Title

The effect of psychotropic drugs on cortical excitability and plasticity measured with transcranial magnetic stimulation: Implications for psychiatric treatment

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- Repetitive transcranial magnetic stimulation (rTMS) is a promising intervention for patients with treatment-resistant mood disorders
- The potential interaction between psychotropic medications and rTMS may have important clinical implications
- Psychotropic medications exert significant effects on cortical excitability and plasticity as measured with TMS
- These drug effects vary substantially across medication classes, and may have differential consequences for clinical response to rTMS
- A better understanding of these drug effects will be important to optimize the multi-modal treatment of treatment-resistant patients

Abstract

Objective: Repetitive transcranial magnetic stimulation (rTMS) is an emerging treatment for neuropsychiatric disorders. Patients in rTMS treatment typically receive concomitant psychotropic medications, which affect neuronal excitability and plasticity and may interact to affect rTMS treatment outcomes. A greater understanding of these drug effects may have considerable implications for optimizing multi-modal treatment of psychiatric patients, and elucidating the mechanism(s) of action (MOA) of rTMS. **Method**: We summarized the empirical literature that tests how psychotropic drugs affect cortical excitability and plasticity, using varied experimental TMS paradigms. **Results**: Glutamate antagonists robustly attenuate plasticity, largely without changes in excitability *per se*; antiepileptic drugs show the opposite pattern of effects, while calcium channel blockers attenuate plasticity. Benzodiazepines have moderate and variable effects on plasticity, and negligible effects on excitability. Antidepressants with potent 5HT transporter inhibition reduce both excitability and alter plasticity, while antidepressants with other MOAs generally lack either effect. Catecholaminergic drugs, cholinergic agents and lithium have minimal effects on excitability but exhibit robust and complex, non-linear effects in TMS plasticity paradigms. **Limitations**: These effects remain largely untested in sustained treatment protocols, nor in clinical populations. In addition, how these medications impact clinical response to rTMS remains largely unknown. **Conclusions**: Psychotropic medications exert robust and varied effects on cortical excitability and plasticity. We encourage the field to more directly and fully investigate clinical pharmaco-TMS studies to improve outcomes.

Keywords: transcranial magnetic stimulation; pharmacology; excitability; plasticity

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Introduction

TMS: Biophysical Aspects

Transcranial magnetic stimulation (TMS) is one of a family of non-invasive, device-based technologies for modulating the function of the human brain, and the most widely-adopted in both clinical and experimental settings. When the simulator pulses the magnetic field at the scalp, this field passes across the skull and intervening tissues to reach the brain without attenuation, where it induces a low-amplitude current in the cortex, flowing parallel to the surface of the coil. The magnetic field strength falls sharply with distance from the coil, under general conditions penetrating approximately 2 cm beneath the cortical surface. However, higher stimulation intensities can induce fields to a depth of 3-4 cm (Terao and Ugawa 2002), and the cortical volume of stimulation can be as large as several cm^3 (Opitz et al., 2011). The neuronal populations affected, their cellular sites of depolarization, and the dynamics of local circuit effects are generally complex and very sensitive to the intensity, pattern and spatial orientation of stimulation, and is further described elsewhere (Muller-Dahlhaus et al., 2013). In addition, changes in cortical signaling even with lower intensities can lead to downstream effects in cortical circuits, which can be detected with non-invasive methods such as functional MRI (fMRI) or electroencephalography (EEG).

TMS Measures of Cortical Excitability and Plasticity

Single- or multiple pulse TMS is a valuable experimental probe of cortical excitability and plasticity (Ziemann et al., 2008). Neural excitability is typically defined as the threshold for neuronal action potential generation, and excitability is a function of various factors, such as the location and function of post-synaptic receptors that mediate changes in neuronal membrane potential, ion fluxes across diverse membrane-bound ion channels, and structural features such as the location of the axon initial segment (Keck et al., 2017). Cortical excitability in humans is typically evaluated by determining the Motor Threshold (MT), defined by convention as the stimulation intensity that elicits either overt muscle contraction or alternatively compound Motor Evoked Potentials (MEPs) measured by electromyography (EMG) on 50% of single-pulse TMS (spTMS) trials. MT can be assessed as "resting" MT (rMT), i.e. with fully-relaxed target muscles, or "active" MT (aMT), with moderate isometric contraction of target muscles, which generally lowers the threshold from rMT.

Plasticity refers to changes over time in the structure or function of neurons, which can arise from both experience and genetically-programmed effects. The mechanisms subserving plasticity in the central nervous system include changes in excitability via long-term potentiation and long-term depression of synapses, synaptogenesis and synaptic elimination, and neurogenesis (Bruel-Jungerman et al., 2007; Cooke and Bliss, 2006). There are now several experimental TMS paradigms to non-invasively probe cortical plasticity in human subjects. These serve as the experimental measures of plasticity to test pharmacological effects, which in turn may modify rTMS therapeutic effects. In Paired Associative Stimulation (PAS), typically the

median nerve is activated by bipolar stimulation at the wrist, along with spTMS to the representation of the same hand in primary motor cortex (contralateral to that hand) (Carson and Kennedy, 2013; Ziemann et al., 2008). The interstimulus interval (ISI) between these two stimulations determines how the TMS pulse modifies the median nerve stimulation effect, which is observed at the level of the cortex, in a manner consistent with spike-timing dependent plasticity (see discussion in Muller-Dahlhaus et al., 2010). An ISI of 25 milliseconds (PAS25) results in potentiation that resembles long-term potentiation (LTP) in animal studies; longer ISIs have no effect. In contrast, an ISI of 10 ms (PAS10) results in attenuation, analogous to the long-term depression (LTD) observed in animal studies (Ziemann et al., 2008). Another stimulation protocol that is increasingly used in both research and treatment protocols is theta-burst stimulation (TBS). This "patterned" TMS paradigm typically employs 50 Hz pulse triplets applied at 200 ms intervals, i.e. a theta frequency, which replicates a common paradigm used to optimize LTP induction in animal models and tissue preparations (Huang et al., 2005; Ziemann et al., 2008). Trains of TBS repeated at 10 second intervals (intermittent TBS, or iTBS) tend to be facilitatory, i.e. LTP-like, whereas trains that are delivered at 200 ms intervals without interruption (continuous TBS, or cTBS) tend to induce long-term depression (LTD)-like responses (Cardenas-Morales et al., 2010; Suppa et al., 2016). PAS and TBS-induced changes are typically referred to as "LTP-like" or "LTD-like" because they resemble the large-scale physiological (and behavioral) manifestations of enduring physiological changes observed with LTD (or LTD) induction in animal models, yet in humans it remains unclear if these reflect the same cellular processes that mediate LTP/LTD, and in the same neuronal populations (Pell, Roth and Zangen, 2011). In any event, TBS has demonstrated clinical efficacy in depression (Chung et

al., 2015), which may speak to the role of disturbed plasticity in this illness. Other mechanisms may mediate clinical efficacy of TBS, such as the modulation of dysfunctional brain networks (Anderson et al., 2016), which is not necessarily inconsistent with effects on plasticity. Plasticity is also commonly evaluated by single-pulse TMS in conjunction with practice-based changes in neural phenomena such as cortical mapping of motor output to targeted muscles. Measures of higher-order phenomena such as homeostatic plasticity and meta-plasticity can also be achieved using TMS paradigms (Karabanov et al., 2015; Thickbroom, 2007), but have not yet been employed in pharmacology studies. Studies of excitability and plasticity largely have been restricted to motor systems, probably largely due to the objective and reliable measures of output that can be assessed. It is critical that plasticity also be assessed in prefrontal cortical non-motor areas as well because these are the primary targets of therapeutic rTMS in psychiatry (Hill et al., 2016). An emerging literature has employed EEG to study on-line TMS effects in non-motor areas, including in combination with plasticity-inducing TMS paradigms such as TBS (see Chung et al., 2015; Thut and Pascual-Leone, 2010). This literature has identified varied effects of these TMS paradigms on TMS-evoked potentials, oscillatory phenomena, and spatial connectivity changes, which could represent enduring expressions of cortical plasticity. This approach has been recently employed to study the effects of drugs such as GABA-ergic agents, with the potential to understand how drugs may modify TMS-induced plasticity (Premoli et al., 2017). Some of the challenges with the TMS-EEG approach include the resource-intensiveness of EEG in clinical settings; the relatively greater across-subject variability in the functional neuroanatomy of frontal cortical regions, compared to sensorimotor cortex; general limitations on spatial inferences with the use of scalp EEG; and on a conceptual level,

the unresolved question of whether these EEG measures truly reflect plasticity processes such as LTP or LTD (discussed in Cooke and Bliss, 2006, and Pell, Roth and Zangen, 2011).

The variability of TMS-induced effects on excitability and plasticity in motor systems has been evaluated for paradigms such as PAS and TBS (Ziemann et al., 2008). Typically, reasonable within-subject reliability is observed, though interestingly, across-subjects variability is notable, for instance so-called "paradoxical" effects of iTBS on LTD-like effects on MEP amplitude, and the reversal of direction of TBS effects that is dependent on the time interval between TBS cycles. These appear to be important expressions of variability that are not yet well-understood. To date, there is a paucity of information about the reliability of drug-induced changes in these phenomena; this remains an important issue for further empirical study.

Neuronal Ion Channels and Central Neurotransmitter Systems

Biophysical models of magnetic stimulation generally extend the classic Hodgkin and Huxley model, with roles for sodium, potassium, and calcium channels present on neuronal plasma membranes (Wagner et al., 2007). This suggests important implications for the actions of pharmacological agents that directly (e.g. antiepileptic drugs) or indirectly (e.g., monoaminergic drugs) affect fluxes across these channels. Antiepileptic drugs generally have potent effects on ion-channel activity in cortical neurons, especially sodium and/or calcium channels, and as a result robustly modify neuronal and behavioral effects of TMS (see below). As a rule, drugs with

psychotropic effects modify neuronal signaling via neurotransmitter receptor-mediated effects on cell-membrane currents that are modulated on short (e.g. glutamate agents) or long/varied (e.g. monoaminergic agents) time scales. Each of these neurotransmitters is associated with multiple ion-channel types and subtypes, with effects mediated by multiple intracellular second messenger systems. Many also are associated with transmitter receptor subtypes that have opposing effects on second messengers (e.g. D1 vs D2 receptors), with divergent anatomical distributions and cellular localization (Cooper, Bloom and Roth, 2003). These features of brain neurotransmitter systems are the primary basis for the complex, multiphasic and non-linear effects observed when neurotransmission is modified with chemical (i.e. pharmacological) or electrical perturbations. These features also render it difficult to predict the precise effects of psychotropic drugs in modifying magnetic stimulation effects on cortical cells and circuits and associated behavior, especially for those drugs with a multiplicity of actions (e.g. antipsychotics). This is one critical reason why empirical studies of drug-TMS interactions are important to conduct in human subjects, as it is not straightforward to predict how these drugs might ultimately affect clinical responses from animal or tissue models alone (Littman and Williams, 2005). It will be equally essential to conduct these experiments in patient populations (and not just healthy subjects) because many clinical disorders are characterized by disturbances in neurotransmitter system function. There are an insufficient number of these latter studies in psychiatry for an informative review here.

Repetitive TMS: Biological and Clinical Effects

When applied in rhythmic trains or pulses in treatment sessions over a period of weeks (repetitive TMS, or rTMS), changes in excitability, plasticity, and signaling in the brain become sustained and have robust antidepressant effects (Chen et al., 2013; Schutter, 2009; Slotema et al., 2010) with preliminary evidence for efficacy in schizophrenia, treatment-resistant anxiety, and other disorders (Chervyakov et al., 2015; Slotema et al., 2010). While the efficacy trials of rTMS for the treatment of major depressive disorder (MDD) were performed in unmedicated subjects (O'Reardon et al., 2007), the treatment most commonly is administered in routine practice to patients who are concurrently receiving antidepressants, mood stabilizers, anticonvulsants or other drugs known to affect excitability or plasticity (Carpenter et al., 2012; McClintock et al., 2018).

In addition, the mechanisms of action (MOA) for rTMS and psychotropic drugs are likely to have considerable overlap and are not mutually-exclusive of one another. They include changes in neurotransmitter signaling, gene expression, neurotrophic and neuroprotective effects, and oscillatory patterns of distributed brain circuits (Chervyakov et al., 2015; Cirillo et al., 2017). One particularly intriguing line of investigation addresses the restoration of neural plasticity, which has been implicated in both the pathophysiology of depression and the action of antidepressant medication (Cantone et al., 2017; Eliwa et al., 2017). There may be significant interactions between electromagnetically induced neural excitation and cellular drug effects, both of which affect excitability and plasticity. Such potential interactions may have great relevance to clinical rTMS treatment, yet have not been adequately studied. These

pharmacological interactions with TMS, and their potential effects on clinical efficacy, are the subject of this review.

The Present Review

We searched the peer-reviewed literature for studies of psychotropic drug effects on cortical excitability and plasticity as measured in these experimental paradigms. This review updates previous published reviews addressing this topic (Paulus et al., 2008; Ridding and Ziemann, 2010; Ziemann et al., 2015), with a greater emphasis presently on psychotropic drugs and psychiatric treatment implications. We organized the literature by major drug classes as they are configured for clinical indications, rather than according to MOA. This strategy was employed because the members of a clinically-defined drug class are generally very heterogeneous in their MOA, and often neurochemical effects are shared among drugs in different classes (e.g. antidepressants and psychostimulants). These are important considerations when crafting a polypharmacy regimen for patients who are either complicated in symptom profile or treatment-resistant. The heterogeneity within classes, and lesser degree of overlap across classes, does pose challenges for making inferences from the experimental literature reviewed below. Nonetheless, clinically-defined classes map onto clinical indications in the most straightforward manner, and it is this level of organization that clinicians will have to consider when integrating psychopharmacology with TMS to optimize treatment responses (the primary MOA for each drug is indicated in the tables).

This literature predominantly uses experimental TMS paradigms to investigate excitability and plasticity processes, rather than the repetitive TMS protocols which are utilized for clinical interventions, so the relationship of the reported phenomena to TMS as it is used clinically remains to be elaborated. In addition, these studies are almost exclusively conducted in healthy subject samples, so the question of how psychotropic drugs modulate these phenomena in psychiatric populations (which may have disturbances in either neurotransmitter systems, and/or cortical circuits that directly respond to rTMS) is a key research problem deserving of future study.

Method

We conducted a systematic review. We initially searched PubMed for all English-language, peer-reviewed publications with the full text available, using all combinations of search terms A) “transcranial magnetic stimulation”, “excitability”, “motor threshold”, “plasticity”, “paired associative stimulation”, “theta burst”, with B) each of the drug category names indicated below. Existing reviews (and their reference lists) that addressed this topic were also evaluated for additional reports. We excluded papers reporting on studies conducted in animal models, studies using other non-invasive neuromodulation methods such as transcranial direct current stimulation, and the few published TMS/pharmacology papers reporting on studies of clinical populations, because of the limited number of non-systematic studies, and/or heterogeneous patient populations. We also generally excluded papers reporting on drugs which are not

clinically-indicated for psychiatric disorders, with the exception of those which may be informative based on selective MOA (e.g. selective ion-channel blockers) or have implications for psychiatric disorders (e.g., the $GABA_B$ receptor agonist baclofen). This combined search strategy yielded 3525 articles, of which 69 were included based on the inclusion/exclusion criteria.

With exceptions as noted below, the existing literature uses single-dose or very short-term oral dosing designs (e.g., 4-7 days), probably largely based on practicality. It is also important to consider that the doses of many of these drugs are subtherapeutic for psychiatric conditions. We also excluded experimental paradigms that evaluate the several interesting inhibitory/facilitatory phenomena that can be measured with TMS (e.g., short- and long-interval cortical inhibition [SICI and LICI]; cortical silent period [CSP]; intracortical facilitation [ICF]). While these measures appear to be informative of dynamics in local cortical circuitry and are altered in some psychiatric conditions, they are not altered in a disease-specific pattern, with minimal evidence found to date that they are associated with clinical response to rTMS treatment or clinical outcome in general (see discussions in (Bunse et al., 2014; Kaskie and Ferrarelli, 2018). In addition, length considerations preclude the review of these latter measures.

RESULTS

Glutamate Agents

This class of drugs is summarized in table 1. N-Methyl D-Aspartate receptor antagonists (NMDAR) exhibit inconsistent effects on excitability measured as changes in MT. Wohlfarth and colleagues (Wohlfarth et al., 2000) found no effect of acamprosate on MEP facilitation or inhibition in a paired-pulse stimulation paradigm, although the rMT was increased with single-pulse TMS. Similarly, there was no effect of either dextromethorphan (DMX) (Wankerl et al., 2010; Ziemann et al., 1998) or memantine (Huang et al., 2007; Schwenkreis et al., 1999) on rMT. In two studies of ketamine, one found dose-related decreases in rMT and aMT with subanaesthetic doses (Di Lazzaro et al., 2003), while the other study found no effect on rMT with slightly lower doses (Hoffken et al., 2013). It remains unclear if these discrepancies relate to differences in bioavailability, given the differing doses and measures of circulating levels, or other methodological differences.

In contrast, the administration of NMDAR antagonists is associated with robust, consistent attenuation of plasticity. DMX abolished the LTP-like MEP response in the PAS25 paradigm (Stefan et al., 2002; Weise et al., 2017), the LTD-like MEP response to PAS10 (Wolters et al., 2003), as well as the LTP-like MEP response to cTBS300 (Wankerl et al., 2010). Interestingly, DMX also abolished the effect of the calcium channel-blocker nimodipine, which when given alone reversed the MEP facilitation with cTBS300 (Wankerl et al., 2010). In another study, when DMX was administered together with nimodipine, the LTP-like response to PAS25 was abolished in the face of an increase in static excitability (measured by PAS5000, which does not induce plasticity responses) that was not observed for either drug alone (Weise et al., 2017).

Memantine also abolishes both the LTP-like and the LTD-like MEP responses to iTBS and cTBS, respectively (Huang et al., 2007). An 8-day regimen of memantine blocked the shift in topographic mapping for the abducens pollicis brevis muscle with practice, while a single dose had no effect (Schwenkreis et al., 2005). Taken together, these results suggest a robust yet complex pattern of effects of NMDAR antagonists on cortical plasticity processes measured with TMS, potentially mediated by non-linear effects on calcium influx across neuronal membranes.

Antiepileptic Agents

This class of drugs is summarized in table 2. Medications that were originally developed for seizure disorders have found considerable use in a range of psychiatric conditions, especially bipolar-spectrum disorders and other disorders of impulse control (Rogawski and Loscher, 2004b). While the efficacy of anticonvulsants as adjunctive treatment in treatment-resistant unipolar MDD remains to be firmly established, they nevertheless are widely used, often for co-morbid anxiety and/or irritability. As a class, these medications have heterogeneous MOAs (Rogawski and Loscher, 2004a) for their effects on epilepsy and probably also for psychiatric conditions. These MOAs include blockade of voltage-gated (especially sodium and calcium) ion channels and increased gamma-butyric acid (GABA) signaling. A few antiepileptic agents also exhibit glutamate receptor antagonism; the only drug among these that is used in psychiatry is topiramate (with kainate [KA] and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] receptor antagonism) (Rogawski and Loscher, 2004b). We therefore review only the

literature that examines effects of those antiepileptic drugs which are commonly-used in psychiatry (e.g., we exclude levetiracetam and phenytoin).

Given that antiepileptic drugs therapeutically modulate brain excitability, it is appropriate that this is the most widely-tested class for effects on cortical excitability measured with TMS. Carbamazepine, a sodium channel blocker (Rogawski and Loscher, 2004a), shows consistent effects to increase both rMT and aMT with single doses (Lang et al., 2013; Menzler et al., 2014; Ziemann et al., 1996) as well as a 4-week dose escalation schedule (Lee et al., 2005). In contrast, Inghilleri and colleagues (Inghilleri et al., 2004) found no effects on rMT or aMT with 7 days of treatment, while the MEP facilitation observed with 5 Hz rTMS was abolished.

These investigators also tested gabapentin, which blocks high-voltage activated (HVA) calcium channels and increases GABA turnover (Rogawski and Loscher, 2004a). They found a pattern of effects very similar to those they observed with carbamazepine: treatment for 7 days abolished MEP facilitation after 5 Hz rTMS, with no effects on rMT or aMT. Two other studies reported no effects of gabapentin on rMT or aMT (Rizzo et al., 2001; Ziemann et al., 1996).

Lamotrigine shares effects on high voltage activated (HVA)-calcium channels with gabapentin, though it does not have established GABA effects. In contrast to gabapentin, lamotrigine does consistently raise rMT and aMT in single doses (Boroojerdi et al., 2001; Li et al., 2009; Tergau et al., 2003; Ziemann et al., 1996), in a dose-dependent manner during a one-day dose-escalation

(Tergau et al., 2003), and in a 4-day dose escalation protocol up to 200 mg/day (Lee et al., 2005).

Topiramate also exhibits HVA-calcium channel blockade, but it also blocks sodium channels, has $GABA_A$ receptor agonist activity, and KA/AMPA receptor antagonist activity (Rogawski and Loscher, 2004a). Like gabapentin, it generally lacks effects on rMT or aMT, with varied administration protocols including single doses (Reis et al., 2002), 7 days fixed dosing (Inghilleri et al., 2004), or 4-day dose escalation up to 100 mg (Inghilleri et al., 2006). However, each of these multi-day drug administration protocols was associated with abolished MEP facilitation in response to 5 Hz rTMS (Inghilleri et al., 2004; Inghilleri et al., 2006).

Finally, valproic acid is an antiepileptic that is widely-used for bipolar-spectrum conditions, with neurochemical effects that include blockade of sodium channels and T-type calcium channels, and increased GABA turnover (Rogawski and Loscher, 2004a). It appears to have very modest effects on MT, with trend-level (not statistically-significant) effects to raise rMT (Reis et al., 2002; Zunhammer et al., 2011).

Taken together, this literature suggests a highly-variable pattern of effects of antiepileptic drugs on cortical excitability measured with TMS, in both single- and multi-dose administration protocols. Intriguingly, the comparison between gabapentin and lamotrigine effects suggests that the GABA agonist effects (associated with gabapentin) may mitigate the effects of HVA-calcium channel blockade on cortical excitability. Because no other antiepileptic drugs currently

available appear to be pure HVA-calcium channel blockers (Rogawski and Loscher, 2004a), this hypothesis awaits proper testing in humans with TMS paradigms.

Unlike studies of excitability, there is a relative paucity of studies testing antiepileptic drug effects on TMS-related plasticity measures. In one study, lamotrigine decreased both the LTP-like MEP response to PAS 25 (at 0 and 30 minutes post-administration) and the paradoxical LTD-like MEP response to PAS25 (at 60 minutes post-administration) (Delvendahl et al., 2013). Inghilleri and colleagues (Inghilleri et al., 2004, 2006) found the MEP facilitation that is observed with 5 Hz rTMS to be abolished with carbamazepine, gabapentin and topiramate. In contrast, neither gabapentin nor topiramate showed effects on the LTP-like MEP response to PAS25 (Heidegger et al., 2010). It is useful to note that the T-type voltage gated calcium channel blocker ethosuximide reversed the LTP-like MEP response to PAS25 (Weise et al., 2017). While this literature overall remains limited in scope and somewhat variable in aspects of both treatment and measurement design, it suggests that antiepileptic drugs may decrease cortical excitability without affecting cortical plasticity, generally the reverse of NMDAR antagonists. This conclusion must be carefully tempered with the recognition that these drugs are highly heterogeneous and the experimental designs are highly variable.

Other Ion-Channel Antagonists

This class of drugs is summarized in table 2. Drugs with selective actions at voltage-gated ion channels include not only the antiepileptic agents reviewed above, but also other drugs for

conditions such as cardiovascular illness and peripheral neurological conditions. Their selective MOA may inform our understanding of MOA of therapeutic rTMS. In addition, psychiatry patients may also take these medications for medical indications while undergoing rTMS treatment for concurrent psychiatric problems. To date, these medications have not been well-studied for effects on excitability or plasticity via TMS. Nimodipine is an L-type voltage-gated calcium channel (VGCC) blocker which abolished the LTD-like response to PAS10 (Wolters et al., 2003) and the LTP-like MEP response to PAS25 (Weise et al., 2017), and reversed the LTP-like MEP response to cTBS300 (Wankerl et al., 2010). Nimodipine also reversed the LTP-like MEP response to cTBS300 after 90 seconds of voluntary thumb abduction, with a relatively larger effect with the larger dose (Wankerl et al., 2010). Ethosuximide, a T-type VGCC blocker, reversed the LTP-like facilitation of PAS25 into a depressive (LTD-like) pattern (Weise et al., 2017). These findings suggest significant effects of VGCC blockers in inhibiting (or altering) plasticity.

GABA Agonists: Benzodiazepines and Baclofen

This class of drugs is summarized in table 3. Benzodiazepines (BDZ) all strongly bind to the BDZ binding site of $GABA_A$ receptors, but vary considerably in their affinity for $GABA_A$ receptor subunits. The clinical implications of this variability remain unclear. A relatively recent class of quasi-BDZ drugs is FDA-approved for sleep disorders (e.g., zolpidem), and these also act at the $GABA_A$ receptor (at a binding site distinct from the BDZ site). Baclofen is also included in this review as the sole $GABA_B$ receptor agonist in routine clinical use, as its unique MOA may have

implications for rTMS treatment of psychiatric conditions where $GABA_B$ receptor dysfunction is evident (Bowery, 2006).

In general, BDZ as a class do not appear to affect MT as measured in spTMS paradigms. The following drugs (all single oral dose, except where indicated) show no effects on rMT and/or aMT: alprazolam, diazepam (Mohammadi et al., 2006; Palmieri et al., 1999) and lorazepam, given orally (Boroojerdi et al., 2001; Di Lazzaro et al., 2000a; Ziemann et al., 1996) and i.v. (Kimiskidis et al., 2006). Similarly, neither zolpidem (Mohammadi et al., 2006) nor baclofen (Ziemann et al., 1996) altered rMT or aMT. It therefore is clear that, at least in single doses, GABA receptor agonists do not affect cortical excitability as measured by spTMS. These drugs have been studied less in TMS plasticity paradigms. Here, diazepam 20 mg showed a trend-level effect on the LTP-like response to PAS25 (Heidegger et al., 2010) and attenuated the practice-related change in the topographic map for the biceps measured with spTMS and transient ischemic nerve block (Ziemann et al., 2001). On the other hand, baclofen 50 mg attenuated the LTP-like MEP response to PAS20, with a switch to a LTD-like pattern of inhibition in 5/7 subjects (McDonnell et al., 2007). GABA receptor drugs have not been tested to date in stimulation paradigms such as TBS. Therefore, it remains unclear whether they may modify other types of plasticity phenomena.

Antidepressants

This class of drugs is summarized in table 4. Selective Serotonin Reuptake Inhibitors (SSRIs) have variable but generally insignificant catecholaminergic effects. Among these, citalopram and escitalopram are the most highly-selective for the serotonin (5HT) transporter over the norepinephrine (NE) transporter (NET; Owens et al., 2001; Tatsumi et al., 1997). Citalopram appears to increase the rMT, between 0-3.5 hours after i.v. administration (Minelli et al., 2010), and at 2.5 hours after oral administration (Robol et al., 2004). Escitalopram (the pure S-enantiomer of racemic citalopram) has not been studied for effects on cortical excitability measured with TMS. Sertraline (which also has significant NET and dopamine transporter [DAT] inhibition) (Owens et al., 2001; Tatsumi et al., 1997) had no effect on rMT or aMT in one study (Ilic et al., 2002). Paroxetine (which also has modest NET inhibition as well as anti-muscarinic activity; (Sanchez et al., 2014) showed no effect on rMT or aMT (Gerdelat-Mas et al., 2005) with either single-dose or 3-day dosing. Clomipramine, a tricyclic antidepressant that is a highly-potent 5HT inhibitor that also inhibits NET, does increase rMT after i.v. infusion (Manganotti et al., 2001; Minelli et al., 2010), and aMT as well (Manganotti et al., 2001). Interestingly, reboxetine, a selective NET inhibitor (Kasper et al., 2000), decreased rMT in one study (Herwig et al., 2002), though in other studies showed no effect on rMT or aMT (Kuo et al., 2017; Plewnia et al., 2002). Selegiline (also known as L-deprenyl) is a selective and non-reversible inhibitor of monoamine oxidase B isozyme (MAO-B, which preferentially degrades catecholamines over 5HT; (Fisar, 2016), and appears to have no effects on rMT or aMT (Ziemann et al., 1997). Finally, mirtazapine is an antagonist at both α_2 adrenergic and $5HT_{1B/1D}$ receptors (inhibitory autoreceptors for NE and 5HT, respectively) and therefore increases synaptic NE and 5HT. It showed no effect on rMT or aMT (Munchau et al., 2005). Taken together, these results suggest

that antidepressants with potent 5HT transport inhibition (e.g. citalopram, clomipramine), whether accompanied with NET inhibition or not, decrease cortical excitability, whereas antidepressants with either less-potent 5HT transport inhibition (paroxetine), or alternatively other MOAs such as effects on catecholamine transport (reboxetine) or degradation (selegiline), or 5HT/NE autoreceptor inhibition (mirtazepine), are variable or ineffective at altering cortical excitability measured with spTMS.

Only three studies have been conducted testing antidepressant effects on plasticity measures with TMS. In one (Batsikadze et al., 2013), citalopram decreased the LTD-like MEP response in the PAS10 paradigm between 0-90 minutes post-dose, and increased the LTP-like response in the PAS25 paradigm between 0-30 minutes post-dos. In contrast, fluoxetine (an SSRI with relatively greater affinity for NET) had no effect on practice-related changes in topographic mapping of motor activity (Pleger et al., 2004), or on practice-related changes in TMS-induced thumb movements (McDonnell et al., 2018). The relatively rapid effects of citalopram in the first of these studies suggests an effect mediated by 5HT receptor-linked effects on neuronal membrane excitability rather than slower downstream, intracellular effects on second messenger systems and gene expression.

Catecholamine Agents

This class of drugs is summarized in table 5. There is a diversity of drugs in the pharmacopoeia that have primary effects on either NE and/or dopamine (DA). These include the classic

psychostimulants, which are generally potent NET and DAT inhibitors (Minzenberg, 2012). Amphetamine has no effect on rMT (Boroojerdi et al., 2001; Ziemann et al., 1997), and only a trend-level suppression of the increased MEP observed with 0.1 Hz rTMS and transient ischemic nerve block (Ziemann et al., 2002). Neither methylphenidate (Gilbert et al., 2006) nor L-DOPA, a precursor to DA (dosed with benzaseride to block peripheral drug conversion), alter rMT or aMT (Ziemann et al., 1997). No effect on rMT or aMT was observed with the relatively selective D_2 agonists bromocriptine (Ziemann et al., 1997) or cabergoline (Korchounov et al., 2007). Adrenergic drugs appear to have no effect on rMT or aMT, including the highly-selective NET inhibitor atomoxetine (Gilbert et al., 2006), the α_2 agonist guanfacine (Boroojerdi et al., 2001) or the α_2 antagonist yohimbine (Plewnia et al., 2001). Similarly, antipsychotics appear to have no effect on rMT or aMT. This includes the potent (and relatively selective) D2 antagonist haloperidol (Ziemann et al., 1997), the mixed D_2/$5HT_2$ antagonist sulpiride (Ziemann et al., 1997) and quetiapine (a potent $5HT_2$ antagonist but relatively weak D_2 antagonist; (Arnt, 1998), the latter drug administered either as single-dose or once-daily for 5 days (Langguth et al., 2008).

The relative lack of effect on cortical excitability measured with TMS contrasts sharply with the consistent effects of these drugs on plasticity measures with TMS. For example, L-DOPA alters LTP-like responses to PAS25, in a complex, non-linear dose-response pattern. 100 mg enhanced the LTP-like response between 5-120 minutes post-dose in one study (Kuo et al., 2008); in another study using PAS25, 25 mg abolished this response, whereas 100 mg prolonged the LTP-like response after a delay, and 200 mg reversed the LTP-like response altogether

(Thirugnanasambandam et al., 2011b). The MEP response to PAS10 was comparable but not identical in this same study: 25 mg showed the same pattern of effects, 100 mg showed no effect, and 200 mg prolonged rather than reversed the LTP-like effect (Thirugnanasambandam et al., 2011b). Methylphenidate, a transport inhibitor with relatively greater potency at DAT than NET, enhanced the practice effect on spTMS-induced movement, both during and after practice (Meintzschel and Ziemann, 2006), though it failed to modify MEP enhancement with PAS25 (Korchounov and Ziemann, 2011). Amphetamine also enhanced practice-related changes in cortical motor mapping (Tegenthoff et al., 2004). The selective DA agents also show consistent effects on plasticity. Pergolide, a mixed D_1/D_2 agonist, increased the MEP suppression induced with 1 Hz rTMS between 0-20 minutes post-dose (Lang et al., 2008). Bromocriptine attenuated the LTP-like MEP response to PAS25 at 2.5, 10 and 20 mg between 0-30 minutes post-dose, with the high and low doses abolishing the MEP effect; a similar pattern was found in PAS10 though the intermediate 10 mg dose had no effect (Fresnoza et al., 2014). Cabergoline in contrast, had no effect on MEP response to PAS25 (Korchounov and Ziemann, 2011), though it did increase the practice effect on spTMS-induced movement both during and after the practice period (Meintzschel and Ziemann, 2006). And ropinirole, a D_2/D_3 agonist, abolished the LTP-like MEP response to PAS25 at 0.125 and 1 mg, with no effect at the intermediate dose of 0.5 mg, nor drug effect on MEP response to PAS10 at any of these doses (Monte-Silva et al., 2009). Antipsychotics also show consistent effects to attenuate plasticity processes. Haloperidol abolished the MEP response to PAS25 (Korchounov and Ziemann, 2011) and the practice effect on spTMS-induced movement, both during and after practice (Meintzschel and Ziemann, 2006). Sulpiride abolished the LTP-like response to iTBS and the

LTD-like MEP response to cTBS (Monte-Silva et al., 2011), and abolished the LTD-like MEP response to PAS10 (Nitsche et al., 2009). This dose did show a trend-level *increase* in the LTP-like MEP response to PAS25 at 5 minutes post-dose, but otherwise was without effect in this experimental paradigm (Nitsche et al., 2009). Two studies tested the plasticity effects of prazosin, which is a relatively selective α_1 adrenergic receptor antagonist currently in clinical use for nightmares associated with PTSD. Prazosin abolished the LTP-like MEP response to PAS25 (Korchounov and Ziemann, 2011), though it also showed a trend-level increase in the practice effect on spTMS-induced movement, during the practice phase (Meintzschel and Ziemann, 2006).

One notable feature in this literature, particularly observed with DA drug effects on plasticity processes, is the reasonably consistent finding of non-linear effects, typically with intermediate doses showing lesser effects than high or low doses. This may represent non-linear effects at individual DA receptor subtypes or possibly a more complex scenario representing the interaction of DA receptor subtypes. This could include the balance of D_1 to D_2 (or D_3) binding, as D_1- and D_2-like receptors have opposing effects on cyclic-AMP-dependent intracellular processes. Alternatively, it could reflect opposing effects on DA signaling of activation at post-synaptic DA receptors versus presynaptic (terminal) autoreceptors, which generally bind the native ligand with relatively higher affinity and inhibit DA release. For instance, it is well-established that antipsychotics potently block both pre- and post-synaptic D_2 receptors, leading to complex changes in both the balance of DA release versus post-synaptic receptor activation on one hand, and the balance between D_1 and D_2 receptor activation on the other. These

competing scenarios may be addressed using drug-combination study designs. In one such example (Nitsche et al., 2009), co-administration of L-DOPA with sulpiride reversed the attenuated LTD-like MEP response to PAS10 found with sulpiride alone, and also led to a more sustained (though still trend-level) increase in MEP response to PAS25, again compared to sulpiride alone. These latter findings suggest that altering the balance between D_1 and D_2 receptor binding may in turn affect plasticity responses to TMS. One clinical implication of this type of result is that drug treatment regimens that include multiple drugs with divergent actions within the same neurochemical system (e.g., DA) may have complex, paradoxical, or unpredictable effects on the clinical response to TMS.

Cholinergic Agents

This class of drugs is summarized in table 6. Tacrine is an acetylcholine (Ach) esterase inhibitor, used primarily in degenerative disorders of cognition such as Alzheimer's disease. It showed no effect on rMT or aMT (Korchounov et al., 2005). Similarly, atropine, a non-selective muscarinic receptor antagonist, failed to modify rMT (Liepert et al., 2001). In contrast, scopolamine, another non-selective muscarinic antagonist, decreased rMT and showed a trend-level decrease of aMT (Di Lazzaro et al., 2000b). As a class, cholinergic drugs show a general pattern analogous to that of catecholaminergic drugs (i.e., minimal effects on cortical excitability, and significant, consistent effects on cortical plasticity). For example, a different acetylcholinesterase inhibitor, rivastigmine, enhanced and prolonged both the LTP-like MEP response in PAS25, and the LTD-like effect of PAS10 (Kuo et al., 2007); tacrine increased the

practice effect on spTMS-induced movement after the practice period (Meintzschel and Ziemann, 2006), though it had no effect on LTP-like MEP responses to PAS25 (Korchounov and Ziemann, 2011). Direct Ach receptor-binding drugs do show consistent effects on plasticity processes. Biperiden, a non-selective muscarinic antagonist, decreased the LTP-like response to PAS25 (Korchounov and Ziemann, 2011) and the practice effect on spTMS-induced movement, both during and after the practice period (Meintzschel and Ziemann, 2006). Nicotine, in contrast, has complex, non-linear effects on plasticity processes. Nicotine nasal spray decreased the LTP-like MEP response to PAS25 between 0-30 minutes post-dose, and the LTD-like response to PAS10 between 0-90 minutes post-dose (Grundey et al., 2012). A nicotine oral lozenge, however, showed a biphasic effect on the LTP-like response to iTBS, with attenuation at 5 minutes and then enhancement at 10-40 minutes post-dose (Swayne et al., 2009). A transdermal nicotine dose extended the LTP-like MEP response to PAS25 by 30 minutes, yet abolished the LTD-like MEP response to PAS10 (Thirugnanasambandam et al., 2011a). Varenicline, a partial agonist at the $\alpha_4\beta_2$-nicotinic receptor with efficacy for tobacco smoking cessation, increased the LTP-like MEP response to PAS25 between 0-60 minutes post-dose, with the lowest dose decreasing the LTD-like MEP response to PAS10 between 0-60 minutes post-dose (Batsikadze et al., 2013). Taken together, cholinergic modulation of TMS plasticity effects is a complex, multi-phasic or non-linear function of dose, similar to catecholamine effects, reflecting the dynamics of cholinergic signaling (Picciotto et al., 2012).

Miscellaneous Agents

These drugs are summarized in table 7. Lithium had no effect on rMT or aMT at any of 3 doses (Hubers et al., 2014), though the intermediate dose changed the LTD-like MEP response to PAS22 to a LTP-like pattern. There was a non-significant increase in the positive MEP response among subjects who initially showed a "paradoxical" LTP-like MEP response without drug, with no effect observed among LTD-like responders in PAS15 (Voytovych et al., 2012). Rimonabant is a cannabinoid-1 receptor antagonist which was briefly in use for weight loss, though it was later removed from the US market due to concerns about induction of suicidal ideation. This drug decreased aMT with a trend-level decrease in rMT as well (Oliviero et al., 2012). And amantadine, a drug with diverse neurochemical actions (Perez-Lloret and Rascol, 2018), had no effect on rMT or aMT (Reis et al., 2006).

Implications for Clinical Psychiatry and Future Research Directions

Changes in both cortical excitability and plasticity processes have clear consequences for the use of TMS. In routine clinical practice, when patients adjust concurrent medications with excitability effects (e.g. antiepileptic agents), clinicians will typically re-evaluate excitability measured by MT and adjust the stimulation intensity accordingly. This simple strategy compensates for the drug effect and may compensate for any potential diminution of clinical efficacy. Increases in stimulation intensity, however, may result in an increased incidence of adverse events from rTMS such as headache or discomfort, stimulation of peripheral nerves in the head, and other side effects such as anxiety or insomnia. It also should be noted also that it

remains unclear whether changes in the "set-point" of cortical excitability have a clinically significant effect on the brain's potential for plasticity responses and therapeutic efficacy (Keck et al., 2017). For instance, altered excitation/inhibition balance has been suggested in disorders such as schizophrenia and autism (Foss-Feig et al., 2017), and it remains possible that interventions such as rTMS or psychotropic drugs remediate these disturbances. In general, meta-plasticity factors have yet to be fully-investigated in humans, yet it seems likely that the brain's capacity for plasticity may not be a simple linear function of excitability, especially given the myriad cellular and local-circuit processes that affect excitability of individual neurons and populations of neurons. Furthermore, as discussed above, excitability generally is assessed in motor cortex, while treatment usually is administered to association cortices that have a different neuron populations, laminar structure, and short- and long-range connectivity, and may have distinct excitability profiles, including with TMS (Hill et al., 2016; Kahkonen et al., 2004).

In addition, interventions such as TMS or pharmacology are well-known to be state-dependent, i.e. the initial state of the brain determines how the brain responds to the intervention (Silvanto, Muggelton and Walsh, 2008). The effects of arousal state, attentional focus, priming interventions, or recent environmental exposures can each affect the degree or even the direction of brain and behavioral responses to TMS, for instance. Because many classes of psychotropic drugs also affect global processes such as arousal state, it seems likely that the effects of these drugs on physiological (and clinical) responses to TMS could be mediated via these state-dependent processes. This scenario may be challenging to fully-evaluate, given the

need for on-line monitoring of the state-related process that is hypothesized to be in effect, in concert with the intervention and the outcome measure. However, these types of investigations may be uniquely informative of how drugs and TMS effects interact.

Neural plasticity may be manifest in time-varying, experience-dependent changes in excitability, but also can be expressed in changes in other aspects of neural signaling or structural changes (Bruel-Jungerman et al., 2007). Antidepressant action for instance is linked with synaptogenesis and/or neurogenesis (Eliwa et al., 2017; Santarelli et al., 2003), and therefore essential physiological effects of interventions may be independent of direct neurochemical changes in excitability *per se*. Therefore, concurrent medications which alter plasticity processes may exert important effects on therapeutic responses to rTMS. Drugs which have simple, monotonic effects to attenuate plasticity (e.g. ion-channel blockers) may therefore emerge as relatively contraindicated with rTMS treatment, if evidence becomes available that these drugs negatively impact clinical outcome. For many other psychotropic drug classes, the scenario may be more complex, given the non-linear profile of dose-response effects. Dopaminergic drugs represent a paradigmatic example. These drugs as a rule have a restricted dose range where outcomes are optimized (whether biological effects, cognitive performance, or target symptom severity) and beyond which symptoms may be exacerbated. These non-linear dynamics at individual receptor subtypes may reflect not only the degree of receptor activation, but also the balance of activation across receptor subtypes with opponent actions and varying time-scales of effects manifest in target neuron subpopulations. The optimal drug regimen for concurrent rTMS treatment may therefore require careful titration of dose in the

face of ongoing TMS effects, which could be challenging given the time-varying emergence of clinical response in routine rTMS treatment. In addition, the considerable heterogeneity in pharmacological actions of both individual drugs and drug classes has been widely appreciated, and it remains possible that clinical efficacy for major psychiatric illnesses requires the interaction at multiple targets of individual drugs (Roth et al., 2004). Drug combination studies (e.g. Wankerl et al., 2010; Nitsche et al., 2009) may aid in the disambiguation of experimental effects to inform this issue.

It is important to consider that this empirical literature largely employs healthy subject samples, with single-dose or very short-term drug treatment regimens, often with doses that are subtherapeutic for clinical conditions, and almost exclusively with experimental TMS paradigms that differ from the rTMS that is used clinically. Therefore, each of these study design features will have to be adjusted in future work for the clinical scenario, to more directly inform how these modulatory effects may translate to clinical effects and outcomes.

Given the current state of our knowledge, a simple dictum is to aim for parsimony in concurrent drug treatment, with the least-burdensome regimen and highest level of evidence to support the use of specific agents in the clinical conditions under treatment. This can be challenging, given that at present, most TMS treatment candidates are highly treatment-resistant, often with significant co-morbid conditions, and polypharmacy therefore tends to be the rule rather than the exception. Nonetheless, some clinical strategies commonly-used for these patients have scant supporting evidence, such as the use of antiepileptic drugs in unipolar major

depression, or the concurrent use of multiple antidepressants within a single subcategory. These strategies may have additive or even synergistic effects to attenuate plasticity and therefore they should be used only with caution. A more intriguing consideration is the identification or development of drugs which may actually *promote* plasticity in a manner that can augment the clinical response to rTMS. This would represent a major advance, to not merely avoid drugs that blunt rTMS efficacy, but rather to establish multi-modal treatment to enhance outcome over that found in either component alone. Cortical plasticity is either mediated or modulated by a number of neurotransmitter receptors that are targeted by the current pharmacopoeia, such as NMDAR, AMPA, D1 and beta-adrenergic receptors (Gu, 2002), and in principle these drugs could work in a synergistic manner to plasticity-induction with rTMS. While drugs with direct effects on effectors of plasticity (e.g. AMPAkines) have not yet gained use in psychiatry, there is evidence for a causal role of plasticity in the behavioral effects of existing antidepressants (Santarelli et al., 2003). There is also evidence for synergistic effects with the integration of antidepressant medication and psychotherapy, at least for certain patient populations (Karyotaki et al., 2016), and in principle, this should be attainable for integrating drugs and device-based interventions such as TMS. It would be prudent for the field to engage in lines of investigation such as these, to better-serve our patients who do not benefit from simpler, more conventional treatment approaches.

Table 1. Excitability and Plasticity Effects of Glutamate Agents.

Drug	MOA	Reference	Dose	TMS paradigm	Measure	Results
Cortical Excitability						
Ketamine	NDMAR antagonist	Hoffken 2013	10, 30, 50 ng/mL serum	spTMS	MEP	No effect on rMT
Ketamine		Di Lazzaro 2003	0.01, 0.02, 0.04 mg/kg/min i.v.	spTMS	MEP	↓ rMT and ↓ aMT (dose-related)
Memantine	NDMAR antagonist	Schwenkreis 1999	10-30 mg p.o. qd, escalating doses 8 days	spTMS	MEP	No effect on rMT
		Huang 2007	25 mg p.o. x3 days	spTBS	MEP	No effect on rMT
Dextromethorphan	NMDAR Antagonist	Ziemann 1998	150 mg p.o.	spTMS	MEP	No effect on rMT
		Wankerl 2010	120 mg p.o.	spTMS	MEP	No effect on rMT
Acamprosate	NMDAR Antagonist	Wohlfarth 2000	1998 mg p.o. qd x 7 days	spTMS	MEP	↑ rMT
Cortical Plasticity						
Dextromethorphan	NMDAR Antagonist	Stefan 2002	150 mg p.o.	PAS25	MEP Amplitude	↓ LTP-like response (abolished)
Dextromethorphan		Wankerl 2010	120 mg p.o.	cTBS300	MEP Amplitude	↓ LTP-like response (abolished)
Dextromethorphan + Nimodipine	NMDAR Antagonist + L-VGCC Antagonist	Wankerl 2010	120 mg p.o. + 30 mg p.o.	cTBS300	MEP Amplitude	DMX abolished the NDP-induced reversal of

						LTP-like response
Dextromethorphan		Wolters 2003	150 mg p.o.	PAS10	MEP Amplitude	↓ LTD-like response (abolished)
Dextromethorphan	NMDAR Antagonist	Weise 2017	120 mg p.o.	PAS25	MEP Amplitude	↓ LTP-like response (abolished)
Dextromethorphan + Nimodipine	NMDAR Antagonist + L-VGCC Antagonist	Weise 2017	120 mg p.o. + 30 mg p.o.	PAS25	MEP Amplitude	↓ LTP-like response (abolished)
Memantine	NMDAR antagonist	Huang 2007	25 mg p.o./3 days	iTBS	MEP Amplitude	↓ LTP-like response (abolished)
Memantine		Huang 2007		cTBS	MEP Amplitude	↓ LTD-like response (abolished)
Memantine		Schwenkreis 2005	20-30 mg p.o. (weight-adjusted)	spTMS	Practiced APB motor output map shift	No effect
		Schwenkreis 2005	10 or 10-30 mg p.o./day over 8 days	spTMS	Practiced APB motor output map shift	Abolished map shift with practice

Table 2. Excitability and Plasticity Effects of Antiepileptic Drugs and Other Ion Channel Blockers.

Drug	MOA	Reference	Dose	TMS paradigm	Measure	Results
Cortical Excitability						
Carbamazepine	I_{NaF} Inhibition	Lang 2013	300 mg p.o. x2	spTMS	MEP	↑ rMT and aMT
Carbamazepine		Inghilleri 2004	900-1200 mg p.o. x 7 days	spTMS	MEP	No effect on rMT or aMT
Carbamazepine		Lee 2005	200-800 mg p.o./day 4-week dose escalation	spTMS	MEP	↑ rMT ; persisted after acute drug withdrawal
Carbamazepine		Menzler 2014	400 mg p.o.	spTMS	MEP	↑ rMT (no effect of SCN1A genotype)
Carbamazepine		Ziemann 1996	600 mg p.o.	spTMS	MEP	↑ rMT and aMT
Gabapentin	HVA Ca^{2+} ($\alpha 2\delta$) Inhibition ↑GABA turnover	Inghilleri 2004	900-1200 mg p.o. x 7 days	spTMS	MEP	No effect on rMT or aMT
Gabapentin		Rizzo 2001	800 mg p.o.	spTMS	MEP	No effect
Gabapentin		Ziemann 1996	1200 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Lamotrigine	I_{NaF} Inhibition HVA Ca^{2+} Inhibition	Lee 2005	50-200 mg p.o./day 4-week dose escalation	spTMS	MEP	↑ rMT; resolved after acute

						drug withdrawal
Lamotrigine		Tergau 2003	325 mg p.o.	spTMS	MEP	↑ rMT
Lamotrigine		Tergau 2003	25-150 mg p.o. q2hr dose-escalating	spTMS	MEP	↑ rMT dose dependent
Lamotrigine		Li 2004	325 mg p.o.	spTMS	MEP	↑ rMT
Lamotrigine		Li 2009	325 mg p.o.	spTMS	MEP	↑ rMT
Lamotrigine		Ziemann 1996	300 mg p.o.	spTMS	MEP	↑ rMT and aMT
Lamotrigine		Boroojerdi 2001	200 mg p.o.	spTMS	MEP	↑ rMT
Topiramate		Inghilleri 2004	75 mg p.o. x 7 days	spTMS	MEP	No effect on rMT or aMT
Topiramate		Inghilleri 2006	25-100 mg p.o./day 4-week dose escalation	spTMS	MEP	No effect on rMT
Topiramate		Reis 2002	50, 200 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Valproic Acid	I_{NaF} & I_{NaP} Inhibition T-type Ca^{2+} Inhibition ↑GABA Turnover	Reis 2002	1250 mg p.o.	spTMS	MEP	Non-sig ↑ rMT
Valproic Acid		Zunhammer 2011	800 mg p.o.	spTMS	MEP	Trend-level ↑ rMT
Cortical Plasticity						
Carbamazepine		Inghilleri 2004	900-1200 mg p.o. x 7 days	5 Hz rTMS	MEP Amplitude facilitation	↓ facilitation (abolished)

Gabapentin		Inghilleri 2004	900-1200 mg p.o. x 7 days	5 Hz rTMS	MEP Amplitude facilitation	↓ facilitation (abolished)
Gabapentin	HVA Ca^{2+} ($\alpha 2\delta$) Inhibition ↑GABA turnover	Heidegger 2010	1100 mg p.o.	PAS25	MEP Amplitude	No effect on LTP-like MEP response
Lamotrigine	I_{NaF} Inhibition HVA Ca^{2+} Inhibition	Delvendahl 2013	300 mg p.o.	PAS25	MEP Amplitude	↓LTP-like MEP Response (0, 30 min post)
Lamotrigine		Delvendahl 2013		PAS25		↓LTD-like* MEP response (60 min post)
Topiramate	I_{NaF} & I_{NaP} Inhibition HVA Ca^{2+} Inhibition $GABA_A$ Agonist KA/AMPA Antagonist	Inghilleri 2004	75 mg p.o. x 7 days	5 Hz rTMS	MEP Amplitude facilitation	↓ facilitation (abolished)
Topiramate		Inghilleri 2006		5 Hz rTMS	MEP Amplitude facilitation	↓ facilitation (abolished)
Topiramate		Heidegger 2010	100 mg p.o.	PAS25	MEP Amplitude	No effect on LTP-like MEP response

Ethosuximide	T-Type VGCC antagonist	Weise 2017	750 mg p.o.	PAS25	MEP Amplitude	Reversed the LTP-like response
Other Ion-Channel Agents						
Nimodipine	L-type VGCC antagonist	Wankerl 2010	30 mg p.o.	cTBS300	MEP Amplitude	Reversed LTP-like response
Nimodipine		Wankerl 2010	15 mg, 30 mg p.o.	cTBS300 after 1.5 minute vol thumb abduction	MEP Amplitude	Reversed LTP-like response; 30 mg effect > 15 mg effect
Nimodipine		Weise 2017	30 mg p.o.	PAS25	MEP Amplitude	↓ LTP-like response (abolished)
		Wolters 2003	30 mg p.o.	PAS10	MEP Amplitude	↓ LTD-like response (abolished)

Table 3. Excitability and Plasticity Effects of GABA Drugs.

Drug	MOA	Reference	Dose	TMS paradigm	Measure	Results
Cortical Excitability						

Diazepam	$GABA_A$ Receptor Agonist	Mohammadi 2006	5 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Diazepam		Palmieri 1999	3.75 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Lorazepam		Di Lazzaro 2000	2.5 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Lorazepam		Kimiskidis 2006	i.v. to 29 ng/ml plasma	spTMS	MEP Amplitude	↓ Max rMEP recruitment curve; no effect on aMEP curve
Lorazepam		Ziemann 1996	2.5 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Lorazepam		Boroojerdi 2001	0.038 mg/kg p.o.	spTMS	MEP	No effect on rMT or aMT
Zolpidem		Mohammadi 2006	10 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Baclofen	$GABA_B$ receptor agonist	Ziemann 1996	50 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Cortical Plasticity						
Diazepam		Heidegger 2010	20 mg p.o.	PAS25	MEP Amplitude	Trend-level effect on LTP-like MEP response
Diazepam		Ziemann 2001	2 mg p.o.	spTMS + ischemic nerve block	MEP Amplitude	↓ practice-related change in biceps map (abolished)
Baclofen		McDonnell 2007	50 mg p.o.	PAS20	MEP Amplitude	↓ LTP-like MEP response (switch to LTD-

						like in 5/7 subjects)

Table 4. Excitability and Plasticity Effects of Antidepressant Drugs.

Drug	MOA	Reference	Dose	TMS paradigm	Measure	Results
	Cortical Excitability					
Citalopram	5HT Transporter Inhibition	Minelli 2010	40 mg i.v. MDD patients	spTMS	MEP	↑ Resting MT 0-3.5 hours post
Citalopram		Robol 2004	30 mg p.o.	spTMS	MEP	↑ Resting MT 2.5 hours post
Clomipramine	5HT and NE Transporter inhibition	Manganotti 2001	25 mg i.v.	spTMS	MEP	↑ Resting and active MT at 4 hour post
Clomipramine		Minelli 2010	25 mg i.v. MDD patients	spTMS	MEP	↑ Resting MT 0-8 hours post
Mirtazepine	$5HT_{1B/2A}$/$Alpha_2$ AR antagonist	Munchau 2005	30 mg p.o. healthy subjects	spTMS	MEP	No effect on rMT or aMT
Mirtazepine		Munchau 2005	30 mg p.o. Epilepsy patients	spTMS	MEP	↓ aMT; no effect on rMT
Paroxetine	5HT Transporter inhibition	Gerdelat-Mas 2005	20 mg p.o. x 30 days	spTMS	MEP	No effect on resting or active MT

Paroxetine		Gerdelat-Mas 2005	20 mg p.o. single-dose	spTMS	MEP	No effect on resting or active MT
Reboxetine	NET Transporter Inhibition	Herwig 2002	4 mg p.o.	spTMS	MEP	↓ rMT
Reboxetine		Plewnia 2002	4 mg, 8 mg p.o.	spTMS	MEP	No effect on rMT
Reboxetine		Kuo 2017	8 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Selegiline	MAO Inhibitor	Ziemann 1997	5 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Sertraline	5HT and DA Transporter inhibition	Ilic 2002	100 mg p.o.	spTMS	MEP	No effect on resting or active MT
Cortical Plasticity						
Citalopram	5HT Transporter Inhibition	Batsikadze 2013	20 mg p.o.	PAS10	Serial MEP Amplitude	↓ LTD-like response (0-90 minutes)
Citalopram		Batsikadze 2013		PAS25	Serial MEP Amplitude	↑ LTP-like response (0-30 minutes)
Fluoxetine	5HT and NE Transporter Inhibition	Pleger 2004	20 mg p.o.	spTMS	Practiced spTMS-Induced Movement	No effect on practice-related changes in motor map
		McDonnell 2018	20 mg p.o.	spTMS	Practiced spTMS-Induced Thumb Movement	No effect on practice-related changes in movement direction

Table 5. Excitability and Plasticity Effects of Catecholamingeric Drugs.

Drug	MOA	Reference	Dose	TMS paradigm		Measure	Results
Cortical Excitability							
Bromocriptine	D_2 Agonist	Ziemann 1997	5 mg p.o.	spTMS	MEP	No effect on rMT or aMT	
Cabergoline	$D_2/5HT_{2A}$ Agonist	Korchounov 2007	2 mg p.o.		MEP	No effect on rMT or aMT	
l-DOPA	DA Precursor	Ziemann 1997	100/300 mg p.o.	spTMS	MEP	No effect on rMT or aMT	
Amphetamine	DAT/NET Inhibitor	Ziemann 2002	10 mg p.o.	spTMS	MEP	No effect on rMT	
Amphetamine		Ziemann 2002		0.1 Hz rTMS + ischemic nerve block	MEP Amplitude	Trend-level suppression of ↑ MEP	
Amphetamine		Boroojerdi 2001	10 mg p.o.	spTMS	MEP	No effect on rMT	
Methylphenidate	DAT/NET Inhibitor	Gilbert 2006	30 mg p.o.	spTMS		No effect on rMT or aMT	
Antipsychotics							
Haloperidol	D_2 Antagonist; $5HT_2$ and adrenergic antagonist	Ziemann 1997	2.5 mg p.o.	spTMS	MEP	No effect on rMT or aMT	
Quetiapine	$D_2/5HT_2$ antagonist	Langguth 2008	100 mg p.o., or	spTMS	MEP	No effect on rMT or aMT	

			100 mg p.o. qd X 5 days			
Sulpiride	$D_2/5HT_2$ antagonist	Ziemann 1997	200 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Adrenergic Agents						
Atomoxetine	NET Inhibitor	Gilbert 2006	60 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Guanfacine	$Alpha_2$ AR agonist	Korchounov 2003	2 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Yohimbine	$Alpha_2$ AR antagonist	Plewnia 2001	20 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Cortical Plasticity						
Pergolide	D_1/D_2 Agonist	Lang 2008	0.125 mg p.o.	1 Hz rTMS	MEP Amplitude	↑ MEP suppression 0-20 min post
Bromocriptine	D_2 agonist	Fresnoza 2014	2.5, 10, 20 mg p.o.	PAS25	MEP Amplitude	↓ LTP-like response (0-30 minutes) all doses; abolished for 2.5 and 20 mg doses
Bromocriptine		Fresnoza 2014		PAS10		LTD-like response (0-90 minutes) abolished for 2.5 and 20 mg doses; 10 mg no effect
Cabergoline	D_2 agonist	Korchounov 2011	2 mg p.o.	PAS25	MEP Amplitude	No effect
Cabergoline		Meintzschel 2006	2 mg p.o.	spTMS	Practiced spTMS-Induced Movement	↑ practice effect during/after practice
Ropinirole	D_2/D_3 agonist	Monte-Silva 2009	0.125, 0.25, 0.5, 1.0 mg p.o.	PAS25	MEP Amplitude	↓ LTP-like response (abolished) at 0.125 and 1.0 mg; no effect 0.5 mg

Ropinirole		Monte-Silva 2009		PAS10	MEP Amplitude	No effect at any dose
Non-Selective DA Agents						
l-DOPA	DA Precursor	Kuo 2008	100 mg p.o.	PAS25	MEP Amplitude	↑ LTP-like response (5-120 minutes post)
l-DOPA		Thirugnanasambandam 2011a	25, 100, or 200 mg p.o.	PAS25	MEP Amplitude	↓ LTP-like response (abolished) 25 mg; prolonged effect 100 mg; reversed 200 mg
l-DOPA		Thirugnanasambandam 2011a		PAS10	MEP Amplitude	↓ LTD-like response (abolished) 25 mg; no effect 100 mg; prolonged 200 mg
Amphetamine	DAT and NET Inhibitor	Tegenthoff 2004	20 mg p.o.	spTMS	Practiced spTMS-Induced Movement	↑ practice-related changes in motor map
Methylphenidate	DAT and NET Inhibitor	Korchounov 2011	40 mg p.o.	PAS25	MEP Amplitude	No effect
Methylphenidate		Meintzschel 2006	40 mg p.o.	spTMS	Practiced spTMS-Induced Movement	↑ practice effect during/after practice
Antipsychotics						
Haloperidol	D_2 Antagonist; $5HT_2$ and adrenergic antagonist		2.5 mg p.o.	PAS25	MEP Amplitude	↓ LTP-like response (abolished)
Haloperidol		Meintzschel 2006	2.5 mg p.o.	spTMS	Practiced spTMS-Induced Movement	↓ practice effect during/after practice (abolished)

Sulpiride	D_2 and $5HT_2$ Antagonist	Monte-Silva 2011	400 mg p.o.	iTBS	MEP Amplitude	↓ LTP-like response (abolished)
Sulpiride		Monte-Silva 2011		cTBS	MEP Amplitude	↓ LTD-like response (abolished)
Sulpiride	D_2 and $5HT_2$ antagonist	Nitsche 2009	400 mg	PAS25	MEP Amplitude	Trend-level ↑ LTP-like response (5 minutes post)
Sulpiride		Nitsche 2009		PAS10	MEP Amplitude	↓ LTD-like response (abolished)
Sulpiride + l-DOPA	D_2 antagonist + DA precursor	Nitsche 2009	400 mg/100 mg	PAS25	MEP Amplitude	Trend-level ↑ LTP-like response (5-30 minutes post)
Sulpiride + l-DOPA		Nitsche 2009		PAS10	MEP Amplitude	No effect
Adrenergic Agents						
Prazosin	α_1 antagonist	Korchounov 2011	1 mg p.o.	PAS25	MEP Amplitude	↓ LTP-like response (abolished)
Prazosin		Meintzschel 2006	1 mg p.o.	spTMS	Practiced spTMS-Induced Movement	Non-sig ↑ effect during practice

Table 6. Excitability and Plasticity Effects of Cholinergic Drugs.

Drug	MOA	Reference	Dose	TMS paradigm	Measure	Results
Cortical Excitability						

Atropine	Muscarinic antagonist	Liepert 2001	1 mg p.o.	spTMS	MEP	No effect on rMT
Scopolamine	Muscarinic antagonist	DiLazzaro 2000	0.006 mg/kg i.v.	spTMS	MEP	↓ rMT; trend-level ↓ aMT
Tacrine	Acetylcholinesterase Inhibitor	Korchounov 2005	40 mg p.o.	spTMS	MEP	No effect on rMT or aMT
Cortical Plasticity						
Biperiden	Non-Selective Muscarinic Antagonist	Korchounov 2011	8 mg p.o.	PAS25	MEP Amplitude	↓ LTP-like response
Biperiden		Meintzschel 2006	8 mg p.o.	spTMS	Practiced spTMS-Induced Movement	↓ practice effect during/after practice (abolished)
Nicotine	Nicotinic Agonist	Grundey 2012	1 mg nasal spray	PAS25	Serial MEP Amplitude	↓ LTP-like response (0-30 minutes)
Nicotine		Grundey 2012		PAS10		↓ LTD-like response (0-90 minutes)
Nicotine		Swayne 2009	4 mg lozenge p.o.	iTBS	MEP Amplitude	↓ LTP-like response (5 minutes); ↑ LTP-like response

						(10-40 minutes)
Nicotine		Thirugnanasambandam 2011b	15 mg/16 hour transdermal	PAS25	MEP Amplitude	LTP-like response extended 30 minutes
Nicotine		Thirugnanasambandam 2011b		PAS10	MEP Amplitude	↓ LTD-like response (abolished)
Rivastigmine	Acetylcholinesterase Inhibitor	Kuo 2007	3 mg p.o.	PAS25	MEP Amplitude	↑ LTP-like response (20-30 minutes post)
Rivastigmine		Kuo 2007		PAS10	MEP Amplitude	↑ LTD-like response (10-120 minutes post)
Tacrine	Acetylcholinesterase Inhibitor	Korchounov 2011	40 mg p.o.	PAS25	MEP Amplitude	No effect
Tacrine		Meintzschel 2006	40 mg p.o.	spTMS	Practiced spTMS-Induced Movement	↑ practice effect after practice
Varenicline	$\alpha_4\beta_2$-Nicotinic Partial Agonist	Batsikadze 2014	0.1, 0.2, or 0.3 mg p.o. vs PLC	PAS25	Serial MEP Amplitude	↑ LTP-like response (0-60 minutes) all doses
Varenicline		Batsikadze 2014		PAS10		↓ LTD-like response

						(0-60 minutes) 0.1 mg dose only

Table 7. Excitability and Plasticity Effects of Miscellaneous Psychotropic Drugs.

Drug	MOA	Dose	Reference	TMS paradigm	Measure	Results
Cortical Excitability						
Amantadine	Multiple Actions	50, 100 mg p.o.	Reis 2006	spTMS	MEP	No effect on rMT or aMT
Lithium	Multiple Actions	450, 900, 1350 mg p.o.	Hubers 2014	spTMS	MEP	No effect on rMT or aMT
Rimonabant	Cannabinoid 1 Receptor Antagonist	20 mg p.o.	Oliviero 2012	spTMS	MEP	Trend-level ↓ rMT; sig ↓ aMT
Cortical Plasticity						
Lithium	Multiple Actions	900 mg p.o.	Voytovych 2012	PAS22		Reversed LTD-like responders to LTP-like; non-sig ↑ on LTP-like responders
Lithium			Voytovych 2012	PAS15		No effect on LTD-like responders

Table 8. Summary of Drug Class Effects on Cortical Excitability and Plasticity.

Drug Class	Excitability	Plasticity	Notes on Plasticity Effects
Glutamate (NMDAR) Antagonists	±	↓ LTP ↓ LTD	
Antiepileptic Agents			
Carbamazepine	↓	↓ facilitation	
Gabapentin	±	↓ facilitation	
Lamotrigine	↓	↑ LTP ↓ LTD	Effects on paradoxical LTD in PAS25
Topiramate	± (↓ facilitation)	□	
Valproic Acid	±	ND	
Voltage-Gated Ca^{2+} Channel Blockers	ND	↓ LTP	Dose-related
GABA Agonists			
GABA-A Agents	-	±	
GABA-B Agents	-	Switch LTP to LTD	
Antidepressants			
TCAs	↓	ND	
SSRIs	↓	↑ LTP ↓ LTD	
MAOIs	-	ND	
Atypical ADDs	-	ND	
Selective DA Agents	±	↓ LTP	Effects for low & high doses; medium dose no effect
Non-Selective DA Agonists	-	Biphasic ↑ & ↓ LTP	Effects for low & high doses; medium dose no effect
Antipsychotics			
Typical APDs	-	↓ LTP	
Atypical APDs	-	↑ & ↓ LTP ↓ LTD	LTD effect blocked with co-admin l-DOPA
Adrenergic Agonists	-	↓ LTP	
Cholinergic Antagonists	±	↓ LTP	
Cholinergic Agonists			
Nicotine	ND	↓ LTP ↓ LTD	Biphasic ↓ LTP & ↑ LTP with iTBS
Varenicline	ND	↑ LTP ↓ LTD	↑ LTP all doses; ↓ LTD 0.1 mg dose only

AChE Inhibitors	-	↑ LTP	
Lithium	-	Switch LTD to LTP	
Cannabinoid Antagonist	↓	ND	

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Conflicts of Interest

The authors have no conflicts of interest to declare.

Contributors

Dr. Minzenberg was responsible for the literature search, summarizing the findings and the major share of writing the manuscript. Dr. Leuchter was responsible for directing the content area of the manuscript, guiding the organization of the manuscript, and assisting in the writing and editing.

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