Pain Side Effects Analysis in rTMS for Depression: A THREE-D Study

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Introduction

According to WHO, Major Depressive Disorder (MDD) is a leading cause of disability that affects 350 million people worldwide, and 30% of them suffer from treatment-resistant depression (TRD). Repetitive Transcranial Magnetic Stimulation (rTMS) is a first-line treatment for TRD. Newer rTMS protocols are being developed so it is extremely important to characterize their side effect profile and trajectories. The goal of this work is to characterize the most prevalent side effect of rTMS (i.e. pain on the site of stimulation) in two different protocols: High Frequency Left (HFL) and Intermittent Theta Burst Stimulation (iTBS), from the THREE-D study sample by Blumberger et al. in 2018.

Results

The most prevalent side effect for both protocols was confirmed to be pain on the site of stimulation (97%). Two patients withdrew before starting treatment, 29 patients dropped out of the study before completing a full course of rTMS (i.e. 20 treatments), and one patient did not complete the baseline BSI anxiety survey. This resulted in 384 patients included in the primary analysis.

Exploratory Data Analysis

Before testing any LME models, EDA was used first by plotting the average pain scores over time, also by dividing the data based on several variables as shown below:

![Fig 1: Average of Pain Score over Time](image)

Linear Mixed Effects Model

Since EDA can only draw preliminary conclusions, LME modelling was applied next to present reliable statistical findings. After comparing several models, we found that the best pain model for 384 patients includes variables such as time, treatment protocol, the percentage decrease in HRSD score, baseline anxiety score, age, sex, and baseline anxiety score intensity. The summary of significant results as well as the LME model that we used are shown below:

![Table 1: Summary of LME Model for Pain (n=384)](image)

Conclusions

To summarize, pain on the site of stimulation was reported to be the most common side effect for both rTMS protocols (97%), and the LME model and Tables 1 & 2 show the following significant conclusions:

- Pain severity score decreased over the treatment course, but it decreased at a slower rate over time;
- Patients who received iTBS protocol reported higher severity of pain than those who received HFL protocol;
- Female patients reported higher pain severity scores than male patients;
- Patients with more decrease in HRSD score reported less severity of pain;
- Older patients reported higher severity of pain than younger patients;
- Patients who had higher BSI anxiety baseline score reported higher severity of pain than those who had lower BSI anxiety baseline score;
- Pain severity score is positively correlated with the stimulation intensity of the treatment.

Discussion

To our knowledge, this study is the first to compare the pain side effect profiles of the HFL and iTBS rTMS protocols for TRD. The finding of increased pain overall in the iTBS group compared with the HFL group presents a comparative advantage of this protocol.

Our finding that pain severity score decreased significantly over the course of treatment, and rapidly during the first two weeks, provides support for the concept of side effect adaptation during a course of rTMS, and reassurance for patients where pain is a potential barrier to pursuing treatment. Finally, we identified several covariates, including change in HRSD score, time, age, sex, baseline BSI anxiety score, and stimulation intensity, which demonstrated potential utility as predictors of pain severity during treatment.

The results of this work provide useful guidance for clinicians in determining rTMS protocol selection, and as a reference for patients during the informed consent process.

![Fig 2: Average of Pain Score over Time for HFL vs. iTBS](image)

![Fig 3: Average of Pain Score over Time for Male vs. Female](image)

![Table 2: Details of the LME Model for Pain (n=384)](image)