

Is this for real?

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SUMMARY

This thesis offers a valuable contribution to the field of neuropsychiatry by exploring the potential applications of repetitive Transcranial Magnetic Stimulation (rTMS) in treating several neuropsychiatric disorders, including depression, nicotine addiction, epilepsy, and Parkinson's disease (PD). In addition, the presented research highlights the importance of taking into account the placebo effect in rTMS studies, as well as exploring alternative treatment options, such as ketamine, for these disorders. Overall, this thesis sheds light on the potential benefits of rTMS in treating various neuropsychiatric conditions and suggests avenues for further research in this promising field.

In **Chapters 2** and **3** we conducted a randomized, double-blind study to evaluate the effectiveness of accelerated intermittent theta burst stimulation (aiTBS) for smoking cessation. Our study also aimed to investigate the impact of smoking-related cues versus neutral cues during rTMS treatment on cigarette consumption. TMS was delivered over five consecutive days to the left dorsolateral prefrontal cortex (DLPFC). In the study, participants were divided into three groups: the first group received active iTBS stimulation while watching neutral videos, the second group received active iTBS stimulation while watching smoking-related videos, and the last group received sham stimulation while watching smoking-related videos.

The results presented in **Chapter 2** demonstrate that aiTBS is a well-tolerated treatment that leads to similar reductions in cigarette consumption, nicotine dependence, craving, and perceived stress across all treatment groups. Moreover, the treatment's positive effects on nicotine dependence, general craving, and perceived stress persist for at least one week after the therapy. In **Chapter 3**, our follow-up study shows that the benefits of aiTBS on nicotine dependence and tobacco craving remain significant for at least one month after treatment completion, although their magnitude decreases after six months.

Our findings indicate that the therapeutic effectiveness of aiTBS, whether active or sham, does not differ significantly between groups exposed to smoking-related cues or neutral cues. These results add to the mounting evidence supporting TMS as a promising non-pharmacological approach for treating addiction and underscore the importance of accounting for placebo effects in assessing brain stimulation therapies' efficacy.

The results have important implications for developing targeted smoking cessation therapies, emphasizing the need to understand the mechanisms underlying the therapeutic benefits of brain stimulation techniques and to control for placebo effects during clinical investigations. An advantage of this study is the use of innovative placebo coil technology, which allows researchers to differentiate between the effects of the actual treatment and the placebo treatment.

In **Chapter 4** of this thesis, our objective was to compare the immediate antidepressant efficacy of intramuscular (IM) ketamine and rTMS in patients with TRD in a real-world clinical setting. We collected clinical data from 24 TRD patients seeking treatment at a naturalistic mental health clinic. Half of the patients (n=12) received IM ketamine twice a week for eight sessions,

while the other half received 30 sessions of left DLPFC-iTBS. We conducted a retrospective evaluation of patients' symptom severity before and after treatment.

The study's findings indicate that both ketamine and rTMS treatments were effective in reducing depressive and anxiety symptoms in TRD patients, with no significant differences in efficacy between the two treatments. These results highlight the potential utility of both IM ketamine and rTMS as effective treatment options for TRD in a real-world clinical setting. Furthermore, findings revealed high remission and response rates in both groups, with no differences between the ketamine and rTMS groups.

This study tackles a critical challenge in mental health treatment, specifically the issue of treating patients with TRD. The findings contribute significantly to our existing knowledge on the effectiveness of ketamine and rTMS in treating depression, and provide valuable insights into their use in real-world clinical settings and research.

The study emphasizes the importance of personalized treatment plans for patients with TRD, as healthcare professionals can assess each patient's unique needs and preferences to determine the most suitable treatment option. Both ketamine and rTMS have shown potential as viable treatment options, but further research is necessary to identify the factors that influence the efficacy of each treatment and determine which patients would benefit most from each approach.

Overall, this study is a significant contribution to our understanding of how to improve the treatment of patients with TRD. Its insights can help clinicians better address the challenges of treating this population, ultimately leading to more effective and personalized treatment options.

Chapter 5 and **6** contain case reports that investigate the effectiveness of rTMS in treating two persistent neurological conditions: epilepsy and PD. **Chapter 5** presents a case study of a patient with frontal lobe epilepsy, in which the feasibility, safety, and potential clinical effectiveness of bilateral orbitofrontal (OFC) low-frequency rTMS (LF-rTMS) for managing epileptic seizures are explored. This study provides valuable insights into the potential of LF-rTMS as a treatment option for patients with epilepsy and highlights the importance of further research in this area. By examining the specific case of this patient, we can better understand the potential benefits and limitations of using LF-rTMS for managing seizures and develop more effective treatment approaches for epilepsy patients. As managing frontal lobe epilepsy with medication alone is challenging, alternative treatments like rTMS are being investigated. After undergoing 30 sessions of rTMS, the patient reported a significant reduction in seizure frequency, and the fear and panic that previously preceded the seizures were eliminated. The patient continued to experience less seizures with reduced intensity and duration during the maintenance period. The patient reported a high level of satisfaction with the rTMS treatment, as it helped reduce the frequency of the focal attacks, allowed for a reduction in anti-seizure medication dosage, and resulted in a reduction in the side effects caused by the medication.

While the limitations of the study's design require careful interpretation of the findings, this case report provides valuable insights into the potential of rTMS as a treatment option for patients with refractory frontal lobe epilepsy. However, further studies with larger sample sizes and controlled designs are necessary to investigate the effectiveness of rTMS in managing refractory frontal lobe epilepsy more comprehensively. These studies would provide a more significant understanding of the treatment's potential and its limitations, which could help inform the development of more effective and personalized treatment plans for epilepsy patients. Overall, the findings from this case study suggest that rTMS may be a promising treatment option for patients with refractory frontal lobe epilepsy, but more research is needed to confirm its efficacy. In **Chapter 6**, a patient with PD is presented, who underwent an accelerated form of high-frequency rTMS (HF-rTMS). The study aimed to evaluate the clinical effectiveness of rTMS in managing health-related quality-of-life (QoL) symptomatology and depressive symptoms in PD, as well as the long-term effects of rTMS during the maintenance phase. PD is a debilitating neurodegenerative disorder, and depression is a common comorbidity that further worsens the quality of life of patients. The results indicate that HF-rTMS over the right M1 is a safe and well-tolerated treatment that improved the patient's health-related QoL and depressive symptoms, with these positive effects persisting for at least five months after treatment. Hence, HF-rTMS over the right M1 may be a potential treatment option for PD patients. However, it is important to note that this is a single case study, and therefore, further research is necessary to establish the safety and effectiveness of rTMS in larger patient populations. Both reports demonstrate that rTMS treatment can successfully suppress seizures in frontal lobe epilepsy and improve depressive symptoms and overall quality of life in PD. These findings suggest that rTMS may be a viable therapeutic option for certain cases of neurological disorders. However, further research is necessary to establish the safety and effectiveness of rTMS in larger patient populations, and the results may have implications for the development of new treatment strategies for other neurological conditions.

In **Chapter 7** of the thesis we focus on safety concerns of TMS treatment, which have become increasingly important due to advancements in TMS coil technology. While TMS is generally considered safe and well-tolerated, the safety of new coil geometries is still not fully established. Inducing a seizure is a potential serious adverse event during any rTMS treatment. Although rTMS has shown promise in treating treatment-resistant obsessive-compulsive disorder (OCD), the optimal target area and stimulation frequency are still controversial. The case report in this chapter presents a patient with OCD who experienced a seizure during her 7th session of rTMS treatment using the FDA-approved 20-Hz protocol for OCD, applied bilaterally over the left and right dorsomedial prefrontal cortex (DMPFC) with a double-cone coil. However, it remains uncertain whether the seizure was a direct result of the rTMS treatment or if the patient had preexisting risk factors for seizures. Therefore, it is crucial to consider individual patient characteristics when selecting treatment protocols and to take appropriate measures to ensure patient safety. While caution is necessary during rTMS administration, the study's findings are limited by the use of a single case report, which may

restrict the generalizability of the results. In conclusion, this study provides valuable insights into the potential risks and benefits of TMS treatment and emphasizes the importance of careful patient selection, monitoring, and adverse effects management to ensure patient safety. This study lays the foundation for further research on the safety and efficacy of TMS treatment and the development of effective protocols to minimize the risk of adverse effects. However, more research is necessary to fully comprehend the potential risk factors and mechanisms underlying TMS-induced seizures and to develop effective strategies to prevent or manage such adverse effects.

The studies conducted in this thesis make a significant contribution to our understanding of the effectiveness and potential applications of rTMS in neuropsychiatry. The research findings provide valuable insights into the potential of rTMS as a treatment option for various mental health conditions, including depression, nicotine addiction, PD, and epilepsy. However, it is crucial to exercise caution and careful monitoring to avoid any potential adverse effects associated with rTMS treatment.

Furthermore, the thesis highlights the significance of the placebo effect in rTMS studies and the importance of exploring alternative treatment options such as ketamine. The placebo effect can have a significant impact on the outcomes of rTMS studies, and researchers must account for it when interpreting the results. Moreover, exploring alternative treatment options like ketamine could lead to the development of more effective and personalized treatment plans for patients with neuropsychiatric conditions.

In conclusion, the studies conducted in this thesis provide important insights into the potential applications of rTMS in neuropsychiatry. While caution is necessary to prevent any adverse effects, the findings suggest that rTMS could be a promising treatment option for various mental health conditions. Future research in this area should continue to explore the efficacy of rTMS and alternative treatments to further improve patient outcomes.