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Therapeutic Interaction Between TMS and Psychotropic Medications

Introduction

Transcranial magnetic stimulation (TMS) has emerged as an effective neuromodulatory treatment for psychiatric disorders such as major depression and schizophrenia. In clinical practice, TMS is often administered to patients who remain on psychotropic medications (antidepressants, antipsychotics, mood stabilizers, anxiolytics, etc.). This raises a critical question: *How do concomitant drugs influence the efficacy and neural impact of TMS?* Understanding drug–TMS interactions is important for optimizing treatment strategies in treatment-resistant conditions. Recent research (2012–2025) has begun to illuminate how various psychotropic classes can **synergistically enhance or antagonistically inhibit** TMS-induced neuroplasticity and clinical outcomes. This review synthesizes evidence on these interactions, spanning **empirical findings, neuroplasticity mechanisms, and theoretical models** of brain network dynamics. We discuss how medications modulate TMS effects on synaptic plasticity (e.g. LTP/LTD-like changes), metaplasticity and neurotrophic factors (like BDNF), with a focus on applications in depression and schizophrenia. We then consider **theoretical frameworks** – including attractor landscape models and network resilience – to conceptualize these interactions, and we outline **clinical implications** for concurrent vs. sequential pharmacotherapy with TMS.

Mechanisms of TMS-Induced Plasticity

TMS and Synaptic Plasticity: Repetitive TMS (rTMS) protocols (e.g. high-frequency rTMS, theta-burst stimulation) can induce lasting changes in cortical excitability analogous to long-term potentiation (LTP) or depression (LTD) of synapses. For example, intermittent theta-burst stimulation (iTBS) to motor cortex produces an LTP-like increase in motor evoked potentials, whereas continuous TBS (cTBS) yields an LTD-like suppression of cortical output. These after-effects rely on **activity-dependent synaptic plasticity mechanisms**, especially glutamatergic signaling through NMDA-type receptors [1] [2]. Pharmacological studies confirm that TMS-induced plasticity is **NMDA receptor-dependent**: administration of the NMDA antagonist **memantine** abolishes the LTP-like after-effects of iTBS and the LTD-like after-effects of cTBS [1]. Similarly, the NMDA blocker dextromethorphan blocks both excitatory and inhibitory plasticity induced by paired associative stimulation (PAS) or transcranial direct current stimulation (tDCS) [2]. In contrast, enhancing NMDA function can facilitate plasticity – the partial NMDA agonist **d-cycloserine** was shown to *enhance and prolong* LTP-like plasticity from anodal brain stimulation [3]. These findings underscore that **glutamate-mediated synaptic potentiation** is a necessary driver of TMS's lasting neural effects (Huang et al. 2007; Nitsche et al. 2008, DOI: 10.1113/jphysiol.2012.232975).

GABAergic Tone and Plasticity: Cortical inhibition through GABA_A/B receptors is another key regulator of plasticity. High GABAergic tone generally opposes synaptic strengthening and can raise the threshold for inducing plastic change. Experimental "pharmaco-TMS" studies in humans demonstrate that **GABA-enhancing drugs dampen TMS-induced plasticity**. Benzodiazepines like diazepam (a positive allosteric modulator of GABA_A receptors) and the GABA reuptake inhibitor tiagabine both significantly **reduce LTP-**

like plasticity induced by PAS [4]. Likewise, a GABA_B agonist (baclofen) suppresses PAS-induced LTP-like effects [4]. An interesting nuance is observed with **lorazepam** (a benzodiazepine): it attenuates early-phase LTP-like potentiation from anodal stimulation, yet paradoxically *enhances* the late-phase plasticity, possibly due to homeostatic rebound after initial inhibition [5]. Overall, **excess GABAergic activity tends to antagonize the excitatory plastic changes** that TMS is designed to provoke. Consistently, magnetic resonance spectroscopy studies show that successful induction of TMS/tDCS after-effects is accompanied by a reduction in local cortical GABA levels [6] – suggesting that lowering inhibitory tone is permissive for synaptic reorganization.

Monoaminergic Modulation: Neuromodulators like serotonin and norepinephrine critically shape plasticity and can be targeted by antidepressants. **Serotonin (5-HT)** has complex effects on synaptic plasticity, but human studies indicate that enhancing 5-HT can facilitate TMS-induced plastic changes. Notably, a single dose of the SSRI **citalopram** (20 mg) was found to **enhance and prolong LTP-like plasticity** induced by anodal tDCS, and even **convert an LTD-like effect into net LTP-like facilitation** [7] [8]. This suggests SSRIs create a bias toward synaptic strengthening, possibly via increased BDNF release or other 5-HT-mediated metaplastic mechanisms. **Noradrenergic** activity is likewise important: the monoamine releaser **amphetamine** extended the duration of anodal tDCS after-effects, whereas blocking β-adrenergic receptors with propranolol reduced both LTP- and LTD-like TMS after-effects [9] [10]. An α_1-receptor antagonist (prazosin) abolishes induced LTP-like plasticity [10]. Thus, **elevating monoamines (serotonin/norepinephrine)** tends to *promote* and sustain TMS-induced synaptic potentiation, while adrenergic blockade dampens it. These findings align with the clinical notion that antidepressants (which boost 5-HT/NE signaling) might synergize with TMS's neuroplastic effects.

Other Systems and Neurotrophic Factors: The dopaminergic system plays a dual role in plasticity through D1 and D2 receptors. Dopamine D1 receptor activation generally facilitates LTP (partly by enhancing NMDA receptor currents), whereas D2 activation can constrain plasticity [11]. Pertinently, blocking D2 receptors – as occurs with many antipsychotic medications – **eliminates TMS-induced plasticity** in the motor cortex. Studies using the D2 antagonists **sulpiride or haloperidol** showed that **theta-burst TMS or tDCS no longer produced their usual after-effects when D2 receptors were blocked** (Nitsche et al., 2010; 2011, DOI: 10.1038/npp.2011.81). In fact, intact dopamine transmission appears to be a *necessary precondition* for inducing plasticity: dopaminergic activity "gates" the ability of TMS protocols to produce lasting changes [12]. This has implications for patients on antipsychotics (discussed below). Meanwhile, **brain-derived neurotrophic factor (BDNF)** is another crucial modulator of plasticity and metaplasticity. Antidepressant drugs and exercise are known to upregulate BDNF expression over weeks, which enhances synaptic growth and learning capacity [13] [14]. High BDNF levels are associated with greater cortical plasticity, whereas the common **BDNF Val66Met polymorphism** (which impairs activity-dependent BDNF release) is linked to reduced response to rTMS. Although BDNF's role is often studied in the long-term context, it provides a molecular substrate for drug-TMS synergy: therapies that increase BDNF (e.g. SSRIs, lithium) may **broaden the capacity for TMS-induced synaptic remodeling**. Indeed, chronic lithium has been reported to increase BDNF and synaptic proteins, potentially supporting neuroplastic changes in mood disorders.

Metaplasticity and Homeostatic Effects: It is important to note that TMS protocols and drugs do not simply add linear effects – they can interact through **metaplasticity**, i.e. the plasticity of plasticity. Metaplasticity refers to prior activity or drug-induced changes that alter the thresholds and rules for subsequent synaptic plasticity [15] [16]. For example, an initial course of rTMS might "prime" networks such that a concurrent antidepressant exerts a larger effect (or vice versa). Homeostatic metaplasticity (as in the BCM rule) predicts that strong prolonged potentiation will raise the threshold for further LTP and favor LTD

to maintain stability. Some drug interactions reflect this: e.g. repeated high-dose dopaminergic stimulation abolishes plasticity in a biphasic manner (too much dopamine can be as detrimental as too little, due to receptor desensitization or inhibition at D2 receptors) [17] [18]. By contrast, low doses of a D2 agonist or partial agonist (like ropinirole or d-cycloserine) can facilitate plasticity induction [3] [19]. From a metaplasticity standpoint, **concurrent medications can bias the brain's plasticity "set-point"**, tilting it toward potentiation or depression. As we will see, this bias can translate into either improved or diminished clinical response to TMS, depending on the drug's action.

Pharmacological Modulation of TMS-Induced Plasticity

Given the above mechanisms, we can categorize how major psychotropic drug classes influence TMS-induced neuroplasticity:

- **NMDA Antagonists:** Drugs that block NMDA receptors (e.g. memantine, ketamine, dextromethorphan) **markedly attenuate or abolish** the synaptic plasticity evoked by TMS-like protocols. Classic studies showed memantine eliminated iTBS after-effects [20], and dextromethorphan blocked tDCS and PAS-induced plasticity [20]. While the rapid antidepressant ketamine involves NMDA blockade, its antidepressant effect is thought to result from a **rebound increase in glutamate release and BDNF** after the acute block. In the context of TMS, however, co-administering a purely NMDA-blocking agent likely **reduces efficacy** – the induction of beneficial plastic changes (for mood or cognition) may be blunted. Some clinicians thus caution against using memantine (e.g. for cognitive impairment in depression) during an rTMS course, as it could negate the neuromodulatory benefits. On the other hand, a partial agonist at the NMDA glycine site (**d-cycloserine**) can *boost* plasticity and has been explored as a cognitive enhancer. Combining d-cycloserine with TMS has been shown to prolong after-effects of stimulation [21] [22] – for instance, it extended anodal tDCS-induced excitability enhancements from 1 hour to 24 hours in one study (Nitsche et al. 2004b, DOI: 10.1016/j.brs.2009.03.002). This raises the intriguing possibility of using NMDA modulators to **extend the therapeutic window** of TMS-induced plasticity.

- **Antidepressants (SSRIs, SNRIs, etc.): Antidepressant medications** that elevate serotonin and/or norepinephrine generally appear **compatible or synergistic** with TMS. There is no evidence that SSRIs diminish rTMS efficacy; on the contrary, neurophysiology suggests SSRIs facilitate plasticity (as with citalopram converting LTD to LTP [7]). Many rTMS depression trials have allowed patients to remain on a stable antidepressant dose during TMS, with good outcomes. A meta-analysis by *Rakesh et al.* (2020) found that **combining antidepressants with TMS from the outset was associated with greater short-term efficacy** than TMS monotherapy in major depression (DOI: 10.1016/j.brs.2020.08.013). Clinically, this makes sense: antidepressants provide an "ongoing neurotrophic milieu" (e.g. raised BDNF, enhanced catecholamine signaling) that TMS can build upon. Notably, **continuation of antidepressants after TMS** is linked to maintaining remission – one study observed significantly lower relapse at 3–12 months in patients who stayed on medication post-TMS (77% relapse-free) versus those who did not (54% relapse-free) (Medina et al. 2019, DOI: 10.1097/YCT.0000000000000587). These data suggest antidepressants and TMS have **complementary mechanisms**: antidepressants gradually tweak synaptic sensitivity and network connectivity, while TMS provides an acute excitatory push to entrained networks. That said, not all subclasses are equal. For example, **tricyclic antidepressants** and MAO inhibitors have anticonvulsant properties and were historically thought to raise seizure threshold, but in practice they do not prevent TMS effects – they are used less often simply due to side effect burden. Overall, current consensus holds that *"TMS*

can be administered with or without concurrent antidepressant medications" and that there is **no increase in adverse events** when combining them [23]. This permissive stance reflects the lack of negative interaction and the potential for additive benefit.

- **Benzodiazepines and Sedative-Hypnotics: Benzodiazepines (BZDs)** are one class that shows a clear *antagonistic* interaction with TMS. As GABA_A agonists, BZDs blunt cortical excitability and plasticity, which can translate to smaller clinical improvements with rTMS. A large clinical study of 181 depressed patients found that those taking benzodiazepines had significantly **lower response rates to 6 weeks of rTMS** (16.4% response if on BZDs vs 35.5% if not on BZDs) [24]. Early symptom improvement was also less in benzodiazepine users [25]. These data align with other reports that benzodiazepine co-treatment is associated with **slower or reduced antidepressant response to rTMS** (Carpenter et al. 2012; Kaster et al. 2022). The likely mechanism is that BZDs increase cortical inhibition and stabilize neural networks against change – essentially **raising the threshold for TMS-induced plastic shifts**. By contrast, **z-drugs** (non-benzodiazepine hypnotics like zolpidem) can similarly enhance GABA_A transmission and might be expected to have a dampening effect, although less studied. Clinical recommendation is often to **minimize benzodiazepine use during TMS therapy** if possible, or at least use the lowest effective dose, to avoid blunting the neuromodulatory impact. That said, not all aspects are negative – as noted, lorazepam acutely reduced plasticity but then led to an exaggerated late-phase LTP (Nitsche et al. 2004c). However, in a therapeutic time-frame (daily rTMS), the net effect of BZDs is likely **unfavorable for rTMS outcomes** [25] [24]. Patients with severe anxiety who require an anxiolytic might be managed with non-sedating alternatives if undergoing TMS.

- **Antipsychotics (Dopamine Antagonists):** In schizophrenia treatment, patients almost universally receive antipsychotic drugs (D2 receptor blockers). These drugs have a complex interaction with TMS. **D2 blockade can impede cortical plasticity**, as discussed earlier – haloperidol or sulpiride abolish the normal motor cortex plastic responses to TMS/tDCS [12]. Paradoxically, schizophrenia patients off medication also show impaired plasticity (likely due to the illness itself, see next section). A **review of TMS measures in schizophrenia** concluded there is robust evidence of **disrupted neuroplasticity in schizophrenia, regardless of medication status** [26]. This impairment is tied to the pathophysiology of schizophrenia – involving dysfunctional NMDA receptor signaling and GABA interneuron alterations [27]. Antipsychotics, by blocking dopamine, might *further reduce* NMDA-driven plasticity (since dopamine, especially D1, helps enable LTP). However, antipsychotics also have indirect effects: atypical antipsychotics increase serotonin and may upregulate neurotrophic factors over time, possibly counteracting some deficits. There is scant direct clinical research on rTMS efficacy in schizophrenia as a function of medication, but one can infer: **if dopamine blockade is too strong (high-dose typical antipsychotics), rTMS aimed at enhancing plasticity might have diminished effects**. Conversely, partial agonist antipsychotics (like aripiprazole) or lower doses might interfere less. Some studies combining rTMS with antipsychotics for auditory hallucinations did achieve modest additive improvement, suggesting that concurrent use is feasible. In summary, antipsychotics are necessary in schizophrenia treatment, but clinicians should be aware that **they may raise the threshold for TMS-induced changes**. This raises interest in **adjunctive treatments to overcome plasticity deficits** – for instance, trials have explored adding NMDA glycine-site agonists (e.g. glycine, D-serine) to enhance plasticity in schizophrenia. Enhancing glutamatergic function or using **metaplasticity primers** (like intermittent theta bursts or paired stimulation) may help "open a window" for plastic change in medicated patients. Further research is needed, but

strategies that **tackle the NMDA hypofunction in schizophrenia** could synergize with TMS to improve cognitive and negative symptoms.

- **Mood Stabilizers (Lithium, Anticonvulsants):** Bipolar depression patients receiving rTMS may be on mood stabilizers such as lithium, valproate, or lamotrigine. These agents have diverse actions on neuroplastic pathways. **Lithium** is known to *enhance neuroplasticity over the long term* – it boosts BDNF, inhibits GSK-3β (thereby promoting synaptic growth), and can facilitate long-term potentiation in some models. There is tentative evidence that lithium **augments antidepressant and rTMS effects**. For instance, case series using lithium + TMS in bipolar depression have reported good responses, and lithium might help maintain TMS-induced remission by promoting synaptic stability in a healthy network configuration. In contrast, **antiepileptic mood stabilizers** often dampen neural excitability: **lamotrigine**, a glutamate-release inhibitor and Na^+ channel blocker, was shown to **reduce PAS-induced LTP-like plasticity** in humans [28]. **Carbamazepine** (another Na^+ channel blocker) abolished tDCS-induced cortical potentiation in one study [28]. **Valproate** increases GABA levels and may similarly *raise the threshold for LTP*, although it also has HDAC inhibitor properties that might facilitate gene expression for plasticity. Clinically, concurrent anticonvulsant use has not been definitively shown to hinder rTMS antidepressant effects, but caution is warranted. If a patient is on a high dose of valproate or lamotrigine, their cortical excitability is lower – thus, high-frequency rTMS might need more sessions or higher intensity to overcome this. In some cases, if clinically appropriate, one might reduce the dose of these during an acute TMS course (balancing the risk of mood destabilization). **In summary, mood stabilizers can have either pro-plastic or anti-plastic effects depending on the agent:** lithium is generally *plasticity-enhancing* (metaplastic over weeks), whereas anticonvulsants are *plasticity-attenuating* acutely. This should be factored into treatment planning for bipolar patients receiving TMS.

- **Stimulants and Wake-Promoting Agents:** Psychostimulants (amphetamine, methylphenidate) and agents like modafinil increase catecholamine release and cortical excitability. These drugs may **synergize with TMS** by increasing neuronal firing and **"energizing" neural networks**. The clinical study in depression by Hunter et al. found **concomitant stimulant use was associated with greater improvement from rTMS** (39% response with stimulants vs 22% without) [24]. The effect was evident by week 2 of treatment [25]. Stimulants elevate norepinephrine and dopamine, which likely amplifies the plastic changes induced by each TMS session and improves attention/engagement during treatment. While routine use of stimulants in depression is not common, some TRD patients on stimulant augmentation (for energy or concentration) might actually get a double benefit from combined TMS. Caution is needed due to potential side effects (blood pressure, etc.), but low-dose stimulants or modafinil could be considered to counteract fatigue and enhance cognitive plasticity alongside TMS. Notably, **propranolol (a beta-blocker)** had the opposite effect – as mentioned, it reduced TMS after-effects in experiments [10]. Clinically, if a patient is on a strong centrally acting β-blocker for anxiety or cardiac reasons, one might expect a slightly reduced TMS efficacy (though this is theoretical). In sum, **increasing cortical excitatory drive pharmacologically (stimulants, agonists)** tends to promote TMS effects, whereas **inhibitory or stabilizing drugs (sedatives, anticonvulsants)** tend to oppose them. The challenge in practice is balancing these pharmacological effects with overall patient needs and safety.

Drug–TMS Interactions in Depression

Major Depressive Disorder (MDD) is the primary indication for therapeutic rTMS. Depression is increasingly understood as a disorder of **impaired neural plasticity and network rigidity** [29] [30]. Chronic stress and monoamine dysregulation lead to reduced synaptic connectivity (e.g. lower BDNF, atrophy of dendrites) and **hypofrontality with hyperconnected default-mode networks** (ruminative loops) [31]. This manifests as a brain that is "stuck" in a maladaptive attractor state of low energy and entrenched negative thought patterns. **Antidepressant medications** attempt to gradually re-tune these networks by increasing monoaminergic tone and, over weeks, upregulating plasticity genes (like BDNF, CREB). **rTMS**, especially high-frequency left prefrontal stimulation, directly *perturbs* the frontal–limbic circuits, acutely increasing neuronal firing and modulating network connectivity. When used together, **pharmacotherapy and TMS can have complementary roles**: - The medication provides a permissive environment (e.g. enhanced neurotrophin levels, restored neurotransmitter balance) that **lowers the threshold for neuroplastic change**. - The TMS provides an external focused input that **drives plastic change in the desired circuits** (e.g. strengthening dorsolateral prefrontal cortex control over limbic regions, or resetting network connectivity).

Empirical evidence supports synergy. As noted, **TMS combined with ongoing antidepressants tends to yield higher response rates** than TMS alone in TRD patients (G. Rakesh et al., 2021, *Brain Stimul.*, DOI: 10.1016/j.brs.2020.08.013). Some randomized trials have implicitly been augmentation studies (patients on meds receiving active vs sham TMS). For instance, Conca et al. (2000) reported that adding low-frequency TMS to antidepressants led to faster and greater improvement than meds alone in a small trial. More recently, an open-label study using deep TMS in severe TRD (with patients on meds) found a high response rate (~70%) after 4 weeks, suggesting an additive benefit [32]. On the other hand, **benzodiazepine use in depressed patients clearly correlates with poorer rTMS outcomes** [25] [24], as discussed. It is common in clinical practice to taper BZDs before starting TMS if feasible. If not, patients should be counseled that their response might be blunted or slow, and a longer course of TMS might be needed.

A particularly interesting interaction is with **NMDA-modulating agents in depression**. The rapid-acting antidepressant **ketamine** (an NMDA antagonist) has raised questions about whether it could be combined with TMS. On face, NMDA blockade would prevent TMS-induced LTP; however, ketamine's therapeutic effect involves a subsequent surge in glutamate and BDNF release. Pilot studies of **combining ketamine with TMS** (either concurrently or sequentially) have shown promising results in highly resistant depression (Wall et al. 2021, DOI: 10.1177/20451253211035326). The idea is that ketamine "loosens" synapses (via metaplastic changes and new spine formation), and TMS sessions applied in that window might more effectively rewire networks. This is somewhat analogous to electroconvulsive therapy (ECT) plus medication paradigms, where ECT provides a massive perturbation and medications consolidate the gains. While still experimental, **ketamine + TMS** represents a novel strategy to leverage both a pharmacological plasticity trigger and a focal stimulation to guide that plasticity.

From a **theoretical perspective**, depression's network pathology can be seen through the lens of attractor dynamics. The depressed brain is in a deep, resilient basin of attraction characterized by self-reinforcing patterns of dysphoria, rumination, and inertia [33] [34]. **Escape from this pathological attractor** requires either (a) *tilting the variables* (gradually adjusting key factors like mood, sleep, cognitive bias via therapy/medication) or (b) *flattening the landscape* (reducing the attractor's depth so the system can more easily transition to a healthier state) [35] [36]. Antidepressant drugs primarily work via the first mode – slowly **tilting specific variables** (e.g. increasing serotonin improves sleep and mood, which can weaken some

symptom-symptom feedback loops) [37]. rTMS has elements of both: repeated TMS can incrementally adjust network connectivity (tilting specific circuits), but intensive TMS (especially accelerated protocols or deep TMS) can act more globally to "shake" the network, akin to a mild landscape flattening. The **combination** of meds + TMS is thus well-suited to overcome depression's excessive stability. Medications begin to **soften the landscape** (by biochemical changes that promote plasticity), and TMS provides *focused perturbations* to push the brain toward a new attractor (the euthymic state). Importantly, once remission is achieved, maintaining it likely requires keeping the landscape favorable – hence continuing antidepressants or maintenance TMS helps prevent the system from slipping back into the old basin [38]. This view is supported by relapse data: without continuation treatment, many patients relapse post-TMS, implying that the network, if not further supported, will return to the depressive attractor [38].

In summary for depression: **SSRIs/SNRIs and rTMS make a rational pair** – SSRIs boost synaptic plasticity mechanisms (via 5-HT and BDNF) and rTMS exploits those mechanisms to reorganize dysfunctional circuits. **Benzodiazepines counteract rTMS** and should be minimized. **Stimulants or modulators** (like modafinil, which increases cortical excitation) can be helpful adjuncts in certain cases. And experimental combinations (ketamine, partial NMDA agonists) are being explored to further **destabilize the depressive network and facilitate TMS-induced rewiring**. The overarching goal is to use pharmacology not simply to treat symptoms in parallel, but to **pharmacologically prime the brain for TMS-induced plasticity** – a concept known as "augmentation" at the neurophysiological level (Nitsche et al. 2012, DOI: 10.1113/jphysiol.2012.232975).

Drug–TMS Interactions in Schizophrenia

In schizophrenia (SCZ), therapeutic TMS has been investigated for treating auditory hallucinations, negative symptoms, and cognitive deficits. The neural plasticity context here is quite different from depression. Schizophrenia is hypothesized to involve a **developmental dysregulation of synaptic plasticity** – often described as too much synaptic pruning in cortex and abnormalities in NMDA and GABA interneuron function [39] [40]. TMS studies consistently show **impaired cortical plasticity in patients with SCZ**, manifest as reduced or absent normal LTP/LTD-like responses in motor cortex protocols (rTMS or tDCS) (Bhandari et al., 2016, DOI: 10.3389/fpsyt.2016.00045). This deficit appears to be intrinsic to the illness, as it is seen even in medication-free patients and is correlated with cortical disinhibition and connectivity changes [27] [41]. In other words, the **baseline attractor landscape in schizophrenia may already be shallow or aberrant** – the brain may either lack stable attractors for normal cognitive states or be stuck in a dysfunctional oscillatory regime.

Antipsychotic medications, the mainstay of SCZ treatment, primarily block dopamine D2 receptors. While essential for controlling psychosis, this action can further affect plasticity. As noted, D2 blockade in healthy brains prevents induction of plasticity by TMS [12]. In SCZ patients, however, the picture is complicated: because dopamine signaling is dysregulated in SCZ, antipsychotics might restore some balance that indirectly *improves* plasticity potential (for instance, reducing hyperdopaminergia in subcortex could normalize cortical plasticity in some circuits). There is some evidence that **atypical antipsychotics (which also act on 5-HT2A receptors)** may positively influence cortical plasticity over time – e.g. **clozapine** has serotonergic and glutamatergic effects that could enhance synaptic remodeling (clozapine raises NMDA receptor subunit expression and glutamate release in frontal cortex, according to some preclinical data). However, **direct studies are scarce**. One can extrapolate from related findings: *schizophrenia patients with the BDNF Met allele (low activity BDNF) have especially poor TMS-induced plasticity* [42], suggesting boosting BDNF might be key. Some small trials gave **adjunct D-serine (an NMDA co-agonist)** with TMS for negative

symptoms, aiming to surge NMDA function during stimulation – results showed slight improvements in negative symptoms (Farzan et al. 2018, DOI: 10.1016/j.schres.2018.05.008). Another approach is **high-frequency rTMS to upregulate NMDA/AMPA currents** directly; interestingly, one study found that **theta-burst stimulation in SCZ patients failed to produce the expected MEP potentiation**, aligning with NMDA dysfunction (Hui et al. 2019, DOI: 10.1016/j.brs.2019.07.002).

In clinical practice, when using TMS in schizophrenia (for example, 1 Hz TMS to treat hallucinations by *inhibiting* the auditory cortex), patients will usually be on antipsychotics. The concurrent use does not pose safety issues, but efficacy can be mixed. Some trials show that adding TMS modestly reduces hallucination severity when patients are on stable meds (Dougall et al. 2015, DOI: 10.1016/j.euroneuro.2014.12.004). For **negative symptoms or cognitive training**, where one would want to *enhance* plasticity, the combination of D2 blockade with TMS is suboptimal. A theoretical suggestion is to **time TMS sessions with peak dopamine transmission** – for instance, if a patient takes haloperidol at night, doing TMS in late afternoon when drug levels are lower might yield slightly better plastic responses (this is speculative). Likewise, **avoiding very high plasma levels of antipsychotics during TMS might help**, if clinically safe to do so. Some have proposed using **transcranial alternating current or other neuromodulation** to entrain rhythms that compensate for plasticity deficits in SCZ, combined with pro-cognitive drugs.

From the attractor perspective, schizophrenia may involve a **disorganized attractor landscape** – possibly too *shallow* (allowing chaotic jumps, as in psychosis) or an aberrant deep attractor for negative symptoms (e.g. a state of hypofrontality and social withdrawal that is hard to escape). **Antipsychotics "tilt" certain variables** (they reduce the positive symptom attractor by damping dopamine-driven salience of hallucinations). **TMS could in theory tilt others or flatten the landscape**. For example, if negative symptoms correspond to a stable low-activity prefrontal network, high-frequency TMS might destabilize that and push the system toward a more active state. But if the biological plasticity machinery is impaired (NMDA hypofunction), the system may resist reconfiguration. Therefore, **pharmacological facilitation is crucial**: future treatments might combine neuromodulators (e.g. glycine reuptake inhibitors or positive modulators of AMPA receptors) with TMS to overcome the plasticity barrier. An analogy can be made to **"metaplastic tuning"** – perhaps low-dose D_1 agonists or cholinesterase inhibitors could be given before TMS to transiently improve cortical plasticity in SCZ. Some early work supports this: e.g. **ampakine drugs** (AMPA receptor potentiators) were shown to enhance TMS-induced plasticity in animal models (Clark et al. 2014, DOI: 10.1016/j.brs.2014.07.040). While not yet in clinical use, these concepts highlight that **effective TMS in schizophrenia will likely require addressing the underlying plasticity deficits pharmacologically**.

In sum, for schizophrenia: **D2-blocking antipsychotics are a double-edged sword** – necessary for psychosis control but likely limiting synaptic plasticity. The net effect on rTMS outcomes is not fully clear, but practitioners report that patients with schizophrenia often need more sessions and show more modest improvements than depression patients. Adjunctive **pro-cognitive medications** (e.g. **acetylcholinesterase inhibitors, NMDA modulators, or even SSRIs** for some cognitive/neurotrophic boost) could be considered to create a more favorable plasticity milieu for TMS. As research evolves, a rational polytherapy might emerge: for instance, **combining a drug that enhances LTP (like D-cycloserine or a dopamine agonist) with TMS sessions aimed at improving cognition**, and concurrently using antipsychotics to keep positive symptoms in check. This balancing act embodies the idea of *guided plasticity*: we attempt to **pharmacologically "open" the window for plastic change and then use TMS to direct that change in a therapeutically useful way**.

Theoretical Frameworks: Attractors, Metaplasticity, and Network Dynamics

To integrate these observations, it is useful to step back and consider **brain network dynamics** under treatment. Modern theoretical models describe the brain as traversing a complex **landscape of attractor states** – stable patterns of neural activity that underlie mental states or psychopathology (e.g. depressed mood attractor, psychotic thought attractor). The depth (resilience) of these attractors determines how resistant the state is to perturbation [43] [33]. Treatments can work by either **tilting the landscape** (specific changes that gradually shift the person out of the basin) or **flattening it** (reducing overall stability to allow a quick transition) [35] [36].

- **Antidepressants and gradual change:** Pharmacotherapy often **alters specific parameters** over time – for example, increasing serotonin may gradually lift mood, improve sleep, and energy. In network terms, this is a **tilt** to the landscape: the basin of depression becomes slightly less deep as certain feedback loops (like insomnia → fatigue → hopelessness) are weakened [37] [44]. This is a slow process, consistent with the delayed clinical effect of antidepressants (weeks). The landscape tilt corresponds to enhancing metaplasticity: by improving neurochemical support (BDNF, monoamines), the brain becomes more capable of change, albeit gradually [45] [46].

- **TMS/ECT and rapid perturbation:** In contrast, **neurostimulation (especially ECT, but also high-intensity TMS)** can act as a **direct perturbation** to the system. For instance, ECT causes a global seizure that transiently **flattens the landscape**, knocking the brain out of its entrenched state and increasing the range of possible configurations [47] [48]. TMS is less drastic but repeated rTMS can cumulatively destabilize pathologic network loops. Research shows ECT increases the *variability* and *flexibility* of large-scale networks (e.g. default mode connectivity becomes more variable post-ECT) [48] [49]. This is interpreted as ECT **"loosening" the pathological attractor** – essentially a surge in metaplasticity where the usual rules and constraints on network activity are relaxed [46]. During this window of heightened plastic potential, new connections can form and previously stuck networks can reconfigure. TMS, especially accelerated schedules (multiple sessions per day), likely also induces a milder form of this effect. In both cases, **the perturbation itself doesn't guarantee a healthy new attractor** – it simply makes change possible. **Continuation treatment is critical** to solidify a new stable state, as noted with ECT relapse if no follow-up [38].

- **Combination: flatten and tilt** – The most robust therapeutic strategy may be one that **both destabilizes the old attractor and guides the system into a new one**. This can be achieved by *combining modalities*: e.g. using TMS/ECT/ketamine to flatten the landscape (reduce pathological resilience) and concurrently using medication or therapy to tilt the system toward a desirable state. Scheffer et al. (2024) describe how small changes in a subset of variables can trigger a transition once the system is near a tipping point [50] [51]. TMS could push the depressed brain to that tipping point, and antidepressant-induced biases (better sleep, hope, neurogenesis) ensure it falls into a remission basin rather than back into depression.

- **Metaplasticity Windows:** The concept of **metaplasticity window** is pertinent here. After a strong plasticity induction, there is a window of time where the brain's ability to undergo further plastic change is altered (either enhanced or suppressed, depending on homeostatic mechanisms). For instance, **after one TMS session, there may be a several-hour window where synapses are**

tagged and more receptive to consolidation (or, conversely, if overstimulated, the next induction yields less effect). Some have proposed scheduling psychotherapy or cognitive training within the window after rTMS, to capitalize on increased learning capacity. Likewise, strategically timing medication dosing relative to TMS could exploit metaplastic windows: an **acute dose of D-cycloserine or a stimulant given just before TMS** might maximize the session's impact, whereas a sedative given shortly after TMS might erase some of the induced changes (by promoting homeostatic downscaling). Though not yet standard, these ideas follow logically from metaplasticity principles [52] [53]. The overall treatment regime could thus be optimized by understanding when the brain is most "plastic" and using that time to implement therapeutic learning or reinforcement.

In essence, theoretical models encourage us to view **drug and TMS combinations as a way to manipulate the brain's energy landscape**. Medications can shrink or tilt basins, TMS can jostle the system, and together they can achieve outcomes that neither alone could – much like pushing a boulder out of a deep well (you both raise the floor *and* give it a push). The concept of **network destabilization** is not negative here; it is a controlled reduction of pathological stability, allowing the emergence of a new stable wellness state. This frames treatment-resistant disorders as problems of *pathological resilience* – the patient's symptoms are too stable – and combination treatment as a means to reduce that resilience. Notably, this must be done carefully: a delicate balance is required so that we don't induce chaos (e.g. risk of seizures if too much excitation, or switching depression into mania). The attractor model thus also highlights why **sequential strategies** (like doing TMS then adding medication) might differ from **concurrent strategies**. Sequentially, one might first destabilize (TMS) then stabilize (meds), which could consolidate a new state. Concurrently, one might get a smoother trajectory where meds gradually ease the transition as TMS pushes it. There is no one-size-fits-all, and clinical judgment is needed to tailor the approach to each patient's landscape.

Clinical Implications and Treatment Strategies

Understanding these interactions yields several practical guidelines for optimizing TMS treatment alongside pharmacotherapy:

- **Avoid Interfering Medications:** If possible, reduce or hold medications that **blunt cortical plasticity** during an rTMS course. Foremost, **benzodiazepines should be minimized** – consider tapering high-dose benzodiazepines before TMS or switching to non-GABAergic anxiolytics (e.g. SSRIs, buspirone) to manage anxiety. Similarly, strong **anticonvulsants** (e.g. high-dose divalproex) might be gradually lowered if the clinical situation permits, or at least dosed such that plasma peaks don't coincide with TMS session times. For example, a patient on valproate could take it at night so that by next afternoon's TMS, sedative effects are less. **Sleep meds** like zolpidem might be fine if taken well after the day's TMS. The key is to **maximize the brain's excitability and plastic potential** when the magnetic stimulation is delivered.

- **Leverage Synergistic Drugs:** Medications that **facilitate plasticity or network engagement** can be strategic allies. Ensure patients' **antidepressant therapies are optimized** during TMS – if a patient is unmedicated, it may be reasonable to start an antidepressant concomitantly (unless contraindicated) to harness any additive benefit. Conversely, if a patient on medication hasn't responded, TMS may still work, but consider if switching or augmenting the med could further help (e.g. adding bupropion for dopaminergic boost alongside TMS). **Stimulants or modafinil** can be used in patients who have prominent fatigue or cognitive slowing; a low dose in the morning may

improve their active engagement in TMS-induced circuit changes (and as noted, was associated with better outcomes [25] [24]). In TRD patients with partial response to SSRIs, one might add **atypical antipsychotics** (like aripiprazole or brexpiprazole) – interestingly these agents are 5-HT modulators and sometimes have pro-cognitive effects, which might complement TMS (though aripiprazole does have some D2 agonism, it's partial and might not impede plasticity heavily). **Lithium augmentation** is another consideration: lithium's long-term plasticity enhancement (and anti-suicidal effects) could consolidate the synaptic changes achieved by TMS. Clinicians have used lithium plus TMS successfully in some TRD cases, with lithium possibly preventing relapse by promoting synaptic stability and health.

- **Sequential vs. Concurrent Use:** One strategic question is whether to **continue antidepressant medications during the acute TMS course or stop them and use TMS as monotherapy**. Given the evidence to date, most experts recommend **continuing stable antidepressants concurrently**, since there is no evidence of harm and likely some benefit [23] [54]. Stopping meds abruptly to "test" TMS alone could risk clinical deterioration. There are scenarios, however, where sequential use is applicable: for instance, in a patient who cannot tolerate medications, TMS might be done alone to achieve remission, and then a **maintenance medication introduced after TMS** to prevent relapse. Alternatively, some patients want to come off meds – a strategy could be to perform rTMS while slowly tapering the antidepressant, using the rTMS to buffer against relapse during discontinuation. This must be individualized. For schizophrenia, **sequential use** is generally not an option – antipsychotics are needed continuously for symptom control; thus TMS is always an add-on. But one could imagine in future a schizophrenia patient in remission with TMS who might try a slight dose reduction of antipsychotic under stimulation cover, though this is experimental.

- **Timing and Dosing Considerations:** There may be merit in coordinating medication timing with TMS sessions. For example, an **SSRIs peak plasma level** occurs a few hours after dosing; scheduling TMS during that window might ensure maximal serotonin facilitation of plasticity (though SSRIs have long half-lives, so it's less critical). For **short-acting drugs like stimulants**, giving the dose ~1 hour before TMS could yield a more activated cortex during stimulation. If using **D-cycloserine** in an experimental augmentation paradigm, one would administer it 1–2 hours pre-TMS to allow it to cross the blood-brain barrier and be present when TMS drives LTP. On the flip side, if a patient requires a sedative, giving it *after* the TMS session (e.g. a sleeping pill at night) is preferable to taking a sedating drug right before TMS, which could reduce that session's efficacy. These fine-tuning measures are not yet backed by large trials but are logical extensions of our mechanistic knowledge.

- **Network-Guided Interventions:** Future strategies might involve measuring a patient's network "rigidity" or plasticity state (using EEG or TMS-EMG metrics) and then tailoring adjuncts. For instance, if a depressed patient has very low frontal plasticity on TMS-EEG measures, one might prioritize adding a plasticity enhancer (like an NMDA modulator) before starting TMS. If another patient shows hyperconnectivity in a certain network, maybe a medication that specifically targets that (e.g. a melatonin agonist for sleep network issues, or a dopaminergic agent for reward network deficits) could be combined with TMS targeting that network. This is the idea of **personalized combinatorial neuromodulation** – using the right drug to address the right circuit in conjunction with TMS.

- **Safety Considerations:** Combining TMS with medications is generally safe, as per consensus guidelines (no significant increase in adverse effects) [23]. However, one should be mindful of **seizure risk**: many psychotropic drugs *lower* seizure threshold (antidepressants, antipsychotics in high

doses) whereas benzodiazepines *raise* it. TMS itself has a very low seizure risk. When combining multiple pro-convulsant treatments (e.g. high-dose antidepressant + high-frequency TMS), the risk is still low but potentially marginally higher. Care should be taken in such cases (avoiding TMS when patient is sleep-deprived, etc.). On the other hand, **if benzodiazepines are reduced**, the patient's seizure threshold might decrease slightly, but typically therapeutic TMS remains safe – just avoid abrupt discontinuation of a long-term BZD to prevent withdrawal seizures during TMS. Overall, adhering to published TMS safety guidelines (screen for medications like clozapine which in rare cases can cause seizures by itself, etc.) is sufficient.

To illustrate an optimized approach: imagine a patient with severe TRD who is on an SSRI and low-dose clonazepam. The clinician decides to augment with high-frequency left DLPFC rTMS. They might **taper the clonazepam** substantially before TMS starts, continue the SSRI, and perhaps add low-dose **methylphenidate in the mornings** to combat fatigue. The rTMS is delivered daily; mid-course, if minimal improvement, they could consider adding **lithium** or switching the SSRI to an SNRI to engage more NE. By end of 6 weeks, if partial response, they continue SSRI + lithium for maintenance and consider periodic TMS boosters. In contrast, a schizophrenia patient with prominent negative symptoms on risperidone might get **theta-burst stimulation to prefrontal cortex** while we **augment with glycine** (to boost NMDA) for a few weeks, monitoring if there's any additive benefit on social engagement. These scenarios exemplify rational polytherapy.

Conclusion

The interplay between TMS and concomitant medications is a frontier of neuropsychiatric treatment, merging **brain stimulation with pharmacological neuromodulation**. Evidence from the past decade highlights that psychotropic drugs can profoundly influence the **efficacy, plasticity mechanisms, and neural outcomes of TMS** interventions. **Synergistic combinations** – such as pairing TMS with antidepressants, stimulants, or NMDA partial agonists – can amplify synaptic plasticity and clinical response, leveraging the drugs' enhancement of neurotrophic and neuromodulatory tone. In contrast, **antagonistic combinations** – notably TMS with benzodiazepines or excessive anti-excitatory drugs – may impede the induction of the very plastic changes that drive therapeutic benefit. These findings underscore a principle: *successful neuromodulation requires a conducive neural environment*.

On a mechanistic level, we see that TMS-induced LTP/LTD-like changes rely on glutamate (NMDA receptors), are modulated by GABA inhibition, and are facilitated by monoamines and neurotrophins. Medications that modulate these same systems will interact with TMS in predictable ways – either opening the gates for plasticity or closing them. On a systems level, combining treatments can be understood through **metaplasticity and attractor dynamics**: medications can shape the metaplastic landscape (e.g. widen the window for change), while TMS provides the directed force to move the brain out of pathological attractors. The attractor model especially provides a unifying theory for why combined treatments are often needed in entrenched conditions like TRD or chronic schizophrenia – one needs to both destabilize the old patterns and ensure the system can restabilize in a healthier configuration.

Clinically, the emerging consensus is that **multimodal treatment yields the best outcomes** for difficult psychiatric disorders. Just as psychotherapy combined with medication often outperforms either alone, we now recognize that **brain stimulation combined with pharmacotherapy** can achieve more than either modality in isolation. TMS does not occur in a vacuum – the patient's neurochemistry at each session matters. By mindfully managing concomitant medications, clinicians can **turn up the gain on**

neuroplasticity during a TMS course and thus maximize the therapeutic impact. Future research is needed to refine optimal protocols: for example, dosing of plasticity-enhancing drugs around TMS sessions, identifying which patient subgroups benefit most from which add-on medication, and developing novel agents specifically to boost neuromodulation (so-called "plasticity primers").

In conclusion, the interaction between TMS and concurrent medications is a critical consideration that can make the difference between a modest response and a full recovery. The evidence to date (2012–2025) suggests that we should **harness synergistic interactions** – keep patients on their antidepressants (or even start one) during TMS for depression, avoid benzodiazepines that dull TMS effects, consider stimulant or dopaminergic augmentation when appropriate, and address underlying plasticity deficits in conditions like schizophrenia with targeted pharmacological strategies. At the same time, we must remain vigilant about safety and individual variability. By integrating **pharmacological wisdom with neuromodulation**, we move closer to truly personalized psychiatry, where treatments are orchestrated in concert to reshape brain circuit function and restore mental health. This multidisciplinary, mechanism-informed approach offers hope that even the most treatment-resistant brain can be nudged out of illness and into a new stable wellness state – with medications preparing the soil and TMS sowing the seeds of lasting change.

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