Review Paper

CCNP Young Investigator Award

# Pharmacological adjuncts and transcranial magnetic stimulation-induced synaptic plasticity: a systematic review

**Myren N. Sohn, BSc; Joshua C. Brown, MD, PhD; Prayushi Sharma, BSc; Ulf Ziemann, MD; Alexander McGirr, MD, PhD**

**Background:** Transcranial magnetic stimulation (TMS) is a noninvasive neurostimulation modality that has been used to study human synaptic plasticity. Leveraging work in ex vivo preparations, mechanistically informed pharmacological adjuncts to TMS have been used to improve our fundamental understanding of TMS-induced synaptic plasticity. **Methods:** We systematically reviewed the literature pairing pharmacological adjuncts with TMS plasticity-induction protocols in humans. We searched MEDLINE, PsycINFO, and Embase from 2013 to Mar. 10, 2023. Studies published before 2013 were extracted from a previous systematic review. We included studies using repetitive TMS, theta-burst stimulation, paired associative stimulation, and quadripulse stimulation paradigms in healthy and clinical populations. **Results:** Thirty-six studies met our inclusion criteria (28 in healthy and 8 in clinical populations). Most pharmacological agents have targeted the glutamatergic *N*-methyl-D-aspartate (NMDA; 15 studies) or dopamine receptors (13 studies). The NMDA receptor is necessary for TMS-induced plasticity; however, sufficiency has not been shown across protocols. Dopaminergic modulation of TMS-induced plasticity appears to be dose-dependent. The GABAergic, cholinergic, noradrenergic, and serotonergic neurotransmitter systems have small evidence bases supporting modulation of TMS-induced plasticity, as do voltage-gated calcium and sodium channels. Studies in clinical populations suggest that pharmacological adjuncts to TMS may rescue motor cortex plasticity, with implications for therapeutic applications of TMS and a promising clinical trial in depression. **Limitations:** This review is limited by the predominance in the literature of studies with small sample sizes and crossover designs. **Conclusion:** Pharmacologically enhanced TMS largely parallels findings from ex vivo preparations. As this area expands and novel targets are tested, adequately powered samples in healthy and clinical populations will inform the mechanisms of TMS-induced plasticity in health and disease.

## Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive neurostimulation technique that induces electrical currents in underlying brain parenchyma through electromagnetic induction.[1] It is one of the most established noninvasive neurostimulation modalities and has unique advantages over others that deliver current or mechanically deform neural membranes to impact neuronal function. Specifically, TMS can generate rapidly alternating fields with the precision of cubic centimetres in cortical targets.[1] This property sets TMS apart from the other techniques because it can approximate synaptic plasticity protocols in ex vivo preparations and tractable species, in vivo, and in the human brain.

Synaptic plasticity refers to the activity-dependent changes to the electrochemical communication between neurons.[2,3] At the tripartite synapse, this communication depends on vesicular release at the presynaptic terminal, reuptake from the synaptic cleft, and activation of both synaptic and extrasynaptic ionotropic and metabotropic receptors, which then cause a cascade of intracellular programs to strengthen or weaken synaptic weights. Although synaptic plasticity occurs at multiple timescales, here we focus on the long-term induction of synaptic plasticity, namely long-term potentiation (LTP) and long-term depression (LTD).[4] In the field of human TMS, these activity-dependent changes are termed "LTP-like" and "LTD-like," principally because the spatial resolution of TMS results in population-level neuronal firing,

**Correspondence to:** A. McGirr, 3280 Hospital Drive NW, Calgary, AB, T2N 4Z6; alexander.mcgirr@ucalgary.ca

Submitted June 2, 2023; Revised Oct. 23, 2023; Revised Nov. 3, 2023; Accepted Nov. 8, 2023

**Cite as:** *J Psychiatry Neurosci* 2024 February 15;49(1). doi: 10.1503/jpn.230090

and cellular-level changes are inferred rather than shown.[5,6] Moreover, alterations to different neuronal populations may underlie the facilitation or attenuation of TMS responses following plasticity-induction protocols. For instance, similar changes may be observed with decreased inhibition (i.e., GABAergic reduction) or increased excitability (i.e., glutamatergic enhancement).[7–9]

The noninvasive neurostimulation field, and TMS more specifically, has leveraged pharmacology and our understanding of synaptic plasticity in ex vivo preparations in tractable species to inform LTD-like and LTP-like processes (Figure 1).[10] Over the last 2 decades, many groups have used repetitive TMS (rTMS) including theta-burst stimulation (TBS), paired associative stimulation (PAS) and, more recently, quadripulse stimulation (QPS) in conjunction with pharmacological adjuncts to determine how LTP-like and LTD-like processes are modulated in the human brain.[10] We are witnessing a renaissance in this area, as certain intersectional approaches have matured to the point of extension into therapeutic applications of TMS, with the goal of pharmacologically augmenting treatment effects.[11]

## *Synaptic plasticity and metaplasticity*

Hebbian-type plasticity denotes synapse-specific modification in synaptic strength following afferent stimulation.[12] It is a tightly regulated process that is dependent on the *N*-methyl-D-aspartate (NMDA) receptor to produce strengthening (LTP) or weakening (LTD) of synaptic communication.[4,12,13] Tetanic stimulation activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, generating a positive inward current in the postsynaptic membrane that triggers release of the voltage-dependent magnesium block in NMDA receptors.[12,14] A subsequent influx of calcium ions triggers the molecular cascade that leads to the insertion of AMPA receptors into the postsynaptic membrane, allowing this synapse to respond more effectively to future inputs. Conversely, low-frequency stimulation results in a small influx of intracellular calcium due to incomplete magnesium block of the NMDA receptor, activating protein phosphatases and the endocytosis of AMPA receptors to produce LTD.[12] As such, the induction of LTD rather than LTP occurs, with smaller increases in intracellular calcium that occur when the postsynaptic neuron is less depolarized. However, glutamatergic signalling does not act alone in activity-dependent adaptation, and in TMS the population-level output from stimulation reflects the integration of excitatory and inhibitory (i.e., GABAergic) neurotransmission as well as neuromodulators, including acetylcholine, norepinephrine, dopamine, and serotonin, that have both local- and circuit-level effects on neural states.[10,15]

Another important consideration is metaplasticity, referring to the plasticity of plasticity, or how prior activity-dependent changes modify the ability of the neuron to adapt

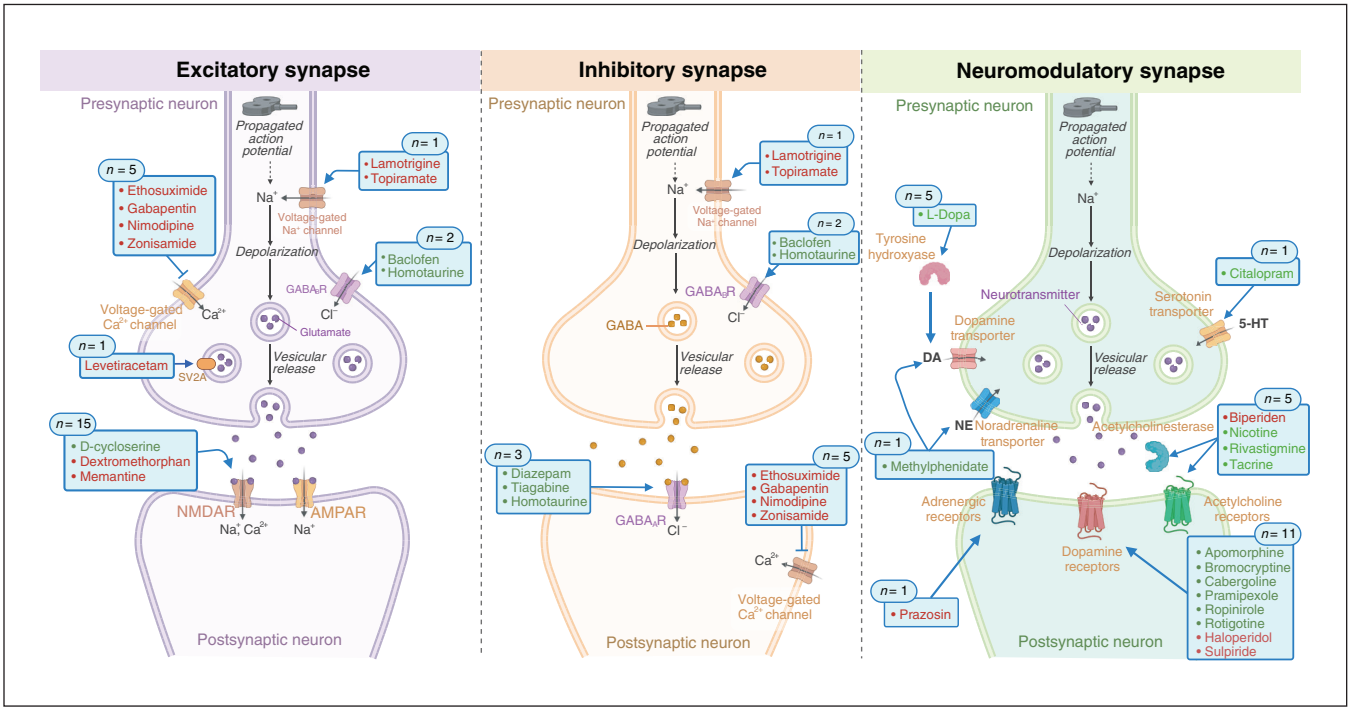


**Figure 1:** Pharmacological adjuncts used in conjunction with TMS plasticity protocols. The panels are organized according to compounds predominantly targeting excitatory synapses (left panel), inhibitory synapses (middle panel), and synapses where neuromodulators are released (right panel). Compounds are colour coded as green when the net effect is to facilitate synaptic plasticity and red when the net effect is to decrease synaptic plasticity resulting from TMS plasticity protocols. The number of studies for each mechanism is denoted in the oval above each grouping. Not depicted are piracetam and lovastatin in participants with neurofibromatosis, and home dosing of olanzapine/quetiapine/risperidone in participants with schizophrenia.

to subsequent LTP- or LTD-inducing patterns of neural activity.[16,17] A longstanding model of synaptic plasticity and metaplasticity is the Bienenstock–Cooper–Munro (BCM) model, whereby LTP and LTD are proposed to occur on a threshold that changes based on previous postsynaptic activity.[18] Previously low levels of postsynaptic activity favour the induction of LTP, while high levels of postsynaptic activity will favour the induction of LTD. Metaplasticity regulates Hebbian-type plasticity to stabilize neuronal networks and maintain activity within physiologic range.[17,19,20] Thus, the duration of the interstimulation interval is critical to how circuits can adapt to subsequent stimuli. The cell must have sufficient time for local protein synthesis, such that prior activity does not occlude the effect of subsequent tetani.[21] Increasing data suggest that 40–90 minutes are required between tetani, just as in ex vivo preparations.[22–25]

Moreover, pivotal work has shown that "more is not better" with TMS.[26,27] In keeping with BCM predictions, variations in the parameter space drive fundamentally different neural adaptations.[21] For instance, delivering TBS intermittently more commonly results in LTP-like changes, whereas its continuous application more commonly results in LTD-like changes.[28] An important caveat to this oversimplification is that TMS applied to the human brain will result in the expected LTP-like/LTD-like process in only about 60% of healthy participants,[29] although optimization of parameter selection could increase this percentage.[30] Similarly, modifications to the number of pulses delivered[26,31] or duration of pulse train[32] while keeping all other parameters identical can produce opposite effects.[27] We highlight this to remind ourselves that the interplay between the TMS parameter space and synaptic plasticity is complex. The type of TMS paradigm used and the timing of stimulation have important implications for plasticity induction. Pharmacological adjuncts add a layer of complexity that must be considered carefully in study design and interpretation.

### *TMS plasticity protocols*

With TMS, pulses may be patterned to induce LTP-like and LTD-like adaptation. These are most commonly in the form of trains of TMS pulses at specific frequencies, or bursts of TMS pulses delivered at the theta frequency.[33] Although informed by the ex vivo synaptic plasticity literature, the early investigation of pharmacological enhancement of rTMS suffered from engineering constraints limiting high-frequency rTMS to 5 Hz–20 Hz trains. In ex vivo preparations, high-frequency or tetanic stimulation most commonly involves 100 Hz trains, whereas paired protocols, where stimulation is paired with membrane depolarization, reliably produce LTP at low frequencies (< 3 Hz).[34] It is tempting to speculate that with the broad magnetic fields of TMS affecting apical and basal dendritic regions, in contrast to the spatially precise stimulation of ex vivo electrical stimulation, we may be employing a sort of paired protocol leading to LTP[9] and LTP-like effects.[35,36] However, this has yet to be shown. LTD-like protocols, on the other hand, have been directly informed by the ex vivo synaptic plasticity literature, where long trains of 1 Hz stimulation induce LTD.[37]

Theta-burst stimulation paradigms leverage biologically relevant hippocampal physiology to induce synaptic LTP-like or LTD-like plasticity through intermittent (iTBS) or continuous TBS (cTBS), respectively.[28] Although TBS is also informed by the ex vivo literature, it typically involves more bursts within a train and a larger number of pulses than are used in slice; therefore, direct correlations with the ex vivo literature to inform pharmacological augmentation must also be made with caution. Further challenges in comparing ex vivo slice preparations and in vivo human plasticity include the isolated circuits studied in slice preparations relative to the intact brain, brain state changes unique to living organisms, and heterogeneity of the metabolic environment of the brain, such as glucose levels, caffeine,[38,39] or prior experience.[40]

Another approach used to induce LTP-like and LTD-like changes with TMS involves PAS, whereby peripheral stimulation of somatosensory afferents (e.g., median nerve at the wrist) is combined with a TMS pulse over the contralateral motor cortex.[41] The timing of the 2 pulses modifies the effect on the synapse. Specifically, motor cortex TMS following median nerve stimulation at 25 ms (PAS25) leads to synchronous motor cortical responses to both inputs, strengthening synaptic efficacy and increasing the amplitude of motor-evoked potentials (MEPs).[41] Conversely, when the cortex is stimulated 10 ms (PAS10) after the median nerve, asynchronous arrival of stimuli has an LTD-like effect.[42]

Quadripulse stimulation is a TMS stimulation protocol that has also shown the induction of LTP-like and LTD-like changes.[43] It consists of 4 monophasic TMS pulses with 1.5 ms interpulse intervals that, when repeated at 0.2 Hz for 30 minutes, induce LTP-like facilitation in the motor cortex.[43] Changing the interstimulus interval changes the effect on synaptic plasticity. Specifically, short interpulse intervals (i.e., 1.5 ms/666 Hz, 5 ms/200 Hz, or 10 ms/100 Hz) result in LTP-like effects while longer interpulse intervals (i.e., 50 ms/20 Hz) result in LTD-like effects.[44] Studies to date typically use paradigms of 5 ms/200 Hz (QPS5) to induce LTP-like and 50 ms/20 Hz (QPS50) to induce LTD-like effects.[45]

### *Measuring LTP-like and LTD-like processes after TMS*

To study LTP-like and LTD-like processes with TMS, the dominant approach to date has used the motor cortex as a model circuit to measure changes in corticospinal excitability as indexed by MEP amplitude before and after intervention.[10,46] The 2 most common measurements of cortical plasticity include the change of MEP amplitude measured at a fixed intensity and the stimulus response curve (SRC), which consists of the MEP amplitude measured at a range of intensities.

A TMS pulse to the motor cortex can directly (D-waves) or indirectly (I-waves) activate corticospinal neurons.[47,48] D-waves represent direct stimulation of layer V pyramidal axons resulting from the first descending volley following high-intensity stimulation. I-waves follow about 1.5 ms after a D-wave, representing indirect activation of corticospinal neurons through cortical interneurons. Notably, different types of I-waves with different origins are recruited at

different stimulus intensities. I1-waves are recruited by TMS at threshold intensities and are thought to represent monosynaptic excitation of layer V pyramidal neurons. As such, increased amplitude of I1-waves reflects increased pyramidal tract excitability. As stimulation intensity increases, I1-waves increase in size and are followed by later volleys (late I-waves). Late I-waves are associated with the interconnections of GABAergic interneurons between layer II, III, and V pyramidal neurons. The most commonly applied approach to measure the peak-to-peak amplitude of MEPs at a fixed proportion of motor threshold, typically 120% of motor threshold, is to assay I-waves before and after the TMS plasticity protocol.

Another commonly applied measure of corticospinal excitability involves leveraging the input–output function associated with TMS stimulus intensity (the stimulus response curve).[49–51] With increasing stimulus intensities, a sigmoidal increase in MEP amplitudes is observed, representing a larger volume of cortex reaching firing threshold until the volume of excited parenchyma exceeds the anatomic representation of a given muscle and no further neurons are recruited with a stronger stimulus. Stimulus response curves, or recruitment curves, are thus an informative metric of corticospinal excitability within these circuits and expansion/reduction of neuronal ensembles.

### *Pharmacological augmentation of TMS plasticity protocols*

To the best of our knowledge, the field of pharmacological adjuncts and TMS-associated plasticity has not been systematically reviewed in the last decade, despite significant growth in TMS-related research and a renaissance with the first proof of principle demonstration that clinical applications of TMS can be enhanced by leveraging mechanistically informed pharmacological augmentation.[11] As such, the goal of the present review is to summarize and critically analyze the literature using TMS plasticity protocols and pharmacological adjuncts in human participants. We aim to help identify areas of convergence and gaps to inform future experiments.

We systematically reviewed the literature with a focus on studies that have used the intersection of mechanistically informed adjuncts and rTMS, TBS, PAS, or QPS in the human brain. We organized the literature first by the neurotransmitter system targeted by the adjunct, and then according to the health status of the participants.

## Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[52] The protocol was preregistered on the international register of prospective systematic reviews (PROSPERO; CRD42023396267).

### *Search strategy*

The MEDLINE, Embase, and PsycINFO databases were searched from 2013 to Mar. 10, 2023. Articles published before 2013 were extracted from an earlier study.[10] The full search strategy can be found in Appendix 1, Figure 1, available at https://www.jpn.ca/lookup/doi/10.1503/jpn.230090/tab-related-content. The reference lists of included studies were reviewed to identify studies that may not have been captured by our search.

### *Selection criteria*

Articles examining the effects of pharmacological augmentation to synaptic plasticity–inducing TMS protocols were included in this review. This includes high-frequency rTMS, low-frequency rTMS, iTBS or cTBS, PAS, and QPS protocols. To be included, studies must have reported assessment of some measure of change in physiology and/or behaviour following TMS with a pharmacological adjunct. We included studies conducted with human participants of any age, sex, or gender. Studies in both healthy participants and individuals with neuropsychiatric conditions were included. We did not consider studies using TMS to quantify the effect of other neurostimulation modalities, such as transcranial direct current stimulation. We similarly did not consider the influences of pharmacological adjuncts on neurophysiological measures (e.g., resting motor threshold, active motor threshold, and cortical silent period) or paired pulse experiments to quantify intracortical facilitation or inhibition unless these metrics were used as an outcome measure following a plasticity-induction protocol.

### *Data collection*

Titles and abstracts were screened by 2 reviewers (M.N.S., A.M.), and 2 independent reviewers extracted data from eligible studies (M.N.S., P.S., or J.C.B.). Discrepancies were resolved by consensus or a third reviewer (A.M.). The following items were systematically extracted from included studies:

(1) Study design (e.g., parallel groups, crossover)
(2) Drug and dosage
(3) Mean age of population
(4) Percentage of male participants
(5) Number of participants
(6) Disease state of participants
(7) TMS plasticity-induction protocol
(8) TMS target site, muscle of interest, and/or electroencephalography site of interest
(9) Measurement and intervention timing
(10) Physiologic and/or behavioural changes following the intervention

### *Risk of bias*

The quality of included studies was assessed (M.N.S.) using the Cochrane Risk of Bias (RoB) 2 tool for randomized trials. Any nonrandomized trials included were assessed using the Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) tool.

## Results

The results of our literature search are summarized in Figure 2. Risk of bias assessments are reported in Appendix 1, Figure 2. Thirty-six studies met our inclusion criteria. Twenty-eight studies were conducted in healthy participants and 8 in clinical populations (Alzheimer disease $n = 1$, major depressive disorder [MDD] $n = 2$, mild cognitive impairment $n = 1$, neurofibromatosis $n = 1$, Parkinson disease $n = 2$, and schizophrenia $n = 1$).

Pharmacological augmentation targeting the glutamatergic (healthy participants $n = 13$, MDD $n = 2$), GABAergic (healthy participants $n = 2$, mild cognitive impairment $n = 1$), dopaminergic (healthy participants $n = 9$, Alzheimer disease $n = 1$, Parkinson disease $n = 2$, and schizophrenia $n = 1$), serotonergic (healthy participants $n = 1$), cholinergic (healthy participants $n = 3$, Alzheimer disease $n = 1$), and adrenergic (healthy participants $n = 1$) systems were identified. Pharmacological augmentation targeting voltage-gated calcium (VGCC; healthy participants $n = 4$) and sodium (VGSC; healthy participants $n = 1$) channels were also present. Most studies applied PAS ($n = 14$) or TBS ($n = 11$), though QPS ($n = 2$) and 10 Hz rTMS ($n = 3$) interventions have also been conducted.

### *Glutamate (15 studies)*

#### Healthy participants (13 studies)

The effect of glutamatergic drugs on TMS-induced synaptic plasticity has been studied pairing NMDA receptor antagonists[42,53–58] and agonists[35,36,59–62] with TBS,[53–55,60–62] 10 Hz rTMS,[35,36,59] and PAS protocols.[42,56–58,63] The effects of glutamatergic modulation in healthy individuals have been assessed measuring MEP amplitudes at fixed stimulus intensites, SRCs, and using saccadic eye movements. Study sample sizes ranged from 6 to 30 participants, with only 6 samples from 5 studies having more than 10 participants.[54,55,57,61,62] Results are presented in Table 1.

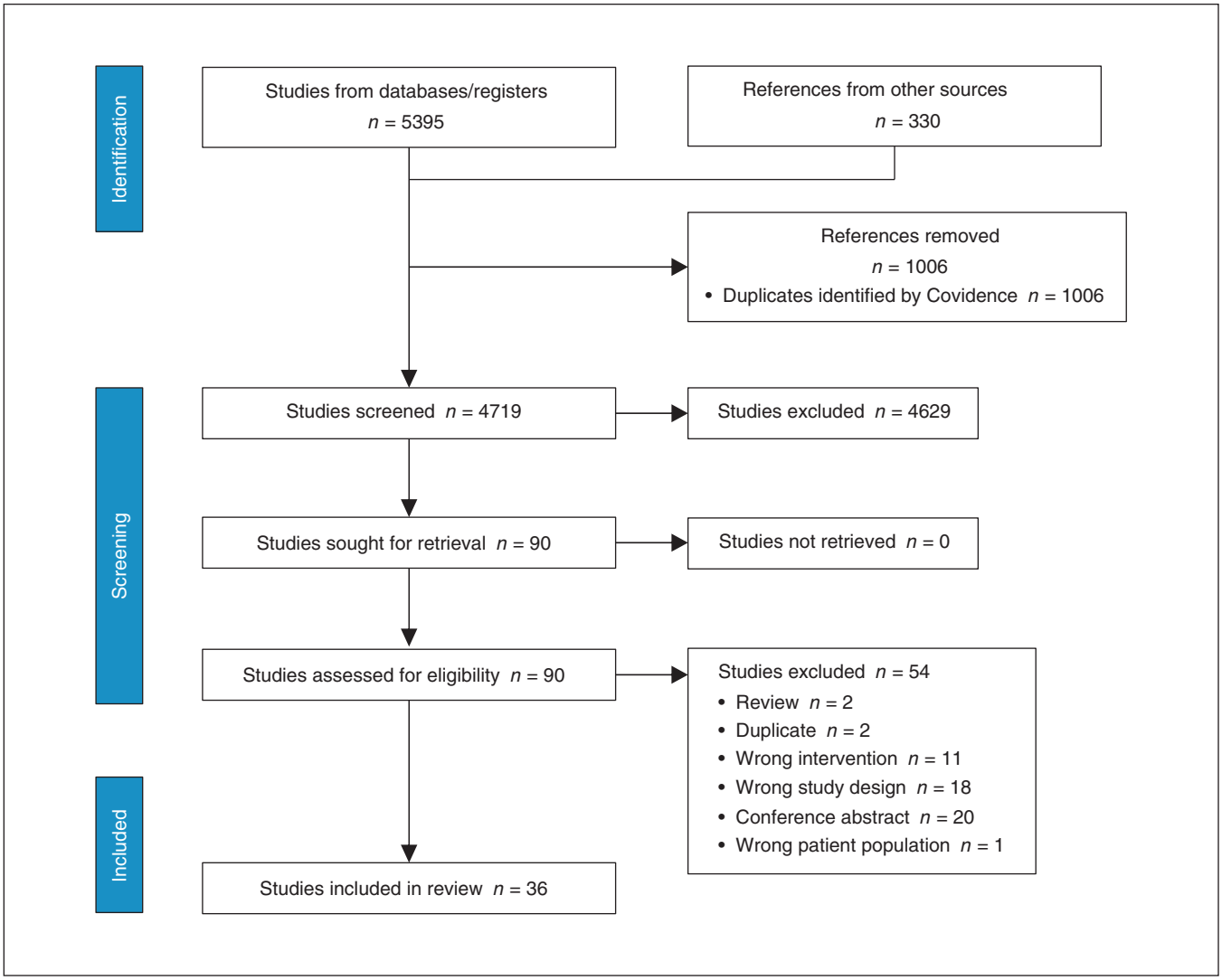


**Figure 2:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

**Table 1: Glutamatergic system and TMS plasticity protocols**

| Study | Design (*n*) | Age, yr* | Male, % | Protocol | Drug (dose) | TMS target | Mechanism of action | Effect |
|---|---|---|---|---|---|---|---|---|
| **Healthy participants** | | | | | | | | |
| Stefan et al.[56] | C/O (6) | 27 ± 6 | 78.5 | PAS25 | Dextromethorphan (150 mg) | M1 | NMDAR antagonist | Blocked LTP-like |
| Weise et al.[57] | C/O (11) | 21.8 ± 3.1 | 45.5 | PAS25 | Dextromethorphan (120 mg) | M1 | NMDAR antagonist | Blocked LTP-like |
| | C/O (13) | 22.3 ± 3.3 | 53.85 | PAS25 | Dextromethorphan (120 mg) + nimodipine (30 mg) | M1 | NMDAR antagonist + L-type VGCC blocker | Increased LTP-like |
| Wolters et al.[42] | C/O (10) | 27.8 ± 5.7 | 55.9 | PAS10 | Dextromethorphan (150 mg) | M1 | NMDAR antagonist | Blocked LTD-like |
| Suppa et al.[58] | C/O (8) | 27 ± 3 | 41.2 | Laser-PAS50 | Memantine (10 mg) | M1 | NMDAR antagonist | Blocked LTP-like |
| Wankerl et al.[54] | C/O (15) | 26.5 ± 3.7 | 40 | cTBS300 | Dextromethorphan (120 mg) | M1 | NMDAR antagonist | Blocked cTBS-LTP; blocked cTBS + nimodipine-LTD |
| Huang et al.[53] | C/O (6) | 29 ± 67 | 16.67 | iTBS cTBS | Memantine (10 mg) | M1 | NMDAR antagonist | Blocked LTP-like and LTD-like |
| Colnaghi et al.[55] | Parallel (30) | 27.3 ± 5.35 | 50 | cTBS | Memantine (10 mg) | Cerebellum | NMDAR antagonist | Blocked occulomotor metrics of plasticity |
| Teo et al.[60] | C/O (6) | NR | 66.7 | iTBS | D-cycloserine (100 mg) | M1 | NMDAR partial agonist | Switched LTP-like to LTD-like |
| Selby et al.[61] | C/O (12) | 29.66 ± 6.37 | 41.7 | iTBS | D-cycloserine (100 mg) | M1 | NMDAR partial agonist | Blocked early LTP-like followed by enhanced LTP-like after 60 min; blocked 16-hr SRC rightward shift |
| Wrightson et al.[62] | C/O (20) | 33.7 | 60 | Repeat iTBS (2 × 60 min apart) | D-cycloserine (100 mg) | M1 | NMDAR partial agonist | Increased LTP-like after both tetani |
| Brown et al.[35] | C/O (10) | 26–37 | 60 | 10 Hz rTMS | D-cycloserine (100 mg) | M1 | NMDAR partial agonist | Increased LTP-like |
| Brown et al.[36] | C/O (10) | 26–37 | 60 | 10 Hz rTMS | D-cycloserine (100 mg) | M1 | NMDAR partial agonist | Decreased ICF and increased ICI |
| Kweon et al.[59] | C/O (10) | 28 ± 6 | 40 | 10 Hz rTMS | D-cycloserine (100 mg) | M1 | NMDAR partial agonist | No effect on MEP amplitude post-10 Hz; decreased SRC intercept |
| **MDD** | | | | | | | | |
| Cole et al.[64] | C/O (12 MDD, 12 HC) | 35.8 ± 15.3 | 58.3 | iTBS | D-cycloserine (100 mg) | M1 | NMDAR partial agonist | Normalized SRC shift in MDD and stabilized LTP-like |
| Cole et al.[11] | Parallel (50) | 40.8 ± 13.4 | 38 | iTBS (20 sessions) | D-cycloserine (100 mg) | Left DLPFC | NMDAR partial agonist | Improved antidepressant effects |

C/O = crossover; cTBS = continuous theta-burst stimulation; DLPFC = dorsolateral prefrontal cortex; HC = healthy controls; ICF = intracortical facilitation; ICI = intracortical inhibition; iTBS = intermittent theta-burst stimulation; LTD = long-term depression; LTP = long-term potentiation; M1 = motor cortex; MDD = major depressive disorder; MEP = motor-evoked potential; NMDAR = *N*-methyl-D-aspartate receptor; NR = not reported; PAS = paired associative stimulation; rTMS = repetitive transcranial magnetic stimulation; SRC = stimulus response curve; TBS = theta-burst simulation; TMS = transcranial magnetic stimulation; VGCC = voltage-gated Ca2+ channel.
*Data are presented as mean ± standard deviation.

The necessity of the NMDA receptor in rTMS-induced LTP-like and LTD-like plasticity has been probed in crossover studies using NMDA receptor antagonists, specifically memantine and dextromethorphan. For these acute dosing experiments, the memantine regimen calls for a 5 mg oral dose 2 days before the experiment followed by 5 mg twice daily, and 10 mg 2 hours[53] or 3 hours[55] before the start of the experimental protocol. This regimen corresponds to an accelerated titration relative to clinical practice.[53] It abolished iTBS-induced LTP-like plasticity and cTBS-induced LTD-like plasticity in the motor cortex[53] and blocked the inhibitory effects of cTBS to the posterior cerebellar vermis on saccadic eye movements.[55] Similarly, a single oral dose of 120 mg of dextromethorphan has been shown to cross the blood–brain barrier and block NMDA receptors.[65,66] When taken 2.5 hours before TBS, dextromethorphan blocks the LTP-like effects of cTBS300 (a short version of cTBS with the application of only 300 rather than 600 pulses) and the LTD-like effects of cTBS300 + 30 mg oral nimodipine (an antagonist of the VGCC, which is also necessary for LTP and LTD[54]). Based on the evidence generated using memantine and dextromethorphan, the NMDA receptor appears to be necessary for TBS-induced LTP-like and LTD-like plasticity.

In addition, NMDA receptor antagonism modifies the effects of PAS protocols.[42,56–58] Two crossover studies have shown that acute doses of 150 mg and 120 mg of oral dextromethorphan, taken 2.5 hours before stimulation, block the LTP-like effects of PAS25, measured by MEP amplitude.[56,57] However, in the presence of nimodipine, dextromethorphan no longer blocked PAS25-induced LTP.[57] Memantine, taken in the same dosing schedule as noted previously,[53] blocked the LTP-like effects of PAS on MEP amplitudes where the PAS protocol used an associative laser stimulus to evoke pain 50 ms before a TMS pulse (Laser-PAS50).[58] Similarly, 150 mg of oral dextromethorphan blocked the LTD-like effects of PAS10.[42] Collectively, these findings support NMDA receptor dependency of PAS25-plasticity, though the mechanisms underlying laser-PAS50 and PAS10 have been less thoroughly investigated.

D-cycloserine is a partial NMDA receptor agonist and, therefore, would provide the possibility of testing both necessity and sufficiency of the NMDA receptor in rTMS-induced LTP-like and LTD-like effects. Unfortunately, all studies to date have used an acute low dose of D-cycloserine (100 mg, oral dosing), and therefore have tested the relevance of the NMDA receptor in pharmacologically augmenting the LTP-like effects of TMS,[35,36,60–62] but no study to date has investigated protocols that are designed to induce LTD-like effects. Two studies involving 10 participants tested the augmentation of LTP-like effects induced by 10 Hz rTMS in a crossover design.[35,59] While the findings from these studies were varied, they differed predominantly in their effect size. Both studies revealed increased facilitation of MEPs to a constant intensity, but only 1 reported results that reached statistical significance, and 1 study showed a significant leftward shift in SRCs when pairing 10 Hz rTMS with D-cycloserine.[35,59] In a secondary analysis of this first study, the investigators also showed that 10 Hz rTMS paired with D-cycloserine appears to occlude post-rTMS intracortical facilitation while enhancing intracortical inhibition.[36] Incidentally, post hoc analysis of covariate demographic factors from these studies suggest that repeated motor practice and daily caffeine use may account for some of the notable variability found in MEPs, with the largest LTP-like effects coming from a small number of caffeine nonusers, musicians, and athletes.[38,40]

Three crossover studies have paired iTBS with an acute dose of 100 mg of D-cycloserine in healthy individuals.[60–62] Teo and colleagues[60] reported that D-cycloserine changed the effects of iTBS from LTP-like to LTD-like. Conversely, Selby and colleagues[61] showed that an initial attenuation of MEP amplitude was followed by potentiation 60 minutes after iTBS and, while there was no immediate effect on SRCs, it appeared to blunt SRC changes the following day. Recently, a crossover study assessed the importance of NMDA receptor agonism in the metaplastic effects of repeated-spaced iTBS by pairing 2 sessions separated by an hour with a single 100 mg dose of D-cycloserine.[62] D-cycloserine resulted in greater facilitation of MEPs in response to a fixed intensity and increased excitability as measured by the SRCs. Moreover, D-cycloserine did not occlude metaplasticity, and resulted in potentiation of MEPs in response to a fixed stimulus intensity after both tetani as well as greater change of the SRC after both iTBS tetani.

**Major depressive disorder (2 studies)**

One study to date has examined the relevance of NMDA receptor agonism with an acute 100 mg dose of D-cycloserine in LTP-like plasticity in individuals with MDD[64] (Table 1). In a crossover design with a sample of 12 patients and 12 controls, impairments in iTBS-induced MEP facilitation in participants with MDD were not rescued by D-cycloserine.[64] However, opposing shifts in SRCs in participants with MDD (increased excitability) and healthy participants (decreased excitability) were rescued and normalized in participants with MDD by D-cycloserine. Importantly, at the individual participant level, changes in SRCs from baseline to the following day were persistent when iTBS was paired with D-cycloserine but not placebo, suggesting that NMDA receptor agonism can lead to persistent effects of iTBS synaptic plasticity.

This study was followed by a double-blind randomized placebo-controlled parallel group trial in which adjunctive iTBS and 100 mg D-cycloserine was used as a treatment for MDD.[11] Intermittent TBS was delivered to the left dorsolateral prefrontal cortex, and a single dose of D-cycloserine or placebo was taken 1–2 hours before iTBS for the first 2 weeks of a 4-week course of iTBS. No synaptic plasticity assays were included in this trial; however, there was a large effect size (Hedges $g$ = 0.99) favouring pharmacologically augmented iTBS, and the rate of clinical responders doubled relative to iTBS delivered with a placebo (74% v. 33%). It is worth noting that these clinical observations support the unproven supposition that plasticity detected by neurophysiology may underly clinical rTMS response.

*Dopamine (13 studies)*

**Healthy participants (9 studies)**

The effect of dopaminergic drugs on rTMS-induced plasticity has been studied using dopamine receptor agonists[67–72] and antagonists.[69,72–75] Seven of these studies have used PAS,[67,70–75] 1 has used TBS,[73] and 1 has used QPS[69] protocols. Studies examining the modulatory effects of dopaminergic agents have assessed only changes in MEP amplitudes assayed at constant stimulus intensity using crossover designs. Study sample sizes ranged from 8 to 12 participants. Results are presented in Table 2.

The modulatory role of dopamine in TMS-induced LTP-like and LTD-like plasticity has been assessed in studies using dopamine receptor agonists, specifically acute oral doses of bromocriptine, cabergoline, ropinirole, the dopamine precursor levodopa (L-Dopa), and subcutaneous injections of apomorphine. These have consistently shown dose-dependent effects such that low doses of oral L-Dopa (25 mg), bromocriptine (2.5 mg), ropinirole (0.125 mg), and subcutaneous apomorphine (0.1 mg) block LTP-like facilitation (PAS25).[67,68,70,71] Conversely, low-dose ropinirole had no effect on PAS10 LTD-like plasticity,[68] while the LTD-like effects of PAS10 were blocked by low-dose bromocriptine[71] and L-Dopa,[67] and

**Table 2 (part 1 of 2): Dopaminergic system and TMS plasticity protocols**

| Study | Design (*n*) | Age, yr* | Male, % | Protocol | Drug (dose) | TMS target | Mechanism of action | Effect |
|---|---|---|---|---|---|---|---|---|
| **Healthy participants** | | | | | | | | |
| Monte-Silva et al.[68] | C/O (*n* = 12) | 28.92 ± 5.77 | 50 | PAS25<br>PAS10 | Ropinirole (0.125 mg, 0.5 mg, 1.0 mg) | M1 | Dopamine D2/ D3 receptor agonist | 0.125 mg: blocked PAS25 LTP-like effect, no effect on PAS10 LTD-like effect<br>0.5 mg: no effect on LTP-like or LTD-like<br>1.0 mg: blocked PAS25 LTP-like effect, no effect on PAS10 LTD-like effect |
| Korchounov and Ziemann[72] | C/O (*n* = 8) | 19–26 | 62.5 | PAS(N20) + 2ms | Cabergoline (2 mg) | M1 | D2 receptor agonist | No effect |
| Fresnoza et al.[71] | C/O (*n* = 12) | 28.4 ± 1.0 | 58.33 | PAS25<br>PAS10 | Bromocriptine (2.5 mg, 10 mg, 20 mg) | M1 | Dopamine receptor agonist | 2.5 mg: blocked PAS25 LTP-like and PAS10 LTD-like<br>10 mg: decreased PAS25 LTP-like and no effect on PAS10 LTD-like<br>20 mg: decreased PAS25 LTP-like and PAS10 LTD-like |
| Fresnoza et al.[70] | C/O (*n* = 12) | 28.33 ± 4.46 | 50 | PAS25<br>PAS10 | Apomorphine (0.1 mg, 0.2 mg, 0.3 mg) | M1 | Dopamine agonist | 0.1 mg: blocked PAS25 LTP-like and switched PAS10 LTD-like to LTP-like<br>0.2 mg: blocked PAS25 LTP-like and switched PAS10 LTD-like to LTP-like<br>0.3 mg: blocked PAS25-LTP-like and switched PAS10 LTD-like to LTP-like |
| Thirugnanasambandam et al.[67] | C/O (*n* = 12) | 29.67 ± 8.04 | 50 | PAS25<br>PAS10 | L-Dopa (25 mg, 100 mg, 200 mg) | M1 | Dopamine precursor | 25 mg: blocked PAS25 LTP-like and PAS10 LTD-like<br>100 mg: prolonged PAS25 LTP-like; no effect on PAS10 LTD-like<br>200 mg: switched PAS25 LTP-like to LTD-like; no effect on PAS10 LTD-like |
| Fresnoza et al.[75] | C/O (*n* = 12) | 26.91 ± 4.23 | 58.33 | PAS25<br>PAS10 | L-Dopa (25 mg, 100 mg, 200 mg) + sulpiride (400 mg) | M1 | Dopamine precursor + D2 receptor antagonist | 25 mg: blocked PAS25 LTP-like effect and switched PAS10 LTD-like to LTP-like<br>100 mg: blocked PAS25 LTP-like effect and switched PAS10 LTD-like to LTP-like<br>200 mg: reduced PAS25 LTP-like effect and switched PAS10 LTD-like to LTP-like |
| Nitsche et al.[74] | C/O (*n* = 12; *n* = 10) | 30.67 ± 10.53<br>27.1 ± 6.1 | 41.67<br>50 | PAS25<br>PAS10 | Sulpiride (400 mg) + L-Dopa (100 mg) | M1 | D2 receptor antagonist + Dopamine precursor | Sulpiride: no effect on PAS25 LTP-like and blocked PAS10 LTD-like<br>Sulpiride + L-Dopa: no effect on PAS25 LTP-like or PAS10 LTD-like |
| Korchounov and Ziemann[72] | C/O (*n* = 8) | 19–26 | 62.5 | PAS(N20) + 2ms | Haloperidol (2.5 mg) | M1 | D2 receptor antagonist | Blocked LTP-like |
| Monte-Silva et al.[73] | C/O (*n* = 12) | 25.75 ± 5.11 | 50 | iTBS<br>cTBS | Sulpiride (400 mg) | M1 | D2 receptor antagonist | Blocked LTP-like and LTD-like |
| Enomoto et al.[69] | C/O (*n* = 10) | 43.4 ± 8.8 | 90 | QPS5<br>QPS50 | Pramipexole (1.5 mg) | M1 | Dopamine receptor agonist | No effect on LTP-like or LTD-like |
| Enomoto et al.[69] | C/O (*n* = 10) | 43.4 ± 8.8 | 90 | QPS5<br>QPS50 | L-Dopa (100 mg) | M1 | Dopamine precursor | Increased LTP-like and LTD-like |

low-dose apomorphine switched LTD-like to LTP-like facilitation.[70] A moderate dose (100 mg) of L-Dopa prolonged the LTP-like effect of PAS25 until the afternoon after the protocol but had no effect on PAS10-induced LTD-like plasticity, while a high dose (200 mg) switched the LTP-like effect of PAS25 to an LTD-like effect and did not influence the LTD-like effect of

**Table 2 (part 2 of 2): Dopaminergic system and TMS plasticity protocols**

| Study | Design (*n*) | Age, yr* | Male, % | Protocol | Drug (dose) | TMS target | Mechanism of action | Effect |
|---|---|---|---|---|---|---|---|---|
| **Parkinson disease** | | | | | | | | |
| Guerra et al.[76] | C/O (*n* = 13) | 66.2 ± 9.4 | 84.62 | iTBS with active/ sham-tACS | Home regimen of L-Dopa ON v. OFF (dose not specified) | M1 | Dopamine precursor | No effect on LTP-like effects with iTBS + sham tACS or iTBS + active tACS |
| Carrillo et al.[77] | C/O (*n* = 16) | 60.06 ± 11.86 | 50 | cTBS | Home regimen of L-Dopa, ropinirole, pramipexole, or selegiline (ON v. OFF) | Cerebellum-M1† | Parkinson disease medications | No effect on LTD-like |
| **Alzheimer disease** | | | | | | | | |
| Koch et al.[78] | Parallel (*n* = 30) | NR | NR | iTBS cTBS | Rotigotine (40 mg/d for 4 wk [subsample for 12 wk]) | M1 | Nonspecific dopamine receptor agonist | Increased LTP-like effect of iTBS after 4 and 12 wk of treatment; no effect on cTBS after 4 or 12 wk |
| **Schizophrenia** | | | | | | | | |
| Fitzgerald et al.[79] | Parallel (*n* = 26) | 32.2 ± 8.8 (medicated) 32.6 ± 8.3 (unmedicated) | 62.5 (medicated) 80.0 (unmedicated) | 1Hz rTMS | Home regimen of olanzapine, risperidone, or quetiapine | M1 | Dopamine receptor antagonist | No effect on MEP amplitudes, RMT, AMT, or CSP |

AMT = active motor threshold; C/O = crossover; CSP = cortical silent period; cTBS = continuous theta-burst stimulation; iTBS = intermittent theta-burst stimulation; L-Dopa = levodopa; LTD = long-term depression; LTP = long-term potentiation; M1 = motor cortex; MEP = motor-evoked potential; NR = not reported; PAS = paired associative stimulation; QPS = quadripulse stimulation; RMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation; tACS = transcranial alternative current stimulation.
*Data are reported as mean ± standard deviation or as a range.
†cTBS targeting the cerebellum, plasticity outcomes measured from M1.

PAS10.[67] Moderate (0.2 mg) and high (0.3 mg) doses of apomorphine blocked the PAS25-induced LTP-like increase in excitability.[70] At all doses of apomorphine, PAS10-induced LTD-like MEP inhibition was switched to LTP-like facilitation.[70] Finally, cabergoline (2 mg) had no modulating effect on an excitatory PAS protocol using an interstimulus interval equivalent to the N20 latency of the median nerve somatorsensory-evoked cortical potential plus 2 ms (PAS[N20] + 2 ms) compared with placebo.[72] The evidence to date suggests that dopaminergic agonists modulate the induction of LTP-like and LTD-like plasticity with dose-dependent effects, and while there may be differences associated with specific agents, additional studies and validation are needed.

Antagonizing the dopamine D2 receptor has yielded inconsistent results. Haloperidol (2.5 mg) blocked the LTP-like effects of PAS(N20) + 2ms,[72] while sulpiride in isolation had no effect on PAS25 LTP-like plasticity and blocked PAS10 LTD-like plasticity.[74] Sulpiride has also been used in combination with L-Dopa to favour D1 receptor activation.[71,74] Results showed that in combination with a low (25 mg) dose of L-Dopa, sulpiride blocked LTP-like effects of PAS25.[75] However, in combination with a moderate (100 mg) dose of L-Dopa, 1 study found no effect,[74] while another study revealed a block of PAS25 LTP-like plasticity.[75] When sulpiride was combined with a high dose (200 mg) of L-Dopa, the LTP-like effects of PAS25 were reduced.[75] Moreover, sulpiride alone abolished the effects of PAS10,[74] while in combination with L-Dopa (100 mg) there was either no effect[74] or a switch to LTP-like plasticity (25 mg, 100 mg, 200 mg).[75] Indeed, studies using dopaminergic antagonists suggest that specific dopaminergic receptors may play different roles in modulating LTP-like and LTD-like effects of PAS protocols.

One study has examined the relevance of D2 receptor activation in iTBS and cTBS protocols in healthy individuals using an acute 400 mg oral dose of the D2 antagonist sulpiride.[73] In a sample of 12 participants, changes in MEP amplitudes in response to a fixed stimulus intensity were measured for up to 60 minutes following TBS. Findings showed that antagonizing the D2 receptor prevented the LTP-like and LTD-like effects of iTBS and cTBS, respectively. This initial finding suggests that the D2-receptor plays an important role in modulating the LTP-like and LTD-like effects of TBS.

One study to date has assessed the role of pramipexole, a dopaminergic agonist, and L-Dopa in QPS.[69] In a placebo-controlled crossover design involving 10 participants, Enomoto and colleagues[69] measured fixed-intensity MEPs before and following high-frequency QPS (QPS5) for induction of LTP-like plasticity and low-frequency QPS (QPS50) for induction of LTD-like plasticity.[44] Participants received an oral dose of either 100 mg of L-Dopa, 1.5 mg of the D2 agonist pramipexole, or a placebo adjunct before stimulation. L-Dopa enhanced both the LTP-like and LTD-like plasticity effects of QPS5 and QPS50, respectively, and the most pronounced effect was observed 30 minutes following stimulation. However, the dopamine receptor agonist pramipexole had no influence on QPS5-induced LTP-like plasticity and QPS50-induced LTD-like plasticity.[69]

**Parkinson disease (2 studies)**

Two studies to date have assessed the effects of dopamine on cortical plasticity in individuals with Parkinson disease (Table 2).[76,77] These studies reported blunted effects of TBS to the motor cortex[76] and cerebellum[77] in individuals with

Parkinson disease compared with healthy controls. In a crossover design involving 13 participants, Guerra and colleagues[76] assessed the effects of iTBS with active or sham transcranial alternating current stimulation (tACS) to the motor cortex in patients with Parkinson disease who were either ON or OFF their daily regimen of L-Dopa. They found no effect of medication on MEPs measured at a fixed intensity following iTBS + sham tACS or iTBS + active tACS. Carrillo and colleagues[77] assessed MEPs at a fixed stimulus intensity as well as short-interval corticial inhibition and intracortical facilitation following cTBS to the cerebellum in 16 patients with Parkinson disease who were either ON or OFF their daily home regimen of Parkinson disease medications. The study identified no effect of medication on any outcomes following cerebellar cTBS. These 2 studies emphasize no effect of dopaminergic modulation on TMS-induced cortical plasticity in individuals with Parkinson disease.

**Alzheimer disease (1 study)**

One study has examined dopaminergic modulation of TMS plasticity in participants with Alzheimer disease (Table 2).[78] Thirty participants with a suspected Alzheimer disease diagnosis were randomized in a parallel group design to receive the nonspecific dopamine receptor agonist rotigotine (4 mg), the acetylcholinesterase inhibitor rivastigmine (4.6 mg), or placebo in the form of a daily transdermal patch for 4 weeks. Ten controls matched for age, sex, and education were recruited for baseline comparison. Measuring MEP amplitude at a fixed stimulus intensity showed a blunted response in participants with Alzheimer disease compared with healthy controls following iTBS but not cTBS. Four weeks of rotigotine, but not rivastigmine or placebo, in participants with Alzheimer disease increased iTBS LTP-like plasticity but not cTBS effects. A subset of 7 participants continued rotigotine treatment for an additional 8 weeks (total treatment duration of 12 wk). After 12 weeks of treatment, enhanced iTBS LTP-like plasticity was observed in this subset of participants. Rotigotine continued to have no effect on MEP amplitudes following cTBS. These findings highlight the need to test both acute and chronic dosing and their effects on TMS plasticity.

**Schizophrenia (1 study)**

One study has examined dopaminergic modulation of TMS plasticity in participants with schizophrenia (Table 2).[79] This study suggested blunted mortor cortical plasticity in both medicated and unmedicated individuals with schizophrenia compared with healthy controls who received no pharmacological adjunct with stimulation. In a parallel group design, Fitzgerald and colleagues[79] compared cortical plasticity in 26 participants with schizophrenia, 16 of whom were medicated with an oral antipsychotic for at least 1 month and 10 of whom were not being treated with antipsychotic medications (i.e., no oral antipsychotic medicationin the last 3 months and no long-acting injectable antipsychotic in the last 12 months). Medications included olanzapine ($n$ = 7), risperidone ($n$ = 4) and quetiapine ($n$ = 5), all of which nonspecifically antagonize the D2 receptor.[80] The MEP amplitude was measured at a fixed intensity before and 15 minutes after 1 Hz rTMS, as was resting motor threshold, active motor threshold, and cortical silent period. Though no comparisons between medicated and unmedicated participants with schizophrenia reached significance, there were opposite directions of effect suggesting LTP-like increases in MEPs after 1 Hz stimulation in medicated participants and LTD-like decreases in MEPs after 1 Hz stimulation in unmedicated participants.

*γ-Aminobutyric acid (3 studies)*

**Healthy participants (2 studies)**

Two studies to date have examined the effects of GABA agonism during the PAS paradigm[81,82] (Table 3). In a placebo-controlled crossover study ($n$ = 7), McDonnell and colleagues showed that 50 mg of the specific $GABA_B$ receptor agonist baclofen blocked the LTP-like effects of PAS(N20) + 2 ms.[81] In a crossover study ($n$ = 10), Heidegger and colleagues[82] compared the influence of 7 antiepileptic medications on PAS(N20) + 2 ms, and among these were 2 GABAergic compounds: diazepam (20 mg), a positive allosteric modulator at the $GABA_A$ receptor, and tiagabine (15 mg), a GABA reuptake inhibitor. Both diazepam and tiagabine decreased PAS(N20) + 2 ms LTP-like plasticity; however, this did not survive correction for multiple comparisons in either condition. This pair of studies shows that facilitating GABAergic signalling reduces PAS-induced LTP-like synaptic plasticity.

**Mild cognitive impairment (1 study)**

Homotaurine is a glycosaminoglycan that partially agonizes the $GABA_A$ and $GABA_B$ receptors and has been proposed to prevent β-amyloid plaque aggregation.[83] In a sample of 10 participants with mild cognitive impairment (MCI), Martorana and colleagues[84] measured intermittent and continuous TBS-induced changes in MEP amplitude following 4 weeks of a daily 100 mg homotaurine treatment (Table 3). Corticospinal plasticity was measured at baseline and after 4 weeks. Measured at a fixed stimulus intensity, there was no effect of homotaurine treatment on iTBS or cTBS-induced LTP-like or LTD-like change in MEP amplitude.

*Serotonin (1 study in healthy participants)*

To date, 1 study has examined the role of serotonin on PAS10 and PAS25-induced plasticity[85] (Table 4). Fourteen healthy individuals participated in a placebo-controlled crossover trial pairing an acute dose of 20 mg of citalopram, a selective serotonin reuptake inhibitor, or placebo with PAS10 and PAS25 in separate sessions. Changes in corticospinal excitability were measured using MEP amplitudes when single-pulse TMS was delivered at a fixed intensity. In this sample, citalopram, administered 2 hours before PAS, reduced the LTD-like effects of PAS10 for 90 minutes and facilitated the LTP-like effects of PAS25 30 minutes after the intervention. This preliminary evidence supports a modulatory role of the serotonergic system in both PAS10 LTD-like and PAS25 LTP-like plasticity.

**Table 3: GABAergic system and TMS plasticity protocols**

| Study | Design (*n*) | Age, yr* | Male, % | Protocol | Drug (dose) | TMS target | Mechanism of action | Effect |
|---|---|---|---|---|---|---|---|---|
| **Healthy participants** | | | | | | | | |
| McDonnell et al.[81] | C/O (7) | 28.7 ± 7.9 | 42.86 | PAS(N20) + 2 ms | Baclofen (50 mg) | M1 | $GABA_B$ agonist | Blocked LTP-like |
| Heidegger et al.[82] | C/O (9) | 21–30 | 60 | PAS(N20) + 2 ms | Diazepam (20 mg) | M1 | $GABA_A$ agonist | Decreased LTP-like |
| Heidegger et al.[82] | C/O (8) | 21–30 | 60 | PAS(N20) + 2 ms | Tiagabine (15 mg) | M1 | GABA reuptake inhibitor | Decreased LTP-like |
| **MCI** | | | | | | | | |
| Martorana et al.[84] | OL (10) | 61.9 ± 1.9 | 60 | iTBS cTBS | Homotaurine (100 mg/d for 4 wk) | M1 | $GABA_A$ and $GABA_B$ partial agonist | No effect |

C/O = crossover; cTBS = continuous theta-burst stimulation; GABA = γ-aminobutyric acid; $GABA_A$ = γ-aminobutyric acid type A; $GABA_B$ = γ-aminobutyric acid type B; iTBS = intermittent theta-burst stimulation; LTP = long-term potentiation; M1 = motor cortex; MCI = mild cognitive impairment; OL = open label; PAS = paired associated stimulation; TMS = transcranial magnetic stimulation.
*Data are presented as either mean ± standard deviation or as a range.

**Table 4: Serotonergic system and TMS plasticity protocols**

| Study | Design (*n*) | Age, yr* | Male, % | Protocol | Drug (dose) | TMS target | Mechanism of action | Effect |
|---|---|---|---|---|---|---|---|---|
| **Healthy participants** | | | | | | | | |
| Batsikadze et al. [85] | C/O (14) | 28.1 ± 4.7 | 50 | PAS25 PAS10 | Citalopram (20 mg) | M1 | SRI | Increased PAS25 LTP-like; reduced PAS10 LTD-like |

C/O = crossover; LTD = long-term depression; LTP = long-term potentiation; M1 = motor cortex; PAS = paired associative stimulation; SRI = serotonin reuptake inhibitor; TMS = transcranial magnetic stimulation.
*Data are presented as mean ± standard deviation.

*Acetylcholine (4 studies)*

**Healthy participants (3 studies)**

Three studies to date have examined the role of the cholinergic system in PAS25 and PAS10 paradigms using rivastigmine (3 mg), tacrine (40 mg), and nicotine (15 mg)[72,86,87] (Table 5). Two studies using cholinesterase inhibitors, rivastigmine and tacrine, have presented conflicting results.[72,86] An initial study with 10 participants suggested that 3 mg of rivastigmine increased the effects of both PAS25 and PAS10 when MEP amplitudes were measured at a fixed intensity.[86] Specifically, LTP-like PAS25 facilitation was extended from 20 to 60 minutes, and LTD-like PAS10 inhibition was maintained until the morning after the PAS protocol. Conversely, a study with 8 participants revealed no significant effect of 40 mg of tacrine compared with placebo on PAS(N20) + 2 ms–induced LTP-like plasticity.[72] Moreover, agonism of the nicotinic acetylcholine receptor was assessed in a sample of 12 participants using a 15 mg transdermal nicotine patch.[87] Nicotine slightly prolonged PAS25-induced LTP-like plasticity from 90 to 120 minutes and blocked PAS10-induced LTD-like plasticity.

One study to date has examined muscarinic receptor (M1) antagonism with biperiden on the PAS(N20) + 2 ms protocol.[72] In a sample of 8 participants, MEP amplitude was measured at a fixed stimulus intensity. In this study, 8 mg of biperiden blocked LTP-like plasticity compared with placebo.[72]

Together, these preliminary findings suggest that the presence of acetylcholine may facilitate the effects of PAS25 and block the effects of PAS10, while antagonizing the M1 receptor appears to block LTP-like plasticity following PAS(N20) + 2 ms. However, further examination into the role of specific cholinergic receptors is needed.

**Alzheimer disease (1 study)**

To date, 1 study has examined the effects rivastigmine, an acetylcholinesterase inhibitor, in participants with Alzheimer disease (Table 5).[78] In the aforementioned study, 30 participants with a suspected diagnosis of Alzheimer disease were randomized in a parallel group design to receive rivastigmine (4.6 mg), rotigotine (4 mg), or placebo in the form of a daily transdermal patch for 4 weeks. Ten healthy controls matched for age, sex, and education were recruited for baseline comparison. Measuring MEP amplitude at a fixed stimulus intensity revealed a blunted response in those with Alzheimer disease compared with healthy controls following intermittent but not continuous TBS to the primary motor cortex. Four weeks of treatment with rivastigmine had no effect on LTP-like or LTD-like plasticity following iTBS or cTBS compared with placebo. These findings highlight blunted TBS-induced plasticity in patients with Alzheimer disease that is not rescued by inhibiting acetylcholinesterases.

**Table 5: Cholinergic system and TMS plasticity protocols**

| Study | Design (*n*) | Age, yr* | Male, % | Protocol | Drug (dose) | TMS target | Mechanism of action | Effect |
|---|---|---|---|---|---|---|---|---|
| **Healthy participants** | | | | | | | | |
| Kuo et al.[86] | C/O (10) | 28 ± 4<br>27 ± 4 | 60<br>50 | PAS25<br>PAS10 | Rivastigmine (3 mg) | M1 | Cholinesterase inhibitor | Increased PAS25 LTP-like; increased PAS10 LTD-like |
| Korchounov and Ziemann[72] | C/O (8) | 19–26 | 62.5 | PAS(N20) + 2 ms | Tacrine (40 mg) | M1 | Cholinesterase inhibitor | No effect |
| Thirugnanasambandam et al.[87] | C/O (12)<br>C/O (12) | 24.5 ± 1.3<br>25.9 ± 2.1 | 50<br>50 | PAS25<br>PAS10 | Nicotine (15 mg) | M1 | Nicotinic ACh agonist | Prolonged PAS25 LTP-like; blocked PAS10 LTD-like |
| Korchounov and Ziemann[72] | C/O (8) | 19–26 | 62.5 | PAS(N20) + 2 ms | Biperiden (8 mg) | M1 | M1 antagonist | Blocked LTP-like |
| **AD** | | | | | | | | |
| Koch et al.[78] | Parallel (30) | NR | NR | iTBS<br>cTBS | Rivastigmine (4.6 mg/d for 4 wk) | M1 | Cholinesterase inhibitor | No effect |

AD = Alzheimer disease; C/O = crossover; cTBS = continuous theta-burst stimulation; iTBS = intermittent theta-burst stimulation; LTD = long-term depression; LTP = long-term potentiation; M1 = motor cortex; NR = not reported; PAS = paired associative stimulation; TBS = theta-burst stimulation; TMS = transcranial magnetic stimulation.
*Data are presented as either mean ± standard deviation or as a range.

*Norepinephrine (1 study in healthy participants)*

To date, the influence of adrenergic agonism and antagonism during a PAS protocol for induction of LTP-like plasticity (PAS[N20] + 2 ms) has been assessed in 1 study[72] (Table 6). This study used both 40 mg of methylphenidate, an inhibitor of noradrenaline and dopamine reuptake, and 1 mg of prazosin, an α-1-adrenergic receptor antagonist. In a sample of 8 healthy participants, methylphenidate had no significant effect on LTP-like plasticity compared with placebo when MEP amplitude was measured at a fixed stimulus intensity (Cohen $d$ = 0.13). Conversely, prazosin significantly reduced LTP-like plasticity compared with placebo, with a large effect size (Cohen $d$ = –2.49). This preliminary evidence suggests a modulatory role of the α-1-adrenergic receptor in PAS-induced plasticity, while dopamine and noradrenaline reuptake inhibition had a smaller, nonsignificant effect.

*Ion channels (5 studies)*

**Voltage-gated calcium channels (5 studies in healthy participants)**

Voltage-gated calcium channels mediate the increase in intracellular calcium concentration.[88] To date, 4 studies have examined the relevance of VGCCs in TMS-induced plasticity using the VGCC blockers nimodipine, ethosuximide, and gabapentin, which differentially target L-type and T-type VGCCs[42,54,57,82] (Table 7). T-type VGCCs transiently open at approximately –70 mV, while L-type VGCCs open at around –20 mV; thus, drugs targeting these different types of VGCCs may have different effects on rTMS-induced plasticity.[89]

The effects of L-Type VGCCs have been the most thoroughly investigated using PAS and cTBS300 protocols. Three separate studies have shown that 30 mg of nimodipine, an L-type VGCC antagonist, blocks the LTD-like effects of PAS10 ($n$ = 10),[42] and the LTP-like effects of PAS25 ($n$ = 13),[57] and cTBS300 ($n$ = 22).[54] Pairing nomidipine (30 mg) with the NMDA receptor antagonist dextromethorphan (120 mg) had different effects on PAS and cTBS300 plasticity. Specifically, this combination restored PAS25 LTP-like plasticity to the level of a plabeco intervention,[57] whereas the combination did not rescue cTBS300 LTP-like effects.[54] The combination also did not significantly change the effects of PAS5000 relative to placebo. Wankerl and colleagues[54] also assessed the influence of low- (15 mg) and high-dose (30 mg) nimodipine with and without 1.5 minutes of voluntary isometric thumb abduction before cTBS300. This crossover study ($n$ = 20) suggested metaplastic effects, whereby a low dose of nimodipine had no impact on LTP-like effects of cTBS300; however, in the presence of isometric contraction of the muscle, this low dose blocked LTP-like effects. Further, a high dose of nimodipine blocked the LTP-like effects of cTBS300, and in the presence of isometric muscle contraction switched LTP-like to LTD-like effects. These findings highlight a role of L-type VGCCs in metaplasticity.

Three studies have examined the effects of other VGCC antagonists on TMS plasticity paradigms. One crossover study ($n$ = 13) showed that ethosuximide, a T-type VGCC antagonist, switched the LTP-like effects of PAS25 to LTD-like and blocked the LTP-like effects of cTBS300.[57] A crossover study in 10 participants assessed the influence of gabapentin, a medication that has an unclear mechanism of action but is thought to block presynaptic VGCCs. That study reported no effect of gabapentin on PAS(N20) + 2 ms–induced LTP-like MEP facilitation, as measured at a constant stimulus intensity.[82] Finally, 1 study in 24 participants has examined the influence of zonisamide (25 mg), a T-type VGCC antagonist,

**Table 6: Adrenergic system and TMS plasticity protocols**

| Study | Design (*n*) | Age, yr* | Male, % | Protocol | Drug (dose) | TMS target | Mechanism of action | Effect |
|---|---|---|---|---|---|---|---|---|
| **Healthy participants** | | | | | | | | |
| Korchounov and Ziemann[72] | C/O (8) | 19–26 | 62.5 | PAS(N20) + 2 ms | Methylphenidate (40 mg) | M1 | Adrenergic and dopaminergic reuptake inhibitor | No effect |
| Korchounov and Ziemann[72] | C/O (8) | 19–26 | 62.5 | PAS(N20) + 2 ms | Prazosin (1 mg) | M1 | α-1 antagonist | Blocked LTP-like |

C/O = crossover; LTP = long-term potentiation; M1 = motor cortex; PAS = paired associative stimulation; TMS = transcranial magnetic stimulation.
*Data are expressed as a range.

**Table 7: Voltage gated ion channels and TMS plasticity protocols**

| Study | Design (*n*) | Age, yr* | Male, % | Protocol | Drug (dose) | TMS target | Mechanism of action | Effect |
|---|---|---|---|---|---|---|---|---|
| **Healthy participants, VGCCs** | | | | | | | | |
| Weise et al.[57] | C/O (13) | 22.3 ± 3.3 | 46.15 | PAS25 | Nimodipine (30 mg) | M1 | L-type VGCC antagonist | Blocked LTP-like |
| Wolters et al.[42] | C/O (10) | 27.8 ± 5.7 | 55.88 | PAS10 | Nimodipine (30 mg) | M1 | L-type VGCC antagonist | Blocked LTD-like |
| Weise et al.[57] | C/O (13) | 22.3 ± 3.3 | 46.15 | PAS25 PAS5000 | Nimodipine (30 mg) + dextromethorphan (120 mg) | M1 | L-type VGCC antagonist + NMDAR antagonist | No effect on LTP-like |
| Weise et al.[57] | C/O (13) | 24.7 ± 4.0 | 22.73 | PAS25 | Ethosuximide (750 mg) | M1 | T-type VGCC antagonist | Switched LTP-like to LTD-like |
| Heidegger et al.[82] | C/O (10) | 24 ± 6 | 62.5 | PAS(N20)+2ms | Gabapentin (1100 mg) | M1 | Blocks VGCCs (unclear mechanism) | No effect |
| Wankerl et al.[54] | C/O (22) | 24.7 ± 4.0 | 22.73 | cTBS300 | Nimodipine (30 mg) | M1 | L-type VGCC antagonist | Blocked LTP-like |
| Wankerl et al.[54] | C/O (22) | 24.7 ± 4.0 | 22.73 | cTBS300 | Nimodipine (30 mg) + dextromethorphan (120 mg) | M1 | L-type VGCC antagonist + NMDAR antagonist | Blocked LTP-like |
| Wankerl et al.[54] | C/O (20) | 24.4 ± 4.8 | 15 | cTBS300 +/– isometric contraction | Nimodipine (15 mg or 30 mg) | M1 | L-type VGCC antagonist | Low dose (15 mg): no effect on LTP-like without contraction but blocks LTP-like with contraction; high dose (30 mg): blocks LTP-like without contraction and switches to LTD-like with contraction |
| Weise et al.[57] | C/O (16) | 23.1 ± 2.6 | 50 | cTBS300 | Ethosuximide (750 mg) | M1 | T-type VGCC antagonist | Blocked LTP-like |
| Tanaka et al.[90] | C/O (24) | 65.8 ± 2.4 | 50 | QPS5 | Zonisamide (25 mg) | M1 | T-type VGCC | No effect |
| **Healthy participants, VGSCs** | | | | | | | | |
| Heidegger et al.[82] | C/O (10) | 21–30 | 60 | PAS(N20)+2ms | Lamotrigine (300 mg) | M1 | VGSC antagonist | Reduced LTP-like |
| Heidegger et al.[82] | C/O (10) | 21–30 | 60 | PAS(N20)+2ms | Topiramate (100 mg) | M1 | VGSC antagonist (antagonizes AMPA/ kainite, inhibits carbonic anhydrase) | No effect |

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; C/O = crossover; LTD = long-term depression; LTP = long-term potentiation; M1 = motor cortex; PAS = paired associative stimulation; QPS = quadripulse stimulation; TBS = theta-burst stimulation; TMS = transcranial magnetic stimulation; VGCCs = voltage-gated calcium channels; VGSCs = voltage-gated sodium channels.
*Data are presented as either mean ± standard deviation or as a range.

using QPS5.[90] In a crossover design, participants received either zonisamide or placebo before QPS5. The MEP amplitude trended higher with zonisamide on board, though this effect was not statistically significant.

Together, these findings show the necessity of L-type VGCC activation for PAS-induced plasticity and the modulatory role of T-type VGCCs in facilitating LTP- or LTD-like effects of PAS, TBS, and potentially QPS paradigms.

**Voltage-gated sodium channels (1 study in healthy participants)**
Though voltage-gated sodium channels are crucial in the generation and propagation of action potentials in neurons, only 1 study to date has examined VGSC blockade during a PAS protocol for LTP-like plasticity induction (Table 7). In a sample of 10 healthy volunteers, Heiddeger and colleagues[82] used 300 mg of lamotrigine, a VGSC antagonist, as an adjunct to PAS(N20) + 2 ms. When MEPs were measured at a fixed stimulus intensity, lamotrigine slightly reduced PAS-induced LTP-like MEP facilitation, though this effect did not survive correction for multiple comparisons. The same study tested 100 mg of topiramate, which blocks VGSCs, antagonizes AMPA/kainate receptors, and inhibits carbonic anhydrase. Topiramate did not influence the PAS(N20) + 2 ms–induced LTP-like plasticity. These preliminary findings failed to show the necessity of VGSCs in PAS-induced plasticity, though further study in larger samples is needed.

*Other mechanisms of action*

**Antiepileptic compounds (1 study in healthy participants)**
In their study of antiepileptic compounds at standard clinical doses, Heiddeger and colleagues[82] included a 3000 mg dose of levetiracetam (Table 8). Although its primary anticonvulsant mechanism of action is binding to the synaptic vesicle glycoprotein 2A (SV2A) and lowering release probability,[92] levetiracetam has other actions relevant to LTP-like plasticity.[93] Compared with placebo, levetiracetam resulted in a suppression of PAS(N20) + 2 ms LTP-like plasticity and was the only compound among 7 considered that did so completely. Also included in their study of antiepileptic compounds was a characterization of piracetam (3600 mg), a nootropic and antimyoclonic agent for which the mechanism of action is poorly understood and includes effects on cerebral microvasculature.[94] Compared with placebo, piracetam reduced the effect of PAS(N20) + 2 ms LTP-like plasticity, though this finding did not survive correction for multiple comparisons.[82]

**Statin (1 study in neurofibromatosis)**
One study to date has examined the influence of lovastatin on PAS25 in participants with neurofibromatosis type 1 (Table 8).[91] At baseline, the authors showed that participants with neurofibromatosis type 1 ($n$ = 11) had blunted LTP-like plasticity, such that MEP amplitudes measured at a fixed intensity did not change following PAS25, whereas a statistically significant increase is seen in healthy controls ($n$ = 11). Lovastatin, a medication used to treat high cholesterol, competitively inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis. It also reduces inflammation, has anticoagulant effects, and increases catabolism of low-density lipoprotein cholesterol.[95] The effects of 200 mg of oral lovastatin were tested following a single dose and after 4 days of daily treatment in individuals with neurofibromatosis type 1. Measured at a fixed intensity, a single dose did not change MEP amplitude after PAS25, whereas after 4 days of lovastatin treatment PAS25 increased MEP amplitudes to levels of healthy controls. The study showed that blunted PAS-induced plasticity in patients with neurofibromatosis type 1 may be rescued using multi-day treatment with lovastatin.

*Bias in the literature*

Sources of bias in randomized trials were assessed using the Cochrane RoB 2 tool (Appendix 1, Figure 2). Across 30 crossover trials and 4 randomized group comparison studies, the majority revealed a moderate to high risk of bias. The main source of bias came from an unclear discussion of the randomization process, a lack of double-blinding, and no preregistration of protocols, making it unclear whether the outcome measures presented were those initially planned. Two nonrandomized studies were assessed using the ROBINS-I tool, which revealed moderate risk of bias owing to a lack of preregistration.[79,84] Confounding owing to the inclusion of individuals using different medications and/or doses was identified in 2 crossover studies[76,77] and 1 nonrandomized trial.[81] To overcome these common sources of bias in future work, all studies should preregister protocols and clearly report randomization and blinding procedures.

**Table 8: Other mechanisms of action**

| Study | Design ($n$) | Age, yr* | Male, % | Protocol | Drug (dose) | TMS target | Mechanism of action | Effect |
|---|---|---|---|---|---|---|---|---|
| **Healthy participants** | | | | | | | | |
| Heidegger et al.[82] | C/O (10) | 21–30 | 60 | PAS(N20)+2ms | Levetiracetam (3000 mg) | M1 | SV2A binding | Reduced LTP-like |
| Heidegger et al.[82] | C/O (10) | 21–30 | 60 | PAS(N20)+2ms | Piracetam (3600 mg) | M1 | Unknown | Reduced LTP-like |
| **NF1** | | | | | | | | |
| Mainberger et al.[91] | Parallel (11) | 28 (17–44) | 54.54 | PAS25 | Lovastatin (200 mg) single dose | M1 | HMG-CoA inhibition | No Effect |
| Mainberger et al.[91] | Parallel (11) | 28 (17–44) | 54.54 | PAS25 | Lovastatin (200 mg), 4 daily doses | M1 | HMG-CoA inhibition | Increased LTP-like |

C/O = crossover; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; LTP = long-term potentiation; M1 = motor cortex; NF1 = neurofibromatrosis type 1; PAS = paired associative stimulation; SV2A = synaptic vesicle glycoprotein 2A; TMS = transcranial magnetic stimulation.
*Data are expressed as a mean with a range or as a range.

## Discussion

Here, we synthesize the literature using pharmacological adjuncts to enhance rTMS-induced synaptic plasticity. This technique, building on preclinical understanding of synaptic plasticity in the form of LTP and LTD, has been applied most commonly to the human motor cortex to examine the mechanisms of TMS-induced cortical changes. The literature to date has predominantly examined glutamatergic and dopaminergic modulation of PAS, 10 Hz rTMS, 1 Hz rTMS, TBS, and QPS protocols. Fewer studies have examined the influence of other neuromodulatory systems and voltage-gated ion channels on plasticity-inducing TMS protocols.

### *Healthy participants*

The literature examining pharmacological augmentation of TMS in healthy participants reveals the complex interplay between neurotransmitter systems underlying TMS-induced synaptic plasticity in the human brain. Most of the literature to date involves the NMDA receptor and dopaminergic modulation. Whereas NMDA experiments use a common set of antagonists (memantine and dextromethorphan) and agonists (D-cycloserine) at similar doses, the dopaminergic literature has the advantage of dose-finding studies but there is less consistency in adjuncts used and, accordingly, less consistency in mechanisms. The NMDA receptor literature suggests that this receptor is necessary but may not be sufficient for TMS-induced synaptic plasticity, whereas the dopamine literature reveals a dose-dependent modulatory role of the dopaminergic system in plasticity induction. Other neurotransmitter and ion channel systems have been studied, but the evidence base has not achieved a critical mass, with few individual experiments using disparate agents in small samples and, accordingly, the findings from these studies are more variable. Overall, however, findings largely mimic those from the animal and ex vivo literature, confirming similar mechanisms of LTP-like and LTD-like synaptic plasticity in the human brain.[96–98]

Studies in healthy participants further highlight the importance of study design, including the specificity and dose of pharmacological adjunct, the type of TMS paradigm, and the type of output measurements. It is increasingly evident that future studies should consider multiple measures to identify TMS-induced LTD-like and LTP-like change the brain. For example, though the majority of studies have measured MEP at a fixed intensity, studies using D-cycloserine have found that where fixed intensity does not identify a consistent effect, the incorporation of an SRC provides a different lens on synaptic plasticity with more consistent findings across several plasticity-inducing protocols.[59,62,64] As such, future work considering multiple measurements of plasticity may further inform our understanding of how pharmacological enhancement can be used to facilitate the effects of TMS.

### *Clinical populations*

A nascent literature using pharmacologically enhanced rTMS plasticity protocols in clinical populations highlights that blunted cortical plasticity may, in some cases, be rescued with a mechanistically and pathologically informed pharmacological adjunct.[64,78,91] Given the small number of studies in clinical populations (7 studies), it remains to be determined what can be generalized from mechanistically informed adjuncts in healthy participants to rTMS in the clinical setting. As an example of nonlinearities and discrepancies that may arise between healthy and clinical populations, D-cycloserine has been associated with conflicting findings in healthy individuals,[36,60–62] but normalizes impaired LTP-like effects in individuals with MDD.[64] Yet, it remained an empirical question whether pairing stimulation with an adjunct that normalizes LTP-like effects would be associated with improved clinical outcomes. A recent randomized placebo-controlled trial showed the remarkable potential of the strategy, with more than double remission and response rates compared with standard-of-care iTBS.[11] Although this initial test showed statistical superiority of pharmacological enhancement with clinically meaningful separation, this requires independent replication. Moreover, caution is required before concluding that findings from a particular clinical population can be extended to any other, and the same process of systematically examining the effect of mechanistically informed adjuncts to TMS on LTP-like and LTD-like processes in healthy and in clinical populations is required before proceeding to treatment studies.

### *Limitations*

An important caveat to the literature to date is the predominance of small sample sizes and crossover designs, with only 4 studies using samples of 20 or more participants per group or crossover arm.[11,54,62,90] As such, while there appears to be broad alignment between the ex vivo tractable species literature and the human TMS literature, more adequately powered studies are required to determine if pharmacological adjuncts to rTMS plasticity protocols deviate from the preclinical literature.

Finally, though the motor cortex is an accessible and important model circuit from which to test synaptic plasticity in the human brain, the generalizability of the data may be limited by anatomic, circuit, and receptor differences in other brain regions. In brain regions without a measurable motor output, electroencephalography paired with TMS permits measuring TMS-evoked potentials (TEP) and spectral properties of cortical activation with TMS.[99–102] To date, there have been no studies using EEG to examine TMS-synaptic plasticity protocols; however, single- and paired-pulse paradigms have tested glutamatergic,[103–108] GABAergic,[106,109] SV2A vesicles,[105,107] VGCCs,[103] and VGSCs[105,107] using TMS-EEG. Dedicated comparisons of how pharmacological adjuncts impact LTP-like and LTD-like effects of TMS protocols in different brain regions would be an informative line of inquiry, as it may be that findings from the motor cortex may not map on to other regions of interest.

## Conclusion

Informed by a large preclinical literature examining the fundamental principles of synaptic plasticity, the noninvasive neurostimulation field is leveraging pharmacological insights to test principles of plasticity in the human brain. Although there is some inconsistency in findings, the human TMS mechanistically informed adjunct literature largely parallels the ex vivo synaptic plasticity literature. The literature, however, remains small and is dominated by inadequately powered samples, and few studies have examined pharmacological adjuncts in clinical populations. To resolve these limitations, harmonizing methods and rigorous testing in adequately powered healthy and clinical samples is required, with potential extension to therapeutic TMS applications where indicated.

**Affiliations:** From the Hotchkiss Brain Institute, University of Calgary, Calgary, Alta., Canada (Sohn, McGirr); the Department of Psychiatry, University of Calgary, Alta., Canada (Sohn, McGirr); the Mathison Centre for Mental Health Research and Education, Calgary, Alta., Canada (Sohn, McGirr); the McLean Hospital, Division of Neurotherapeutics, Belmont, Mass., USA (Brown, Sharma); the Department of Psychiatry, Harvard Medical School, Boston, Mass., USA (Brown); the Department of Neurology & Stroke, Eberhard-Karls University, Tübingen, Germany (Ziemann); and the Hertie-Institute for Clinical Brain Research, Eberhard-Karls University, Tübingen, Germany (Ziemann).

**Competing interests:** J. Brown is supported by the Brain & Behavior Research Foundation (#31748) and by Department of Defense Advanced Research Projects Agency (HR00112320037), and McLean Hospitals Center of Excellence in Depression and Anxiety Disorders. He reports honoraria for lectures at the Annual Clinical TMS Society meeting 2023 and the Brainbox Initiative Conference 2023. He is a member (unpaid) of the Board of Directors, member at large, and research committee cochair of the Clinical TMS Society. U. Ziemann is supported by a European Research Council Synergy Grant under the European Union's Horizon 2020 research and innovation programme (grant agreement no. 810377), a German Research Foundation grant (ZI 542/13-1), and an Else Kröner Fresenius Foundation Grant (2022_EKTP22). He has received travel support from the International Federation of Clinical Neurophysiology and Elsevier. He declares consulting fees from Cortec GmbH Freiburg im Breisgau. He is an ExCo member of the International Federation of Clinical Neurophysiology and the German Society of Clinical Neurophysiology and Functional Neuroimaging A. McGirr is supported by the Canadian Institutes of Health Research as a principal investigator (PI) of Enhancing repetitive transcranial magnetic stimulation in major depression with adjunctive D-cycloserine (2022-2027), and by the Natural Sciences and Engineering Research Council of Canada as a PI of Modules of spontaneous cortical activity inmouse cortex during quiet wakefulness: key nodes and shaping by neuromodulators. He holds patents 63/282,297 ("adjunctive D-cycloserine augmentation of transcranial magnetic stimulation [TMS] therapy for obsessive compulsive disorder"; Nov. 24, 2021) and 63/193,643 ("adjunctive D-cycloserine augmentation of transcranial magnetic stimulation [TMS] therapy for major depressive disorder"; May 27, 2021). No other competing interests were declared.

**Contributors:** M. Sohn, U. Ziemann, and A. McGirr designed the study. P. Sharma acquired the data, which J. Brown analyzed. M. Sohn and A. McGirr wrote the article. All of the authors revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.



## References

1. Hallett M. Transcranial magnetic stimulation and the human brain. *Nature* 2000;406:147-50.
2. Turrigiano GG, Nelson SB. Homeostatic plasticity in the developing nervous system. *Nat Rev Neurosci* 2004;5:97-107.
3. Campanac E, Debanne D. Plasticity of neuronal excitability: hebbian rules beyond the synapse. *Arch Ital Biol* 2007;145:277-87.
4. Bliss TVP, Lømo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol* 1973;232:331-56.
5. Ziemann U. TMS induced plasticity in human cortex. *Rev Neurosci* 2004;15:253-66.
6. Cooke SF, Bliss TV. Plasticity in the human central nervous system. *Brain* 2006;129:1659-73.
7. Lenz M, Vlachos A. Releasing the cortical brake by non-invasive electromagnetic stimulation? rTMS Induces LTD of GABAergic Neurotransmission. *Front Neural Circuits* 2016;10:96.
8. Lenz M, Galanis C, Muller-Dahlhaus F, et al. Repetitive magnetic stimulation induces plasticity of inhibitory synapses. *Nat Commun* 2016;7:10020.
9. Vlachos A, Muller-Dahlhaus F, Rosskopp J, et al. Repetitive magnetic stimulation induces functional and structural plasticity of excitatory postsynapses in mouse organotypic hippocampal slice cultures. *J Neurosci* 2012;32:17514-23.
10. Ziemann U, Reis J, Schwenkreis P, et al. TMS and drugs revisited 2014. *Clin Neurophysiol* 2015;126:1847-68.
11. Cole J, Sohn MN, Harris AD, et al. Efficacy of adjunctive D-cycloserine to intermittent theta-burst stimulation for major depressive disorder: a randomized clinical trial. *JAMA Psychiatry* 2022;79:1153-61.
12. Abbott LF, Nelson SB. Synaptic plasticity: taming the beast. *Nat Neurosci* 2000;3:1178-83.
13. Bliss T. The NMDA receptor 30 years on. *Neuropharmacology* 2013;74:2-3.
14. Watt AJ, Van Rossum MCW, Macleod KM, et al. Activity coregulates quantal AMPA and NMDA currents at neocortical synapses. *Neuron* 2000;26:659-70.
15. Foehring RC, Lorenzon NM. Neuromodulation, development and synaptic plasticity. *Can J Exp Psychol* 1999;53:45-61.
16. Muller-Dahlhaus F, Ziemann U. Metaplasticity in human cortex. *Neuroscientist* 2015;21:185-202.
17. Brown JC, Higgins ES, George MS. Synaptic plasticity 101: the story of the AMPA receptor for the brain stimulation practitioner. *Neuromodulation* 2022;25:1289-98.
18. Bienenstock EL, Cooper LN, Munro PW. Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. *J Neurosci* 1982;2:32-48.
19. Turrigiano G. Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. *Cold Spring Harb Perspect Biol* 2012;4:a005736.
20. Turrigiano GG. The self-tuning neuron: synaptic scaling of excitatory synapses. *Cell* 2008;135:422-35.
21. Goldsworthy MR, Pitcher JB, Ridding MC. Spaced noninvasive brain stimulation: prospects for inducing long-lasting human cortical plasticity. *Neurorehabil Neural Repair* 2015;29:714-21.
22. Abraham WC, Huggett A. Induction and reversal of long-term potentiation by repeated high-frequency stimulation in rat hippocampal slices. *Hippocampus* 1997;7:137-45.
23. Lynch G, Kramar EA, Babayan AH, et al. Differences between synaptic plasticity thresholds result in new timing rules for maximizing long-term potentiation. *Neuropharmacology* 2013;64:27-36.
24. Cao G, Harris KM. Augmenting saturated LTP by broadly spaced episodes of theta-burst stimulation in hippocampal area CA1 of adult rats and mice. *J Neurophysiol* 2014;112:1916-24.
25. Rioult-Pedotti MS, Friedman D, Donoghue JP. Learning-induced LTP in neocortex. *Science* 2000;290:533-6.
26. Gamboa OL, Antal A, Moliadze V, Paulus W. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. *Exp Brain Res* 2010;204:181-7.

27. Caulfield KA, Brown JC. The problem and potential of TMS' infinite parameter space: a targeted review and road map forward. *Front Psychiatry* 2022;13:867091.
28. Huang YZ, Edwards MJ, Rounis E, et al. Theta burst stimulation of the human motor cortex. *Neuron* 2005;45:201-6.
29. Young-Bernier M, Tanguay AN, Davidson PSR, et al. Short-latency afferent inhibition is a poor predictor of individual susceptibility to rTMS-induced plasticity in the motor cortex of young and older adults. *Front Aging Neurosci* 2014;6:182.
30. Goldsworthy MR, Pitcher JB, Ridding MC. A comparison of two different continuous theta burst stimulation paradigms applied to the human primary motor cortex. *Clin Neurophysiol* 2012; 123:2256-63.
31. McCalley DM, Lench DH, Doolittle JD, et al. Determining the optimal pulse number for theta burst induced change in cortical excitability. *Sci Rep* 2021;11.
32. Jung SH, Shin JE, Jeong YS, et al. Changes in motor cortical excitability induced by high-frequency repetitive transcranial magnetic stimulation of different stimulation durations. *Clin Neurophysiol* 2008;119:71-9.
33. Ziemann U, Paulus W, Nitsche MA, et al. Consensus: motor cortex plasticity protocols. *Brain Stimul* 2008;1:164-82.
34. Chen HX, Otmakhov N, Lisman J. Requirements for LTP induction by pairing in hippocampal CA1 pyramidal cells. *J Neurophysiol* 1999;82:526-32.
35. Brown JC, DeVries WH, Korte JE, 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* 2020;13:530-2.
36. Brown JC, Yuan S, DeVries WH, et al. NMDA-receptor agonist reveals LTP-like properties of 10-Hz rTMS in the human motor cortex. *Brain Stimul* 2021;14:619-21.
37. Chen R, Classen J, Gerloff C, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 1997;48:1398-403.
38. Vigne M, Kweon J, Sharma P, et al. Chronic caffeine consumption curbs rTMS-induced plasticity. *Front Psychiatry* 2023;14:1137681.
39. Specterman M, Bhuiya A, Kuppuswamy A, et al. The effect of an energy drink containing glucose and caffeine on human corticospinal excitability. *Physiol Behav* 2005;83:723-8.
40. Kweon J, Vigne MM, Jones RN, et al. Practice makes plasticity: 10-Hz rTMS enhances LTP-like plasticity in musicians and athletes. *Front Neural Circuits* 2023;17:1124221.
41. Stefan K, Kunesch E, Cohen LG, et al. Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain* 2000;123:572-84.
42. Wolters A, Sandbrink F, Schlottmann A, et al. A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. *J Neurophysiol* 2003;89:2339-45.
43. Hamada M, Hanajima R, Terao Y, et al. Quadro-pulse stimulation is more effective than paired-pulse stimulation for plasticity induction of the human motor cortex. *Clin Neurophysiol* 2007;118:2672-82.
44. Hamada M, Terao Y, Hanajima R, et al. Bidirectional long-term motor cortical plasticity and metaplasticity induced by quadripulse transcranial magnetic stimulation. *J Physiol* 2008;586:3927-47.
45. Hamada M, Ugawa Y. Quadripulse stimulation–a new patterned rTMS. *Restor Neurol Neurosci* 2010;28:419-24.
46. Darmani G, Ziemann U. Pharmacophysiology of TMS-evoked EEG potentials: a mini-review. *Brain Stimul* 2019;12:829-31.
47. Di Lazzaro V, Profice P, Ranieri F, et al. I-wave origin and modulation. *Brain Stimul* 2012;5:512-25.
48. Di Lazzaro V, Ziemann U. The contribution of transcranial magnetic stimulation in the functional evaluation of microcircuits in human motor cortex. *Front Neural Circuits* 2013;7:18.
49. Kukke SN, Paine RW, Chao C-C, et al. Efficient and reliable characterization of the corticospinal system using transcranial magnetic stimulation. *J Clin Neurophysiol* 2014;31:246-52.
50. Carroll TJ, Riek S, Carson RG. Reliability of the input-output properties of the cortico-spinal pathway obtained from transcranial magnetic and electrical stimulation. *J Neurosci Methods* 2001;112:193-202.
51. Peri E, Ambrosini E, Colombo VM, et al. Intra and inter-session reliability of rapid Transcranial Magnetic Stimulation stimulus-response curves of tibialis anterior muscle in healthy older adults. *PLoS One* 2017;12:e0184828.
52. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev* 2021;10:89.
53. Huang Y-Z, Chen R-S, Rothwell JC, et al. The after-effect of human theta burst stimulation is NMDA receptor dependent. *Clin Neurophysiol* 2007;118:1028-32.
54. Wankerl K, Weise D, Gentner R, et al. L-type voltage-gated Ca2+ channels: a single molecular switch for long-term potentiation/long-term depression-like plasticity and activity-dependent metaplasticity in humans. *J Neurosci* 2010;30:6197-204.
55. Colnaghi S, Colagiorgio P, Versino M, et al. A role for NMDAR-dependent cerebellar plasticity in adaptive control of saccades in humans. *Brain Stimul* 2017;10:817-27.
56. Stefan K, Kunesch E, Benecke R, et al. Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. *J Physiol* 2002;543:699-708.
57. Weise D, Mann J, Rumpf J-J, et al. Differential regulation of human paired associative stimulation-induced and theta-burst stimulation-induced plasticity by L-type and T-type Ca2+ channels. *Cerebral cortex* 2017;27:4010-21.
58. Suppa A, Biasiotta A, Belvisi D, et al. Heat-evoked experimental pain induces long-term potentiation-like plasticity in human primary motor cortex. *Cereb Cortex* 2013;23:1942-51.
59. Kweon J, Vigne M, Jones R, et al. A replication study of NMDA receptor agonism sufficiency to enhance 10-Hz rTMS-induced motor cortex plasticity. *Brain Stimul* 2022;15:1372-4.
60. Teo JTH, Swayne OB, Rothwell JC. Further evidence for NMDA-dependence of the after-effects of human theta burst stimulation. *Clin Neurophysiol* 2007;118:1649-51.
61. Selby B, Macmaster FP, Kirton A, et al. D-cycloserine blunts motor cortex facilitation after intermittent theta burst transcranial magnetic stimulation: a double-blind randomized placebo-controlled crossover study. *Brain Stimul* 2019;12:1063-5.
62. Wrightson JG, Cole J, Sohn MN, et al. The effects of D-cycloserine on corticospinal excitability after repeated spaced intermittent theta-burst transcranial magnetic stimulation: a randomized controlled trial in healthy individuals. *Neuropsychopharmacology* 2023;48:1217-24.
63. Suppa A, Bologna M, Berardelli A. L-Dopa and cortical associative plasticity in Parkinson's disease. *Clin Neurophysiol* 2013;124:638-9.
64. Cole J, Selby B, Ismail Z, et al. D-cycloserine normalizes long-term motor plasticity after transcranial magnetic intermittent theta-burst stimulation in major depressive disorder. *Clin Neurophysiol* 2021;132:1770-6.
65. Hollander D, Pradas J, Kaplan R, et al. High-dose dextromethorphan in amyotrophic lateral sclerosis: phase I safety and pharmacokinetic studies. *Ann Neurol* 1994;36:920-4.
66. Steinberg GK, Bell TE, Yenari MA. Dose escalation safety and tolerance study of the N-methyl-D-aspartate antagonist dextromethorphan in neurosurgery patients. *J Neurosurg* 1996;84:860-6.
67. Thirugnanasambandam N, Grundey J, Paulus W, et al. Dose-dependent nonlinear effect of L-DOPA on paired associative stimulation-induced neuroplasticity in humans. *J Neurosci* 2011;31:5294-9.
68. Monte-Silva K, Kuo MF, Thirugnanasambandam N, et al. Dose-dependent inverted U-shaped effect of dopamine (D2-like) receptor activation on focal and nonfocal plasticity in humans. *J Neurosci* 2009;29:6124-31.
69. Enomoto H, Terao Y, Kadowaki S, et al. Effects of L-Dopa and pramipexole on plasticity induced by QPS in human motor cortex. *J Neural Transm (Vienna)* 2015;122:1253-61.
70. Fresnoza SM, Batsikadze G, Muller LE, et al. Inhibitory effect of apomorphine on focal and nonfocal plasticity in the human motor cortex. *Pharmaceutics* 2021;13:718.
71. Fresnoza S, Stiksrud E, Klinker F, et al. Dosage-dependent effect of dopamine D2 receptor activation on motor cortex plasticity in humans. *J Neurosci* 2014;34:10701-9.
72. Korchounov A, Ziemann U. Neuromodulatory neurotransmitters influence LTP-like plasticity in human cortex: a pharmaco-TMS study. *Neuropsychopharmacology* 2011;36:1894-902.
73. Monte-Silva K, Ruge D, Teo JT, et al. D2 receptor block abolishes theta burst stimulation-induced neuroplasticity in the human motor cortex. *Neuropsychopharmacology* 2011;36:2097-102.
74. Nitsche MA, Kuo MF, Grosch J, et al. D1-receptor impact on neuroplasticity in humans. *J Neurosci* 2009;29:2648-53.

75. Fresnoza S, Paulus W, Nitsche MA, et al. Nonlinear dose-dependent impact of D1 receptor activation on motor cortex plasticity in humans. *J Neurosci* 2014;34:2744-53.
76. Guerra A, D'Onofrio V, Asci F, et al. Assessing the interaction between L-dopa and gamma-transcranial alternating current stimulation effects on primary motor cortex plasticity in Parkinson's disease. *Eur J Neurosci* 2023;57:201-12.
77. Carrillo F, Palomar FJ, Conde V, et al. Study of cerebello-thalamocortical pathway by transcranial magnetic stimulation in Parkinson's disease. *Brain Stimul* 2013;6:582-9.
78. Koch G, Di Lorenzo F, Bonni S, et al. Dopaminergic modulation of cortical plasticity in Alzheimer's disease patients. *Neuropsychopharmacology* 2014;39:2654-61.
79. Fitzgerald PB, Brown TL, Marston NA, et al. Reduced plastic brain responses in schizophrenia: a transcranial magnetic stimulation study. *Schizophr Res* 2004;71:17-26.
80. Seeman P. Atypical antipsychotics: mechanism of action. *Can J Psychiatry* 2002;47:27-38.
81. McDonnell MN, Orekhov Y, Ziemann U. Suppression of LTP-like plasticity in human motor cortex by the GABAB receptor agonist baclofen. *Exp Brain Res* 2007;180:181-6.
82. Heidegger T, Krakow K, Ziemann U. Effects of antiepileptic drugs on associative LTP-like plasticity in human motor cortex. *Eur J Neurosci* 2010;32:1215-22.
83. Manzano S, Aguera L, Aguilar M, et al. A review on tramiprosate (homotaurine) in Alzheimer's disease and other neurocognitive disorders. *Front Neurol* 2020;11:614.
84. Martorana A, Di Lorenzo F, Manenti G, et al. Homotaurine induces measurable changes of short latency afferent inhibition in a group of mild cognitive impairment individuals. *Front Aging Neurosci* 2014;6:254.
85. Batsikadze G, Paulus W, Kuo M-F, et al. Effect of serotonin on paired associative stimulation-induced plasticity in the human motor cortex. *Neuropsychopharmacology* 2013;38:2260-7.
86. Kuo MF, Grosch J, Fregni F, et al. Focusing effect of acetylcholine on neuroplasticity in the human motor cortex. *J Neurosci* 2007;27:14442-7.
87. Thirugnanasambandam N, Grundey J, Adam K, et al. Nicotinergic impact on focal and non-focal neuroplasticity induced by non-invasive brain stimulation in non-smoking humans. *Neuropsychopharmacology* 2011;36:879-86.
88. Rioult-Pedotti M-S, Donogue JP. The nature and mechanisms of plasticity. In: *Plasticity in the human nervous system: investigations with transcranial magnetic stimulation*. Cambridge: Cambridge University Press; 2003:1-25.
89. Kopecky BJ, Liang R, Bao J. T-type calcium channel blockers as neuroprotective agents. *Pflugers Arch* 2014;466:757-65.
90. Tanaka N, Hanajima R, Tsutsumi R, et al. Influence of zonisamide on the LTP-like effect induced by quadripulse transcranial magnetic stimulation (QPS). *Brain Stimul* 2015;8:1220-2.
91. Mainberger F, Jung NH, Zenker M, et al. Lovastatin improves impaired synaptic plasticity and phasic alertness in patients with neurofibromatosis type 1. *BMC Neurol* 2013;13:131.
92. Lynch BA, Lambeng N, Nocka K, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proc Natl Acad Sci U S A* 2004;101:9861-6.
93. Rigo JM, Hans G, Nguyen L, et al. The anti-epileptic drug levetiracetam reverses the inhibition by negative allosteric modulators of neuronal GABA- and glycine-gated currents. *Br J Pharmacol* 2002;136:659-72.
94. Winblad B. Piracetam: a review of pharmacological properties and clinical uses. *CNS Drug Rev* 2005;11:169-82.
95. Duong H, Bajaj T. Lovastatin. StatPearls: Treasure Island (FL); 2023.
96. Luscher C, Malenka RC. NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). *Cold Spring Harbor Perspectives in Biology* 2012;4:a005710-a.
97. Gjedde A, Kumakura Y, Cumming P, et al. Inverted-U-shaped correlation between dopamine receptor availability in striatum and sensation seeking. *Proc Natl Acad Sci U S A* 2010;107:3870-5.
98. Otani S, Bai J, Blot K. Dopaminergic modulation of synaptic plasticity in rat prefrontal neurons. *Neurosci Bull* 2015;31:183-90.
99. Bonato C, Miniussi C, Rossini PM. Transcranial magnetic stimulation and cortical evoked potentials: a TMS/EEG co-registration study. *Clin Neurophysiol* 2006;117:1699-707.
100. Ilmoniemi RJ, Kicic D. Methodology for combined TMS and EEG. *Brain Topogr* 2010;22:233-48.
101. Tremblay S, Rogasch NC, Premoli I, et al. Clinical utility and prospective of TMS-EEG. *Clin Neurophysiol* 2019;130:802-44.
102. Gedankien T, Fried PJ, Pascual-Leone A, et al. Intermittent theta-burst stimulation induces correlated changes in cortical and corticospinal excitability in healthy older subjects. *Clin Neurophysiol* 2017;128:2419-27.
103. Belardinelli P, König F, Liang C, et al. TMS-EEG signatures of glutamatergic neurotransmission in human cortex. *Sci Rep* 2021;11:8159.
104. Premoli I, Kiraly J, Muller-Dahlhaus F, et al. Short-interval and long-interval intracortical inhibition of TMS-evoked EEG potentials. *Brain Stimul* 2018;11:818-27.
105. Premoli I, Biondi A, Carlesso S, et al. Lamotrigine and levetiracetam exert a similar modulation of TMS-evoked EEG potentials. *Epilepsia* 2017;58:42-50.
106. Premoli I, Rivolta D, Espenhahn S, et al. Characterization of $GABA_B$-receptor mediated neurotransmission in the human cortex by paired-pulse TMS-EEG. *Neuroimage* 2014;103:152-62.
107. Darmani G, Bergmann TO, Zipser C, et al. Effects of antiepileptic drugs on cortical excitability in humans: a TMS-EMG and TMS-EEG study. *Hum Brain Mapp* 2019;40:1276-89.
108. Darmani G, Zipser CM, Bohmer GM, et al. Effects of the selective alpha5-GABAAR antagonist S44819 on excitability in the human brain: a TMS-EMG and TMS-EEG phase I study. *J Neurosci* 2016;36:12312-20.
109. Premoli I, Bergmann TO, Fecchio M, et al. The impact of GABAergic drugs on TMS-induced brain oscillations in human motor cortex. *Neuroimage* 2017;163:1-12.