Pain Side Effect 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. Click on the audio files below to listen to the differences:

![HFL vs iTBS](image)

Fig 1: Mean Pain Score over Time (Protocol, Sex, Response)

Design & Methods
Four hundred and fourteen patients with TRD were randomized to either HFL or iTBS in a multicenter study across three university hospitals in Canada.

414 Patients Diagnosed with TRD

- HFL (205 pt)
- iTBS (209 pt)

![Randomization](image)

Fig 2: Four Distinct Trajectories of Pain Score over Time

Each side effect was systematically assessed after every treatment using a Likert scale ranging from 0 to 10. Linear mixed-effects modelling was used to test several variables that might be significantly associated to the most prevalent side effect during rTMS, and multinomial logistic regression was used to confirm the significance of variables associated with distinct pain trajectories.

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.

![Trajectories](image)

Fig 2: Four Distinct Trajectories of Pain Score over Time

Exploratory Data Analysis & Latent Class Analysis
Before further analysis, EDA was used first by plotting the average pain scores over time, also by dividing the data based on several variables as shown in Figure 1 below. Additionally, LCA was also performed, and it resulted in four distinct trajectories of pain score (Figure 2).

Linear Mixed Effects Model
Since EDA can only draw preliminary conclusions, LME modeling 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, anxiety score, age, sex, and stimulation 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)

<table>
<thead>
<tr>
<th>Variable</th>
<th>CTR</th>
<th>SE</th>
<th>p-value</th>
<th>Patient-Oriented statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.04</td>
<td>0.03</td>
<td>0.04</td>
<td>Lower, the more painful</td>
</tr>
<tr>
<td>Age</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>(0.2 points per year)</td>
</tr>
<tr>
<td>Female</td>
<td>0.39</td>
<td>0.17</td>
<td>0.01</td>
<td>Female may hurt (0.39</td>
</tr>
<tr>
<td>Responder</td>
<td>-0.46</td>
<td>0.17</td>
<td>0.01</td>
<td>Those who will get better</td>
</tr>
<tr>
<td>BSI-A</td>
<td>0.03</td>
<td>0.02</td>
<td>0.01</td>
<td>The more anxious the higher</td>
</tr>
<tr>
<td>iTBS</td>
<td>0.79</td>
<td>0.22</td>
<td>0.01</td>
<td>iTBS may hurt (0.79 points)</td>
</tr>
<tr>
<td>Time</td>
<td>-0.12</td>
<td>0.02</td>
<td>0.01</td>
<td>For every day 0.12 less</td>
</tr>
<tr>
<td>Time by iTBS</td>
<td>-0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>Pain during iTBS decreases</td>
</tr>
<tr>
<td>Time by BSI-A</td>
<td>0.001</td>
<td>&lt;0.01</td>
<td>0.01</td>
<td>Anxious matters more early</td>
</tr>
<tr>
<td>Time by Stim_Int</td>
<td>0.001</td>
<td>&lt;0.01</td>
<td>0.01</td>
<td>Intensity of stimulation</td>
</tr>
<tr>
<td>Baseline Anxiety</td>
<td>0.08</td>
<td>0.02</td>
<td>0.01</td>
<td>May hurt more early in the</td>
</tr>
<tr>
<td>Baseline Anxiety</td>
<td>0.001</td>
<td>&lt;0.01</td>
<td>0.01</td>
<td>treatment, and then become</td>
</tr>
</tbody>
</table>

LME Model for Pain:

\[ \text{Pain} = 0.05 + \text{Age}^*0.02 + \text{Female}^*0.39 + \text{BSI-A}^*0.08 + \text{Time}^*0.79 + \text{Stim_Int}^*0.07 + \text{Time}^*0.12 - \text{Time}\text{ITBS}^*0.02 - \text{Time}\text{Stim_Int}^*0.001 + \text{Time}^2*0.003 \]

![Table](image)

Table 2: Summary of Significant Results as well as the LME Model that we used are shown below:

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 showed the following significant conclusions:

- Pain severity score decreased over the treatment course with 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;
- Responders to rTMS reported less severity of pain than non-responders;
- Pain severity score is positively correlated with age;
- Pain severity score is positively correlated with the stimulation intensity (dose) of the treatment;
- Pain severity score is positively correlated with baseline anxiety score.

Additionally, we found four distinct trajectories of pain severity score as reported over the course of rTMS, where MLR analysis confirmed that higher stimulation intensity and non-response to rTMS were significantly associated to the two less favorable pain trajectories: “High pain, delayed decrease” and “High pain, no change” groups.

Discussion
This study is the first to compare the pain side effect profiles of the HFL and iTBS rTMS protocols for TRD. 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 (clinical outcome, time, age, sex, baseline anxiety score, stimulation intensity), as well as four distinct pain trajectories, 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.