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Letter to the Editor

Modulating corticospinal excitability with transcranial ultrasound stimulation: meta-analytic evidence of online and offline effects

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Transcranial ultrasound stimulation (TUS) is an emerging brain stimulation technique, enabling non-invasive modulation of the nervous system with high spatial resolution (Kim et al., 2021; Sarica et al., 2022; P. Wang et al., 2019). Following evidence of animal TUS neuromodulation (Kim et al., 2021; P. Wang et al., 2019), data have been accumulating that showcase the feasibility, safety, and potential neuromodulatory effects of TUS on humans (Sarica et al., 2022), as well as its therapeutic potential with clinical populations (J. Wang et al., 2025).

An early review of the literature reported that non-primate animal studies demonstrated both excitatory and inhibitory TUS effects, but only inhibitory TUS effects were observed in primates (Kim et al., 2021). This review included only two human studies. Since, multiple human TUS studies demonstrated that excitatory TUS neuromodulation is possible (e.g., Shamli Oghli et al., 2023; Zeng et al., 2022; for reviews Sarica et al., 2022; J. Wang et al., 2025). This growing evidence of human TUS neuromodulation has not yet been systematically assessed.

Systematically identifying human TUS neuromodulation studies equips the field with a dataset representative of the state-of-the-art, where information about sonication protocols and potential effects is gathered. Further, quantitively assessing these studies provides robust estimates of TUS effects in terms of both magnitude and direction for different protocols, while minimising single study bias and controlling for between- and within-study variability. Hence, we considered that it is timely to systematically gather and quantitively assess the reported effects of TUS on corticospinal excitability.

To measure human corticospinal excitability, researchers typically record transcranial magnetic stimulation induced motor evoked potentials (MEPs; Phylactou et al., 2024). Combined with TUS, this can be done online (MEPs during/immediately after a TUS burst) or offline (MEPs after the application of a TUS protocol). Here, we present *meta*-analytic evidence for both online and offline MEP TUS effects.

Following similar earlier work (Phylactou et al., 2023, 2024), we conducted a rapid review of the literature to identify studies that measured MEPs online or offline combined with motor cortex TUS on healthy human participants (*Supp. Table S1*). After screening 431 reports, we identified $n = 18$ studies (*Supp. Fig. S1; Supp. Table S2*), which included data from 348 individuals (estimated age *mean* ± *sd* = 28.63 ± 3.38 years; estimated percentage of females = 44.14 ± 15.30%). Collectively, these studies yielded a total of $k = 208$ effect sizes (online: $k = 80$; offline: $k = 128$).

Using the $k = 208$ effects, we developed 10 multi-level random effect *meta*-analytic models, accounting for within-study dependency (Fig. 1). The effects were categorised into five groups: (i) online MEPs, and offline MEPs following (ii) theta-burst TUS (tbTUS), (iii) non-tbTUS low-intensity TUS (LiFU), and—irrespective of tbTUS or LiFU catergorisation—TUS protocols described by the authors of the primary studies as (iv) inhibitory and (v) excitatory.

Each group comprised two *meta*-analyses. One *meta*-analysis was performed on the MEP ratios of Active TUS over Control (online) or Post- over Pre-TUS (offline) conditions. For ratios, values greater than 1 indicate excitation and values less than 1 indicate inhibition (Fig. 1 top panels). The other *meta*-analysis was performed on the Active versus Sham standardised differences (Hedge's *g*), with time of MEP recordings post stimulation as a moderator. For standardised differences, positive *g* values indicate excitation and negative *g* values indicate inhibition (Fig. 1 bottom panels). Details describing the search strategy and data analysis procedures are provided in the *Supplementary Material*. All data sets, analysis code, and a table with the included studies' details (including sonication parameters for each effect) are openly available on the *Open Science Framework* repository (https://doi.org/10.17605/OSF.IO/78XES).

Results showed that online TUS consistently resulted in inhibition of corticospinal excitability, as reflected in both MEP ratios (ratio = 0.874, *95% CIs* = [0.834, 0.916], $p < 0.001$; Fig. 1A) and Active versus Sham comparisons (g = –1.916, *95% CIs* = [–2.465, –1.367], $p < 0.001$; Fig. 1B). The *meta*-analysis of Post/Pre-tbTUS ratios supported an excitatory effect (ratio = 1.189, *95% CIs* = [1.085, 1.303], $p < 0.001$; Fig. 1C), which was sustained up to 60 min post tbTUS (*Supp. Table S3*). However, when comparing Active versus Sham tbTUS post stimulation, no neuromodulatory effects were evident ($g = 0.254$, *95% CIs* = [–0.681, 1.188], $p = 0.595$; Fig. 1D) at any timepoint post stimulation (*Supp. Table S3*). For LiFU protocols, no significant effects were found for either Post/Pre-LiFU ratios (ratio = 1.044, *95% CIs* = [0.912, 1.196], $p = 0.531$; Fig. 1E; *Supp. Table S3*) nor Active versus Sham LiFU

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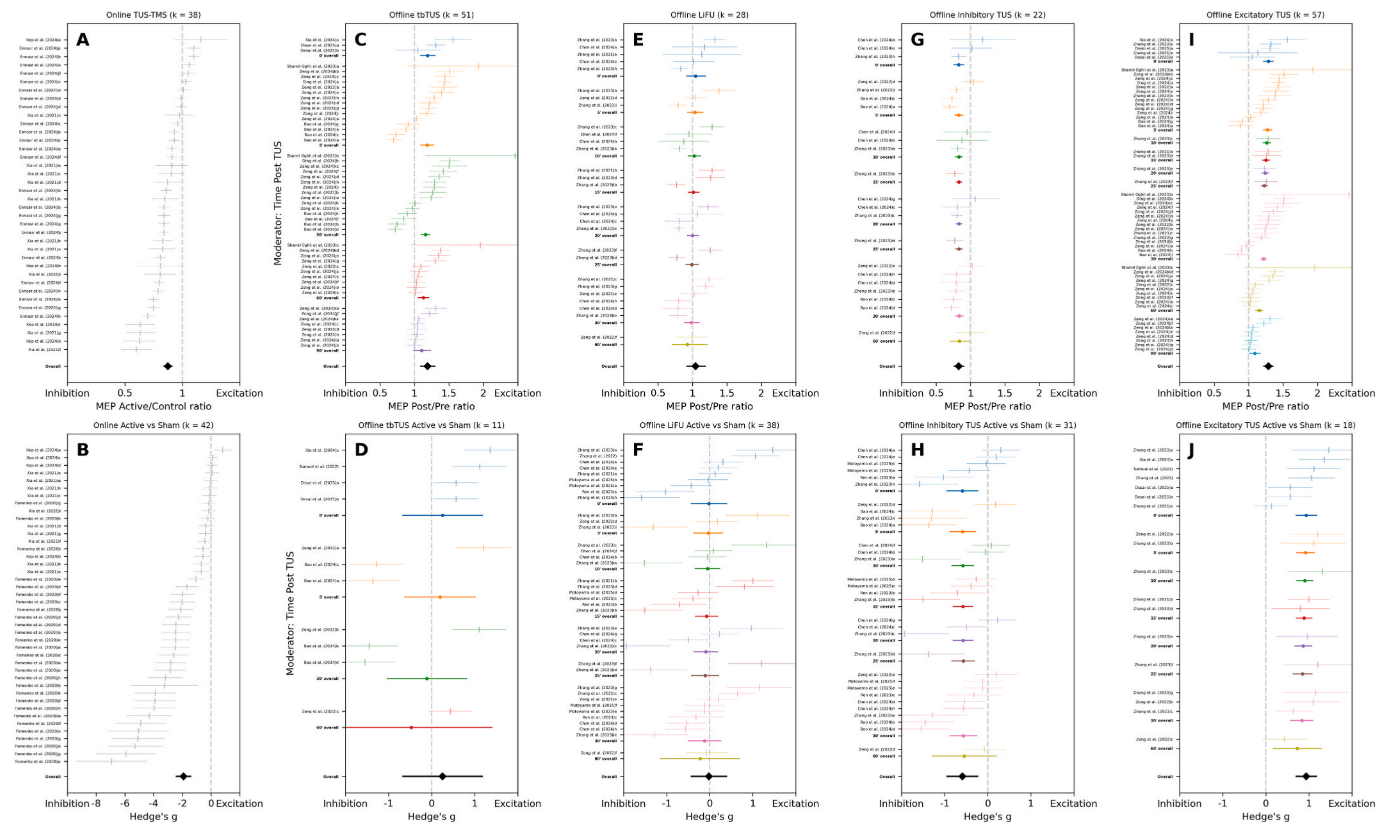

Fig. 1. Meta-analyses performed on online and offline MEPs assessing the effects of TUS. Two sets of analyses were performed for five categorisations. The top panel illustrates *meta*-analyses performed on MEP ratios (Active/Control or Post/Pre MEP ratios), while the bottom panel presents *meta*-analyses performed on Active versus Sham standardised differences. The five categories include (**A, B**) online MEP effects, offline (**C, D**) tbTUS MEP effects, (**E, F**) LiFU MEP effects, (**G, H**) inhibitory TUS MEP effects, and (**I, J**) excitatory TUS MEP effects. Line markers represent individual effects, dot markers moderator effects, and diamond markers overall effects. Different colours illustrate effects included in each moderator level. *Notes.* Error bars depict 95% Confidence Intervals. LiFU: low intensity focused ultrasound; MEPs: motor evoked potentials; tbTUS: theta-burst transcranial ultrasound stimulation; TUS: transcranial ultrasound stimulation.

differences ($g = -0.019$, *95% CIs* = [–0.441, 0.403], $p = 0.930$; Fig. 1F; *Supp. Table S3*). Irrespective of protocol type (i.e., tbTUS or LiFU), decreased corticospinal excitability was confirmed for inhibitory protocols in both Post/Pre ratios (ratio = 0.828, *95% CIs* = [0.756, 0.907], $p < 0.001$; Fig. 1G) and Active versus Sham differences ($g = -0.588$, *95% CIs* = [–0.956, –0.220], $p = 0.002$; Fig. 1H), for up to 30 min (*Supp. Tables S3 and S4*). Finally, increased corticospinal excitability via excitatory protocols was evident for up to 90 min (*Supp. Table S3*) through Post/Pre ratios (ratio = 1.286, *95% CIs* = [1.215, 1.362], $p < 0.001$; Fig. 1I) and up to 60 min (*Supp. Table S4*) through Active versus Sham differences ($g = 0.940$, *95% CIs* = [0.691, 1.189], $p < 0.001$; Fig. 1J).

In summary, our analyses indicate that, to date, online MEPs primarily result in inhibitory effects. This can likely be attributed to TUS increasing $GABA_A$-mediated inhibition mechanisms, similar to short-interval intracortical inhibition (Fomenko et al., 2020). As for offline MEP measures, tbTUS potentially drives excitation, however, such neuromodulatory effects were not present when comparing active to sham tbTUS. LiFU protocols did not show any consistent effects on corticospinal excitability in either direction. Although, when analyses were based on whether a protocol was defined as inhibitory or excitatory (by the primary study authors), both inhibition and excitation were echoed in their respective *meta*-analyses. This illustrates that changes to the tbTUS and LiFU sonication parameters can induce effects on corticospinal excitability in both directions (Bao et al., 2024).

Conclusively, the *meta*-analyses confirm the neuromodulatory effects of TUS and illustrate the bidirectionality of offline TUS neuromodulation. Further, our work provides the community with an openly available, up-to-date, systematically identified dataset of the state-of-the-art of the TUS-MEP literature on the healthy human motor cortex.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2026.2112330.

References

Bao, S., Kim, H., Shettigar, N.B., Li, Y., Lei, Y., 2024. Personalized depth-specific neuromodulation of the human primary motor cortex via ultrasound. J. Physiol. 602 (5), 933–948. https://doi.org/10.1113/JP285613.

Fomenko, A., Chen, K.-H.-S., Nankoo, J.-F., Saravanamuttu, J., Wang, Y., El-Baba, M., Xia, X., Seerala, S.S., Hynynen, K., Lozano, A.M., Chen, R., 2020. Systematic examination of low-intensity ultrasound parameters on human motor cortex excitability and behavior. Elife 9, e54497. https://doi.org/10.7554/eLife.54497.

Kim, T., Park, C., Chhatbar, P.Y., Feld, J., Mac Grory, B., Nam, C.S., Wang, P., Chen, M., Jiang, X., Feng, W., 2021. Effect of low intensity transcranial ultrasound stimulation on neuromodulation in animals and humans: an updated systematic review. Front. Neurosci. 15. https://doi.org/10.3389/fnins.2021.620863.

Phylactou, P., Pham, T.N.M., Narskhani, N., Diya, N., Seminowicz, D.A., Schabrun, S.M., 2024. Phosphene and motor transcranial magnetic stimulation thresholds are correlated: a meta-analytic investigation. Prog. Neuropsychopharmacol. Biol. Psychiatry 133, 111020. https://doi.org/10.1016/j.pnpbp.2024.111020.

Phylactou, P., Traikapi, A., Konstantinou, N., 2023. One in four people fail to perceive phosphenes during early visual cortex transcranial magnetic stimulation. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation 16 (1), 23–24. https://doi.org/10.1016/j.brs.2022.12.012.

Sarica, C., Nankoo, J.-F., Fomenko, A., Grippe, T.C., Yamamoto, K., Samuel, N., Milano, V., Vetkas, A., Darmani, G., Cizmeci, M.N., Lozano, A.M., Chen, R., 2022. Human studies of transcranial ultrasound neuromodulation: a systematic review of effectiveness and safety. Brain Stimul. 15 (3), 737–746. https://doi.org/10.1016/j.brs.2022.05.002.

Shamli Oghli, Y., Grippe, T., Arora, T., Hoque, T., Darmani, G., Chen, R., 2023. Mechanisms of theta burst transcranial ultrasound induced plasticity in the human motor cortex. Brain Stimul. 16 (4), 1135–1143. https://doi.org/10.1016/j.brs.2023.07.056.

Wang, J., Wang, H., Jiang, T., Wang, Y., Li, N., Qie, S., 2025. Transcranial ultrasound stimulation parameters for neurological diseases: a systematic review. Front. Neurol. 16. https://doi.org/10.3389/fneur.2025.1567482.

Wang, P., Zhang, J., Yu, J., Smith, C., Feng, W., 2019. Brain modulatory effects by low-intensity transcranial ultrasound stimulation (TUS): a systematic review on both animal and human studies. Front. Neurosci. 13. https://doi.org/10.3389/fnins.2019.00696.

Zeng, K., Darmani, G., Fomenko, A., Xia, X., Tran, S., Nankoo, J.-F., Shamli Oghli, Y., Wang, Y., Lozano, A.M., Chen, R., 2022. Induction of human motor cortex plasticity by theta burst transcranial ultrasound stimulation. Ann. Neurol. 91 (2), 238–252. https://doi.org/10.1002/ana.26294.

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