantly, these differences extended to the treatment of SI, a critical outcome in TRD. Because the SI item is also one component of the total PHQ-9 score, there is a risk of overlapping information when we look at 'overall PHQ-9 response' and then again at SI specifically. By isolating the SI item in its own survival analysis, we ensure we're capturing the unique trajectory of suicidality, an outcome with distinct clinical urgency, rather than simply reflecting broader depressive symptom change. Statistically, the two analyses remain distinct because the total-score survival endpoint ($\geq 50\%$ PHQ-9 reduction) and the SI endpoint (≥ 1 -point SI drop) employ different event definitions and censoring schemes, which creates separate risk sets and hazard estimates and thus mitigates bias from the shared measurement. Median time to SI improvement was significantly shorter for esketamine (9 days) than for TMS (26 days), and survival probabilities at every early interval showed esketamine outperforming TMS. This finding aligns with esketamine's current FDA approval for acute suicidality and further validates its use in clinical scenarios requiring urgent symptom alleviation (Canuso et al., 2019).

To further examine the shape and timing of treatment response, plotted the derivatives of the KM survival curves were plotted to estimate the instantaneous likelihood of first response events over time. These smoothed derivative plots showed that esketamine response rose sharply early on, both by day and by session, whereas TMS demonstrated a more gradual and continuous

accumulation of new responders across the treatment period. The esketamine curves reflected a concentrated period of early benefit, while TMS maintained a steady increase in response likelihood throughout. These patterns illustrate distinct therapeutic profiles: esketamine may be preferred when early relief is critical, whereas TMS may be more appropriate for individuals likely to benefit from a slower, sustained approach. The overall distribution of responses adds valuable context to median response estimates, emphasizing not only how soon but how consistently each treatment facilitates improvement.

The finding that esketamine leads to a faster clinical response whereas TMS has a slower onset is consistent with patterns observed in other real-world studies. Retrospective outcomes indicate that intranasal esketamine can induce notable symptom improvements within the first few weeks of therapy (Popova et al., 2019). For instance, a multicenter observational study reported a rapid reduction in depression scores by the 1-month follow-up of esketamine treatment, with response and remission rates substantially rising by month three (Martinotti et al., 2022). This aligns with the drug's known rapid-onset pharmacology in TRD. In contrast, observational TMS cohorts have shown that patients typically require multiple weeks of stimulation before achieving significant improvement. Real-world TMS data suggest clinical benefits usually emerge during the second to fourth week of a rTMS course, and some patients may only reach response after completing the full 4–6 week acute treatment series (Prodi et al., 2024). These comparative samples reinforce that esketamine tends to provide faster relief in TRD, while rTMS gains accumulate more gradually over the course of treatment.

When examining overall response and remission rates at any point throughout treatment, esketamine again demonstrated an advantage, with response and remission rates of 68.82% and 45.16%, respectively, compared to 58.42% and 40.14% for TMS. Notably, the observed 58.6%

TMS response rate aligns with meta-analytic estimates of 49–55% in controlled TMS studies, (Brunoni et al., 2017) while the 68.2% esketamine response closely matches the 64–70% range reported in Phase III trials (Canuso et al., 2019). This concordance suggests that these naturalistic findings recapitulate the efficacy frequently seen under trial conditions. Cox regression and logistic regression modeling revealed that, in contrast to esketamine, response to rTMS was significantly modulated by patient-specific clinical features. In particular, individuals with comorbid anxiety disorders had a significantly lower likelihood of achieving response with rTMS. This is consistent with literature suggesting that anxiety comorbidity blunts response to neuromodulation, potentially due to overlapping pathophysiological mechanisms or heightened limbic reactivity (George et al., 2013). Additionally, benzodiazepine use negatively predicted rTMS response, potentially due to its known dampening effects on cortical excitability, which could counteract the excitatory intent of rTMS protocols (Hunter et al., 2019). Interestingly, former tobacco use was associated with improved outcomes, possibly reflecting underlying neurobiological differences related to dopaminergic tone or neuroplasticity. These were all consistent with previous findings on a smaller subset of the rTMS database (Benster et al., 2025). In contrast, none of these predictors reached significance in the esketamine group. Although this could be partially attributed to smaller sample size and limited power, it may also suggest that esketamine operates via mechanisms less dependent on cortical modulation or psychiatric comorbidity profiles, making it a more broadly effective option across diverse patient populations. The rTMS finding that comorbid anxiety halves (HR 0.69) the hazard of response, echoes a recent systematic review identifying anxiety disorder as one of the strongest negative predictors of rTMS efficacy (Wang et al., 2021), reinforcing the need to screen for and potentially treat anxiety symptoms prior to neuromodulation. Notably, even baseline depression

severity did not significantly predict treatment outcomes, although a trend was observed in the esketamine model. This calls for further investigation into whether baseline symptom burden meaningfully influences ketamine response or whether it is largely agnostic to initial severity. Substance use, including alcohol, cannabis, and illicit drugs, was an important factor in treatment response, particularly for rTMS. Our analysis showed that concurrent substance use was associated with higher odds of sustained response in the rTMS group. This aligns with previous studies suggesting that substance use can influence neural circuits or reward pathways, potentially enhancing the effects of rTMS by modulating dopaminergic systems, which are involved in mood regulation (Hunter et al., 2019). However, no such association was found for esketamine, which suggests that its efficacy may be less influenced by substance use compared to rTMS. This is consistent with findings from Al-Sabbagh et al. (2022), who suggested that esketamine's effects may be more independent of external substance use factors, operating via its glutamatergic modulation (Al-Sabbagh et al., 2022). Interestingly, trauma history did not emerge as a significant predictor of treatment response in either treatment group, despite a notable difference in trauma history between the two treatment groups. The esketamine group had a higher prevalence of individuals with psychological trauma, which may indicate a potential interaction between treatment modality selection and trauma exposure. This finding contrasts with some prior studies that have shown that trauma can influence treatment outcomes, particularly for psychotherapies and pharmacological interventions (Feder et al., 2014). However, this suggests that neuromodulation treatments like rTMS and esketamine may be less susceptible to the impact of trauma compared to traditional therapies. This highlights the need for further research to examine how trauma, especially in its more severe forms, might interact with the effects of neuromodulatory treatments.

Similarly, baseline depression severity did not predict response to either rTMS or esketamine, which contrasts with findings from studies on other antidepressants where baseline severity often plays a significant role in treatment outcomes (e.g., Rush et al., 2006). This finding suggests that rTMS and esketamine may be more broadly effective across different levels of depression severity, indicating their potential utility in treating patients with varying levels of symptom burden. These results are consistent with Brotman et al. (2021), who reported that rTMS had significant efficacy regardless of baseline severity.

In contrast, anxiety comorbidity was identified as a negative predictor for rTMS response. Patients with comorbid anxiety experienced a slower time-to-response, potentially due to overlapping neurobiological pathways, such as heightened limbic reactivity, that may interfere with the effects of rTMS (e.g., George et al., 2013). However, anxiety did not have the same effect on esketamine response, suggesting that esketamine may be more robust to the influence of comorbid psychiatric conditions. This supports the notion that esketamine, with its action on the glutamatergic system, may bypass some of the neural networks implicated in anxiety and depression, which could explain its broader effectiveness across comorbid populations.

Our study also found that former tobacco use was associated with improved rTMS outcomes, potentially due to nicotine's modulation of dopaminergic tone and cortical excitability. This is consistent with Sabesan et al. (2015), who suggested that nicotine can enhance the effects of neuromodulation by increasing cortical excitability. However, tobacco use did not influence esketamine outcomes, indicating that the effect of nicotine may be specific to rTMS. This finding warrants further exploration to determine the specific mechanisms by which nicotine interacts with rTMS.

Finally, BMI was not a significant predictor of treatment response in either group. While some studies have suggested that BMI may affect the pharmacokinetics of antidepressant medications (e.g., Kohli et al., 2018), our findings suggest that rTMS and esketamine are less influenced by BMI compared to traditional pharmacological approaches. This could imply that these treatments may offer more consistent efficacy across different body weights, potentially reducing the need for dose adjustments based on BMI.

Another critical point concerns the difference in response rate definitions. Whereas KM analyses captured response at any point during treatment, the logistic models defined sustained response as response at treatment endpoint. As expected, this resulted in lower response rates, particularly in the TMS group (44.8%), suggesting that some patients respond transiently or late in the course of TMS. This highlights the importance of evaluating both early and sustained outcomes in neuromodulation studies, particularly when informing clinical decision-making. The higher proportion of individuals in the esketamine group who had previously undergone rTMS (47% vs. 11.8% in the TMS group) could suggest that these patients had a more complex treatment history, possibly reflecting greater treatment resistance. Despite this, the esketamine group demonstrated a higher response, which may indicate that esketamine is effective even for those with a history of neuromodulatory treatments like rTMS. This suggests that esketamine may be a viable treatment option for patients who have not responded to prior treatments, underscoring its potential in the treatment-resistant depression pathway. Further studies exploring the interaction between previous neuromodulatory treatments and esketamine's efficacy are warranted.

Despite its strengths (including the use of real-world clinical data, rigorous statistical methods, and survival-based modeling) this study has several limitations. Because this was a

real-world clinical sample, treatment assignment was not randomized, and differences in baseline characteristics, clinician judgment, or patient preferences may have introduced selection bias. Additionally, there was some overlap between individuals in the rTMS and esketamine treatment groups, with a small number of patients included in both. This overlap was minimal and is unlikely to significantly influence the overall findings of the study. Treatment protocols were not fully standardized, with variability in frequency, pulse intensity, and duration of treatment across participants. The retrospective design and naturalistic follow-up schedule may also have influenced PHQ-9 assessment timing, introducing potential measurement bias. Additionally, differences in esketamine and rTMS mechanisms, timing, and tolerability challenges the ability to draw firm conclusions when comparing the two. These limitations notwithstanding, our findings contribute insights into how esketamine and rTMS perform in clinical practice, particularly in terms of speed of response, modulation by clinical features, and treatment durability. Moving forward, prospective studies are needed to replicate these results, ideally with harmonized protocols and randomization. Additional predictors, especially neurophysiological, genetic, or cognitive biomarkers, could greatly enhance our ability to tailor treatments to individual patients (Appelbaum et al., 2022).

In sum, this study demonstrates that while both TMS and esketamine can be effective in TRD, their clinical profiles differ meaningfully. Esketamine provided faster, more robust early symptom relief, especially for SI, while TMS response appears more dependent on patient-specific factors such as comorbid anxiety and medication use. These findings underscore the importance of aligning treatment modality with clinical presentation, offering a framework for more personalized and timely interventions in the treatment of TRD.

5. CONCLUSION

This study provides a real-world comparison of two key treatments for TRD: TMS and esketamine. The results highlight significant differences in response speed and overall treatment trajectories. Esketamine demonstrated a notably faster time-to-response, particularly for alleviating suicidal ideation, making it a compelling option for patients in acute distress. TMS, while effective, showed a more gradual response, with clinical predictors such as anxiety comorbidity, benzodiazepine use, and former tobacco use significantly influencing treatment outcomes. These findings underscore the need for personalized treatment approaches, where the choice of intervention is tailored to individual patient profiles. Esketamine may be particularly beneficial for those requiring rapid symptom relief, whereas TMS may be more suitable for patients whose response is influenced by specific clinical factors. Future studies should focus on refining treatment protocols, exploring additional predictors of response, and further assessing the long-term effects of these interventions in broader, more diverse patient populations. Ultimately, this research contributes to a deeper understanding of the clinical dynamics between TMS and esketamine, offering valuable insights for optimizing treatment strategies in TRD and informing future clinical decision-making.

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Chapter 3: Examining the role of the Cortical Silent Period (CSP) in treatment response to
neuromodulatory interventions in TRD

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ABSTRACT

Treatment-resistant depression (TRD) poses substantial clinical challenges, underscoring the need for reliable biological measures that can be used to predict treatment response. The cortical silent period (CSP), a measure of GABA_B-mediated cortical inhibition elicited by transcranial magnetic stimulation (TMS) – is such a biomarker that reflects neurophysiological states relevant to neuromodulatory treatments. The following were tested: (1) whether baseline CSP predicted post-treatment PHQ-9 scores via analysis of covariance controlling for baseline symptoms, (2) whether baseline CSP moderated longitudinal symptom change using a linear mixed-effects model, and (3) whether within-individual changes in CSP correlated with changes in PHQ-9 scores using robust regression and nonparametric correlation. Twenty-five adults underwent baseline CSP and depressive symptom assessment (PHQ-9); 16 completed post-treatment (8 TMS, 8 esketamine) evaluations. CSP duration did not differ between treatment groups at baseline or follow-up. ANCOVA revealed that longer baseline CSP was associated with higher post-treatment (collapsed over TMS and esketamine) PHQ-9 scores, despite the overall model not reaching significance. Mixed-effects modeling, however, revealed a significant CSP-by-time interaction, indicating that participants with longer baseline CSP showed greater symptom reduction. These seemingly conflicting findings likely arise from differences in methodology: the ANCOVA captures the influence of baseline CSP on post-treatment severity at a single time point, whereas the mixed-effects model accounts for changes in symptoms over time. Change-score analyses yielded a positive but non-significant trend between the change in CSP duration and the change in PHQ-9 scores (Δ CSP and Δ PHQ-9). Depressive severity did not predict CSP duration in analyses testing the reverse association (CSP predicting depression severity). Baseline CSP may index individual differences in responsiveness to neuromodulatory

treatments across modalities, however, the associations with clinical outcomes were modest and inconsistent, and CSP changes did not reliably track symptom improvement. These findings underscore the need for larger, randomized studies to validate CSP as a biomarker for treatment response.

INTRODUCTION

Major depressive disorder (MDD) is a leading contributor to disability worldwide, with an estimated lifetime prevalence of 10–20% (Ferrari et al., 2013; Hasin et al., 2018). While many individuals respond to first-line antidepressant treatments, up to 30% fail to achieve remission despite multiple adequate trials—a condition classified as treatment-resistant depression (TRD) (Rush et al., 2006). Patients with TRD often experience prolonged depressive episodes, greater functional impairment, elevated suicide risk, and increased health care utilization (Lundberg et al., 2023; McIntyre et al., 2023). These challenges underscore the urgent need for alternative interventions and objective biomarkers that can guide treatment selection.

Neuromodulatory treatments, including repetitive transcranial magnetic stimulation (rTMS) and intranasal esketamine, have emerged as promising options for individuals with TRD. These treatments differ substantially in their mechanisms of action: rTMS is a non-invasive brain stimulation technique that delivers pulsed magnetic fields to modulate cortical excitability, while esketamine acts as a glutamatergic modulator, rapidly inducing synaptic plasticity via NMDA receptor antagonism (Zarate et al., 2006) (Daskalakis et al., 2006). While both modalities have demonstrated efficacy in subsets of patients, treatment response remains highly variable, and no reliable physiological marker currently exists to identify which patients will respond, or across which treatment modality. A better understanding of individual neurobiological traits that confer responsiveness across neuromodulation could enable more personalized, mechanism-informed treatment selection.

One such candidate biomarker is the cortical silent period (CSP), a measure of cortical inhibition that has been linked to neuroplasticity and responsiveness to treatments (Fitzgerald et al., 2004). The CSP is a brief interruption of voluntary muscle activity following suprathereshold

TMS delivered to the primary motor cortex during tonic contraction (Cantello et al., 1992).

When a suprathreshold TMS pulse is applied over the primary motor cortex during an ongoing voluntary contraction, it generates a motor evoked potential (MEP) followed by a transient cessation of electromyographic (EMG) activity in the target muscle (Spampinato et al., 2023).

This pause in EMG activity, typically lasting 100–300 ms, is thought to reflect the suppression of cortical output and is widely considered a functional index of intracortical inhibition (Škarabot et al., 2019). Thus, the CSP has been used in research as an *in vivo* proxy for cortical inhibitory function.

Pharmacological and paired-pulse TMS studies have demonstrated that CSP duration is primarily mediated by GABA_B receptor activity (Ahern et al., 2023; McDonnell et al., 2006), distinguishing it from short-interval intracortical inhibition (SICI), which reflects GABA_A-mediated processes. Pharmacological studies have demonstrated that agents enhancing GABA_B receptor activity tend to prolong the CSP, whereas those that block these receptors shorten it (Ziemann, Lönnecker, et al., 1996). Prior research has demonstrated that altered CSP durations may be linked to depressive states, suggesting a disruption in intracortical inhibitory processes (Kinjo et al., n.d.). Prior studies have demonstrated that CSP is altered in MDD, often showing reduced duration relative to healthy controls (Levinson et al., 2010)(Radhu et al., 2013; Voineskos et al., 2019). These findings are consistent with broader evidence implicating reduced GABAergic tone in depression, particularly in dorsolateral prefrontal cortex (Sanacora et al., 2004). Results across studies, however, are not uniform, and methodological variability—including differences in stimulation parameters, motor target selection, and patient subtypes—has made it difficult to establish normative CSP profiles for depression (Hupfeld et al., 2020).

While there is no definitive consensus or established normative CSP profile for depression, a growing number of studies have examined whether CSP or other TMS-derived markers can predict clinical response to neuromodulatory treatment. For instance, longer baseline CSP has been associated with better outcomes following electroconvulsive therapy (Voineskos et al., 2016). This is likely due to CSP serving as a proxy for cortical inhibition, which plays a critical role in ECT's mechanism of action. ECT is known to induce neuroplastic changes in the brain, and preserved cortical inhibition, as indicated by a longer baseline CSP, may reflect a neural environment that is more receptive to these changes. Similarly, baseline CSP has been linked to better outcomes with rTMS, suggesting that individuals with more intact cortical inhibition may be more responsive to neuromodulatory effects (Fitzgerald et al., 2004). These findings point to CSP as a potential biomarker of treatment efficacy, reflecting the integrity of GABAergic inhibitory circuits. To date, however, no study has directly compared CSP's predictive utility across different neuromodulatory modalities, and limited studies have examined whether changes in CSP correspond to treatment-induced symptom improvement.

Importantly, while CSP has been examined in relation to rTMS outcomes, less is known about its relevance to treatments like esketamine, which also appear to modulate cortical inhibition and GABAergic systems (Duman & Aghajanian, 2012). Given this shared neurotransmitter target, CSP may represent a cross-modality biomarker of responsiveness, rather than a treatment-specific predictor. That is, individuals with more intact inhibitory tone at baseline may be more likely to benefit from neuromodulatory interventions broadly, regardless of whether they receive rTMS or esketamine.

To investigate this possibility, the present study examined the utility of baseline CSP duration as a predictor of symptom improvement in a naturalistic sample of patients with TRD

undergoing either rTMS or esketamine treatment. Rather than comparing the two treatments, this study sought to determine whether CSP reflects an individual difference that moderates responsiveness across modalities and whether within-individual changes in CSP over the course of treatment are associated with concurrent changes in depressive symptom severity. This approach aims to clarify both the prognostic and mechanistic relevance of CSP and address prior inconsistencies in the literature through a carefully characterized clinical dataset. Specifically, this study investigates (1) whether baseline CSP duration predicts symptom improvement following neuromodulatory intervention, and (2) whether treatment-related changes in CSP duration are associated with concurrent changes in depressive symptom severity. It was hypothesized that individuals with longer baseline CSP durations, suggestive of greater GABA_B-mediated inhibition, would experience greater reductions in depressive symptoms following neuromodulatory intervention. Additionally, it was predicted that increases in CSP duration over the course of treatment would be positively associated with symptom improvement, supporting a role for CSP as a state-sensitive biomarker reflecting treatment-induced plasticity. Establishing CSP as a transdiagnostic and cross-modality predictor of treatment response could inform the development of physiologically guided personalized treatment pathways in TRD.

METHODS

Sample and Treatment

Participants were adults (aged 18 and older) with TRD seeking care for depression at the UC San Diego Interventional Psychiatry Program. Participants were excluded if they endorsed any contraindication of TMS, as assessed by the TMS Adult Safety Screen (TASS) per site standard-of-care, if the treating clinician determined treatment termination was warranted for

safety reasons, or if the patient terminated treatment for any reason. All participants provided informed consent to participate in a research protocol approved by the UC San Diego Institutional Review Board. All participants were enrolled in a larger biomarker research protocol investigating neuromodulation-related predictors of treatment response, which included neurophysiological, clinical, and self-report measures collected pre- and post-treatment. CSP assessments were conducted early in the protocol, following reliably establishing the resting motor threshold (rMT). Participants received modest monetary compensation for their time and participation in research procedures, separate from their clinical care.

TMS or esketamine treatment was prescribed based on clinician judgment as part of standard clinical care. TMS treatment involved protocols that included intermittent theta burst stimulation (iTBS) and bilateral TBS (BiTBS) as well as 10 Hz low-frequency repetitive stimulation (LFR) to the right dorsolateral prefrontal cortex (DLPFC), with the type of protocol based on clinician judgment, guided by the patient's previous treatment history and relevant medical information. For all participants, the rMT was determined by locating the motor hotspot and applying the lowest stimulation intensity required to provoke movement in the contralateral abductor pollicis brevis (APB) muscle in 50% of attempts. Once rMT was established, the treatment session parameters were set. Coil placement was guided by the Beam F3 method, and the procedure was carried out following standard protocols (20). For patients starting the iTBS protocol (set at 120% rMT), which includes 600 pulses delivered in bursts of three with 8-second inter-train intervals, the treatment was adapted to either BiTBS (90% rMT; 3600 total pulses, split into 1800 pulses via 3-iTBS and 1800 pulses via cTBS at 120% rMT targeting the left and right hemispheres, respectively) or 3-iTBS (three consecutive iTBS sessions, as described by Li et al. 2014 (21), if efficacy was suboptimal or tolerability was an issue). High-frequency left

(HFL; 19 minutes) and low-frequency right (LFR; 10 minutes) protocols were less frequently used, both at 120% rMT. These sessions were conducted several times per week, with most treatment series comprising 36 sessions.

Esketamine was administered intranasally in accordance with FDA-approved protocols for treatment-resistant depression. Treatments were delivered two or three times per week under direct clinical supervision in a specialized outpatient setting. The majority of patients completed approximately 16 sessions, reflecting the standard course of treatment across the induction and maintenance phases. However, the precise number of sessions and pacing were tailored based on clinical need, patient tolerability, response trajectory, and logistical considerations such as patient availability and co-occurring medical conditions. Initial dosing followed FDA guidelines, beginning at 56 mg and titrated to 84 mg as tolerated. Dose adjustments were made at the discretion of the treating psychiatrist in response to side effects or insufficient clinical response. Each session included a minimum two-hour observation period during which vital signs, dissociative symptoms, and adverse effects were monitored by trained nursing staff. Safety protocols included routine blood pressure and heart rate assessments before and after administration, and the presence of on-site medical personnel in the event of adverse reactions.

As this was a naturalistic treatment setting, patients who demonstrated meaningful improvement but did not meet formal remission thresholds could continue beyond 16 sessions based on shared decision-making between provider and patient. Likewise, treatment could be discontinued earlier in cases of lack of efficacy, intolerable side effects, or patient preference. Clinical outcome measures, including the PHQ-9, were administered at each session to track symptom changes in real time and inform treatment adjustments.

Cortical Silent Period

CSP was assessed at baseline and after the final treatment session as part of a biomarker protocol. TMS pulses were delivered to the left motor cortex using a Magstim BiStim² stimulator with a figure-of-eight coil (Magstim, Whitland, United Kingdom). The motor cortex was identified through the BrainSight Neuronavigation system (Rogue Research, Montreal Canada), with targeting guided by individually identifying each participant's motor hotspot. Hotspots were marked in the neuronavigation system to ensure consistent delivery of stimulation with minimal variation across pulses. Electromyographic (EMG) recordings were acquired from the APB muscle using surface electrodes in a belly–tendon montage during sustained voluntary contraction set to 20% of each participant's maximum output, recorded via the Intronix Model 2024F system. Participants were visually guided to maintain ~20% of their maximum pinch grip force using a pinch gauge. The stimulus intensity was set at 140% of each participant's rMT, which had been determined according to standard procedures. RMT was defined as the lowest stimulation intensity that reliably elicited motor-evoked potentials (MEPs) with a peak-to-peak amplitude of at least 50 μ V in 5 out of 10 consecutive trials in the contralateral APB muscle at rest. EMG data were band-pass filtered and digitized for offline analysis. Ten CSP trials were collected per participant pre and post treatment, and the average CSP duration was used for analyses. Trials were excluded in cases of excessive noise or unclear CSP onset or offset. CSP duration was manually calculated and defined as the interval from the offset of the MEP to the resumption of spontaneous EMG activity, and was manually marked through visual inspection of the signal in Signal.

Depression Outcome Variable

The primary clinical outcome was depressive symptom severity, assessed using the 9-item Patient Health Questionnaire (PHQ-9). The PHQ-9 is a validated self-report instrument that

assesses core DSM-5 symptoms of major depressive disorder over the preceding two weeks. Each item is rated on a 4-point scale (0 = “Not at all” to 3 = “Nearly every day”), producing total scores ranging from 0 to 27. Established thresholds indicate severity as follows: 0–4 = none, 5–9 = mild, 10–14 = moderate, 15–19 = moderately severe, and 20–27 = severe depression. PHQ-9 scores were collected at baseline (pre-treatment) and again following the completion of the treatment course. Treatment response was defined as a $\geq 50\%$ reduction in PHQ-9 score from baseline to post-treatment.

Statistical Analyses

All statistical analyses were conducted using Python (v3.9). Analyses were designed to evaluate the relationship between CSP duration and depression severity using three complementary approaches: (1) the predictive association between baseline CSP duration and post-treatment PHQ-9 scores, controlling for baseline symptoms; (2) the moderating effect of baseline CSP on symptom change over time via mixed-effects modeling; and (3) the association between changes in CSP duration and changes in depressive symptoms from pre- to post-treatment. All models were conducted across the combined MDD sample, without stratification by treatment type, due to limited statistical power. Statistical significance was defined as $\alpha = 0.05$ (two-tailed) for all inferential tests.

To evaluate the relationship between CSP duration and depression severity, a linear mixed-effects model (LMM) was employed. The model included fixed effects for time (pre- vs. post-treatment), baseline CSP duration, and their interaction (CSP $\times$ time), with participant ID specified as a random intercept to account for repeated measures. This model tested whether individual differences in baseline CSP moderated changes in depressive symptoms across the treatment period. To further assess the predictive utility of baseline CSP, an analysis of

covariance (ANCOVA) was conducted with post-treatment PHQ-9 score as the dependent variable, controlling for both baseline PHQ-9 score and baseline CSP duration. This model evaluated whether CSP duration predicted post-treatment depressive symptom severity above and beyond initial symptom burden. In a complementary analysis, a linear regression model was used to examine whether PHQ-9 scores predicted CSP duration across timepoints. The model included an interaction term ($\text{PHQ} \times \text{time}$) to evaluate whether the relationship between depression severity and CSP differed between baseline and post-treatment assessments. Change scores from pre-to-post treatment ($\Delta\text{PHQ-9}$ and ΔCSP) were computed to explore dynamic relationships between neural and clinical change. A robust linear regression model, using Huber's T norm, was fit to estimate the association between ΔCSP and $\Delta\text{PHQ-9}$. Additionally, a nonparametric Spearman correlation was conducted to assess the strength and direction of the relationship between change scores, accounting for potential violations of normality and small sample size. Logistic regression models tested whether CSP duration predicted treatment response. All plots were created using matplotlib and seaborn to visualize relationships between clinical and neurophysiological measures, including stratification by treatment group. Model residuals and assumptions were checked in all parametric analyses to ensure validity. Notably, due to small sample sizes, some models may lack statistical power.

RESULTS

Participant Characteristics

Twenty-five individuals (male = 3; female = 19; other = 2; undefined = 1) with TRD completed baseline assessments of CSP duration and depressive symptoms using the PHQ-9. The participants had a mean age of 52.08 years ($\text{SD} = 17.24$), with ages ranging from 22 to 82 years.

Of these, 16 participants (male = 2; female = 13; other = 1) also completed post-treatment assessments following a full course of neuromodulatory treatment, eight of which underwent esketamine and eight underwent rTMS. No significant differences in CSP duration were observed between the esketamine and rTMS groups at baseline ($t[22] = 1.21, p = .238$) or post-treatment ($t[13] = 0.575, p = .575$). For those that completed a pre-treatment visit, 64% (16/25) had one or more concomitant antidepressant medications prescribed. For those that completed both visits, 68.75% (11/16) endorsed concomitant antidepressant medication treatment. Out of the 16 that completed a treatment series, there were nine responders, reflecting a 56% response rate (50%+ reduction in PHQ-9 scores) in the sample. Descriptive statistics for CSP duration and PHQ-9 scores at each time point are presented in **Table 6**. A Wilcoxon signed-rank test revealed a highly significant reduction in depressive symptoms from pre- to post-treatment (PHQ-9: $W = 0.00, p < .001$), whereas CSP duration showed a non-significant trend toward increase ($W = 26.00, p = .053$).

Table 6: Descriptive Statistics.

Measure	All Patients at Baseline (n=25)	rTMS at Baseline (n=14)	Esketamine at Baseline (n=10)	Combined at Follow-up (n=16)	rTMS at Follow-Up (n=8)	Esketamine at Follow-Up (n=8)
Age (years): Mean (SD), Range	52.08 (17.24), 22–82	50.50 (19.35),	54.22 (15.34),	56.44 (16.96), 22-82	54.88 (22.11),	58.00 (11.06),
Gender – M/F/O	3/19/2	1/10/2	2/7/X	2/14/1	0/7/1	2/6/0
PHQ-9 Score: Mean (SD)	18.6 (4.2)	18.92 (4.25)	18.10 (4.23)	9.07 (5.56)	10.6 (5.95)	6.5 (4.60)
CSP Duration (ms): Mean (SD)	82.85 (33.18)	77.37 (27.13)	93.84 (39.62)	101.9 (35.7)	96.89 (28.34)	106.64 (36.10)
Tx Response, n (%)	-	-	-	9 (56.25%)	3 (37.5%)	6 (75%)
Concomitant Antidepressants, n (%)	16 (64%)	9 (64.2%)	6 (60%)	11 (68.8%)	6 (75%)	6 (75%)

Normality Tests

Prior to conducting primary analyses, Shapiro-Wilk tests were performed to assess the normality of key variables. Results indicated that post-treatment CSP durations and total PHQ-9 scores approximated normality ($p = .72$ and $p = .34$, respectively), whereas baseline PHQ-9 scores and item-level symptom scores deviated significantly from a normal distribution ($ps < .01$). Given these findings and the small sample size, supplementary robust or non-parametric methods (e.g., Spearman correlation, robust regression) were employed where normalcy assumptions were violated. All summary statistics were computed using cleaned and verified data in Python; discrepancies from spreadsheet-derived values were likely due to missingness or averaging procedures that included different subsets of participants.

Baseline CSP as a Predictor of Post-Treatment Depression Severity

To assess whether baseline CSP duration predicted post-treatment depression severity, an ANCOVA was conducted using ordinary least squares (OLS) regression, controlling for baseline depressive severity. The overall model explained 27.8% of the variance in post-treatment depressive symptoms but was not statistically significant ($R^2 = 0.278$, $F(2,13) = 2.50$, $p = .120$). However, baseline CSP duration significantly predicted post-treatment PHQ-9 scores ($\beta = 0.080$, $p = .048$), suggesting longer CSP at baseline was associated with higher post-treatment depressive symptom severity. Baseline PHQ-9 scores were not significantly predictive ($\beta = 0.045$, $p = .897$). Results available in **Table 7**. The scatterplot in **Figure 13A-B** illustrates individual change scores in CSP duration versus the change in depressive symptoms (Δ CSP and Δ PHQ-9). A least-squares regression line is included to demonstrate the trend in the data.

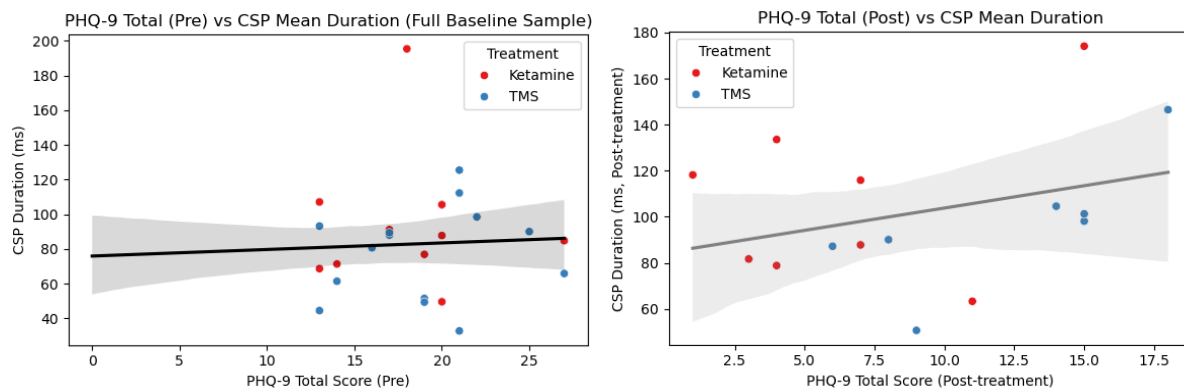


Figure 13: Scatterplot of change in CSP vs. change in PHQ-9. Scatterplot of individual change scores in CSP duration versus reduction in depressive symptoms. Each point represents one participant ($n = 25$ at baseline, $n=16$ at follow-up); Δ CSP = $CSP_{post} - CSP_{pre}$, Δ PHQ-9 = $PHQ_{pre} - PHQ_{post}$. The black line represents the least-squares regression, with the shaded band indicating the 95% confidence interval around the fit.

Table 7: ANCOVA Results.

Variable	Coefficient	Std. Error	t	p-value	95% CI Lower	95% CI Upper
Intercept	0.5808	6.551	0.089	0.931	-13.571	14.733
Baseline PHQ-9	0.0455	0.344	0.132	0.897	-0.698	0.789
CSP Duration	0.0803	0.037	2.182	0.048*	0.001	0.16

Baseline CSP as a Moderator of Symptom Change

To further explore the predictive role of baseline CSP, a linear mixed-effects model was conducted examining depressive symptom severity over time. Fixed effects included baseline CSP duration, time (baseline vs. post-treatment), and their interaction; participant ID was modeled as a random intercept, full results depicted in **Table 8**. A significant CSP-by-time interaction was found ($\beta = 0.074, p = .011$), indicating participants with longer baseline CSP durations experienced greater reductions in PHQ-9 scores following treatment. A significant main effect of time ($\beta = -16.387, p < .001$) confirmed overall improvement in depressive symptoms from baseline to post-treatment. The main effect of baseline CSP duration alone was not significant ($\beta = -0.001, p = .973$). However, it's important to note that the ANCOVA results indicated an opposite relationship, with longer baseline CSP being associated with higher post-treatment depressive symptom severity. This contradiction may stem from differences in how baseline symptoms were controlled for in each model, as well as the distinct methodological approaches, with the ANCOVA focusing on post-treatment outcomes while the mixed-effects model captures changes over time. As shown in **Fig. 14A-D**, the mean CSP duration and PHQ-9 scores were compared between baseline and post-treatment for participants receiving either TMS or esketamine. **Fig. 14A** presents the mean CSP duration at both time points, while **Fig. 14B**

shows the corresponding mean PHQ-9 scores. **Fig. 14C** and **Fig. 14D** illustrate these measures separated by treatment modality, providing a clearer view of the differences between groups.

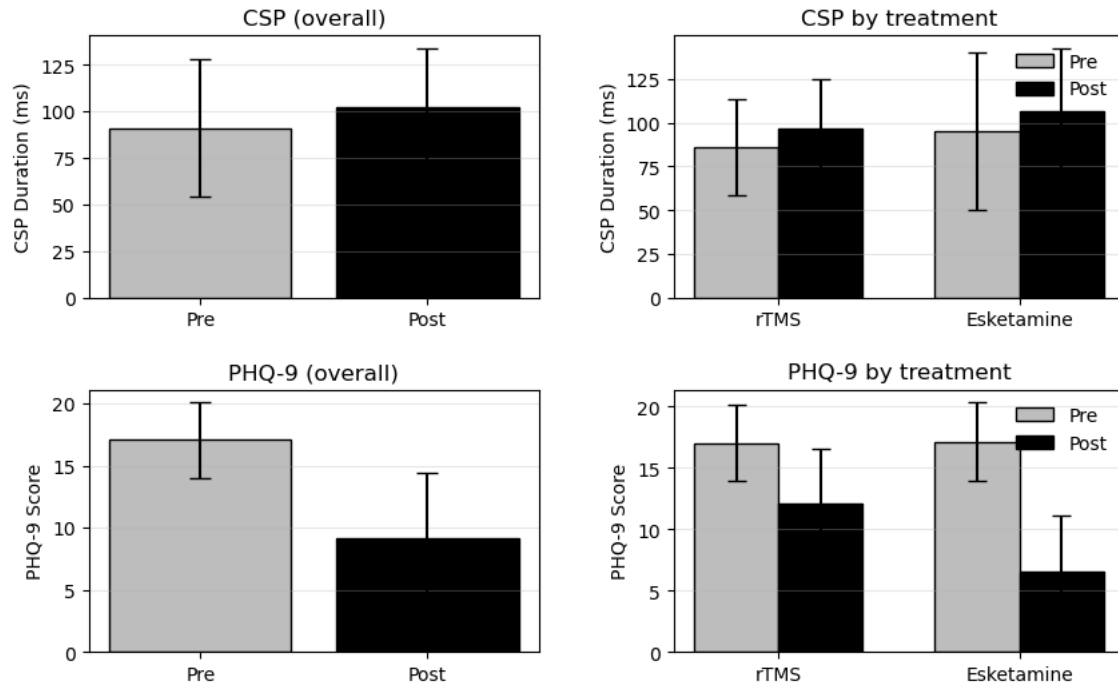


Figure 14: Pre and post CSP and PHQ-9 bar graphs. Fig. 14A-D. Bars show group means; error bars denote ± 1 SD. Fig. 14A. Mean CSP duration at baseline and after treatment for participants receiving either TMS or esketamine ($n = 16$). Fig. 14B. Mean PHQ-9 score at baseline and after treatment for participants receiving either rTMS or esketamine ($n = 16$). Fig. 14C. Mean CSP duration at baseline and after treatment separated by treatment type. Fig. 14D. Mean PHQ-9 total score at baseline and after treatment separated by treatment type.

Table 8: Linear Mixed Effects Model Results Predicting PHQ Over Time.

Effect	Coefficient	Std. Error	z-value	p-value	95% CI Lower	95% CI Upper
Intercept	18.920	2.518	7.513	<0.001	13.984	23.856
CSP Duration (baseline)	-0.001	0.028	-0.034	0.973	-0.056	0.054
Time	-16.387	2.738	-5.985	<0.001*	-21.753	-11.021
CSP Duration $\times$ Time	0.074	0.029	2.558	0.011*	0.017	0.131

Depression Severity as a Predictor of CSP

To assess the reverse association, whether depressive symptoms predicted neurophysiological functioning, a linear model examined CSP duration as the outcome with PHQ-9 scores, time, and their interaction as predictors. The overall model was not statistically significant ($p = .248$), and no predictors reached significance: PHQ-9 ($\beta = 4.41, p = .144$), timepoint ($\beta = 36.34, p = .056$), or PHQ-9 $\times$ time interaction ($\beta = -2.47, p = .473$). This analysis suggests depressive severity did not meaningfully predict CSP duration across timepoints.

Exploratory Therapeutic Mechanism Analysis

To assess if treatment-related changes in CSP duration represented a possible therapeutic mechanism, a robust regression model was conducted examining associations between change in CSP (Δ CSP) and change in depressive symptoms (Δ PHQ-9) from pre- to post-treatment. Although not statistically significant, the association approached significance ($\beta = 0.073, p = .097, 95\% \text{ CI } [-0.013, 0.160]$), suggesting a possible trend wherein greater CSP increases were weakly associated with greater symptom improvement. This observation suggests that, although CSP changes may not be the primary mechanism of symptom improvement, there may be a trend indicating that individuals who experienced greater increases in CSP also showed more substantial reductions in depressive symptoms. However, it is important to note that this finding is modest and not statistically significant, and further investigation with a larger sample size is needed to clarify the relationship. Complete model outputs are provided in **Supplementary Materials**. **Fig. 15** depicts the robust regression model results, which explore the association between changes in CSP and depressive symptoms (Δ CSP and Δ PHQ-9), highlighting the trends observed in the data.

Table 9: Robust Regression Model.

Variable	Coefficient	Std. Error	z-value	p-value
Intercept	7.117	1.178	6.042	<0.001
Δ CSP Duration	0.073	0.044	1.662	0.097

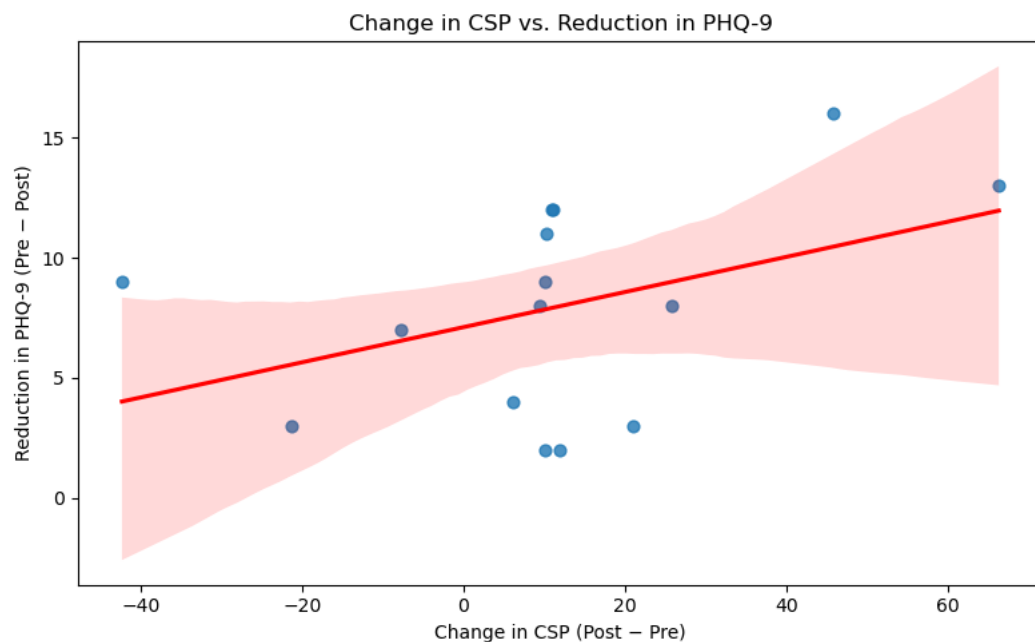


Figure 15: Scatterplot showing change in CSP and change in PHQ-9. Scatterplot showing the relationship between the change in CSP from pre- to post-treatment and the reduction in PHQ-9 scores. The red regression line indicates a positive trend, with the shaded area representing the confidence interval.

DISCUSSION

This study investigated whether CSP duration might serve as a biomarker of treatment response or mechanism of therapeutic change in individuals with TRD undergoing neuromodulatory interventions. Overall, the data show a substantial reduction in depressive

symptoms, as indicated by the mean PHQ-9 scores, which decreased from 18.6 at baseline to 9.07 at follow-up for the combined group. This reduction is consistent across both treatment modalities, with the esketamine group showing a more pronounced improvement, achieving a mean PHQ-9 score of 6.5, compared to the rTMS group, which showed a post-treatment score of 10.6. These findings suggest that both treatments are effective in reducing depressive symptoms, with esketamine potentially yielding a more significant improvement.

Similarly, CSP duration increased from a baseline mean of 82.85 ms to 101.9 ms post-treatment, with both treatment groups showing an increase in CSP duration, which aligns with the expected neurophysiological response to these interventions. However, the change in CSP duration did not correlate with symptom improvement, indicating that while both CSP duration and depressive symptoms change following treatment, the relationship between these changes remains complex and warrants further investigation.

The primary hypothesis was that baseline CSP duration, as a marker of cortical inhibition, would predict symptom improvement following treatment, while the secondary hypothesis posited that changes in CSP duration during treatment would correlate with changes in depressive symptoms. While the results support the hypothesis that baseline CSP duration is a potential predictor of symptom change, the relationship between CSP and treatment response remains inconsistent across different models, underscoring the complexity of identifying reliable biomarkers for TRD. In adjusted models, baseline CSP duration significantly predicted post-treatment depressive symptom severity, and a significant CSP-by-time interaction in the mixed-effects model indicated that participants with longer CSPs at baseline tended to experience greater symptom reduction. These findings align with prior reports suggesting that greater cortical inhibition may reflect a neurophysiological state more responsive to neuromodulatory

interventions and enhance neuroplasticity (Poleszczyk et al., 2018)(Ghosal et al., 2020) (Appelbaum et al., 2022).

However, the effect was not consistent across all analyses. In the linear mixed-effects model, which examined depressive symptom severity over time, baseline CSP duration did not emerge as a significant main effect. This suggests that, although baseline CSP may play a role in determining symptom change, it does not fully account for the individual variability observed in treatment response. Similarly, although change in CSP duration showed a modest trend toward predicting symptom improvement, this association was not statistically significant. These conflicting findings between models likely arise from fundamental differences in the methods used to analyze the data. The ANCOVA approach controls for baseline symptoms at a single time point, reflecting a snapshot of symptom severity, and therefore, it only captures the influence of baseline CSP on post-treatment severity. In contrast, the mixed-effects model accounts for changes in symptoms over time and emphasizes the trajectory of symptom change. This dynamic approach allows for the consideration of individual variability and the timing of treatment effects, which may be a more accurate reflection of how baseline CSP relates to symptom progression. Consequently, while baseline CSP predicts higher post-treatment depressive symptom severity in the ANCOVA, it is not significant in the mixed-effects model that incorporates symptom change over time. These methodological differences may explain the apparent contradiction, suggesting that baseline CSP's predictive power could vary depending on the analytic approach. These null results underscore the limited explanatory power of CSP alone and suggest that its clinical utility may depend on additional moderating factors or patient-specific contexts.

The secondary hypothesis, that changes in CSP during treatment would correlate with changes in depressive symptoms, was not fully supported. While a modest trend toward a significant association between changes in CSP duration (Δ CSP) and changes in depressive symptoms (Δ PHQ-9) was observed, this relationship was not statistically significant, suggesting that the therapeutic effects of rTMS and esketamine may not be directly reflected in changes in CSP. This is consistent with findings from other studies that have reported weak or inconsistent associations between neurophysiological markers and clinical outcomes following neuromodulatory treatment (Voineskos et al., 2016). It is important to note that changes in CSP duration may not be a direct mechanism of symptom improvement but may instead represent broader alterations in cortical excitability or inhibition that interact with multiple treatment-related processes. Moreover, the potential therapeutic mechanism underlying the observed change in CSP remains unclear. While CSP is thought to reflect cortical GABAergic inhibition, a crucial system implicated in depression, the relationship between changes in CSP and clinical improvements is likely influenced by the complex and multifactorial nature of TRD. Both rTMS and esketamine aim to modulate brain circuits implicated in depression, but they do so through different neurochemical pathways. TMS modulates cortical excitability through electromagnetic pulses, while esketamine modulates glutamatergic neurotransmission via NMDA receptor antagonism. The differing mechanisms of action may explain the lack of a direct link between changes in CSP and depressive symptom reduction, highlighting the need for further exploration of the interactions between GABAergic and glutamatergic systems in depression (Duman & Aghajanian, 2012). Additionally, given the modest sample size, the study may have been underpowered to detect small but meaningful effects, particularly in exploratory models examining change trajectories.

Nevertheless, the observed interaction between CSP and time in predicting symptom reduction supports ongoing investigation into inhibitory tone as a feature of treatment responsiveness. CSP is thought to reflect the integrity of cortical GABA_B circuits, with longer durations suggesting more intact inhibitory control (McDonnell et al., 2006). In this context, individuals with longer CSP durations may possess more adaptive neurophysiological substrates, potentially enabling greater responsiveness to interventions that recalibrate E/I balance, such as rTMS or ketamine. These findings build on mechanistic theories suggesting that modulation of GABAergic tone may play a role in recovery from depression and offer preliminary evidence that CSP could index such capacity. However, prior literature on CSP in depression has been mixed. Fitzgerald et al. (2004) reported longer CSP durations in individuals with MDD who did not respond to rTMS, contrasting with the more favorable outcomes observed here. Discrepancies across studies may reflect methodological differences, sample heterogeneity, or inconsistencies in how CSP is quantified. The results suggest that CSP, while potentially valuable, should not yet be interpreted as a stand-alone biomarker, and future work should consider combining it with other markers (e.g., resting-state connectivity, SICI, clinical phenotypes) to improve predictive accuracy.

Several limitations warrant mention. First, the sample size was small and limited by time-sensitive recruitment, and while results were directionally consistent across models, not all reached statistical significance. The study lacked randomization, which may have introduced potential biases. For example, patients receiving esketamine may present with different clinical characteristics than those receiving rTMS, and these differences may have influenced treatment outcomes. The absence of treatment stratification in the analysis further complicates the interpretation of the results, as the efficacy of CSP as a predictor may vary between treatments.

Manual scoring of CSP introduces potential measurement error, and EMG artifacts may have impacted trial inclusion. The naturalistic design also precludes random assignment to treatment modality, raising the possibility of confounding by indication. Finally, the study focused on short-term symptom change, and longer follow-up may be necessary to assess the persistence of CSP-related effects. Future research should seek to replicate these findings in larger, more diverse TRD cohorts, ideally using randomized treatment designs. Incorporating multimodal biomarkers, exploring moderators (e.g., sex, age, medication status), and extending assessments beyond the motor cortex may also enhance interpretability. Longitudinal analyses tracking CSP and symptom dynamics over the full course of treatment could clarify whether CSP changes precede or follow clinical improvements, strengthening mechanistic inference.

In conclusion, this study provides preliminary evidence that baseline CSP duration may be associated with symptom improvement following neuromodulatory treatment in TRD. However, its utility as a mechanistic or predictive biomarker remains uncertain. While CSP holds theoretical promise as a scalable, physiology-based tool, further research is needed to delineate its specificity, clinical relevance, and integration with other indices of treatment response.

CONCLUSION

This study provides preliminary evidence that baseline CSP duration may be associated with clinical improvement following neuromodulatory interventions in treatment-resistant depression. While longer CSP at baseline was linked to greater symptom reduction over time, CSP was not consistently related to depression severity or treatment-induced change, and several models yielded null results. These findings suggest that CSP may capture aspects of cortical inhibition relevant to treatment responsiveness, but its utility as a standalone predictive or

mechanistic biomarker remains limited. Further research is needed to clarify its role within a broader set of neurophysiological and clinical indicators guiding personalized treatment in TRD.

Chapter 3 has been submitted for publication in *Clinical Neurophysiology*. The dissertation author was the primary investigator and first author of this manuscript, and the co-authors provided mentorship, conceptual guidance, neurophysiological training and support, methodological input, and/or critical feedback on the work.

DISSERTATION DISCUSSION AND SYNTHESIS

The overarching aim of this dissertation was to enhance the understanding and prediction of treatment response in individuals with TRD receiving neuromodulatory interventions, specifically repetitive rTMS and esketamine. Given the complexity and clinical heterogeneity inherent to TRD, identifying reliable predictors and developing robust predictive models are critical to optimizing therapeutic outcomes and personalizing treatment strategies. To achieve these objectives, three complementary studies were conducted, each uniquely contributing to the broader goal of delineating clinical, demographic, and neurophysiological factors associated with neuromodulatory treatment response. Collectively, these studies aimed to improve the precision and efficacy of treatment selection, ultimately reducing symptom burden and enhancing the quality of life for individuals affected by this challenging and debilitating condition.

Common Themes

Several consistent themes emerged across the three studies presented in this dissertation. First, patient-specific characteristics consistently influenced treatment outcomes, reinforcing the need for personalized treatment selection. Psychiatric comorbidities, particularly anxiety disorders, were reliably associated with poorer outcomes across modalities, consistent with prior findings that comorbid anxiety often attenuates antidepressant efficacy and complicates the course of depression (Coplan et al., 2015; Hirschfeld, 2001). These results echo growing calls for transdiagnostic frameworks that address overlapping symptomatology rather than siloed treatment approaches (T. Insel et al., 2010). Similarly, the presence of trauma history exhibited inconsistent predictive value, enhancing rTMS outcomes in some contexts while showing minimal effects in others, suggesting that trauma's role may interact with factors such as

chronicity, dissociation, or neurobiological adaptation, which remain underexplored.

Concomitant medication use, particularly benzodiazepines and antipsychotics, consistently predicted diminished treatment response. These findings align with prior work suggesting that GABAergic agents such as benzodiazepines may interfere with neuroplasticity mechanisms crucial for the efficacy of rTMS and esketamine (Vashchinkina et al., 2014). The observed negative impact of antipsychotics may reflect dopaminergic antagonism counteracting reward and motivation circuits implicated in depression recovery (Costello et al., 2024). These results support recommendations for cautious pharmacological optimization prior to initiating neuromodulation. Discussion of each of these is expanded upon in the next section.

Second, important distinctions emerged in treatment trajectories between rTMS and esketamine. As observed in this dissertation, esketamine was associated with rapid symptomatic improvement--consistent with Phase III trials reporting significant reductions in depressive symptoms within 24 hours (Popova et al., 2019). In contrast, rTMS exhibited a slower yet more sustained course of improvement, paralleling patterns reported in large observational cohorts and meta-analyses (Berlim et al., 2014; Carpenter et al., 2012). These timing differences are clinically relevant, especially in triaging patients with SI or urgent symptom burden, where esketamine may offer a more appropriate front-line intervention. Conversely, rTMS may be more suitable for patients with chronic symptomatology, comorbidities, or preferences for non-pharmacological treatment options.

Third, the exploration of a neurophysiological biomarker, the CSP, highlighted both promise and limitations of using such indices in predicting treatment outcomes. CSP was found to associate with treatment outcomes in some models, yet its predictive consistency was limited. This mixed utility reflects broader challenges in psychiatry regarding the clinical translation of

neurophysiological biomarkers, where signal variability and inter-individual differences complicate single-marker interpretations (Drysdale et al., 2017; Olbrich & Arns, 2013). Recent studies have proposed that instead of reflecting a fixed inhibitory state, CSP may index cortical adaptability, resonating with emerging views that neuroplastic potential, rather than baseline activation alone, better predicts treatment response (Kraus, Wasserman, et al., 2019). As such, CSP may hold greatest utility within a multimodal framework rather than as a standalone predictor. This will also be expanded upon in a later section of this synthesis.

Beyond these thematic domains, the methodological rigor embedded across the studies, particularly the application of ML and survival analysis, enabled a more nuanced modeling of response trajectories and interactions. ML models allowed for the identification of complex, nonlinear patterns in a large clinical dataset, overcoming the limitations of traditional linear regression approaches (Chekroud et al., 2016; Orrù et al., 2012). Likewise, survival analysis provided essential insights into the temporal dynamics of treatment response, which are frequently neglected in static outcome models. Importantly, this dissertation emphasized the value of using real-world data to enhance generalizability and clinical applicability. The reliance on EMR reflects a growing trend in psychiatry toward practice-based evidence, where the richness of naturalistic clinical data can inform predictive modeling and decision support tools (Oliver et al., 2024). These findings collectively support the shift toward multimodal, integrative approaches. As no single variable class (i.e., clinical, demographic, or neurophysiological) proved sufficient on its own, the future of personalized psychiatry will likely depend on hybrid models that combine multi-domain information to enhance accuracy and applicability (Fernandes et al., 2017; Kapur et al., 2012). Together, these themes not only reinforce the complex

heterogeneity inherent to TRD but also point to viable avenues for optimizing care through more tailored and comprehensive evaluation strategies.

Integrated Analysis of Predictive Factors

The integrated analysis of predictors across studies in this dissertation revealed several consistent and divergent variables influencing treatment outcomes. Among consistent findings, anxiety comorbidity emerged as a reliable negative predictor of response to both rTMS and esketamine. This observation aligns with previous literature indicating that co-occurring anxiety disorders often attenuate antidepressant treatment efficacy and complicate symptom resolution (Fava et al., 2008). Anxiety may interfere with the engagement of prefrontal regulatory systems targeted by neuromodulation, thus reducing the likelihood of full clinical response. Tobacco use history also revealed a consistent and somewhat unexpected association: former tobacco use was linked to improved outcomes in rTMS-treated individuals. While the mechanisms underlying this finding remain unclear, it may reflect neuroadaptive changes related to dopaminergic modulation or altered cortical excitability among individuals with past nicotine exposure, possibilities suggested in prior studies exploring the neuromodulatory effects of nicotine (Subramaniam & Dani, 2015). Pharmacological variables, particularly current benzodiazepine and antipsychotic use consistently predicted poorer treatment outcomes across studies. These results are supported by prior work demonstrating that benzodiazepines may dampen the neuroplasticity mechanisms central to both rTMS and esketamine efficacy. Similarly, the dopaminergic antagonism associated with antipsychotic medications may counteract therapeutic neuromodulatory effects, particularly in brain regions implicated in motivation and reward processing.

In addition to these consistent predictors, several variables demonstrated divergent or context-dependent predictive value. Trauma history, for example, predicted better outcomes in the rTMS cohort within a large retrospective dataset, but did not demonstrate significant predictive effects in smaller prospective esketamine samples. This discrepancy may reflect differences in how trauma-related neural adaptations interact with each treatment's mechanisms of action. rTMS may preferentially engage prefrontal-limbic circuits affected by trauma exposure, enhancing top-down regulation, whereas esketamine's rapid glutamatergic modulation may not engage these pathways in the same targeted manner (Bremner et al., 2008; Philip et al., 2018).

In sum, this integrated analysis of predictive factors illustrates the multifaceted nature of treatment response in TRD. While some variables, such as anxiety comorbidity and benzodiazepine use, consistently predict poorer outcomes, others demonstrate differential effects based on modality, sample characteristics, and methodological approach. These findings reinforce the need for predictive models that are flexible, multimodal, and attuned to the complex interplay of clinical, demographic, neurophysiological, and contextual factors. Future research leveraging larger, diverse samples and hybrid modeling techniques may further clarify these relationships, contributing to more accurate and individualized treatment pathways.

Comparative Analysis of Treatment Modalities

The comparative analysis of treatment modalities across the second study underscores significant distinctions between rTMS and esketamine in their clinical trajectories and responsiveness in TRD. Notably, esketamine demonstrated a more rapid onset of antidepressant effects and overall higher response rates compared to rTMS. This rapid therapeutic response,

evident as early as within the first few treatments, aligns with previous clinical trial findings emphasizing esketamine's unique potential in acute symptom alleviation, particularly in cases involving severe depressive symptoms or acute suicidality (Daly et al., 2018; Popova et al., 2019). Such findings suggest esketamine's suitability in clinical scenarios where rapid intervention is paramount, providing clinicians with a critical option for immediate symptom management and stabilization (Canuso et al., 2018).

Conversely, rTMS demonstrated a comparatively gradual improvement trajectory, typically requiring several sessions before achieving clinically meaningful reductions in depressive symptoms. The therapeutic trajectory observed for rTMS was notably influenced by patient-specific factors such as comorbid anxiety, medication use, and the total number of sessions administered. These findings are consistent with prior research that characterizes rTMS as a cumulative intervention reliant upon incremental neural plasticity changes over time (Carpenter et al., 2012; Fitzgerald et al., 2016). Such incremental effects reinforce the importance of considering patient engagement, tolerability, and adherence when planning longer-term treatment regimens with rTMS.

This dissertation's findings additionally highlighted how specific comorbidities differentially impact these two treatment modalities. Anxiety disorders, consistently predicting poorer outcomes with rTMS in this dissertation and previously reported studies, appear to exert less influence on esketamine's efficacy (Fitzgerald et al., 2020)(Ionescu et al., 2014). This differential impact may stem from distinct neural mechanisms underlying each treatment; esketamine's rapid modulation of glutamatergic systems might effectively circumvent anxiety-related neural disruptions more readily than the slower, network-based adaptations targeted by

rTMS (Abdallah et al., 2018; Murrough et al., 2013). Thus, understanding comorbidity profiles becomes vital in selecting the optimal treatment modality.

An additional novel finding emerged concerning prior medication exposure, notably benzodiazepines and antipsychotics, which negatively impacted the efficacy of rTMS but exhibited less consistent influence on esketamine outcomes. This distinction aligns with prior work suggesting pharmacodynamic interactions between medications like benzodiazepines and neuroplasticity-promoting treatments such as rTMS (Hunter et al., 2019; Kaster et al., 2020). Such differential medication interactions underscore the clinical necessity for thorough pharmacological reviews when initiating neuromodulatory interventions, advocating for individualized medication adjustments that could optimize treatment response.

Furthermore, from a tolerability and patient acceptance standpoint, while esketamine's rapid response offers a distinct clinical advantage, its administration requirements, such as supervised settings due to acute dissociative side effects, contrast notably with the outpatient practicality and relatively minimal adverse effects of rTMS (George et al., 2010b; Popova et al., 2019). These practical considerations further emphasize the importance of individualized treatment matching not only based on symptom severity and urgency but also logistical, tolerability, and patient-preference aspects, enhancing adherence and ultimately, clinical outcomes. Overall, this comparative analysis delineates critical, clinically meaningful differences between rTMS and esketamine, emphasizing the necessity for personalized treatment selection strategies informed by comprehensive patient profiles, symptomatology, comorbidities, and practical considerations. Such nuanced understanding facilitates optimized clinical decision-making and aligns closely with emerging frameworks in precision psychiatry (A. D. Krystal et al., 2020; Williams et al., 2016).

Neurophysiological Biomarkers and Clinical Integration

The clinical implications derived from the comparative analyses and integrated findings across the dissertation are significant, underscoring the necessity of individualized treatment approaches based on specific patient profiles, clinical urgency, and therapeutic goals. Tailored treatment selection becomes particularly important given the distinct temporal response patterns and differing mechanisms of action observed between esketamine and rTMS. Esketamine's rapid onset and higher immediate response rates position it favorably as a frontline option for patients with severe depressive symptoms, acute suicidality, or clinical scenarios necessitating swift therapeutic action. This rapid therapeutic window is particularly relevant in acute inpatient or crisis-intervention settings, where timely symptom management can drastically influence immediate patient safety and subsequent clinical trajectory (Sams et al., 2023).

In contrast, rTMS offers a distinct profile of incremental and sustained symptom improvement over longer treatment courses, aligning it with clinical scenarios where a less urgent, yet robust and enduring, therapeutic effect is sought. This profile is particularly beneficial for outpatient or ambulatory settings, where adherence, tolerability, and patient convenience play pivotal roles in successful treatment implementation. Furthermore, the incremental nature of therapeutic gains with rTMS also provides the clinician an opportunity to iteratively evaluate response and adjust treatment protocols (e.g., adjusting stimulation frequency or coil positioning), potentially enhancing individualized outcomes (Fitzgerald et al., 2016).

These differential clinical profiles highlight the value of a precision psychiatry approach, whereby individual patient characteristics—including comorbid psychiatric conditions, previous medication histories, symptom severity, and risk profiles—inform selection of neuromodulatory interventions. Given the observed negative impact of anxiety comorbidities and certain

psychotropic medications on rTMS response, esketamine may warrant earlier consideration for some patients presenting with such complicating factors (Hunter et al., 2019). Conversely, individuals with fewer complicating clinical features and lower urgency for immediate symptom alleviation might be best served by initiating treatment with rTMS, leveraging its outpatient practicality and favorable side effect profile.

Additionally, this dissertation considered whether neurophysiological measures, notably CSP, may eventually serve as adjunctive tools in treatment decision-making. At present, the findings are too preliminary to support clinical application, but they suggest a possible direction for future integrative work. Assessing neurophysiological markers alongside clinical predictors may yield more accurate and clinically actionable models, potentially guiding clinicians toward the most promising therapeutic options for individual patients (Radhu et al., 2017).

Furthermore, the dissertation findings contribute to existing clinical guidelines and treatment frameworks by clarifying the practical nuances of treatment trajectories and outcomes in real-world settings. While randomized controlled trials (RCTs) remain critical, the real-world evidence presented here bridges important knowledge gaps regarding treatment effectiveness and clinical applicability outside controlled environments, where patient heterogeneity is substantial (Dunner et al., 2014; Trevizol et al., 2020). Thus, these findings advocate for the integration of predictive modeling and real-world data into routine clinical practice, aligning closely with contemporary goals in personalized psychiatry.

Neurophysiological biomarkers offer significant promise for enhancing the accuracy and specificity of predictive models for neuromodulatory interventions. Among such markers, CSP was evaluated in this dissertation as a candidate biomarker with potential clinical relevance. Baseline CSP was found to be associated with symptom improvement following treatment;

however, its predictive value demonstrated considerable variability, indicating a more nuanced and context-dependent role. This finding aligns with prior studies reporting inconsistent CSP predictability across different therapeutic contexts, suggesting that CSP's clinical utility may rely heavily upon integration with complementary measures rather than standing alone as a predictive indicator (Levinson et al., 2010).

One possible interpretation is that CSP may reflect broader aspects of cortical excitability. While CSP has traditionally been understood as a proxy for GABA_B-mediated cortical inhibition (Tremblay et al., 2013), findings from this dissertation propose a broader conceptualization: CSP may reflect cortical flexibility or resilience, properties indicative of an individual's neuroplastic and adaptive capabilities. This reframing positions CSP not merely as a simple inhibitory marker but as indicative of underlying cortical network adaptability, providing insights into individual responsiveness to neuromodulatory treatments. Such a perspective is consistent with emerging evidence in neurophysiology, where biomarkers reflecting neural adaptability and plasticity (rather than pure inhibitory or excitatory states) are increasingly recognized as pivotal in determining treatment response across psychiatric disorders (Voineskos et al., 2021).

Despite these potential implications, significant limitations to CSP's predictive capabilities persist. The complexity inherent to CSP, influenced by various neurophysiological, clinical, and methodological factors (e.g., muscle activation levels, cortical target selection, measurement protocols), likely contributes to its inconsistent predictive value (Farzan et al., 2013). Furthermore, CSP measurements reflect activity from predominantly motor cortical regions; thus, the extent to which motor cortex-based inhibition generalizes to neural circuits involved directly in mood regulation remains uncertain (Kaster et al., 2018; Radhu et al., 2017). This limitation highlights the importance of investigating additional neurophysiological

measures (e.g., TMS-EEG, resting-state EEG connectivity patterns) in future research to enhance the specificity and clinical applicability of predictive biomarker panels. Importantly, the complexity and partial predictive utility of CSP suggest that its integration with comprehensive clinical and EMR-derived predictors could yield more precise and actionable treatment-response models. This multimodal integrative approach is supported by prior research advocating combined clinical-neurophysiological prediction strategies to accurately delineate treatment-responsive phenotypes in TRD. Given that CSP alone has limited standalone utility, future studies are necessary to systematically investigate its combined predictive capacity with demographic variables, clinical severity measures, and medication history—ultimately informing more robust clinical decision-making tools.

In sum, CSP adds an exploratory neurophysiological dimension to this dissertation, but its predictive and mechanistic utility remains uncertain. Given the small sample, methodological constraints, and variable findings, CSP is best understood here as a preliminary signal that may warrant continued study alongside broader clinical and neurophysiological predictors..

Methodological Innovations and Clinical Decision-Making

This dissertation implemented methodological innovations designed to enhance clinical decision-making and bridge key gaps in the prediction of treatment response. Central among these innovations was the integration of ML models with routinely collected EMR data. The application of ML allowed for the exploration and identification of intricate, nonlinear relationships among clinical, demographic, and treatment-related predictors, surpassing conventional statistical approaches in accurately predicting patient outcomes. Leveraging ML algorithms, including random forests and gradient boosting models, permitted the extraction of

clinically actionable insights from complex, high-dimensional datasets commonly found in real-world psychiatric practice (Chekroud et al., 2016; Iniesta et al., 2016). This approach aligns with contemporary trends emphasizing the translation of data-driven insights into pragmatic clinical decision-support tools, underscoring the importance of personalized medicine in psychiatry (Dwyer et al., 2018; Koutsouleris et al., 2021).

Importantly, this dissertation highlighted rigorous model calibration and validation techniques, including internal cross-validation, permutation feature importance, and DCA, to ensure reliability, interpretability, and clinical relevance of findings. DCA was particularly valuable, as it quantifies the net clinical benefit of predictive models across a range of threshold probabilities, effectively guiding clinicians in weighing the potential harms and benefits of applying predictions in practice (Vickers & Elkin, 2006). These methodologies ensure that predictive models not only achieve statistical robustness but also translate meaningfully into actionable clinical guidance; an essential advancement over prior approaches, which often lack explicit evaluations of clinical utility.

Further, survival analysis methods, particularly Kaplan-Meier analyses, were employed to elucidate the temporal dynamics of treatment response and remission trajectories. Unlike traditional cross-sectional outcome measures, survival analyses provided nuanced insights into the onset and progression of therapeutic effects over time, distinguishing the rapid symptomatic alleviation observed with esketamine from the more gradual improvement patterns associated with rTMS. Such temporal insights are critical, enabling clinicians to establish realistic patient expectations, optimize treatment schedules, and intervene appropriately based on individualized therapeutic timelines (Sackeim et al., 2020). The inclusion of survival analyses represents a methodological advancement that addresses prior limitations of time-insensitive analytic

approaches commonly employed in neuromodulation research (Husain et al., 2004; Roth et al., 2021).

Together, the methodological innovations implemented in this dissertation (ML integration with EMR data, comprehensive model validation and clinical utility assessment via DCA, and sophisticated temporal modeling through survival analysis), represent significant contributions toward precision psychiatry. These methods not only improve predictive accuracy and clinical relevance but also highlight the feasibility and importance of translating complex, real-world data into practical tools for clinical decision-making, ultimately enhancing treatment personalization and patient outcomes in TRD.

Integrating neurophysiological biomarkers with clinical predictors presents a promising avenue toward refining treatment strategies in psychiatry, particularly within TRD. While CSP alone showed inconsistent predictive strength, integrating it with clinical profiles may illuminate nuanced differences among patients, guiding more personalized interventions. This aligns with prior studies suggesting that standalone neurophysiological markers often lack the robust predictive capacity required for clinical implementation, yet significantly improve predictive accuracy when embedded within multifactorial models (A. F. Leuchter et al., 2010).

The synthesis of CSP with clinical predictors could specifically aid in stratifying patients according to underlying neurobiological phenotypes, thus offering mechanistic insights into varying degrees of responsiveness to neuromodulation. For instance, longer CSP duration, indicative of enhanced cortical inhibition, might reflect a greater inherent capacity for neuroplastic changes, particularly in individuals without significant anxiety comorbidity or adverse medication influences. Such neurobiological subtyping would represent a critical advancement, addressing the prevalent challenge of heterogeneity within TRD populations that

currently complicates accurate response prediction and treatment planning. Future research should continue to expand these integrative predictive frameworks, incorporating additional neurophysiological measures, such as resting-state EEG power spectra, event-related potentials (ERP), or TMS-evoked potentials (TEPs), alongside clinical, demographic, and genetic predictors. By combining multidimensional datasets, predictive models can evolve to capture the full complexity of TRD, potentially achieving unprecedented accuracy and individualization in treatment recommendations.

Reconceptualizing Neurophysiology and Treatment: New Interpretations

This dissertation offers an opportunity to speculate on reframing traditional views on both the role of neurophysiological biomarkers and the conceptual underpinnings of neuromodulatory treatment within TRD. Specifically, the CSP's role warrants reconsideration beyond its classical interpretation as a direct biomarker reflecting cortical inhibition mechanisms. Instead, CSP may indicate a more comprehensive neurophysiological capacity for adaptive cortical plasticity or resilience. In line with contemporary theories that emphasize adaptability and plasticity as fundamental characteristics of effective therapeutic responses (Pascual-Leone et al., 2005), CSP duration may reflect cortical flexibility or the inherent ability of neural networks to undergo dynamic functional reorganization. Thus, a longer CSP might represent not simply increased inhibitory control but rather enhanced cortical adaptability—an attribute advantageous in responding to neuromodulatory treatments.

Extending this reconceptualization to the broader context of neuromodulatory treatments themselves, this dissertation proposes viewing these interventions not simply as treatments aimed at symptom alleviation, but as structured neurophysiological training programs that facilitate

long-term cortical and subcortical adaptability and resilience. This aligns with emerging perspectives in the literature, which emphasize that neuromodulation may promote sustained network-level adaptations leading to improvements in emotional regulation, cognitive function, and overall psychiatric resilience (Fox et al., 2012; Liston et al., 2014). Within this conceptualization, neuromodulation serves not merely as a passive therapeutic intervention but actively engages and recalibrates dysfunctional neural circuitry toward greater robustness and responsiveness (Cash et al., 2021; Siddiqi et al., 2021).

Further, adopting a "neural training" framework implies that therapeutic benefits extend beyond the period of active intervention, promoting enduring neuroplastic changes that enhance the brain's functional and structural adaptability. Such an expanded conceptual framework is supported by evidence demonstrating neuromodulation-induced neuroplasticity, reflected in increased synaptic density, improved connectivity patterns, and heightened cortical excitability in targeted regions (Vidal-Piñeiro et al., 2015)(Cirillo et al., 2017). Neuromodulatory approaches, therefore, could be better viewed as deliberate and targeted strategies for strengthening neural circuits involved in emotional regulation and cognitive control, subsequently bolstering the overall resilience of the brain to psychiatric distress and relapse (Duman et al., 2016; Krystal et al., 2019). Ultimately, reconceptualizing CSP and neuromodulation through this broader neurophysiological lens underscores the potential for these therapeutic strategies not merely to reduce depressive symptoms temporarily, but to fundamentally reorganize and strengthen neural architecture in a manner analogous to physical training. Future clinical and translational research guided by this innovative perspective could further elucidate mechanisms of therapeutic action, refine intervention strategies, and improve long-term clinical outcomes.

Dissertation's Unique Contribution

This dissertation provides several distinct and novel contributions that significantly advance our understanding of predictors of treatment response in treatment-resistant depression, extending well beyond the findings of the individual studies themselves. Critically, this work uniquely integrates multiple sophisticated methodological approaches, including real-world clinical data extraction, advanced ML techniques, survival analysis methods, and neurophysiological biomarkers, into a coherent and clinically actionable predictive framework. Prior studies have often utilized isolated methodologies or limited data types, restricting their clinical relevance and generalizability (Inieta et al., 2016; Chekroud et al., 2016). In contrast, this dissertation's multi-dimensional approach bridges these gaps by synthesizing diverse sources of predictive information, thereby creating a comprehensive and nuanced predictive model capable of accommodating complex, individualized patient profiles.

The integration of extensive EMR data with advanced ML algorithms represents another key innovation. Although ML has increasingly been applied within psychiatric research, its clinical applicability has frequently been limited by inadequate real-world validation and poor integration with existing clinical decision-making protocols (Chekroud et al., 2021; Torous et al., 2021). This dissertation uniquely addresses these limitations through rigorous validation and calibration processes, enhancing the clinical utility of predictive models by ensuring they can be effectively implemented within routine psychiatric practice. DCAs further demonstrate the clinical relevance of these models, providing tangible insights into their real-world utility by explicitly quantifying clinical benefit across various patient populations and treatment thresholds (Vickers et al., 2019).

Moreover, this dissertation distinctively combines sophisticated statistical methods, including survival analyses, with longitudinal data to elucidate the temporal dynamics of

treatment response, which are critically relevant for clinical decision-making but frequently overlooked in standard predictive modeling approaches (Rush et al., 2006; Trivedi et al., 2006). By highlighting differential treatment trajectories, the current work offers clinicians a valuable temporal dimension for selecting the most appropriate neuromodulation approach based on urgency and anticipated treatment timeline. Finally, the inclusion of neurophysiological markers, specifically CSP, within the predictive framework further enhances this dissertation's novelty. Neurophysiological measures have traditionally been studied separately from clinical predictors, and few studies have effectively integrated these domains into a cohesive clinical decision-making model (Farzan et al., 2016; Tremblay et al., 2019). By explicitly incorporating CSP within broader predictive modeling, this dissertation underscores the potential for neurophysiological biomarkers to refine predictions of individual treatment responsiveness, thereby advancing personalized medicine approaches in psychiatry.

Limitations

Several dissertation-level limitations should be considered when interpreting the findings across this dissertation. Most importantly, the studies relied largely on retrospective, naturalistic, and open-label clinical data, and patients were not randomized to treatment condition. In particular, individuals were not randomly assigned to rTMS versus esketamine, but instead represented clinically derived treatment groups shaped by provider judgment, patient preference, treatment history, access, and other real-world factors. As a result, between-group differences should not be interpreted as evidence of causal superiority of one intervention over another. These designs also introduce the possibility of self-selection effects, expectation effects, and confounding by indication, all of which may have influenced treatment trajectories and

outcomes. In open-label clinical settings, apparent treatment effects may also differ from those observed in randomized controlled trials, where tighter control over treatment allocation and expectancy-related influences can reduce the magnitude of observed effects.

At the same time, these real-world designs provide an important complementary strength. Unlike tightly controlled randomized trials, naturalistic open-label studies capture the heterogeneity, treatment complexity, and decision-making processes that characterize routine interventional psychiatry practice. This enhances ecological validity and offers clinically relevant information about how these interventions function in actual care settings, including among patients who may be excluded from more controlled trials. Thus, the present findings are best understood not as replacements for randomized controlled trials, but as complementary evidence that may be especially informative for real-world clinical decision-making.

Additional limitations are worth noting across the individual studies. The CSP findings should be interpreted with particular caution given the small neurophysiology sample, limited statistical power, and the still-emerging nature of this literature. Accordingly, CSP is best understood here not as a definitive standalone biomarker, but as a preliminary and exploratory neurophysiological signal that warrants continued investigation within broader multimodal predictive frameworks. More broadly, retrospective EMR-based research is constrained by variability in documentation quality, incomplete data capture, and imperfect standardization of assessment timing and treatment delivery, all of which may have introduced measurement error or residual confounding.

If conducted prospectively, this work would ideally incorporate standardized assessment intervals, larger neurophysiology samples, more harmonized treatment protocols, and comparative designs that better address baseline group differences. Where feasible, randomized

or otherwise more tightly controlled studies would strengthen causal interpretation; where randomization is not feasible, prospective observational studies with stronger adjustment for treatment selection factors would represent an important next step.

Future Directions

Future research efforts should aim to validate and extend the integrated predictive framework developed in this dissertation through prospective, multi-modal, and mechanistically grounded investigations. While the current studies demonstrate strong retrospective associations between clinical, demographic, and neurophysiological predictors and treatment outcomes, their predictive value must be tested in prospective and randomized settings to establish real-world clinical utility. Validation of machine learning-derived models in independent cohorts—ideally across multiple treatment centers—would provide critical evidence for their generalizability and scalability in clinical practice (Inieta et al., 2016; Chekroud et al., 2021). Randomized trials that stratify patients based on model-derived risk or response profiles may also offer a pathway for testing personalized treatment allocation strategies, thereby advancing precision psychiatry.

In addition to replication, future research should incorporate a broader array of potential predictors to further refine and optimize predictive accuracy. Multimodal data integration, including genetic markers, structural and functional neuroimaging, cognitive functioning, and psychosocial variables, holds promise for deepening our understanding of the biopsychosocial mechanisms underlying treatment response. Polygenic risk scores, for example, have been linked to antidepressant outcomes and could be used to augment existing clinical predictors (Garcia-Gonzalez et al., 2017). Similarly, neuroimaging markers such as reduced prefrontal-limbic connectivity or altered default mode network activity have been associated with treatment

resistance and may provide additional mechanistic insight when integrated into predictive models (Drysdale et al., 2017; Fonzo et al., 2019). Longitudinal designs will also be essential to clarify the temporal dynamics between neurophysiological changes, such as shifts in CSP duration, and symptom trajectories. While this dissertation suggests that CSP may serve as a marker of treatment responsiveness, its stability over time and sensitivity to intervention remain insufficiently characterized. Repeated CSP assessments during and after treatment could help determine whether changes in cortical inhibition precede, coincide with, or follow clinical improvements, offering mechanistic clues about the causal role of neurophysiological plasticity in depression recovery (Tremblay et al., 2019; Sun et al., 2022).

Finally, future studies should explore the utility of predictive profiles in guiding combined or adjunctive treatment approaches. For example, patients identified as partial responders based on predictive modeling might benefit from integrated protocols involving pharmacotherapy, neuromodulation, and psychotherapy. Trials testing such tailored interventions could help optimize outcomes while minimizing unnecessary treatment exposure. Similarly, stratified augmentation strategies, such as combining rTMS with psychotherapy in patients with high levels of cognitive-affective comorbidity, could be developed using data-driven profiles (Berlim et al., 2013; Carpenter et al., 2021). Such approaches would mark a shift from one-size-fits-all psychiatry toward stratified and adaptive treatment planning rooted in individualized neurobiological and clinical risk. To translate the predictive frameworks developed in this dissertation into clinical practice, it will be crucial to integrate these models into a clinical decision support system (CDSS) that interfaces with EMR. Such a system could automatically flag patients who are likely to benefit from specific treatments, based on their clinical, demographic, and neurophysiological profiles. For example, a CDSS could prompt clinicians to

consider conducting a CSP test for patients exhibiting certain predictors, such as a history of trauma or comorbid anxiety, helping to guide decisions between esketamine and rTMS. Additionally, the system could assist in scheduling follow-up assessments or informing adjustments in treatment plans, such as recommending more intensive neuromodulation or adjunctive psychotherapy for patients showing slower response trajectories. By incorporating real-time data and predictive models into the clinical workflow, these systems could offer personalized treatment pathways that align with each patient's unique treatment response profile, ensuring more targeted, efficient care. Implementing such a system would facilitate timely and data-driven decisions, enhancing treatment outcomes while reducing unnecessary treatment exposure.

Taken together, these future directions underscore the importance of continued methodological innovation, multi-modal integration, and translational implementation to refine predictive models and maximize their clinical utility in the treatment of TRD.

CONCLUSION

This dissertation presents a comprehensive, multi-pronged investigation into the predictors of treatment response in individuals with TRD undergoing neuromodulatory interventions. Across studies, the most consistent contribution of this dissertation is the demonstration that treatment response in TRD is heterogeneous and can be meaningfully informed by real-world clinical characteristics, treatment trajectories, and integrative analytic methods. The strongest findings emerged from the use of EMR-derived clinical data and time-sensitive modeling approaches, which together offer a more practical foundation for personalized treatment selection in routine care. The CSP findings add an exploratory neurophysiological

component to this work, but should be interpreted cautiously given the limited sample size and preliminary nature of the evidence. Through retrospective analyses of real-world EMR data, ML applications, survival analyses, and neurophysiological assessments, this dissertation highlights the value of converging evidence across modalities to inform personalized treatment strategies.

Collectively, these studies underscore the critical importance of tailoring neuromodulation-based interventions to the unique clinical profiles of patients. Findings suggest that response likelihood can be meaningfully estimated through combinations of accessible variables such as comorbidity burden, medication use, and functional status—enhancing the clinical feasibility of predictive tools. Moreover, the exploration of CSP adds a preliminary neurophysiological dimension to this dissertation. However, given the small sample, inconsistent findings, and early stage of this literature, CSP should be interpreted cautiously and not as a clinically established biomarker.

This dissertation contributes to the evolving field of precision psychiatry by demonstrating that predictive models grounded in real-world clinical and neurophysiological data can support more informed and individualized treatment selection. The methodological innovations employed—particularly the combination of survival analysis and machine learning in EMR data—reflect a pragmatic yet forward-thinking approach to psychiatric research. Ultimately, by identifying key predictors of response and proposing integrative, mechanistic frameworks for understanding neuromodulatory efficacy, this work lays the groundwork for more adaptive, personalized, and outcome-driven care pathways for patients with TRD.

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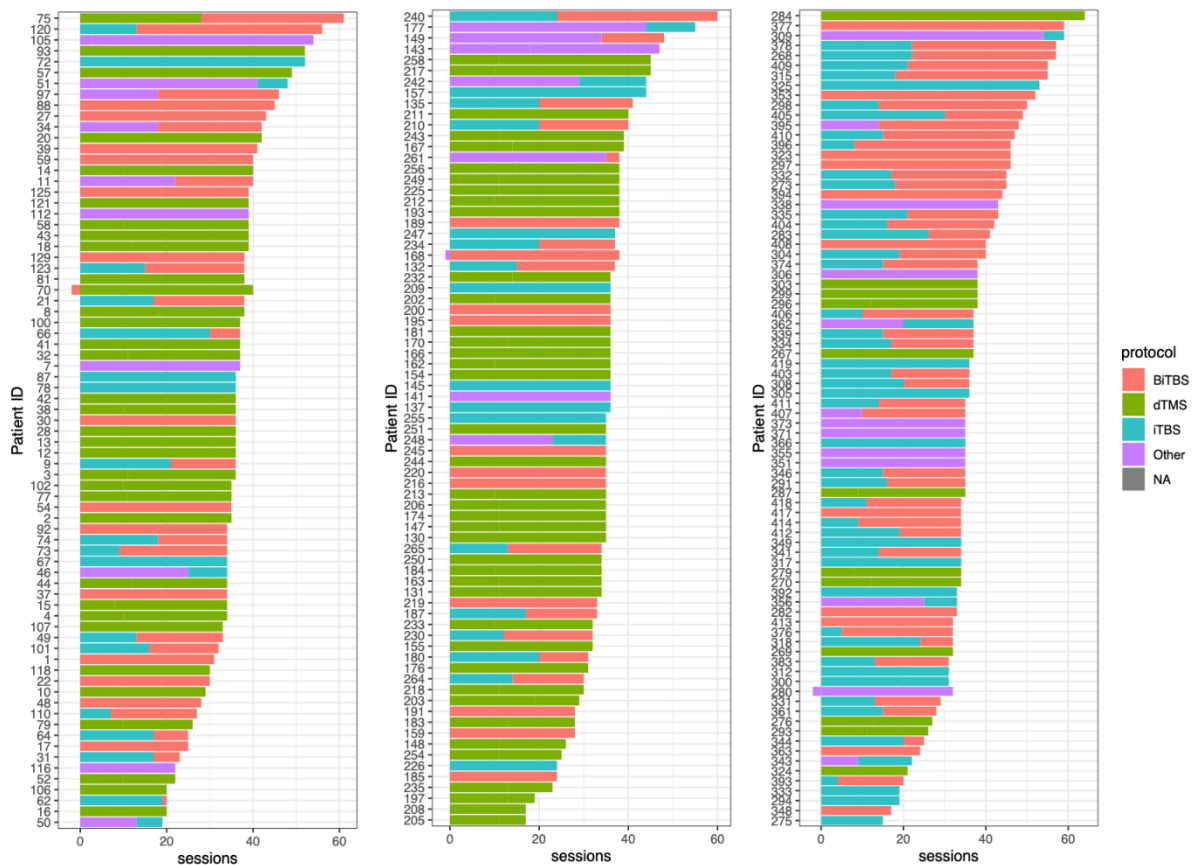
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APPENDIX

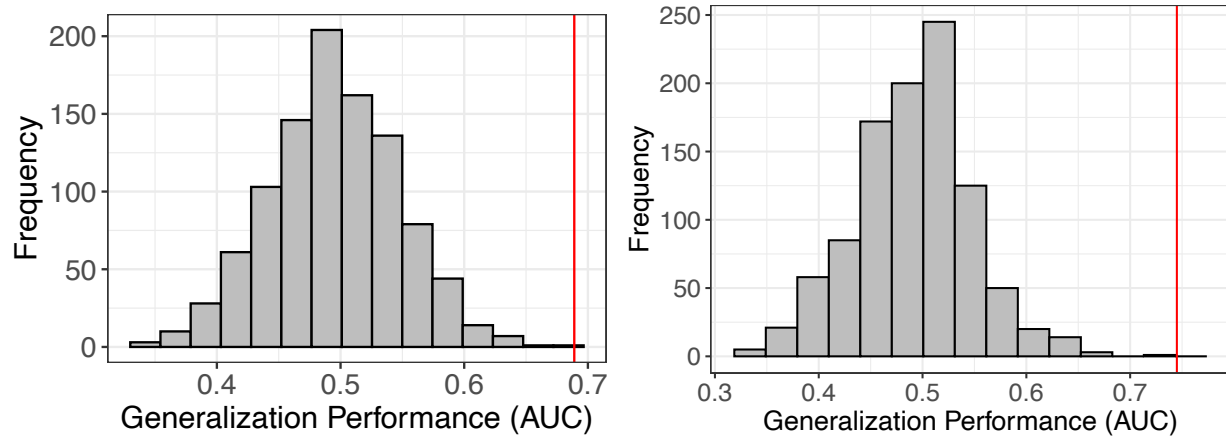
Chapter 1 Supplementary Materials

Coding and Categorization of Psychopharmacological Treatment Variables:

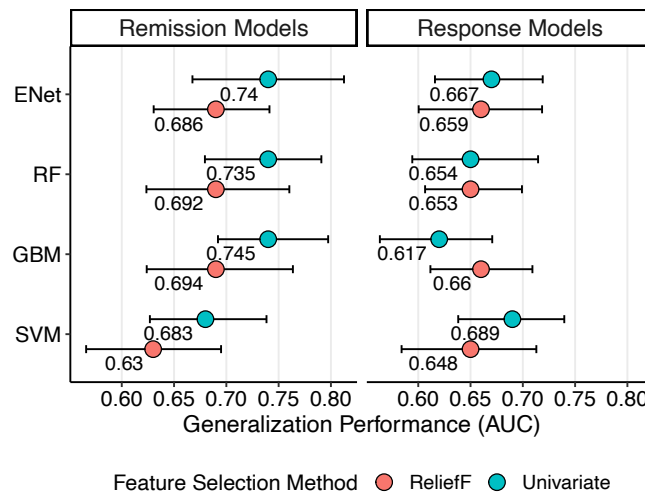
Psychopharmacological treatment variables were recorded as binary indicators of concurrent use (coded as 1 for prescribed, 0 for not prescribed), and a daily dose burden was calculated for each category based on prescribed daily defined doses (DDD). Drug categories included antidepressants, benzodiazepines, non-benzodiazepine sedatives, anxiolytics, antipsychotics, lithium, non-lithium mood stabilizers, stimulants, opioids, and other psychopharmacological medications.



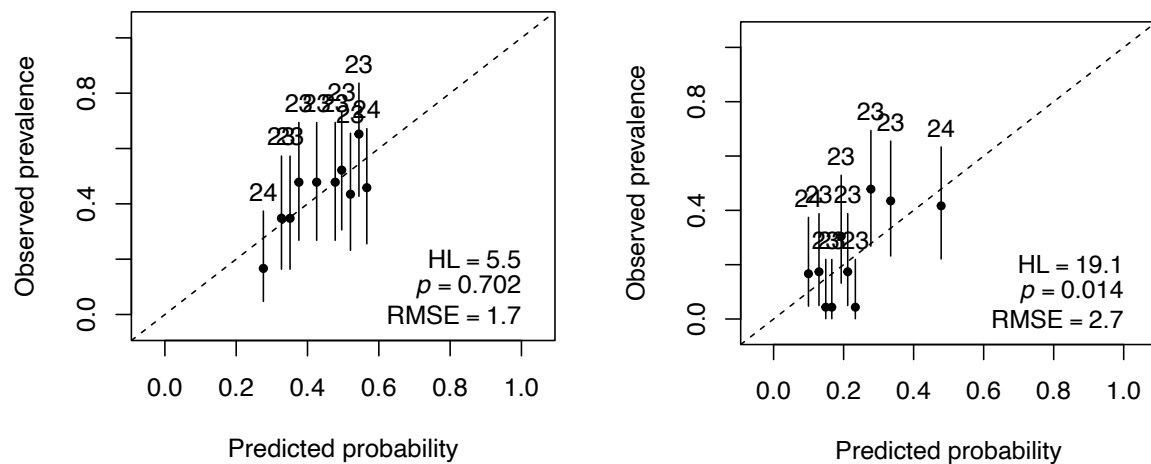
Supplemental Figure 1: rTMS protocol sequencing for all 232 patients included in the analytic sample. Within-patient changes in protocol are indicated by changes in color, and changes in the number of trains delivered per pulse within the same rTMS protocol are indicated by a broken line within the same color.



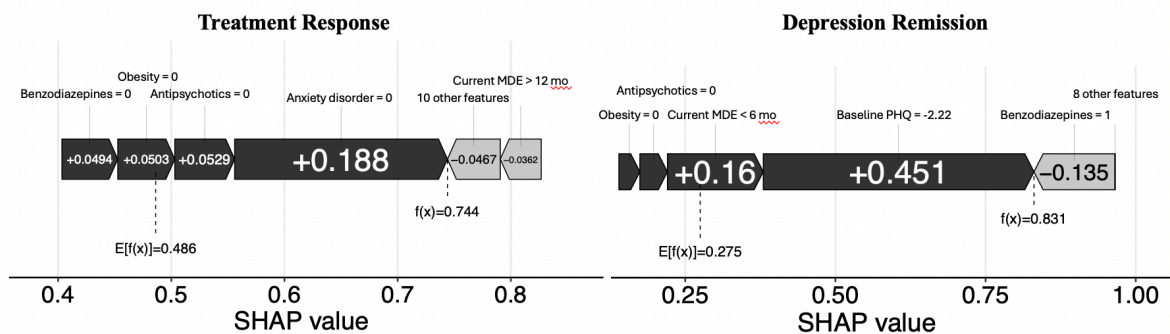
Supplemental Figure 2: Permutation testing (B=99) of selected SVM classifier for treatment response (left, a) and the selected GBM classifier for depression remission (right, b). Red vertical line indicates generalization performance for classification (AUC) models with unpermuted data. Statistical significance is determined by the proportion of permuted samples (p) with superior AUC values relative to the true model (i.e., $p / 100$).



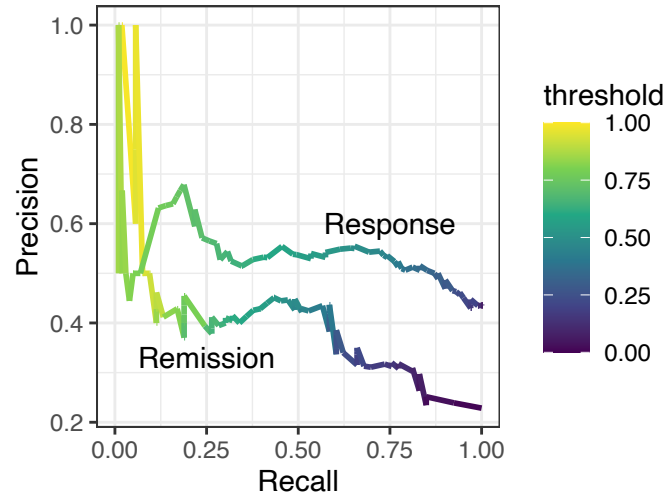
Supplemental Figure 3: Mean generalization performance and 95% confidence intervals across (left panel) classification models in discriminating rTMS treatment remitters from non-remitters and (right panel) classification models in discriminating responders from non-responders. Results based on 20-(outer)fold nested cross-validation. Models using feature selection with univariate filters and ReliefF-based algorithms are shown in blue and red, respectively. SVM: support vector machine. RF: random forest. RFR: random forest regression. ENet: elastic net. GBM: gradient boosted machines. AUC: receiver operating characteristic area under the curve.



Supplemental Figure 4: Calibration plots for the SVM classifier for treatment response (left, a) and the GBM classifier for depression remission (right, b). Predicted probabilities were calibrated using beta regression and binned into deciles (x-axis), then compared against observed probabilities within each bin (y-axis). Hosmer-Lemeshow (HL) test statistic shown to assess goodness-of-fit, as well as root mean squared error (RMSE). P-value derived from HL test.

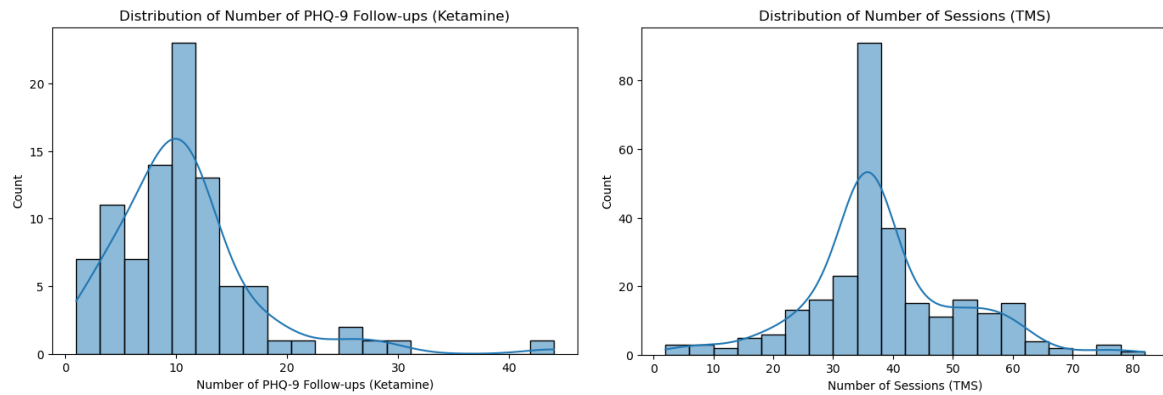


Supplemental Figure 5: SHAP force plots illustrating the additive contribution of individual features to the expected treatment response (a) or depression remission (b) probability for a representative patient from the analytical sample. Features shown in dark grey contribute positively to the patient's response/remission probability, whereas those shown in light grey contribute negatively. (a) The sample mean expected treatment response probability, $E[f(x)]$, is approximately 0.486 (or 48.6%), whereas for the depicted patient, without benzodiazepines, obesity, antipsychotic medication, or a comorbid anxiety disorder, but with a current major depressive episode (MDE) > 12 mo., their expected response probability, $f(x)$, is 0.744 (or 74.4%). (b) The sample mean expected depression remission probability, $E[f(x)]$, is approximately 0.275 (or 27.5%), whereas for the depicted patient, without obesity, antipsychotic medication, a current MDE < 6 mo., and a baseline PHQ-9 score that is 2.22 SD below the sample mean, but currently taking benzodiazepines, their expected remission probability, $f(x)$, is 0.831 (or 83.1%).

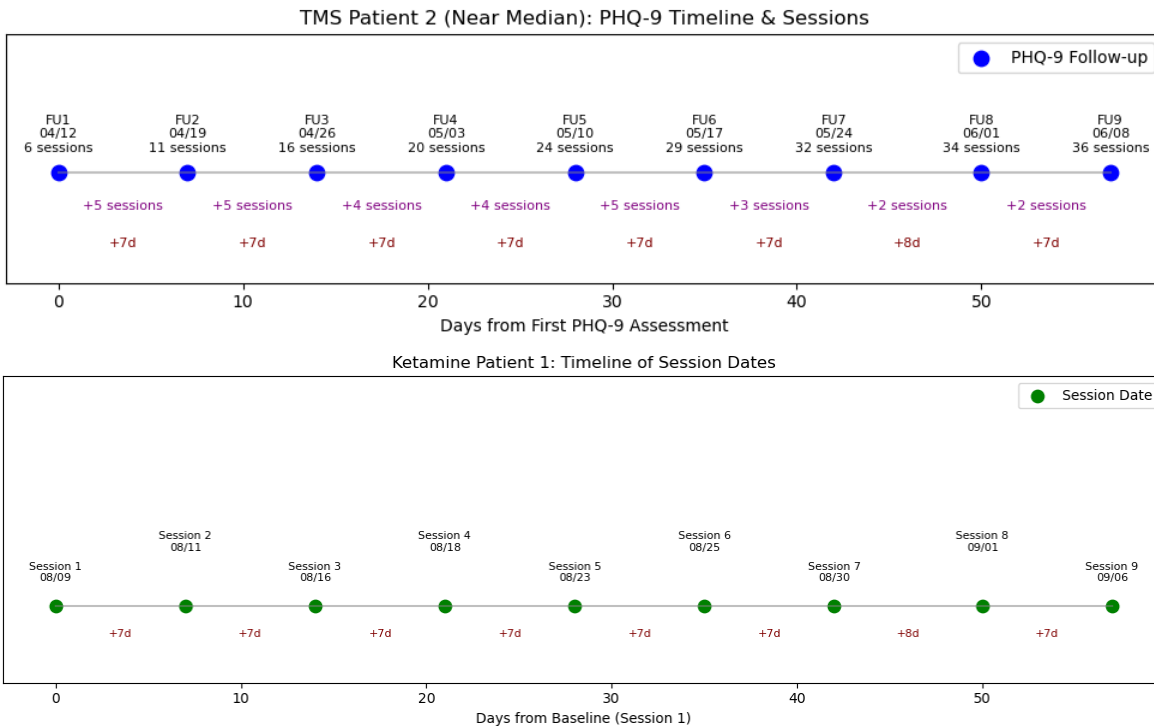


Supplemental Figure 6: Precision-recall (PR) curves for the response and remission models, with color gradients representing thresholds ranging from 0.0 (dark purple) to 1.0 (yellow). The PR AUC values are 0.51 and 0.40 for the response and remission models, respectively, indicating the models' precision-recall trade-offs given the imbalanced class distributions.

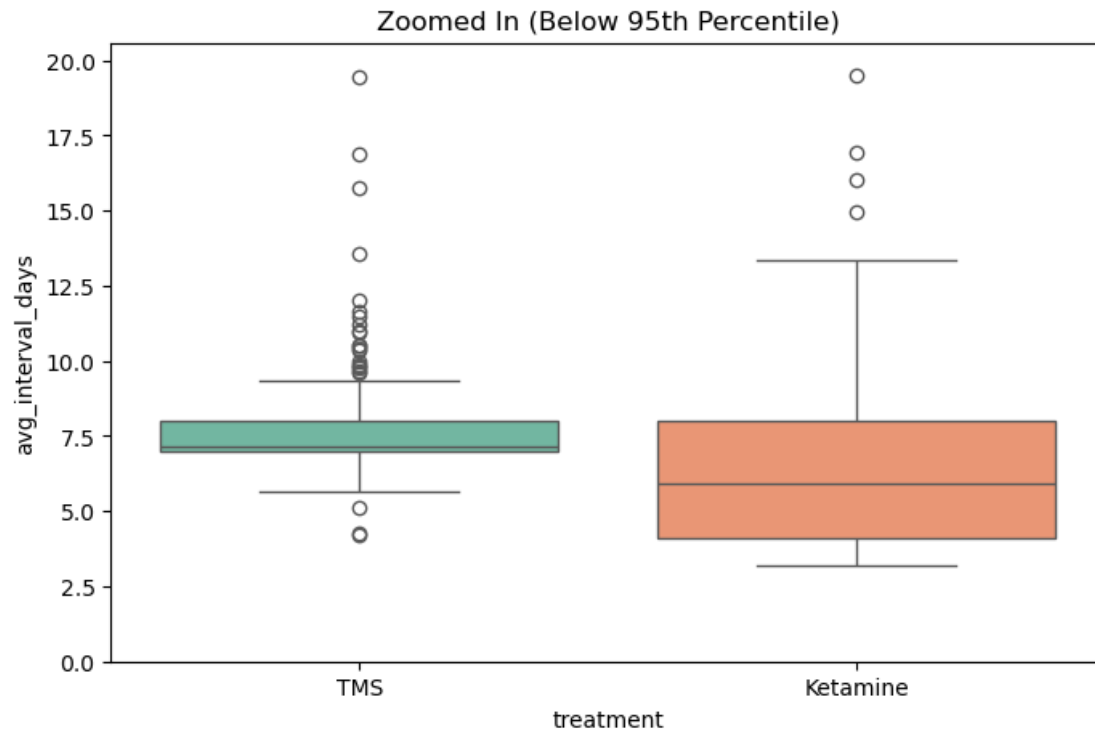
Chapter 2 Supplementary Materials



Supplemental Figure 7: Distribution of number of sessions for ketamine and TMS.



Supplementary Figure 8A-B: Example patient treatment spacing. Fig. 8A illustrates the treatment and PHQ-9 assessment timeline for a TMS patient near the median, showing session and follow-up assessment dates, and the spacing of number of sessions (magenta) and number of days (red). Fig. 8B demonstrates the treatment spacing for a ketamine patient, with session dates spaced consistently with follow-up assessments noted.



Supplemental Figure 9: Treatment spacing for TMS (green) and esketamine (orange). The boxplot illustrates the average interval between treatment sessions for TMS and esketamine, with the data zoomed in to exclude values above the 95th percentile. The green box represents TMS treatment intervals, while the orange box represents those for esketamine, highlighting differences in session spacing between the two modalities.

Supplementary Table 1: Results of Cox Regression.

Predictor	TMS HR (95% CI)	TMS p-value	Esketamine HR (95% CI)	Esketamine p-value
Age	1.01 (1.00-1.02)	0.125	1.00 (0.98-1.02)	0.956
Anxiety Disorder Comorbidity	0.69 (0.49-0.98)	0.039*	0.88 (0.45-1.74)	0.716
BMI Category	0.95 (0.80-1.13)	0.595	0.97 (0.70-1.33)	0.841
Former Tobacco Use	1.31 (1.08-1.59)	0.0059*	1.30 (0.85-1.97)	0.221
Benzodiazepine Use	0.73 (0.53-0.99)	0.0459*	1.19 (0.68-2.09)	0.532
Trauma History	0.84 (0.61-1.15)	0.3006	0.70 (0.40-1.23)	0.217
Session Number	0.99 (0.97-1.00)	0.154	1.02 (0.98-1.06)	0.28

Supplementary Table 2: SI Survival Probabilities.

Time Interval	TMS Survival Probability (No Response)	Ketamine Survival Probability (No Response)
5 days	0.903	0.6
10 days	0.77	0.471
20 days	0.605	0.339
30 days	0.416	0.26
60 days	0.325	0.184
90 days	0.17	0.153
120 days	0.17	0.153
150 days	0.17	0.153
180 days	0.17	0.153
Median Time to Response	26	9
Log-Rank Test Statistic	10.681	0.001082

Supplementary Table 3: Logistic Regression Results.

Predictor	TMS Coef	TMS Std Err	TMS z	TMS p	Ket Coef	Ket Std Err	Ket z	Ket p
Age	0.0095	0.009	1.106	0.269	6.42E-05	0.015	0.004	0.997
Trauma Hx	0.2317	0.263	0.88	0.379	-0.4783	0.508	-0.942	0.346
Benzodiazepines	-0.7053	0.294	-2.401	0.016*	0.6621	0.512	1.224	0.221
Substance Use	0.4135	0.174	2.377	0.017*	0.1652	0.489	0.338	0.625
BMI	-0.1228	0.13	-0.946	0.344	0.0825	0.226	0.365	0.715
Num of Comorbidities	-0.1121	0.114	-0.981	0.327	-0.2058	0.179	-1.15	0.25
Baseline PHQ-9	0.0737	0.102	0.722	0.47	0.2156	0.12	1.803	0.071

Chapter 3 Supplementary Materials

ANCOVA Model Summary:

OLS Regression Results						
Dep. Variable:	PHQ9_Total_post	R-squared:	0.278			
Model:	OLS	Adj. R-squared:	0.167			
Method:	Least Squares	F-statistic:	2.504			
Date:	Fri, 21 Mar 2025	Prob (F-statistic):	0.120			
Time:	15:08:49	Log-Likelihood:	-47.033			
No. Observations:	16	AIC:	100.1			
Df Residuals:	13	BIC:	102.4			
Df Model:	2					
Covariance Type:	nonrobust					
	coef	std err	t	P> t	[0.025	0.975]
Intercept	0.5808	6.551	0.089	0.931	-13.571	14.733
CSP_Mean_pre	0.0803	0.037	2.182	0.048	0.001	0.160
PHQ9_Total_pre	0.0455	0.344	0.132	0.897	-0.698	0.789
Omnibus:	0.532	Durbin-Watson:		1.874		
Prob(Omnibus):	0.767	Jarque-Bera (JB):		0.586		
Skew:	-0.182	Prob(JB):		0.746		
Kurtosis:	2.136	Cond. No.		503.		

Supplementary Figure 10: ANCOVA model exploring the influence of baseline CSP and PHQ-9 scores on post-treatment depression severity.

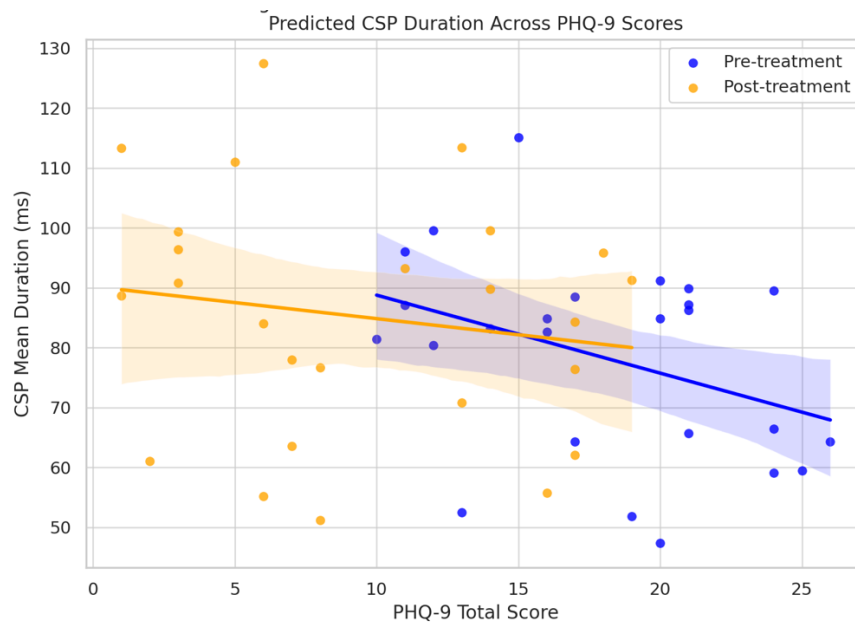
Mixed Linear Model Regression Results

Model:	MixedLM	Dependent Variable:	PHQ9_Total			
No. Observations:	57	Method:	REML			
No. Groups:	25	Scale:	11.9684			
Min. group size:	1	Log-Likelihood:	-165.6286			
Max. group size:	3	Converged:	Yes			
Mean group size:	2.3					
	Coef.	Std.Err.	z	P> z	[0.025	0.975]
Intercept	18.920	2.518	7.513	0.000	13.984	23.856
CSP_Mean_pre	-0.001	0.028	-0.034	0.973	-0.056	0.054
time	-16.387	2.738	-5.985	0.000	-21.753	-11.021
CSP_Mean_pre:time	0.074	0.029	2.558	0.011	0.017	0.131
Group Var	9.184	1.716				

Supplementary Figure 11: Mixed linear model assessing predictors of PHQ-9 change, incorporating time and group effects to further analyze treatment outcomes.

OLS Regression Results						
Dep. Variable:	CSP_Mean	R-squared:	0.144			
Model:	OLS	Adj. R-squared:	0.045			
Method:	Least Squares	F-statistic:	1.460			
Date:	Fri, 28 Mar 2025	Prob (F-statistic):	0.248			
Time:	09:29:54	Log-Likelihood:	-145.81			
No. Observations:	30	AIC:	299.6			
Df Residuals:	26	BIC:	305.2			
Df Model:	3					
Covariance Type:	nonrobust					
	coef	std err	t	P> t	[0.025	0.975]
Intercept	73.4480	14.501	5.065	0.000	43.640	103.256
PHQ9_Total_c	4.4121	2.932	1.505	0.144	-1.614	10.439
time	36.3373	18.200	1.997	0.056	-1.073	73.747
PHQ9_Total_c:time	-2.4726	3.393	-0.729	0.473	-9.447	4.502
Omnibus:	11.000	Durbin-Watson:	1.997			
Prob(Omnibus):	0.004	Jarque-Bera (JB):	10.414			
Skew:	1.073	Prob(JB):	0.00548			
Kurtosis:	4.931	Cond. No.	25.4			

Supplementary Figure 12: OLS and mixed linear regression results for baseline CSP predicting post-treatment PHQ-9 scores. The OLS regression results indicate a weak association between baseline CSP and post-treatment PHQ-9, while the mixed linear model shows a significant interaction between CSP and time, highlighting the change over the treatment period.



Supplementary Figure 13: Interaction plot from the linear mixed model illustrating predicted CSP duration across PHQ-9 scores. This plot demonstrates the relationship between depressive symptom severity (PHQ-9 scores) and CSP duration, showing a stronger correlation for post-treatment compared to pre-treatment, with a clear decrease in CSP as PHQ-9 scores increase.

Spearman correlation between delta_CSP and delta_PHQ:
Correlation coefficient (rho): 0.391, p-value: 0.150

Robust Regression Results (delta_PHQ ~ delta_CSP):
Robust linear Model Regression Results

Dep. Variable:	delta_PHQ	No. Observations:	15
Model:	RLM	Df Residuals:	13
Method:	IRLS	Df Model:	1
Norm:	HuberT		
Scale Est.:	mad		
Cov Type:	H1		
Date:	Fri, 21 Mar 2025		
Time:	11:13:41		
No. Iterations:	2		

	coef	std err	z	P> z	[0.025	0.975]
const	7.1170	1.178	6.042	0.000	4.808	9.426
delta_CSP	0.0733	0.044	1.662	0.097	-0.013	0.160

Supplementary Figure 14: Spearman correlation and robust regression results between change in CSP (Δ CSP) and change in PHQ-9 (Δ PHQ-9). The results from the robust regression model reveal a modest positive correlation between the change in CSP and change in PHQ-9 scores, but the relationship does not reach statistical significance.