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LETTER TO THE EDITOR

Repetitive transcranial magnetic stimulation of the human motor cortex in the gamma band reduces cortical excitability

Transcranial Magnetic Stimulation (TMS) has emerged as a promising therapeutic tool in various neurological and psychiatric conditions [4] owing to its potential to modulate cortical excitability and induce neuroplasticity effects that outlast the stimulation period [3]. Repetitive TMS (rTMS) over the motor cortex has been extensively investigated as a non-invasive treatment to improve motor symptoms in conditions such as multiple sclerosis, Huntington's disease, and amyotrophic lateral sclerosis, providing therapeutic efficacy [1]. Recently, stimulation of the motor cortex has been employed for purposes beyond motor rehabilitation, including the treatment of, amongst others, headaches, sleep disorders and pain [8].

Depending on stimulation parameters, rTMS can suppress cortical excitability [3] in conditions characterized by cortical hyperexcitability [2] or it can enhance cortical excitability, for example in Parkinson's disease [10]. Recently, gamma brain stimulation, particularly at the 40 to 50 Hz frequency, has gained much attention as a potential therapeutic approach for several disorders [7,9]. Additionally, impaired gamma brain activity has been observed in various conditions such as Alzheimer's disease [9] and chronic pain [6], generating the question of whether rTMS stimulation in the gamma band has the potential to regulate the observed gamma band activation disturbances. For instance, increased electroencephalographic activation in the gamma band has been identified in chronic pain patients and has been suggested as a potential marker of pain perception [5]. While evidence suggests that the induction of gamma oscillations using TMS has therapeutic potential, and that impaired gamma band activity can represent a potential biomarker for specific diseases, there are currently no studies investigating the physiological effects of such a high frequency stimulation protocol.

Here we test such a 40 Hz TMS brain stimulation protocol in terms of its potential to modulate cortical excitability that outlasts the stimulation period (for a period of up to 45 minutes after stimulation). We delivered 40 Hz gamma TMS stimulation over the motor cortex and used the resting motor threshold (RMT) as a measure of cortical excitability.

Each participant received 40 Hz TMS at 80% of individual RMT over the primary motor cortex (M1). The influence on cortical excitability was assessed by comparing RMT before stimulation with RMT immediately after (0' time point) and up to 45 minutes after stimulation at 15-minute intervals (i.e., at 0, 15, 30 and 45 minutes post-stimulation).

Fifteen healthy participants took part in the experiment (11 females, 4 males; M = 25 years, SD = 4 years). A safety screening questionnaire was used prior to the experiment to ensure the absence of any contraindications to TMS, and all participants provided written, informed consent. The study was approved by the national bioethics committee (EEBK/EIT/2021/22).

The stimulation protocol consisted of 25 trains, each train consisting of 40 pulses in 1 second (i.e., 40 Hz) followed by 29 seconds of no stimulation (see Fig. 1A). Stimulation was delivered using the Magstim Super Rapid^2 Plus^1 System with a vacuum-cooled D70 figure-of-eight alpha coil. In total, 1000 pulses were delivered to each participant in 12.5 minutes. A neuronavigation system (Visor2, ANT Neuro, Enschede, Netherlands) was used to localize the primary motor cortex hotspot, guide the sessions, and ensure stable coil positioning. The coil was held at an angle of approximately 45° to the midline with the hand pointing laterally and posteriorly such that the current flowed from posterior to anterior. The stimulation was applied contralateral to each participant's dominant hand (i.e., left hemisphere on right-handed participants). After localizing the hot spot, the coordinates of each participant were saved in the neuronavigation system and were used to guide the rTMS session and all the RMT assessments. Thereby, the same stimulation parameters were ensured throughout the experiment for all participants (i.e., coil orientation, distance, and tilt).

RMT was defined as the minimum TMS intensity needed to elicit MEPs of $> 50\mu$V in five out of 10 trials in the relaxed first dorsal interosseous muscle (FDI) and was established using single-pulse TMS. MEPs were obtained by surface electromyography (EMG) leads placed over the left or the right FDI muscle and MEPs were recorded from each participant's dominant hand (i.e., contralateral to the stimulation site). RMT was measured before delivering the gamma stimulation protocol and an additional four times post-stimulation (immediately after stimulation, and every 15 minutes up to 45 minutes post-stimulation). The TMS intensity in the first post-stimulation measurement of RMT was set at the pre-stimulation RMT intensity and during the RMT measurement

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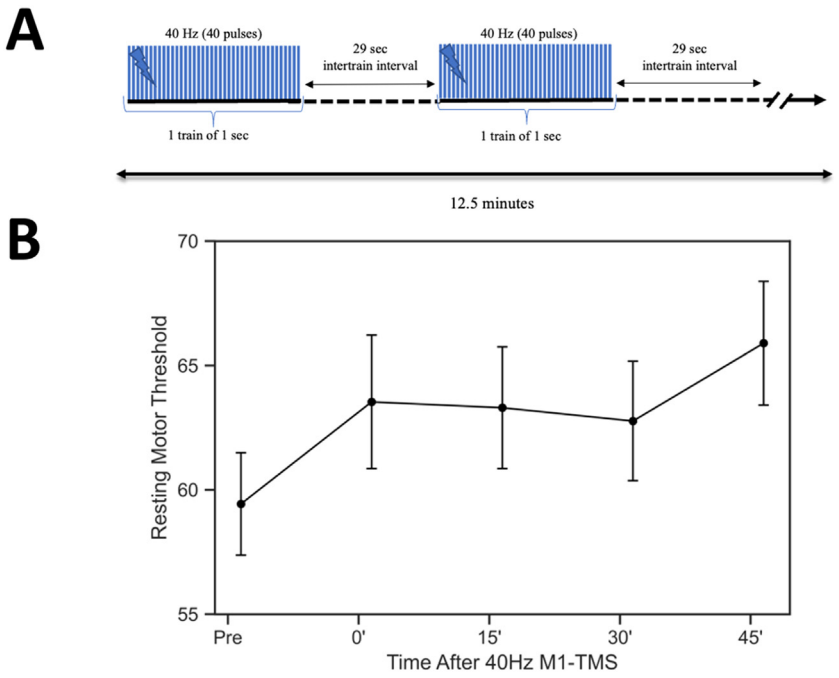

Fig 1 The 40 Hz Transcranial Magnetic Stimulation protocol and its effect on resting motor threshold,
(A) Graphical illustration of the TMS protocol. (B) Mean participant resting motor threshold before receiving the TMS protocol, and at 0, 15, 30, and 45 minutes after receiving the TMS protocol. The increase of the RMT indicates suppression of corticospinal excitability. Error bars depict $\pm$ 1 standard error. TMS; transcranial magnetic stimulation, RMT; resting motor threshold.

phase was being reduced or increased in steps of 1% or 2% until 5 MEPs of $> 50\mu$V out of 10 trials were recorded. Each of the following post-stimulation measurements (i.e., 15', 30' and 45') followed the same procedure and TMS intensity started at the previously identified RMT.

To test the effect of our 40 Hz TMS protocol on cortical excitability we compared the pre-stimulation RMTs with RMTs at the four post-stimulation periods, using a repeated measures analysis of variance (ANOVA). The results provided strong evidence in favor of a TMS timing effect ($BF_{10} = 22.24$), indicating that RMTs differed across the stimulation periods (Fig. 1B). Specifically, compared to the pre-stimulation measures (*Mean* = 59.43 *SD* = 7.99), RMTs were increased in the 0' time point (*Mean* = 63.54 *SD* = 10.39, $BF_{10} = 9.48$), the 15' time point (*Mean* = 63.3 *SD* = 9.47, $BF_{10} = 18.9$), the 30' time point (*Mean* = 62.76 *SD* = 9.3, $BF_{10} = 1.56$), and the 45' time point (*Mean* = 65.89 *SD* = 9.63, $BF_{10} = 34.87$). The inhibitory effect was observed immediately after the stimulation (i.e., time point 0') and reached the highest point at 45 minutes after the stimulation. These results indicate that our 40 Hz TMS stimulation reduces cortical excitability and generates effects on cortical excitability that outlast the stimulation period by at least 45 minutes. The TMS protocol was well tolerated by all participants and there were no complaints of any side effects.

High-frequency TMS at 40 Hz over the human motor cortex can have inhibitory physiological after effects that outlast the stimulation period by at least 45 minutes. Considering that the suppressive effect was at its strongest at 45 minutes after stimulation, a longer lasting effect can be assumed. Overall, our findings revealed that the specific high-frequency gamma TMS protocol is well tolerated and, importantly, it can induce long-lasting effects on neural plasticity. Future work needs to investigate the connection of the effects we report here to known neuronal mechanisms, such as long-term depression.

Declaration of Competing Interest

None.

References

[1] Brown KE, Neva JL, Ledwell NM, Boyd LA. Use of transcranial magnetic stimulation in the treatment of selected movement disorders. Degener Neurol Neuromuscul Dis 2014;4:133–51.
[2] Di Lazzaro V, Dileone M, Pilato F, Contarino MF, Musumeci G, Bentivoglio AR, et al. Repetitive transcranial magnetic stimulation of the motor cortex for hemichorea. J Neurol Neurosurg Psychiatry 2016;77:1095–7.
[3] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201–6.
[4] Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014-2018). Clin Neurophysiol 2020;131:474–528.
[5] May ES, Nickel MM, Ta Dinh S, Tiemann L, Heitmann H, Voth I, et al. Prefrontal gamma oscillations reflect ongoing pain intensity in chronic back pain patients. Hum Brain Mapp 2019;40:293–305.
[6] Mussigmann T, Lefaucheur JP, McGonigal A. Gamma-band activities in the context of pain: a signal from brain or muscle? Neurophysiol Clin 2021;51:287–9.

[7] Strüber D, Herrmann CS. Modulation of gamma oscillations as a possible therapeutic tool for neuropsychiatric diseases: A review and perspective. Int J Psychophysiol 2020;152:15–25.
[8] Tomeh A, Yusof Khan AHK, Inche Mat LN, Basri H, Wan Sulaiman WA. Repetitive transcranial magnetic stimulation of the primary motor cortex beyond motor rehabilitation: a review of the current evidence. Brain Sci 2022;12:761.
[9] Traikapi A, Konstantinou N. Gamma oscillations in alzheimer's disease and their potential therapeutic role. Front Syst Neurosci 2021;15:782399.
[10] Zhang W, Deng B, Xie F, Zhou H, Guo JF, Jiang H, et al. Efficacy of repetitive transcranial magnetic stimulation in Parkinson's disease: A systematic review and meta-analysis of randomised controlled trials. EClinicalMedicine 2022;52:101589.

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