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Mixing Apples and Oranges in Assessing Outcomes of Repetitive Transcranial Stimulation Meta-Analyses

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Dear Editor,

Amad et al. [1] have critically assessed the evidence base for therapeutic application of repetitive transcranial magnetic stimulation (rTMS) in neurological and psychiatric disorders based on the test of excess significance, which statistically compares the expected versus observed number of "positive" datasets. For estimating the effect size of rTMS, the authors selected two large randomized clinical trials (RCTs) that were evaluated as "representative of the field" and "presenting low risk of bias." Afterwards, they compared the combined effect size of these trials with the combined effect size of all datasets for a given disorder. As more "positive" datasets were observed than expected, the authors concluded that "caution is warranted in accepting rTMS as an established treatment for neuropsychiatric disorders."

The whole field of brain stimulation, and rTMS in particular, is experiencing an expansion of the investigation of its clinical applications in neuropsychiatric disorders. In this context, it is of utmost importance to systematically and rationally appraise the literature to better guide patients, clinicians, and policy makers in their decisions. Thus, we appreciate the effort of Amad et al. [1] and also share some of their critical views. However, we would like to discuss important methodological issues that limit the study's overall conclusion.

First, the authors selected two RCTs to represent *all* rTMS interventions. However, these trials employed particular variants of TMS. For instance, Levkovitz et al. [2] employed the H1-coil rTMS ("deepTMS"), which uses a non-focal, bilateral method of brain stimulation [2] and is considered a distinct rTMS modality; whereas the study of Leuchter et al. [3], despite clearly presenting biases (e.g., attrition rate of 40%), used a low-field magnetic stimulation modality. Both rTMS modalities are not commonly used in clinical practice and are delivered by equipment designed specifically for depression. In fact, high-frequency rTMS, the most used modality for depression, has an effect size at least two times higher than estimated by Amad et al. [1] according to recent meta-analyses [4, 5]. As the authors stated that the true effect size of an intervention is "exploratory by nature," it is surprising that they evaluated only specific subvariants of rTMS and did not consider other or additional RCTs, or carefully designed meta-analyses in their estimations.

Second, the authors wrote that the evidence of rTMS "appears [to be] strongly favorable for almost every condition [evaluated]." This is not supported by their own data. For instance, no evidence for this claim was found for any of the psychiatric disorders investigated, except for depression (but see above). For neurologic disorders, the issues arose from two specific meta-analyses: chronic neuropathic pain (18/25 "positive" datasets) and post-stroke depression (22/24 "positive" datasets). However, these studies were methodologically problematic. For instance, the post-stroke depression meta-analysis [6] included several datasets that are not internationally accessible and had low quality, whereas the chronic neuropathic pain meta-analysis [7] included many single-session rTMS trials, which evaluated only short-term rTMS effects and were not necessarily designed to evaluate long-term efficacy.

Third, the authors failed to grasp the particularities involved in different rTMS modalities. Critically, rTMS effects vary according to the frequency, intensity (defined as the percentage applied according to the resting motor threshold), number of pulses, number

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of sessions, coil design, and coil positioning [8]. For instance, some rTMS protocols, such as high-frequency rTMS and intermittent theta-burst stimulation, promote long-term excitatory changes; whereas others such as low-frequency rTMS and continuous theta-burst stimulation can exert inhibitory effects. Therefore, it is methodologically flawed to estimate rTMS effects among several neuropsychiatric disorders without taking into account that different rTMS protocols are employed for these disorders.

In sum, the issue of reproducibility is clearly relevant in rTMS research as in other domains of clinical neuroscience. Correspondingly, key research questions of rTMS efficacy should be addressed with adequately powered and well-designed clinical trials for new indications. However, we do not share the rather generalized conclusions that compared largely varying applications, which are as different as apples and oranges.

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