NMDA-receptor agonist reveals LTP-like properties of 10-Hz rTMS in the human motor cortex

Dear Editor,

Repetitive Transcranial Magnetic Stimulation (rTMS) is a safe and effective treatment for a growing number of neuropsychiatric disorders. While the utilization of clinical rTMS is advancing rapidly, it is happening without a clear mechanistic understanding of how TMS changes the brain. Improved mechanistic understanding could ultimately improve clinical treatments through targeted navigation of the infinite rTMS parameter space and potential pharmacological augmentation.

The early hypothesis that high-frequency (≥5-Hz) rTMS works through long-term potentiation (LTP) at the cellular level was based on limited evidence, and competing hypotheses are gaining attention. However, LTP-like effects have been observed with 10-Hz magnetic stimulation in mouse hippocampal slices, including increased dendritic spine size, increased GluA1-receptor composition, and n-methyl-D-aspartate (NMDA)-receptor-mediated post-synaptic currents [1].

In the human motor cortex, various plasticity-promoting rTMS protocols depend on NMDA-receptors [2–4]. However, specificity is lacking, as it is unclear if NMDA receptor activation is sufficient to enhance rTMS-induced facilitation. For example, NMDA-receptor activation with d-cycloserine (DCS) was insufficient to enhance facilitation induced by intermittent theta burst stimulation (iTBS) in two independent studies [5,6]. By contrast, DCS was sufficient to enhance 10-Hz rTMS-mediated facilitation over 1-hour in a crossover design, again supporting an LTP-like mechanistic hypothesis [7].

Combining pharmacology and rTMS with mechanism-revealing neurophysiology protocols is an unexplored approach. Paired-pulse protocols including intracortical inhibition and intracortical facilitation (ICF and ICI) are well-established. They capitalize on different neural regions, respectively [8]. We hypothesized that ICF and ICI would reveal rTMS-like features underlying previously published 10 Hz rTMS-induced facilitation with DCS from the same cohort [7].

Ten healthy adults (4 female) aged 26–37 years who met TMS safety requirements participated in the study. All participants provided informed consent. This study was approved by the Medical University of South Carolina Institutional Review Board.

Participants were randomly assigned to receive 100 mg DCS or identical microcrystalline cellulose capsules (Tidewater pharmacy, Mt. Pleasant, SC) in a double-blinded, randomized, crossover study. rTMS was administered at the time of peak drug bioavailability, which is 2 hours after oral ingestion (Fig. 1A). Neuronavigated determination of primary motor cortex (M1) hotspot and resting motor threshold (rMT) was previously described [7]. Paired-pulse measures were obtained before and after rTMS, or approximately 1 hour, and 3 hours after drug disbursement, respectively [7].

Paired pulses were separated by inter-stimulus interval (1) of 3 ms for ICI, and 15 ms for ICF [7]. The conditioning stimulus (CS) was subthreshold intensity (80% rMT), and the testing stimulus (TS) was at a predetermined rMT for 1 mV (~120% rMT). We collected single- and paired-pulse MEPs with Magstim 2002 and BiStim capacitors (Magstim, UK) in bins of 20 pulses, jittered 4–7 sec apart. We analyzed MEPs with Spike2 software (Cambridge Electronic Devices, UK). We amplified and filtered the raw signal with CED 1902 and 1401 microprocessors (Cambridge Electronic Devices, UK).

We administered 10-Hz rTMS over the left M1 with MagPro R30 with figure-8 B65 cooled coil (MagVenture, Denmark) because the MagStim device could not deliver rTMS. We delivered 300 pulses over 20 minutes with a 1.5 sec-on/58.5 sec-off duty cycle at 80% rMT (rMT obtained separately for MagVenture system), as previously described [7].

We calculated the average MEP peak-to-peak amplitude for each bin to create a paired-pulse/single-pulse ratio (MEPp/MEPSP) to yield ICF and ICI measures in respective protocols, then calculated change in ICF and ICI associated with rTMS (i.e., Δ = post-rTMS value minus pre-rTMS value) to generate ΔICF and ΔICI. Wilcoxon signed-rank tests compared ΔICF and ΔICI between DCS and PBO conditions within subjects (e.g., ΔICFDCS vs. ΔICFPBO) to assess within-subject relative change. Two-sided P value < 0.05 was considered statistically significant.

Mean ΔICFDCS was –0.48, compared to 0.36 for ΔICFPBO (Fig. 1B, P = 0.037, Cohen’s d = 1.13). Mean ΔICPBO was –0.26 with DCS, compared to 0.25 for ΔICFPBO (Fig. 1D, P = 0.027, Cohen’s d = 1.16).

At face value, these results were paradoxical. In order to better understand them, we examined the raw MEP values before ratios were calculated (Fig. 1C and E, MEP values in legends). The PBO condition produced modest facilitation before rTMS, which then became robust (steeper slope) after rTMS (Fig. 1C). This is consistent with the hypothesis that ‘excitatory’ rTMS would enhance glutamatergic tone in an LTP-like manner. DCS, by contrast, produced robust facilitation (Mean (PBO) ICF: 1.69 vs. 1.25) before rTMS; consistent with a glutamatergic (NMDA receptor) agonist effect. We attribute the modest ICF and lack of facilitation after 10 Hz in the PBO group to the inherent MEP variability from a single time point.
Fig. 1. The effects of NMDA receptor partial agonist D-cycloserine and 10 Hz rTMS on paired-pulse measures intracortical facilitation and intracortical inhibition. Fig. 1A. Study design. Fig. 1B: ICF after rTMS is inhibited under DCS condition relative to PBO. ICF change post-pre rTMS between PBO and DCS conditions. The lines connect the same subjects between two conditions. Each subject is color coded. PBO vs. DCS (Mean ± SEM, 0.36 ± 0.23 vs. 0.48 ± 0.25, *p = 0.037). Orange line represents mean ICF change post-pre rTMS. Fig. 1C: DCS is associated with an "occlusion" effect, an LTP-like property of 10-Hz rTMS. MEP amplitude in ICF protocol pre- and post-rTMS under PBO condition. Red lines represent mean SP and PP MEP amplitudes of pre-rTMS and post-rTMS under PBO condition. Blue lines represent mean SP and PP MEP amplitudes of pre-rTMS and post-rTMS under PBO condition. Red lines represent mean SP and PP MEP amplitudes of pre-rTMS and post-rTMS under DCS condition. Each subject is color coded. MEP values in Mean ± SE. Pre-rTMS: PBO SP-MEP 1.13 ± 0.10, PP-MEP 1.40 ± 0.19; DCS SP-MEP 0.96 ± 0.06, PP-MEP 1.58 ± 0.21. Post-rTMS: PBO SP-MEP 1.13 ± 0.14, PP-MEP 1.75 ± 0.22; DCS SP-MEP 1.55 ± 0.28, PP-MEP 1.78 ± 0.32. Fig. 1D: ICI after rTMS is enhanced under DCS condition relative to PBO. ICI change post-pre rTMS between PBO and DCS conditions. The lines connect the same subjects between two conditions. Each subject is color coded. PBO vs. DCS (Mean ± SEM, 0.25 ± 0.18 vs. 0.26 ± 0.09, *p = 0.027). Orange line represents mean ICI change post-pre rTMS. Fig. 1E: DCS is associated with a "homeostatic" effect, an LTP-like property of 10-Hz rTMS. MEP amplitude in ICI protocol pre- and post-rTMS under PBO condition. Red lines represent mean SP and PP MEP amplitudes of pre-rTMS and post-rTMS under PBO condition. Red lines represent mean SP and PP MEP amplitudes of pre-rTMS and post-rTMS under DCS condition. Each subject is color coded. MEP values in Mean ± SE. Pre-rTMS: PBO SP-MEP 1.13 ± 0.10, PP-MEP 0.46 ± 0.06; DCS SP-MEP 0.96 ± 0.06, PP-MEP 0.58 ± 0.14. Post-rTMS: PBO SP-MEP 1.13 ± 0.14; DCS SP-MEP 0.63 ± 0.18; DCS SP-MEP 1.55 ± 0.28, PP-MEP 0.39 ± 0.07. M1 = Primary Motor Cortex; MT = Motor Threshold; BL = Baseline; rTMS = repetitive Transcranial Magnetic Stimulation; MEP = motor evoked potential; ICF = intracortical facilitation; ICI = intracortical inhibition; SP = single-pulse; PP = paired-pulse; rTMS = repetitive Transcranial Magnetic Stimulation; DCS = D-Cycloserine; PBO = Placebo; SE = standard error. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
point (consider [2]), which can be mitigated through same-subject comparisons enabled by a crossover design. Intriguingly, after rTMS, which creates a high baseline MEPSP (Mean ± SE, 1.55 ± 0.28), the subsequent facilitation is quite modest, suggesting a saturation or ‘occlusion’ effect - a classic finding in LTP studies [9]. Interestingly, observations of numerous human MEP studies suggest there may be a physiologic upper-limit near 75% above baseline.

In contrast to ICF, ICI was mitigated by rTMS alone (i.e., PBO; Fig. 1E), again consistent with the expected effect following an ‘excitatory’ stimulation protocol. DCS, on the other hand, expectedly blunted ICI before rTMS, but unexpectedly, produced the strongest inhibition after rTMS. We speculate that this effect may be the result of concurrent homeostatic depression superimposed excitatory postsynaptic activity. In contrast to ICF, ICI was mitigated by rTMS alone (i.e., PBO; Fig. 1E), again consistent with the expected effect following an ‘excitatory’ stimulation protocol [10]. Animal studies are needed to verify this hypothesis, but we find it remarkable that these results occur in conjunction with the ‘occlusion’ observed with ICF. Moreover, all MEPSP data and PBO data are consistent with what we might expect from ‘excitatory’ rTMS and NMDA receptor agonist activity.

These results suggest that 10-Hz rTMS produces an excitatory effect through glutamatergic activity; and that NMDA receptor partial agonist DCS in combination with 10-Hz rTMS may produce occlusion of ICF, and homeostatic depression unmasked by ICI. In summary, these results suggest LTP-like mechanisms underlying 10-Hz rTMS in the human motor cortex; though our small sample size warrants caution to avoid type I error. Replication is warranted.

Declaration of competing interest

The authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.03.016.

References

[1] Vlachos A, Muller-Dahlhaus F, Rosskopf J, Lenz M, Zieman U, Deller T. Repe- titive magnetic stimulation induces functional and structural plasticity of excit- atriatory postsynapses in mouse organotypic hippocampal slice cultures. J Neurosci 2012;32(48):17514–23.
[2] Huang YZ, Chen RS, Rothwell JC, Wen HY. The after-effect of human theta burst stimulation is NMDA receptor dependent. Clin Neurophysiol 2007;118(5):1028–32.
[3] Suppa A, Biasiotta A, Belvisi D, Maralli L, La Cesca S, Truini A, Crucetti G, Berardelli A. Heat-evoked experimental pain induces long-term potentia- tion-like plasticity in primary human motor cortex. Cereb Cortex 2013;23(8):1942–51.
[4] Stefan K, Kunesch E, Benecke R, Cohen LG, Classen J. Mechanisms of enhance- ment of human motor cortex excitability induced by interventional paired associative stimulation. J Physiol 2002;543(2):699–708.
[5] Teo JTH, Swayne OB, Rothwell JC. Further evidence for NMDA-dependence of the after-effects of human theta burst stimulation. Clin Neurophysiol 2012;123(7).
[6] Selby B, MacMaster FP, Kirton A, McGarr A. D-Cycloserine blunts motor cortex facilitation after intermittent theta burst transcranial magnetic stimulation in multiple sclerosis. Brain Stimul 2013;6:406–7.
[7] Brown JC, DeVries WH, Korte JE, Sahlem GL, Bonilha L, Short EB, et al. NMDA receptor partial agonist, d-cycloserine, enhances 10 Hz rTMS-induced motor plasticity, suggesting long-term potentiation (LTP) as underlying mechanism. Brain Stimul 2019;12(4):1063–5, 2019.
[8] Ziemann U, Rothwell JC, Ridding MC. Interaction between intracortical inhibi- tion and facilitation in human motor cortex. J Physiol 1996;496(3):873–81.
[9] Whitlock JR, Heynens AJ, Shuler MG, Bear MF. Learning induces long-term potentiation in the Hippocampus. Science 2006;313:1091–7.
[10] Turrigiano G. Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. Cold Spring Harb Perspect Biol 2012;4(1): a005736.

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