The final article is available, upon publication, at: Ferro, M., Lamanna, J., Spadini, S., Nespoli, A., Sulpizio, S., & Malgaroli, A. (2022). Synaptic plasticity mechanisms behind TMS efficacy: insights from its application to animal models. *Journal of Neural Transmission, 129*(1), 25–36. https://doi.org/10.1007/s00702-021-02436-7

Synaptic plasticity mechanisms behind TMS efficacy: insights from its application to animal models

Mattia Ferro[1,3]*, Jacopo Lamanna[2,3]*, Sara Spadini[3]*, Alessio Nespoli[1], Simone Sulpizio[4] & Antonio Malgaroli[2,3]

[1]Department of Psychology, Sigmund Freud University, Milan, Italy

[2]Faculty of Psychology, Vita-Salute San Raffaele University, Milan, Italy

[3]Center for Behavioral Neuroscience and Communication (BNC), Vita-Salute San Raffaele University, Milan, Italy

[4]Department of Psychology, University of Milano-Bicocca, Milan, Italy

* Mattia Ferro, Jacopo Lamanna and Sara Spadini equally contributed to this paper.

Authors note

Correspondence should be addressed to: Antonio Malgaroli, Mattia Ferro and Jacopo Lamanna, Center for Behavioral Neuroscience and Communication (BNC), Faculty of Psychology, Vita-Salute San Raffaele University, Via Olgettina 58, Milan 20132, Italy.

Email: malgaroli.antonio@unisr.it (A. M.), m.ferro@milano-sfu.it (M. F.) and lamanna.jacopo@hsr.it (J. L.)

The final article is available, upon publication, at: Ferro, M., Lamanna, J., Spadini, S., Nespoli, A., Sulpizio, S., & Malgaroli, A. (2022). Synaptic plasticity mechanisms behind TMS efficacy: insights from its application to animal models. *Journal of Neural Transmission, 129*(1), 25–36. https://doi.org/10.1007/s00702-021-02436-7

Abstract

Neural plasticity is defined as a reshape of communication paths among neurons, expressed through changes in the number and weights of synaptic contacts. During this process, which occurs massively during early brain development but continues also in adulthood, specific brain functions are modified by activity-dependent processes, triggered by external as well as internal stimuli. Since transcranial magnetic stimulation (TMS) produces a non-invasive form of brain cells activation, many different TMS protocols have been developed to treat neurological and psychiatric conditions and proved to be beneficial. Although neural plasticity induction by TMS has been widely assessed on human subjects, we still lack compelling evidence about the actual biological and molecular mechanisms. In order to support a better comprehension of the involved phenomena, the main focus of this review is to summarize what has been found through the application of TMS to animal models. The hope is that such integrated view will shed light on why and how TMS so effectively works on human subjects, thus supporting a more efficient development of new protocols in the future.

Keywords: TMS, Transcranial Magnetic Stimulation, Brain plasticity, Synaptic plasticity, Mental disorders, Animal model.

The final article is available, upon publication, at: Ferro, M., Lamanna, J., Spadini, S., Nespoli, A., Sulpizio, S., & Malgaroli, A. (2022). Synaptic plasticity mechanisms behind TMS efficacy: insights from its application to animal models. *Journal of Neural Transmission, 129*(1), 25–36. https://doi.org/10.1007/s00702-021-02436-7

Introduction

It is now well-established that repeated activation of neural circuits can lead to changes in their intrinsic transmission strength (Bliss and Lømo 1973). These plastic modifications can be expressed through functional alterations, both positively and negatively directed, variations in gene transcription and translation, as well as through the morphological restructuring of synaptic networks (Citri and Malenka 2008). Originally, plastic changes were induced by electrical stimulation of afferent fibers (Bliss and Lømo 1973); later on, in addition to this standard methodology, we fostered the introduction of additional protocols capable of inducing *bona fide* long-term potentiation (LTP) and long-term depression (LTD), including chemical stimulation (Lamanna et al. 2015) and optogenetics (Fenno et al. 2011). Some of these techniques work *in vivo* on experimental animals, others can be applied only to *in vitro* preparations, but none has been used on humans.

In this respect, transcranial magnetic stimulation (TMS), which non-invasively induces focal electrical activation of neurons and related efferent fibers through a magnetic field, represents an effective tool to induce neural plasticity in the human brain. This technique has already provided important clinical results in psychiatric and neurological diseases (Rossi et al. 2020), all conditions where pathological alteration of brain circuits is hypothesized (Downar et al. 2016). For example, TMS application to patients with major depression produced beneficial effects lasting months, implying that - directly or indirectly - it produces enduring neural modifications (Levkovitz et al. 2015).

The efficacy of TMS, exactly as that of LTP/LTD protocols, varies with stimulation parameters, these affecting associativity and cooperativity of the involved plasticity induction processes, but also according to the target brain areas (Rossi et al. 2020) (see Table 1 for a description of the TMS protocols mentioned in this review). The latter indeed show different levels of plastic potential, presumably a reflection of NMDA receptors distribution and differences in molecular cascades (Oberman and Pascual-Leone 2013). Unfortunately, TMS studies on humans fail to unveil the actual neurobiological modifications subtending those plastic changes. On the other hand, TMS applied to the animal model allows a more direct investigation, addressing if and how TMS can induce the same protein and molecular changes seen after the induction of LTP/LTD. Molecular mechanisms might represent a valuable point of convergence, since homology studies showed similar processes in both animals and humans (Keeler and Robbins 2011). However, it seems appropriate to always keep in mind that, since the rodent brain is much smaller than the human's, stimulation depth is not an issue for most animal studies, but on the other hand these lack the targeting precision achieved with humans. These limitations could be overcome with the development of new stimulation tools for both humans and animal models.

In this review, we first summarize representative evidence available in the literature supporting the capability of TMS to induce functional plastic changes in the brain of human subjects. Then, we collect and discuss studies performed on animal models which shed light on the underlying molecular and biochemical mechanisms. We believe that such parallel view can contribute to better define the involvement of synaptic plasticity in the ameliorating effects of TMS therapy.

The final article is available, upon publication, at: Ferro, M., Lamanna, J., Spadini, S., Nespoli, A., Sulpizio, S., & Malgaroli, A. (2022). Synaptic plasticity mechanisms behind TMS efficacy: insights from its application to animal models. *Journal of Neural Transmission, 129*(1), 25–36. https://doi.org/10.1007/s00702-021-02436-7

Name	Protocol	Purpose
TMS	Single magnetic pulses sent through the coils.	Single stimulation of target areas in brief sessions. Used for evaluation of motor threshold and functional tool together with recording techniques (fMRI or EEG) for brain areas mapping.
rTMS	Repeated magnetic pulses sent through the coils, at either high (>5Hz) or low (~1Hz) frequencies.	Modulation of brain areas activity: high frequency rTMS is commonly used to excite brain areas, while low frequency to inhibit.
ppTMS	Pairs of stimuli at different locations, separated by a variable interval.	Interhemispheric and interregional stimulation (inhibition or facilitation) of the cortex.
TBS	Sequences of stimuli mimicking the hippocampal theta rhythm. Protocol variants: - intermittent TBS (iTBS) - continuous TBS (cTBS)	Enhanced and long-lasting modulation of cortical excitability. TBS was originally used to induce LTP in preclinical models.
dTMS	Pulses that can reach deeper (~ 4 cm) locations beneath the skull and more precise focalization compared to classical TMS.	Enhanced stimulation accuracy, reduced side-effects, stimulation of subcortical regions.

Table 1. Different types of TMS protocols. rTMS: repeated TMS; ppTMS: paired-pulse TMS; TBS: theta-burst stimulation; dTMS: deep TMS.

The endless tale of synaptic plasticity induction and expression

Before addressing the link between TMS action and brain plasticity, it is worth recalling some key aspects that underlie the induction and expression of those functional and structural changes produced by synaptic plasticity phenomena. Of course, the panorama of mechanisms that make possible such changes is boundless and constantly evolving. Hence, we will briefly introduce the topic and provide reference to other reviews for a more in-depth coverage. Functional synaptic plasticity in mammals has been thoroughly characterized *in vitro* using samples from animal models, such as acute brain slices of the hippocampus, by using specific electrical stimulation protocols. High frequency stimulation (~100 Hz), either delivered as a tetanus or a sequence of intermittent bursts (theta-burst stimulation) (Larson & Munkácsy 2015), usually produces potentiation of synapses (LTP), but it can induce both LTP and LTD in specific cortical preparations (such as prefrontal cortex) due to the metaplastic action of neuromodulators (Otani et al., 2003; Lamanna et al., 2021). LTD is more classically obtained through low frequency (~1 Hz), steady stimulation delivered for relatively longer periods of time. One of the most important features of LTP, observed in several brain circuits (the most popular being the Schaffer collaterals of the hippocampus) is associativity, *i.e.* the dependence of potentiation upon almost simultaneous activation of pre- and post- synaptic neurons. Associativity is generally granted by the activation of glutamate NMDA receptors and

the consequent inflow of Ca^{2+} ions (Bliss & Collingridge, 2013). Calcium is pivotal to the induction/expression of both synaptic potentiation and depression, since it directly or indirectly activates protein kinases (such as Ca^{2+}/calmodulin-dependent protein kinase II, CaMKII, cAMP-dependent protein kinase, PKA, and protein-kinase C, PKC) and phosphatases (such as PP1 and PP2A), respectively. Such enzymes mediate complex intracellular cascades leading to the remodeling of synaptic receptors composition, release retrograde messengers, and eventually up- or down-regulate gene expression and protein synthesis/degradation, which is required for the consolidation of synaptic changes in the long-term (Klann & Dever, 2004). Intrinsic excitability of membranes at the level of both soma and neurites can also go through plastic changes and these can be maintained in the long-term, dramatically affecting the function of brain circuits (Daoudal & Debanne, 2003). Furthermore, such changes, together with synaptic scaling, allow for effective stabilization of neural circuits following synaptic potentiation, thus preserving their functionality (Turrigiano & Nelson, 2000). Structural changes can either occur at the level of the dendritic arbor, or affect whole networks of the brain connectome, with heavy consequences on neural dynamics (Bargmann & Marder, 2013). The former kind of modification involves growth factors such as the brain derived neurotrophic factor (BDNF), which is known to be released both constitutively and following synaptic activation (Kuczewski et al, 2009), and recently attracted deep interest in the context of stress-related depressive-like behaviors (Björkholm & Monteggia, 2016). Not only the cellular part of the brain, *i.e.* neurons and synapses, is involved in the structural and functional plastic changes described above. Perineuronal nets (PNNs), formed by chondroitin sulphate proteoglycans (CSPGs), seem to be involved in the inhibition of axon regeneration and act as a glial "scar" blocking new axons growth in neural injured sites (Siebert and Osterhout 2011). In addition, PNNs encapsulate GABAergic fast-spiking interneurons (FSI) expressing parvalbumin (PV), a calcium-binding protein known to play crucial roles in short-term plasticity (Caillard et al. 2000). Therefore, PNNs are thought to regulate the inhibitory action of PV+ cells on principal neurons, hence orchestrating the opening and the closing of the so-called critical period. Critical periods are specific epochs, in the early and late stages of nervous system development, which are characterized by very high plastic potential, and thus contribute to the shaping of most brain functions, such as sensory processing (Levelt & Hübener, 2012). Finally, although most studies focused on clarifying the mechanisms of plasticity at glutamatergic synapses, GABAergic transmission is also known to be highly plastic, and the induction of inhibitory plasticity generally involves different molecular mechanisms, such as changes in the expression of Cl^- transporters (Griffen & Maffei, 2014).

Interpreting TMS effects on human brain in a plasticity perspective

Extended evidence in humans suggests that TMS induces plastic changes and strengthens neural plasticity mechanisms. Nevertheless, the available studies are limited to functional modifications and do not address the underlying biological and molecular mechanisms. In many instances, TMS has been shown to alter specific motor behaviors and the corresponding neurophysiological outputs: the enhancing effect of TMS on the motor evoked potential (MEP) is a classic example. Murray and colleagues, among others, compared the MEP as an index of corticomotor excitability during and after 15-min and 30-min TMS protocols (Murray et al. 2011). In this work, TMS augmented such excitability after the shorter protocol, with no additional advantages with the longer one. In a later study, MEP responses were found potentiated by a paired-pulse TMS (ppTMS) paradigm able to induce a cortical facilitation with different time intervals, from 8 to 30 ms (Cash et al. 2016). The authors suggest that a period of GABAergic late cortical disinhibition (LCD) could underlie this facilitation. All the above transient changes in excitability might refer to a change in action potential activation threshold, which is not a synaptic plastic change *per se*. Nevertheless, in the same study, the authors designed stimulation sequences where each MEP-evoking pulse was preceded by ppTMS. Thanks to the ppTMS-induced cortical

facilitation, this approach produced long-lasting enhancement of motor responses (~60 min), which is suggestive of forms of synaptic plasticity like LTP (Cash et al. 2016).

Other studies indicated synaptic plasticity as the basal mechanism of TMS functional effects by showing how paired associative TMS stimulations induce appreciable long-term transmission effects in terms of physiological changes at the level of M1 (Müller-Dahlhaus et al. 2015). This is reminiscent of Hebbian LTP, but a direct proof of the potentiation of the target circuit is difficult, if not impossible, to achieve. Along this line, TMS has also been shown to change the learning of specific motor behaviors: some examples of these effects are found in the following studies. There is evidence, in fact, that intermittent theta-burst stimulation (iTBS) over primary motor cortex (M1) enhances motor learning across tasks in healthy subjects (Platz et al. 2018), even if the high situation-dependent efficacy of TMS should be considered (Hallett 2001). Another study demonstrated that TMS on M1, delivered simultaneously to motor imagery (MI), induces changes in motor output increasing MEPs in hand and forearm muscles involved in the motor imagination process (Foysal and Baker 2020). Another important concept that links the use of TMS to changes in motor behavior is functional recovery following neurophysiological damage and, also in this case, neural plasticity seems to be the basis of the improvements. Here we present studies that move in this direction. In a clinical trial, Volz and colleagues showed that the enhancement of motor cortex excitability using iTBS-TMS, if applied before physical therapy, promoted recovery of motor functions in a short time span after stroke onset (Volz et al. 2016). Interestingly, the comparison of connectivity maps in motor-related areas revealed that patients with better motor outcome featured a lower decrease in functional connectivity between M1 and bilateral motor areas and this was significantly higher in the M1-stimulation group compared to the control one. In another study BDNF has been hypothesized to play a specific role in modulating the efficacy of repetitive TMS (rTMS) contributing to motor recovery of stroke patients through the induction of LTP-like plasticity (Chang et al. 2014). Based on similar premises, Ackerley and colleagues tested primed upper limb physical therapy with iTBS after stroke (Ackerley et al. 2016). The effectiveness of such therapy resulted significantly increased immediately after TMS and one month later. In addition, a greater improvement was associated with a more balanced corticomotor excitability, explainable by the induction of LTP-like plasticity, with an increase of input receptibility as well as with improved M1 connectivity. Another interesting result on the use of TMS for the plasticity-like functional recovery of specific physiological deficits comes from the application of rTMS to the visual cortex of patients with amblyopia, where it was found that 10 Hz stimulation produced an increase in contrast sensitivity in all participants (Thompson et al. 2008). All the works described above are summarized in Table 2. Although exemplary, these findings support the idea that TMS produces plastic changes on different neural circuits. Similar TMS applications performed on animal models, analyzed in the next section, allow to better investigate synaptic plasticity involvement and suggest molecular and functional mechanisms underlying the observed effects.

The final article is available, upon publication, at: Ferro, M., Lamanna, J., Spadini, S., Nespoli, A., Sulpizio, S., & Malgaroli, A. (2022). Synaptic plasticity mechanisms behind TMS efficacy: insights from its application to animal models. *Journal of Neural Transmission, 129*(1), 25–36. https://doi.org/10.1007/s00702-021-02436-7

Study	Stimulation type and duration	Stimulation area	Results - Humans
Thompson et al., 2008	rTMS at 1 Hz, 600 pulses total; rTMS at 10 Hz, 5 s trains with 45 s inter-train intervals, 900 pulses total; intensity: 100% of motor threshold (MT).	V1	10 Hz increased contrast sensitivity in patients with amblyopia.
Murray et al., 2011	ppTMS, 1.5 ms inter-pulse interval, delivered 0.2 Hz, 15 or 30 min sessions.	Left M1	Increased corticomotor excitability.
Chang et al., 2014	rTMS at 10 Hz, 55 s inter-train intervals, 1000 pulses/day for 10 days; intensity: 90% of MT.	M1	Altered motor cortex excitability; the effect is BDNF-related. BDNF genotyping was performed through PCR on blood samples from tested subjects.
Ackerley et al., 2016	iTBS protocol: 600 stimuli for 10 consecutive days; intensity: 90% of MT.	Ipsilesional M1	Dose-effect improvements in physical therapy efficacy.
Cash et al., 2016	ppTMS, 1.3-1.5 ms inter-pulse interval, 6 trains of 4 doublets at 200-250 ms intervals, 8 s inter-train interval, 48 pulses total. Intensity: maximum at 120% of MT.	Left M1	Increased MEP.
Volz et al., 2016	iTBS for 3.5 min, daily for 5 days.	M1	Improved motor rehabilitation of stroke patients; lower decrease in functional connectivity between M1 and bilateral motor areas.
Platz et al., 2018	iTBS protocol: rTMS at 50 Hz, bursts of 3 pulses, repetition frequency in the theta range (5 Hz), 2 s trains repeated at 0.1 Hz, 600 pulses total (daily for 4 days). Intensity: 80% of active MT.	M1 and S1	Enhancement of motor learning in healthy subjects.
Foysal and Baker, 2020	Six different intervention protocols, pairing TMS with MI of either flexion or extension movements. TMS rate: 0.1 Hz; intensity: 1.1 or 1.2 X RMT; 15 min sessions.	Left M1	Increased MEP of muscles associated to specific motor imagery.

Table 2. Studies using TMS putatively inducing neural plasticity on human subjects.

Plasticity effects of TMS on animal models

Animal models are an unvaluable resource for investigating the biological mechanisms underlying plastic processes that are either induced or enhanced by TMS treatment. The following selection of studies, summarized in Table 3, aims at shedding light on the functional, molecular and anatomical plastic changes of the involved brain circuits.

Visual cortex

Castillo-Padilla and Funke showed that iTBS administration enhanced the visual performance of dark-reared rats, making it indistinguishable from that of rats reared in a normal 12h light/dark cycle (Castillo-Padilla and Funke 2016). Furthermore, a study investigating the stimulation effects on terminal zones (TZs, areas where neurons projections

terminate in a specific cluster or region), suggests that also low-intensity rTMS (LI-rTMS) can induce plastic changes on visual pathways (Makowiecki et al. 2014): after LI-rTMS, the abnormal dispersion of TZs was significantly reduced, as shown by retrograde labelling of geniculo-cortical projections. Such result also suggests that, although TMS stimulation is limited to cortical areas, it can also indirectly drive rearrangement of projections originating in sub-cortical nuclei, at least in those receiving strong cortical feedback, such as the visual thalamus (Montesano et al., 2015). Both the aforementioned studies provide evidence for the involvement of BDNF. As a matter of fact, the deficit in visual performance of dark-rearing rats seemed to come along with a decrease in BDNF and atypical PKC expression, whereas in other groups an enriched environment and iTBS prevented BDNF and PKC from decreasing (Castillo-Padilla and Funke 2016). Accordingly, Makowiecki et al. found an increase in BDNF concentration in the superior colliculus and visual cortex after LI-TMS (Makowiecki et al. 2014).

When applied to the primary visual cortex (V1) of cats, 10 Hz TMS stimulation was shown to induce a temporary state of increased excitability, opening a time window for enhanced plasticity, thus facilitating the reorganization of stimulus-orientation maps (Kozyrev et al. 2018). Such reorganization was stable for hours and characterized by a systematic shift in orientation preference toward the trained orientation. Thus, the authors speculate that TMS may be used to noninvasively trigger a targeted large-scale remodeling of neural connections (Kozyrev et al. 2018).

Prefrontal cortex

High-frequency rTMS protocols conducted on prefrontal cortex of rats significantly increased BDNF expression in hippocampus and prelimbic cortex three days after the stimulation; similarly, augmented levels of the AMPA receptor GluR1 subunit and of phosphorylated GluR1 (pGluR1) were detected solely in hippocampus of awake animals, with a decrease in such neuroplasticity markers if anesthesia was applied (Gersner et al. 2011).

Somatosensory cortex

Mix and colleagues investigated changes in the populations of PV+ expressing GABAergic FSI as a consequence of iTBS-TMS application on rats (Mix et al. 2015). The authors found that the TMS protocol caused a reduction in the number of PV+ cells and that this effect was age-dependent, with no reduction before PD30. It was also shown that such effect was paralleled by the growth of PNNs, suggesting a role of these structures in shaping the network of PV+ neurons. GABA released from PV+ cells also inhibits neural stem cells keeping them quiescent (Mix et al. 2015). Therefore, a reduction in PV+ cells could in turn enhance neural stem cells proliferation (Cullen and Young 2016). In a subsequent study, Hoppenrath et al. (2016) found that the excitability of FSIs was durably increased by iTBS, as assessed through *ex vivo* electrophysiological recordings, but only between postnatal day 29 and 36. The evidence provided by these studies suggest that TMS could exert opposite effects on PNN maturation. However, these findings support the general idea that PV+ FSIs are particularly sensitive to TBS during early cortical development. Based on this, the authors speculate that TMS could be very effective during early development to act on the maturation of neocortical networks before the closing of the critical period (Hoppenrath et al. 2016).

In order to investigate more directly the intracellular pathways and the molecular elements involved in TMS effects, Lu and colleagues studied the action of TMS neurorehabilitation over S1 in an animal model of traumatic brain injury (TBI) (Lu et al. 2015). Authors were able to outline significant differences between the TBI-only and the 4-weeks TMS-TBI treatment group: multi-unit recordings showed a significant increase in the neuronal activity of the TMS group compared to controls, and increased levels of CaMKII expression. A further analysis of local field potentials (LFPs) recorded in the S1 of the same groups confirmed these findings (Lu et al. 2015). Hence, TMS might promote CaMKII expression, which

in turns induces neurite growth by the action of BDNF. Indeed, BDNF is known to regulate synaptic plasticity and neurogenesis, and its signaling impairment has been shown to be central in depressive and anxiety disorders and may also play a role in several other disorders (Bathina and Das 2015).

Based on the evidence described above, TMS might represent a valuable tool for promoting the re-opening of critical periods of plasticity (Hensch and Bilimoria 2012), either by acting on PNNs and PV+ cells or by directly promoting neural plasticity in target neuronal populations.

Motor and sensorimotor cortices

Muller and colleagues demonstrated for the first time that low frequency rTMS (lf-rTMS) induces LTD-like modulation of cortex excitability. Using *in vivo* electrophysiology in anesthetized rats, they proved a long-lasting reduction in the lateralized forelimb MEPs, which may be traced back to LTD-type plasticity due to its frequency- and NMDAR-dependence, with preferential response to 1 Hz stimulation (Muller et al. 2014).

Fujiki and colleagues applied bilateral high frequency rTMS (hf-rTMS) on rats using an electrical stimulation protocol known to induce hippocampal LTP *in vivo* (Fujiki et al. 2020). The authors showed that both rTMS and direct electrical stimulation of the same sensorimotor cortices produced a similar pattern of ribosomal protein S6 phosphorylation in several areas beside the stimulated ones, including the cingulate and the piriform cortices. Since S6 phosphorylation is related to several NMDA-dependent signaling cascades including MAPK/ERK, PI3 kinase and mTOR, the results of this study suggest that hf-rTMS stimulation can enhance synaptic plasticity occurring also at brain sites far from those stimulated. Although S6 phosphorylation seems a promising marker for evaluating TMS efficacy, the reported comparisons remain qualitative and successful induction of functional plasticity was not verified (Fujiki et al. 2020).

Chronic TMS treatment at low frequencies (10-15 Hz) was shown to enhance spatial learning in a mouse model of Alzheimer's disease (AD) based on the accumulation of intracellular amyloid-β deposits (Wang et al. 2015). Interestingly, better cognitive performance of both wild type mice and TMS-treated AD model was followed by higher LTP in hippocampal slices. In addition, the authors found that TMS reduced the accumulation of amyloid-β and rescued the inhibition of large conductance calcium-activated potassium channels (BK) observed in the AD model, likely by promoting Homer-1a expression in the neocortex. These findings support the idea that TMS clinical effects can be related to its ameliorating action on biological processes involved in synaptic plasticity, that can be compromised by pathological conditions.

Yang and colleagues provided evidence for a role of synaptic plasticity in the therapeutic effects of magnetic stimulation of rats' brain with a depressive-like phenotype induced by chronic unpredictable stress (CUS) (Yang et al. 2019). It was shown that 1 Hz stimulation on the rat's head ameliorated cognitive deficits induced by CUS and restored CUS-occluded LTP tested *in vivo* at Schaffer collaterals. The biochemical characterization on hippocampus lysates from the same animals showed an increase in the expression of PSD95 and of the NMDA receptor-channel subunit NR2B, both related to synaptic plasticity and cognitive function (Barkus et al., 2010). The above results suggest that plasticity is enhanced by magnetic stimulation, but the target brain region used in this study cannot be precisely identified.

TMS was also applied to a Parkinson's disease (PD) rat model based on 6-hydroxydopamine lesion in order to test for possible interactions of such phenotype on motor plasticity induced by a TBS rTMS protocol (Hsieh et al. 2015). Interestingly, iTBS-induced potentiation of MEPs shown on healthy controls was occluded in advanced PD animals. Furthermore, such occlusion correlated with both disease severity and the loss of dopaminergic nigral cells and striatal terminals. This result suggests that TMS-induced potentiation of MEPs could be related to dopamine-dependent synaptic

plasticity in the striatum (Kreitzer, A. C., & Malenka, R. C. (2008). Striatal plasticity and basal ganglia circuit function. Neuron, 60(4), 543-554.), which is compromised by dopaminergic deficit in the PD rat model.

rTMS was also applied to cases of spinal cord injury, believing that its effects could improve the symptomatology of the trauma. A recent study examined rats with spinal cord injury at the level of T9 segment (Krishnan et al. 2019). The authors show that high frequency (20 Hz) rTMS administered 10 minutes after injury bilaterally to sensorimotor cortices produced a significant improvement in locomotion measured one week after injury. These results were confirmed by the longer inter-peak latency of MEPs, suggesting a plastic reorganization of motor pathways after the global cortical silencing induced by the injury. Moreover, by using ultra-high field functional magnetic resonance imaging (fMRI), the authors found a greater response after TMS to hindlimb stimulation in the right and left hindlimb primary somatosensory areas. Interestingly, the effects on all these measures were stronger with the acute treatment compared to the chronic one (administered 2 weeks after spinal injury).

Spinal cord

A recent work examined the effects of TMS applied on the spinal injury site (at the C6/7 level) coupled with a locomotor function recovery program performed using treadmill training (Hou et al. 2020). The best results in terms of rehabilitative effects were achieved using both instruments instead of a single one. These effects include the restoration of the forelimb grip strength and limb coordination, a better continuity of the descending fibers around the lesion found using MRI and a better conservation of descending tracts detected via diffusion tensor MRI. Furthermore, an increased expression of BDNF and molecules mediating synaptic inhibition ($GABA_B$ receptors), as well as increased levels of dopamine beta-hydroxylase (DβH), were found through immunohistochemistry. According to the authors, TMS was able to increase the excitability of motor neurons by acting on pre- and post- synaptic GABAergic and noradrenergic signaling, and this action also led to the enhancement of motor plasticity effects induced by the treadmill simulator.

Hippocampus

Further evidence linking TMS to modulation of plasticity comes from a study demonstrating the rescuing effects of low frequency rTMS (lf-rTMS) on L-type Ca^{2+} channel activity, which was long-term inhibited by exposure to sevoflurane during early stages of postnatal development (Liu et al. 2016). Sevoflurane is a volatile anesthetic with complex effects on cortical activity and synaptic transmission (Arena et al. 2017) also known to inhibit hippocampal synaptic plasticity (Xiao et al. 2016). As Liu and colleagues pointed out, voltage-dependent Ca^{2+} channels are crucial for several plasticity-related processes. Hence, TMS action might prevent damages exerted by several different agents during critical periods of brain development (Liu et al. 2016).

Study	**Stimulation type and duration**	**Stimulation area**	**Animal model**	**Results**
Makowiecki et al., 2014	rTMS protocol (10 minutes daily for 14 days): high frequency stimulation comprising 59.9 ms trains of 20 pulses, repeated at 6.67 Hz for 1 min, 10.01 Hz for 8 min, and 6.25 Hz for the final min.	Visual cortex	Ephrin-A2A5-/- mice C57Bl/6J wild-type mice	Significant reduction of the number of ectopic terminal zones and increase in BDNF concentration.

Kozirev et al., 2018	rTMS protocol (25–30 min): 10 Hz protocol composed of high-frequency trains of five pulses triggered every 7 s; 1 Hz protocol composed of three 7-min trains for a total of 1250 pulses.	Visual cortex	Adult cats	Changes in excitatory/inhibitory balance; increased variability in orientation preference and excitability.
Gersner et al., 2011	rTMS (daily for 10 days): 900 daily pulses applied. Low-frequency: continuously at 1 Hz for 900 s; high-frequency: 9 trains of 100 pulses at 20 Hz (5 s each train) with an intertrain interval of 55 s.	Frontal cortex	Male Sprague-Dawley rats; 60 days old	Increased BDNF levels in hippocampus and prelimbic cortex of high-frequency stimulated rats; increased GluR1 and pGluR1 levels in the hippocampus of awake high-frequency stimulated rats.
Lu et al., 2015	rTMS protocol (twice a week for 4 weeks): 9 trains of 100 pulses delivered at 20 Hz and an intertrain rest time of 55 s.	Somatosensory cortex	Male Sprague-Dawley rats; postnatal days 24-52	Enhanced rehabilitative effects in TBI mice.
Mix et al., 2015	iTBS protocol (1 day): three iTBS blocks of 600 pulses at 15 min intervals. Each block consisted of 20 burst trains including ten 50 Hz bursts of three pulses repeated at 5 Hz. Trains lasted two seconds and were repeated at 10 s intervals. Block duration of 192 s.	Somatosensory cortex	Male Sprague-Dawley rats; postnatal days 28-90	Age-dependent reduction of PV+; parallel growth of PNNs.
Castillo-Padilla and Funke, 2016	iTBS protocol (daily for 7 days): 600 pulses grouped as bursts of three pulses at 50 Hz, repeated at 5 Hz. Twenty trains of 2 s repeated at intervals of 10 s.	Somatosensory cortex	Male and female Long-Evans rats, postnatal days 26-32	Improvement of performance in visual tests of dark-reared rats. BDNF and PKC involvement.
Hoppenrath et al., 2016	Same iTBS protocol used in (Mix et al., 2015).	Somatosensory cortex	Male Sprague-Dawley rats; postnatal days 28-90	Durable increase in excitability of FSIs.
Liu et al., 2016	lf-rTMS protocol (daily for 7 days): 1 Hz stimulation for 600 s.	Dorsal hippocampal formation	Male and female Sprague-Dawley rat; 2-5 weeks old	Recovery of activity and Ca^{2+} channels functioning previously inhibited by sevoflurane.
Hsieh et al., 2014	iTBS and cTBS protocols (3-pulse bursts at 50 Hz repeated at 5 Hz). For iTBS, a 2-s train of TBS was repeated every 10 s for 20 repetitions (total 600 pulses); in the cTBS paradigm, a 40-s train of uninterrupted TBS was given (600 pulses).	Motor cortex	Wistar rats (350–400 g); PD animal model based on 6-hydroxydopamine lesion in the same strain	iTBS potentiated MEPs, while cTBS depressed their amplitude; correlation between dopaminergic cells loss and reduction of MEP potentiation in PD model.
Muller et al., 2014	lf-rTMS at 1 Hz, 0.5 Hz, or 0.25 Hz for a total of 300 stimuli.	Motor cortex	Adult male Long-Evans rats	LTD-type MEP suppression by 1 Hz rTMS. NMDAR antagonists prevented MEP depression.

The final article is available, upon publication, at: Ferro, M., Lamanna, J., Spadini, S., Nespoli, A., Sulpizio, S., & Malgaroli, A. (2022). Synaptic plasticity mechanisms behind TMS efficacy: insights from its application to animal models. *Journal of Neural Transmission, 129*(1), 25–36. https://doi.org/10.1007/s00702-021-02436-7

Wang et al., 2015	Chronic TMS: biphasic pulses delivered at 1, 10 or 15 Hz for 5 s daily for 4 weeks.	Sensorimotor cortex	Triple transgenic AD model mice (3xTg) with 129/C57BL6 hybrid background	Better cognitive performance; enhanced LTP in hippocampal acute slices; reduced accumulation of amyloid-β and rescue of BK channels inhibition.
Yang et al., 2019	TMS at 1 Hz; 1 h per day for 14 days.	Sensorimotor cortex	Adult male Wistar rats subjected to a CUS protocol	Occlusion of hippocampal LTP by CUS was rescued by TMS; increase in hippocampal PSD95 and NR2B.
Krishnan et al., 2019	10 Hz TMS trains of 4 s; 26 s inter-train interval; 7 consecutive trains (total of 280 pulses) per day; 3 sessions per week for 6 weeks.	Sensorimotor cortex	Male adult Sprague-Dawley rats	Enhanced locomotor rehabilitation, enhanced MEP responses; increased fMRI responses to hindlimb stimulation in areas for S1 representations.
Fujiki et al., 2020	hf-rTMS: 400 Hz bursts of 8 stimuli; inter-burst interval of 10s; 10-30 min total duration.	Sensorimotor cortex	Adult male Sprague Dawley rats (290–375 g) with spinal cord injury	Phosphorylation of ribosomal protein S6 in several cortical areas.
Hou et al., 2020	TMS stimulation in groups of 5 biphasic pulses per stimulation intensity; 3 s inter-pulse interval; 75 pulses in total; sequence repeated every day for six weeks (total of 18 sessions).	Spinal cord	Young-adult Sprague Dawley rats (275-300 g)	Significant locomotor improvement; upregulation of $GABA_B$ receptors, GAD6, DβH, and BDNF; better conservation of descending axonal tracts.

Table 3. Studies using TMS to induce neural plasticity on animal models.

Discussion

The behavior of any specific brain circuit can change in the short term for many different reasons. Functional variations may depend on changes in neuronal excitability (Turrigiano and Nelson 2000) or alternatively in synaptic strength, what in jargon is called synaptic plasticity. In the long term, anatomical variations can add to this process, with modifications in the number of synapses and in neuronal morphology. In this review, we attempted to understand which biochemical and molecular processes related to synaptic plasticity are recruited by TMS protocols, by analyzing experimental animal studies. This goal is not easily attained, because a full generalization of the findings obtained from these studies to humans would require the same TMS protocols applied to the same target brain areas, as specified in the introduction. Unfortunately, although much effort has been devoted to achieve comparability (Figure 1), the real situation is far from the ideal one.

The final article is available, upon publication, at: Ferro, M., Lamanna, J., Spadini, S., Nespoli, A., Sulpizio, S., & Malgaroli, A. (2022). Synaptic plasticity mechanisms behind TMS efficacy: insights from its application to animal models. *Journal of Neural Transmission, 129*(1), 25–36. https://doi.org/10.1007/s00702-021-02436-7

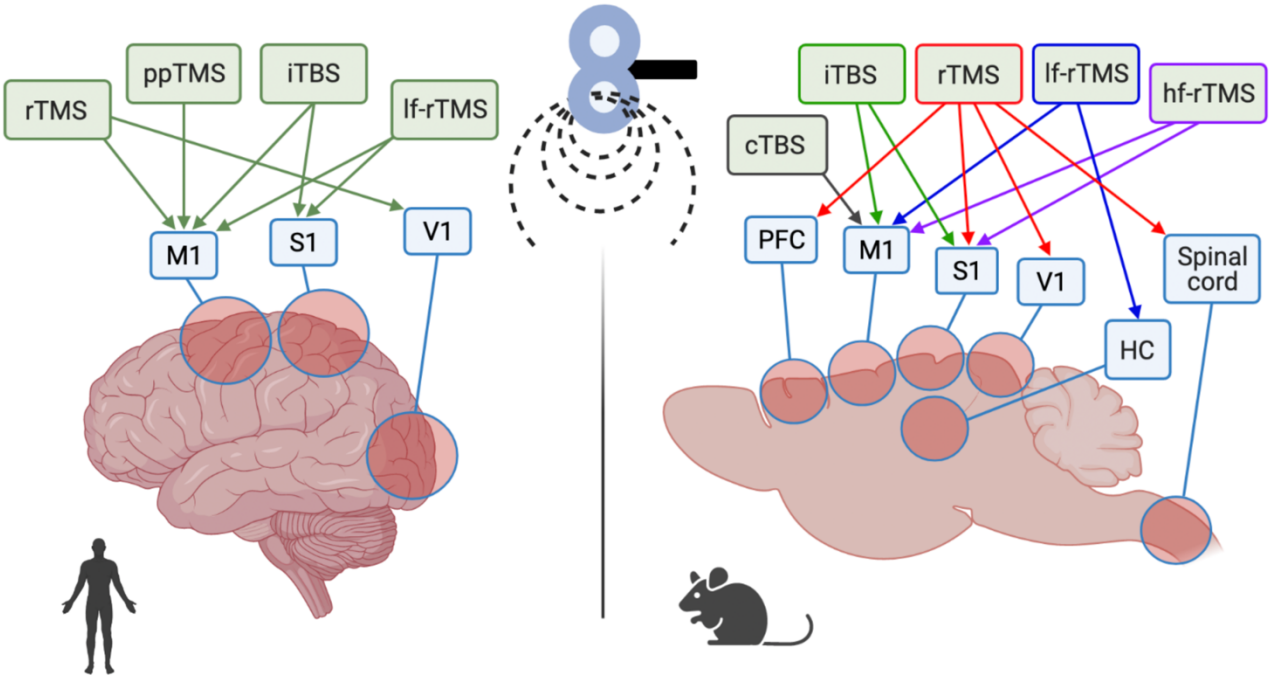

Figure 1. Scheme showing TMS protocols and brain areas already investigated in human (left) and experimental animal (right) models. rTMS: repeated TMS; ppTMS: paired-pulse TMS; iTBS: intermittent theta-burst stimulation; lf-rTMS: low-frequency repeated TMS; cTMS: continuous TMS; hf-rTMS: high-frequency repeated TMS; M1: primary motor cortex; S1: primary sensory cortex; V1: primary visual cortex; PFC: prefrontal cortex; HC: hippocampus; image created with BioRender.com.

Despite this, if we assume a comparable setting, animal studies provide clear-cut evidence that brain cell activation induced by TMS produces many characteristic biological trademarks of synaptic plasticity, including the activation of plasticity-related intracellular signaling cascades involving Ca^{2+}, CaMKII and BDNF. In a clinical perspective, the enhancement of BDNF expression by TMS (Gersner et al. 2011) might be relevant for treating specific conditions and could also be monitored as a biomarker for TMS effectiveness (Peng et al. 2018). Furthermore, based on its effects on geniculocortical map refinement (Makowiecki et al. 2014), a TMS application would be useful for patients presenting impaired or disrupted topographical maps. Beside these more classical plasticity-related changes, other helpful alterations have been observed in animal studies as a consequence of TMS stimulation, such as an improvement on the myelination action of oligodendrocytes (Cullen et al. 2019), possibly favoring a beneficial remodeling of long-range cerebral connectivity. Finally, microRNA is increasingly being studied as a potential biomarker for neurodegenerative illnesses and conditions such as traumatic brain injuries (Müller et al. 2016); TMS has been shown to target and upregulate microRNA to promote neural stem cells proliferation, an evidence supporting its bio-marking potential (Liu et al. 2015). It would also seem useful, in order to have a more direct dissection of the elements involved in neural plasticity, to combine TMS with tools capable to detect *in vivo* changes in synaptic activity (Ferro et al. 2017) at the animal models level. In addition, many models of psychiatric disorders with high validity might be tested to drive future human applications (Lamanna et al. 2019), and TMS could also serve to study plasticity changes induced by behavioral manipulation (Treccani et al. 2014; Lamanna et al. 2021).

Finally, being neural plasticity a broad characteristic of the brain, numerous factors are considered when exploring its properties and uncountable elements rely on the same molecules. On these bases, it appears important to investigate also

The final article is available, upon publication, at: Ferro, M., Lamanna, J., Spadini, S., Nespoli, A., Sulpizio, S., & Malgaroli, A. (2022). Synaptic plasticity mechanisms behind TMS efficacy: insights from its application to animal models. *Journal of Neural Transmission, 129*(1), 25–36. https://doi.org/10.1007/s00702-021-02436-7
the role of secondary plasticity effects, i.e. whether the expression of plasticity-related changes occurs not only in the stimulated area but also in all the other cortical and subcortical regions connected to it.

In conclusion, we believe it is crucial to carefully analyze and discuss the accumulating evidence in this field to eventually clarify the link between TMS efficacy and its action on plasticity processes, also looking at the clinical purpose of creating precise and personalized therapy protocols (Mantovani et al., 2021).

The final article is available, upon publication, at: Ferro, M., Lamanna, J., Spadini, S., Nespoli, A., Sulpizio, S., & Malgaroli, A. (2022). Synaptic plasticity mechanisms behind TMS efficacy: insights from its application to animal models. *Journal of Neural Transmission, 129*(1), 25–36. https://doi.org/10.1007/s00702-021-02436-7

References

Ackerley SJ, Byblow WD, Barber PA, et al (2016) Primed physical therapy enhances recovery of upper limb function in chronic stroke patients. Neurorehabil Neural Repair. https://doi.org/10.1177/1545968315595285

Arena A, Lamanna J, Gemma M, et al (2017) Linear transformation of the encoding mechanism for light intensity underlies the paradoxical enhancement of cortical visual responses by sevoflurane. J Physiol 595:321–339. https://doi.org/10.1113/JP272215

Bathina S, Das UN (2015) Brain-derived neurotrophic factor and its clinical Implications. Arch. Med. Sci. 11:1164–1178

Bliss TVP, Lømo T (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 232:331–356. https://doi.org/10.1113/jphysiol.1973.sp010273

Caillard O, Moreno H, Schwaller B, et al (2000) Role of the calcium-binding protein parvalbumin in short-term synaptic plasticity. Proc Natl Acad Sci U S A 97:13372–13377. https://doi.org/10.1073/pnas.230362997

Cash RFH, Murakami T, Chen R, et al (2016) Augmenting Plasticity Induction in Human Motor Cortex by Disinhibition Stimulation. Cereb Cortex 26:58–69. https://doi.org/10.1093/cercor/bhu176

Castillo-Padilla D V., Funke K (2016) Effects of chronic iTBS-rTMS and enriched environment on visual cortex early critical period and visual pattern discrimination in dark-reared rats. Dev Neurobiol 76:19–33. https://doi.org/10.1002/dneu.22296

Chang WH, Bang OY, Shin Y Il, et al (2014) BDNF polymorphism and differential rTMS effects on motor recovery of stroke patients. Brain Stimul 7:553–558. https://doi.org/10.1016/j.brs.2014.03.008

Citri A, Malenka RC (2008) Synaptic plasticity: Multiple forms, functions, and mechanisms. Neuropsychopharmacology 33:18–41

Cullen CL, Senesi M, Tang AD, et al (2019) Low-intensity transcranial magnetic stimulation promotes the survival and maturation of newborn oligodendrocytes in the adult mouse brain. Glia 67:1462–1477. https://doi.org/10.1002/glia.23620

Cullen CL, Young KM (2016) How does transcranial magnetic stimulation influence glial cells in the central nervous system? Front. Neural Circuits 10:26

Downar J, Blumberger DM, Daskalakis ZJ (2016) The Neural Crossroads of Psychiatric Illness: An Emerging Target for Brain Stimulation. Trends Cogn. Sci. 20:107–120

Fenno L, Yizhar O, Deisseroth K (2011) The development and application of optogenetics. Annu Rev Neurosci 34:389–412. https://doi.org/10.1146/annurev-neuro-061010-113817

Ferro M, Lamanna J, Ripamonti M, et al (2017) Functional mapping of brain synapses by the enriching activity-marker SynaptoZip. Nat Commun 8:. https://doi.org/10.1038/s41467-017-01335-4

Foysal KMR, Baker SN (2020) Induction of plasticity in the human motor system by motor imagery and transcranial magnetic stimulation. J Physiol 598:2385–2396. https://doi.org/10.1113/JP279794

Fujiki M, Yee KM, Steward O (2020) Non-invasive High Frequency Repetitive Transcranial Magnetic Stimulation (hfrTMS) Robustly Activates Molecular Pathways Implicated in Neuronal Growth and Synaptic Plasticity in Select Populations of Neurons. Front Neurosci 14:558. https://doi.org/10.3389/fnins.2020.00558

Gersner R, Kravetz E, Feil J, et al (2011) Long-term effects of repetitive transcranial magnetic stimulation on markers for neuroplasticity: Differential outcomes in anesthetized and awake animals. J Neurosci 31:7521–7526. https://doi.org/10.1523/JNEUROSCI.6751-10.2011

Hallett M (2001) Plasticity of the human motor cortex and recovery from stroke. Brain Res. Rev. 36:169–174

Hensch TK, Bilimoria PM (2012) Re-opening Windows: Manipulating Critical Periods for Brain Development. Cerebrum 2012:11

Hoppenrath K, Härtig W, Funke K (2016) Intermittent Theta-Burst Transcranial Magnetic Stimulation Alters Electrical Properties of Fast-Spiking Neocortical Interneurons in an Age-Dependent Fashion. Front Neural Circuits 10:22. https://doi.org/10.3389/fncir.2016.00022

Hou J, Nelson R, Mohammad N, et al (2020) Effect of Simultaneous Combined Treadmill Training and Magnetic Stimulation on Spasticity and Gait Impairments after Cervical Spinal Cord Injury. J Neurotrauma 37:1999–2013. https://doi.org/10.1089/neu.2019.6961

Hsieh T-H, Huang Y-Z, Rotenberg A, et al (2015) Functional Dopaminergic Neurons in Substantia Nigra are Required for Transcranial Magnetic Stimulation-Induced Motor Plasticity. Cereb Cortex 25:1806–1814. https://doi.org/10.1093/cercor/bht421

Keeler JF, Robbins TW (2011) Translating cognition from animals to humans. Biochem. Pharmacol. 81:1356–1366

Kozyrev V, Staadt R, Eysel UT, Jancke D (2018) TMS-induced neuronal plasticity enables targeted remodeling of visual cortical maps. Proc Natl Acad Sci U S A 115:6476–6481. https://doi.org/10.1073/pnas.1802798115

Krishnan VS, Shin SS, Belegu V, et al (2019) Multimodal Evaluation of TMS - Induced Somatosensory Plasticity and Behavioral Recovery in Rats With Contusion Spinal Cord Injury. Front Neurosci 13:387. https://doi.org/10.3389/fnins.2019.00387

Lamanna J, Isotti F, Ferro M, et al (2021) Facilitation of dopamine-dependent long-term potentiation in the medial prefrontal cortex of male rats follows the behavioral effects of stress. J Neurosci Res 99:662–678. https://doi.org/10.1002/jnr.24732

Lamanna J, Signorini MG, Cerutti S, Malgaroli A (2015) A pre-docking source for the power-law behavior of spontaneous quantal release: application to the analysis of LTP. Front Cell Neurosci 9:1–13. https://doi.org/10.3389/fncel.2015.00044

Lamanna J, Sulpizio S, Ferro M, et al (2019) Behavioral assessment of activity-based-anorexia: how cognition can become the drive wheel. Physiol Behav 202:1–7. https://doi.org/10.1016/j.physbeh.2019.01.016

Levkovitz Y, Isserles M, Padberg F, et al (2015) Efficacy and safety of deep transcranial magnetic stimulation for major depression: A prospective multicenter randomized controlled trial. World Psychiatry 14:64–73. https://doi.org/10.1002/wps.20199

Liu H, Han X hua, Chen H, et al (2015) Repetitive magnetic stimulation promotes neural stem cells proliferation by upregulating MiR-106b in vitro. J Huazhong Univ Sci Technol - Med Sci 35:766–772. https://doi.org/10.1007/s11596-015-1505-3

Liu Y, Yang H, Tang X, et al (2016) Repetitive transcranial magnetic stimulation regulates L-type Ca2+ channel activity inhibited by early sevoflurane exposure. Brain Res 1646:207–218. https://doi.org/10.1016/j.brainres.2016.05.045

Lu H, Kobilo T, Robertson C, et al (2015) Transcranial magnetic stimulation facilitates neurorehabilitation after pediatric traumatic brain injury. Sci Rep 5:. https://doi.org/10.1038/srep14769

Makowiecki K, Harvey AR, Sherrard RM, Rodger J (2014) Low-intensity repetitive transcranial magnetic stimulation improves abnormal visual cortical circuit topography and upregulates BDNF in mice. J Neurosci 34:10780–10792. https://doi.org/10.1523/JNEUROSCI.0723-14.2014

Mantovani A, Neri F, D'Urso G, Mencarelli L, Tatti E, Momi D, Menardi A, Sprugnoli G, Santarnecchi E, Rossi S (2021) Functional connectivity changes and symptoms improvement after personalized, double-daily dosing, repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: A pilot study, Journal of Psychiatric Research, Volume 136, Pages 560-570, ISSN 0022-3956, https://doi.org/10.1016/j.jpsychires.2020.10.030.

Mix A, Hoppenrath K, Funke K (2015) Reduction in cortical parvalbumin expression due to intermittent theta-burst stimulation correlates with maturation of the perineuronal nets in young rats. Dev Neurobiol 75:1–11. https://doi.org/10.1002/dneu.22205

Müller-Dahlhaus F, Lücke C, Lu M-K, et al (2015) Augmenting LTP-Like Plasticity in Human Motor Cortex by Spaced Paired Associative Stimulation. PLoS One 10:e0131020. https://doi.org/10.1371/journal.pone.0131020

Müller M, Jäkel L, Bruinsma IB, et al (2016) MicroRNA-29a Is a Candidate Biomarker for Alzheimer's Disease in Cell-Free Cerebrospinal Fluid. Mol Neurobiol 53:2894–2899. https://doi.org/10.1007/s12035-015-9156-8

Muller PA, Dhamne SC, Vahabzadeh-Hagh AM, et al (2014) Suppression of Motor Cortical Excitability in Anesthetized Rats by Low Frequency Repetitive Transcranial Magnetic Stimulation. PLoS One 9:e91065. https://doi.org/10.1371/journal.pone.0091065

Murray LM, Nosaka K, Thickbroom GW (2011) Interventional repetitive I-wave transcranial magnetic stimulation (TMS): The dimension of stimulation duration. Brain Stimul 4:261–265. https://doi.org/10.1016/j.brs.2010.12.003

Oberman L, Pascual-Leone A (2013) Changes in plasticity across the lifespan: Cause of disease and target for intervention. In: Progress in Brain Research. Elsevier B.V., pp 91–120

Peng S, Li W, Lv L, et al (2018) BDNF as a biomarker in diagnosis and evaluation of treatment for schizophrenia and depression. Discov Med 26:127–136

Platz T, Adler-Wiebe M, Roschka S, Lotze M (2018) Enhancement of motor learning by focal intermittent theta burst stimulation (iTBS) of either the primary motor (M1) or somatosensory area (S1) in healthy human subjects. Restor Neurol Neurosci 36:117–130. https://doi.org/10.3233/RNN-170774

Rossi S, Antal A, Bestmann S, et al (2020) Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. Clin. Neurophysiol. 132:269–306

Siebert JR, Osterhout DJ (2011) The inhibitory effects of chondroitin sulfate proteoglycans on oligodendrocytes. J

The final article is available, upon publication, at: Ferro, M., Lamanna, J., Spadini, S., Nespoli, A., Sulpizio, S., & Malgaroli, A. (2022). Synaptic plasticity mechanisms behind TMS efficacy: insights from its application to animal models. *Journal of Neural Transmission, 129*(1), 25–36. https://doi.org/10.1007/s00702-021-02436-7

Neurochem 119:176–188. https://doi.org/10.1111/j.1471-4159.2011.07370.x

Thompson B, Mansouri B, Koski L, Hess RF (2008) Brain Plasticity in the Adult: Modulation of Function in Amblyopia with rTMS. Curr Biol 18:1067–1071. https://doi.org/10.1016/j.cub.2008.06.052

Treccani G, Musazzi L, Perego C, et al (2014) Acute stress rapidly increases the readily releasable pool of glutamate vesicles in prefrontal and frontal cortex through non-genomic action of corticosterone. Mol. Psychiatry 19:401

Turrigiano GG, Nelson SB (2000) Hebb and homeostasis in neuronal plasticity, Current Opinion in Neurobiology, Volume 10, Issue 3, 2000, Pages 358-364, ISSN 0959-4388, https://doi.org/10.1016/S0959-4388(00)00091-X

Volz LJ, Rehme AK, Michely J, et al (2016) Shaping Early Reorganization of Neural Networks Promotes Motor Function after Stroke. Cereb Cortex 26:2882–2894. https://doi.org/10.1093/cercor/bhw034

Wang F, Zhang Y, Wang L, et al (2015) Improvement of spatial learning by facilitating large-conductance calcium-activated potassium channel with transcranial magnetic stimulation in Alzheimer's disease model mice. Neuropharmacology 97:210–219. https://doi.org/10.1016/j.neuropharm.2015.05.027

Xiao H, Liu B, Chen Y, Zhang J (2016) Learning, memory and synaptic plasticity in hippocampus in rats exposed to sevoflurane. Int J Devl Neurosci 48:38–49. https://doi.org/10.1016/j.ijdevneu.2015.11.001

Yang J, Wang L, Wang F, et al (2019) Low-Frequency Pulsed Magnetic Field Improves Depression-Like Behaviors and Cognitive Impairments in Depressive Rats Mainly via Modulating Synaptic Function. Front Neurosci 13:820. https://doi.org/10.3389/fnins.2019.00820

The final article is available, upon publication, at: Ferro, M., Lamanna, J., Spadini, S., Nespoli, A., Sulpizio, S., & Malgaroli, A. (2022). Synaptic plasticity mechanisms behind TMS efficacy: insights from its application to animal models. *Journal of Neural Transmission, 129*(1), 25–36. https://doi.org/10.1007/s00702-021-02436-7

The final article is available, upon publication, at: Ferro, M., Lamanna, J., Spadini, S., Nespoli, A., Sulpizio, S., & Malgaroli, A. (2022). Synaptic plasticity mechanisms behind TMS efficacy: insights from its application to animal models. *Journal of Neural Transmission, 129*(1), 25–36. https://doi.org/10.1007/s00702-021-02436-7
Funding 'Not applicable'

Conflicts of interest/Competing interests The author reports no biomedical financial interests or potential conflicts of interest.

Availability of data and material 'Not applicable'

Code availability 'Not applicable'