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Reply: Variability in motor threshold

Letter to the editor

We would like to thank Pridmore and colleagues for their interest in our recently published study showing that Motor Threshold (MT) changed significantly on a daily basis during rTMS treatment for depression [1]. Since MT is used to determine the appropriate stimulation intensity for the rTMS treatment, we argue that such variability raises concerns about the safety and efficacy of treatment when MT is only measured at the start of therapy. In the absence of randomized-control-trials that demonstrate the effects of different MT determination frequencies on efficacy and side-effects, we have suggested that the results of our study warrant caution and more regular MT assessments. In the recent letter to the editor by Pridmore and colleagues [2], the authors have argued that such MT determination scheduling is unnecessary since, on one hand, blinded clinical trials have shown clinical efficacy using lower than 110–120% MT stimulation intensity ranges and, on the other hand, MT and seizure threshold may not have a "fixed relationship". We agree with Pridmore and colleagues, that the current evidence in our study should not be regarded as definitive, as highlighted in our limitations section, since our study was not designed to specifically understand if different MT assessment schedules were associated with increase clinical response or risk of side effects. Nevertheless, such evidence is currently lacking and since MT significantly varies across rTMS treatment, we believe the precautionary principle should prevail, and the data suggests at least weekly MT measurements, as others did before [3].

In terms of efficacy from "underdosing" when MT increases during a course of therapy, while Pridmore and colleagues correctly highlight the fact that successful treatment with rTMS has been achieved with lower stimulation intensities, higher stimulation intensities are more likely to elicit a neurophysiologic response [4] and are also associated with higher clinical efficacy [5]. Such evidence lead to the suggestion by TMS Clinical Consensus that stimulation should be performed at 100–120% of MT in the context of rTMS treatment for depression [6]. In terms of safety from "overdosing" with an increased risk of seizures, we agree that the relationship between MT and seizure threshold is still not fully understood and other factors likely also contribute to seizure induction with TMS. Nevertheless, particularly high rTMS stimulation intensities can induce seizures and this is in fact the rationale behind Magnetic Seizure Therapy, where convulsions are intentionally elicited, similar to what is observed in electroconvulsive therapy [7]. Furthermore, the safety parameters for TMS recognize the well-established relationship between TMS intensity and seizure risk [8].

Finally, the present discussion raises another important question: Is MT an adequate metric to define TMS treatment dose? This is particularly challenged by the fact that MT is a neurophysiologic measure acquired in brain motor regions, rather than the dorsolateral prefrontal cortex (DLPFC), the actual rTMS treatment target. Furthermore, a consistent relation between metrics of excitability in motor cortex (including MT) and those in DLPFC has not been shown. One potential solution that may be further explored in future studies is to use a different electrophysiologic measure in DLPFC to determine the stimulation intensity. A number of TMS-EEG measures [9] are being explored and are theoretically better proxies for safety and efficacy of stimulation in DLPFC. We would like to thank Pridmore and colleagues for the opportunity to further discuss the results of our study and their potential impact in clinical practice. We are certain that such scientifically meaningful debates help improve TMS field but most importantly patients' quality of life.

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several issued and pending patents on the real-time integration of noninvasive brain stimulation with electroencephalography and magnetic resonance imaging. None of the aforementioned agencies or companies had a role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, in the preparation, review, or approval of the manuscript, nor in the decision to submit the manuscript for publication. The remaining authors have declared that they have no potential conflicts of interest involving this work, including relevant financial activities outside the submitted work and any other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing what is written.

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