COMMENTARY

COMMENTARY ON: "EFFECTS OF MOTOR IMAGERY-BASED NEUROFEEDBACK TRAINING AFTER BILATERAL REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ON POST-STROKE UPPER LIMB MOTOR FUNCTION: AN EXPLORATORY CROSSOVER CLINICAL TRIAL"

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To the Editor,

We have read the article by Francisco Jose Sanchez-Cuesta et al. (1), with great interest. The introduction is well explained and written. Also, the author had well explained the treatment effect of both rTMS and NFB. We gathered valuable information and wish to congratulate the authors for this successful clinical trial. However, there are some concerns that need to be addressed.

The sample size of the study was well explained in detail related to previous studies. But the subjects were taken from one centre, so identified risk factors may be exclusive to that single centre. This methodological choice may weaken the generalizability of the study findings (2). In the clinical trial, the title is "Transcranial Magnetic Stimulation and Mental Representation Techniques for the Treatment of Stroke Patients", but in the manuscript it is "Effects of Motor Imagery-Based Neurofeedback Training After Bilateral Repetitive Transcranial Magnetic Stimulation on Post-Stroke Upper Limb Motor Function: An Exploratory Crossover Clinical Trial".

While the AB/BA crossover design employed in this study mitigates individual differences and potentially reduces bias (3), the lack of correction for the multiple comparisons and potential learning effects from repeated assessments could compromise the validity of the findings. This broad problem-focused approach, prioritizing a generalizable effect, may neglect the core issue of treatment efficacy for the distinct stroke population (subacute vs chronic). There is a lack of specificity subgroups. A more focused investigation with a clear evaluation of treatment efficacy in subacute and chronic stroke populations is warranted. The potential for bias extends beyond the choice of study design. Selection bias is the concern, as the inclusion criteria are not specific enough to represent the sample. Blinding bias could also occur if either researchers or participants were aware of the intervention assignment, potentially influencing behaviour and skewing the results. Finally, performance bias cannot be ruled out, as the factors not directly related to the intervention could have influenced participant performance (4).

rTMS is a very safe and non-invasive technique used to treat various psychiatric and neurological disorders by stimulating specific brain regions with magnetic fields. rTMS can increase or decrease cortical excitability, which manages the symptoms of the aforementioned conditions (5). While in the study intervention it was not clear if the rTMS was given for 10 consecutive days in therapy group A, then why in therapy group B MI-NFB was it given non-consecutively for 12 days and also why were the first 6 MI-NFB sessions carried out after rTMS and the last 6 sessions, without rTMS?

The results of the study indicate that the combined therapy can be promising treatment for stroke patients in both the subacute and chronic phases. Clinicians may consider incorporating motor imagery-based neurofeedback training and repetitive transcranial magnetic stimulation into rehabilitation programmes for stroke survivors. However, the study did not assess the persistence of intervention effects beyond 1 month. Future research could explore the long-term effects of the combined therapy to better understand its sustainability and impact on functional outcomes.

In addition to our concerns, the study does not represent the size and clinical importance of the effect of MI-NFB or MI-NFB after rTMS. Statistical significance is not the same as clinical significance. Thus, further statistical analysis was performed to obtain the effect size and power of the study by using G*Power because effect size and power are crucial for designing a strong crossover trial. They help researchers to identify the practical significance of treatment effects, plan for an adequate sample size, and avoid both false negatives and false positives in the analysis (6, 7). Multiple formulas were used to compute the effect size, depending on the analysis and type, such as (8):

1. Cohen's d

Cohen's d is used to measure the effect size for the difference between 2 means.

$$d = \frac{M_1 - M_2}{\sqrt{\frac{s_1^2 + s_2^2}{2}}}$$

where M1 and M2 are the means of the 2 groups and s1 and s2 are the standard deviations of the two groups (9).

2. Hedges' g

This is a variation of Cohen's d, but with a correction factor applied for small sample sizes.

$$Hedges'\ g = \frac{M1 - M2}{SD * pooled}$$

where M1 and M2 are differences in mean and SD^*_{pooled} is pooled and weighted standard deviation (10).

Hedges' g and Cohen's d are interpreted similarly. For analysing outcomes, Cohen recommended applying the following general rule of thumb: small effect: < 0.2, medium effect: 0.5, large effect: 0.8) (11).

The Fugl–Meyer Assessment of the Upper Limb (FMA-UL) showed a clinically significant effect size for group AB (Cohen's d = 0.75; power = 0.98) and group BA (Cohen's d = 1.55; power = 1.00). The Hand Grip test revealed a small effect size for group AB (Cohen's d = 0.23, power = 0.30) and a medium effect size for group BA (Cohen's d = 0.54; power = 0.84). The Nottingham Sensory Assessment (NSA) Total Score (TS) showed a medium effect size for group AB (Cohen's d = 0.47; power = 0.75) and a large effect size for group BA (Cohen's d = 1.00; power = 0.99). The NSA Kinesthesia Score (KS) had a large effect size for group AB (Cohen's d = 1.2; power = 0.99) and a small effect size for group BA (Cohen's d = 0.41; power = 0.65). The NSA Stereognosis Score (S) revealed a small effect size for both group AB (Cohen's d = 0.10; power = 0.12) and group BA (Cohen's d = 0.09; power = 0.11). The Nine-Hole Peg Test (9-HPT) showed a medium effect size for group AB (Cohen's d = 0.45; power = 0.72) and a large effect size for group BA (Cohen's d = 0.70; power = 0.96). The Action Research Arm Test (ARAT) had a large effect size for both group AB (Cohen's d = 1.01; power = 0.99) and group BA (Cohen's d = 1.21; power = 0.99). Finally, the Finger Tapping Test (FTT) revealed a small effect size for group AB (Cohen's d = 0.10; power = 0.12) and a medium effect size for group BA (Cohen's d = 0.51; power = 0.81).

This study's findings suggest that combining motor imagery-based neurofeedback training with repetitive transcranial magnetic stimulation can improve upper limb affected patients. This has important implications for enhancing rehabilitation strategies for stroke survivors. The study adds to the existing literature by demonstrating the potential benefits of combining these 2 interventions for stroke rehabilitation. The findings support the efficacy of the combined approach in improving motor outcomes and sensory function. The study provides valuable information, but the above-mentioned points need to be considered for clinical interpretation. We would be interested in the authors' thoughts on these comments.

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RESPONSE TO THE COMMENTARY ON: "EFFECTS OF MOTOR IMAGERY-BASED NEUROFEEDBACK TRAINING AFTER BILATERAL REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ON POST-STROKE UPPER LIMB MOTOR FUNCTION: AN EXPLORATORY CROSSOVER CLINICAL TRIAL"

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Dear Editor,

We sincerely thank Dr Anjali Raghuwanshi, Dr Saliha Rafat, and Dr Adarsh Kumar Srivastav for their thoughtful commentary on our recently published study. We appreciate their interest in our work and the constructive feedback provided. Herein, we address the concerns raised and provide further clarification on specific points.

1. Sample size and single-centre study: While we acknowledge that conducting a study at a single centre may limit the generalizability of our findings, this approach allowed us to maintain a high degree of control over the study environment and intervention protocols. Future research should indeed aim to include multiple centres to enhance the generalizability of the results.

2. Study title discrepancy: We appreciate the observation regarding the discrepancy between the trial registration title and the manuscript title. The registered title, "Transcranial Magnetic Stimulation and Mental Representation Techniques for the Treatment of Stroke Patients", broadly describes the study's scope. The manuscript title was refined to reflect the specific focus on motor imagery-based neurofeedback (MI-NFB) and repetitive transcranial magnetic stimulation (rTMS).

3. Crossover design and potential biases: We selected the AB/BA crossover design to mitigate individual differences and reduce bias. We agree that this design might introduce potential biases such as learning effects. However, the inclusion of a washout period aimed to minimize these effects. The suggestion to address multiple comparisons and blinding in future studies is well taken, and we will incorporate these considerations in subsequent research.

4. Intervention protocol clarification: Regarding the protocols of both therapies, we strictly adhered to the parameters as originally published by their respective authors, ensuring no modifications were made. First, Therapy A consisted of 10 sessions of bilateral rTMS. In contrast, Therapy B was a combination therapy, which included the same 10 sessions of bilateral rTMS from Therapy A, plus an additional 12 sessions of IM-NFB training, conducted at a frequency of 3 sessions per week over 4 weeks. Consequently, in the combined therapy, the initial 6 IM-NFB training sessions were immediately preceded by bilateral rTMS, while the subsequent 6 sessions were not.

5. Long-term effects and clinical significance: We agree on the importance of assessing long-term effects and the clinical significance of our findings. The current study provided preliminary evidence of the combined therapy's efficacy. We plan to conduct follow-up studies to explore the long-term sustainability of these interventions and to further analyse clinical outcomes.

6. Statistical analysis and effect sizes: The commentary emphasizes the necessity of calculating effect sizes and statistical power. Our study included these analyses to provide a comprehensive understanding of the intervention's impact. We acknowledge the critical role of these metrics in interpreting the clinical relevance of our findings and will ensure they are prominently reported in future publications.

Conclusion: We are grateful for the detailed review and valuable suggestions provided by Dr Raghuwanshi, Dr Rafat, and Dr Srivastav. Their insights will undoubtedly enhance the quality of future research in this area. We remain committed to advancing the understanding and application of neuromodulation techniques in stroke rehabilitation.

Thank you once again for the opportunity to address these comments. We look forward to continuing the dialogue and contributing to the field of neurorehabilitation.