

TMS as a tool to investigate the effect of pharmacological medications on cortical plasticity

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Abstract. – The application of medications with a well-defined mode of action on a neurotransmitter or neuromodulator of the central nervous system (CNS) can be utilized to test the pharmacophysiological properties of transcranial magnetic stimulation (TMS) on cortical excitability and plasticity. Similarly, a physiologically well-defined TMS measure of cortical excitability may be exploited to study a particular drug's effect at the level of the cerebrum. In this review, we aim to assess the impact of calcium channel blockers, Selective Serotonin Reuptake Inhibitors (SSRIs), and GABAergic agents on cortical excitability and plasticity while concurrently investigating how TMS can enhance this understanding.

We will begin by reviewing the basics of neuroplasticity, as explored in animal experimentation, and relate this to our knowledge about neuroplasticity induced in humans by TMS techniques. We will then discuss pharmacological modulation of plasticity in humans. Finally, we will review abnormalities of plasticity inherent to certain neuropsychiatric diseases and discuss how the combination of TMS with pharmacological intervention can augment our knowledge of the pathophysiology of these diseases and guide purposeful treatment.

Key Words:

Transcranial magnetic stimulation (TMS), Cortical plasticity, Pharmacological modulation, Neurophysiology.

Introduction

The human brain is a dynamic organ that undergoes constant changes throughout life. Neurogenesis and neuroplasticity characterize the brain's ability to alter itself and adapt to genetic and environmental sensory stimulation and ac-

tivity. The primary motor cortex (M1) provides a magnificent example of cortical reorganization in the human brain. By manipulating the reorganization potential of M1, Transcranial Magnetic Stimulation (TMS) offers a reliable method for altering and observing motor cortical excitability.

First introduced in 1985, TMS provides a safe, effective, and non-invasive method to electromagnetically stimulate the cortex. While some TMS mechanisms may be difficult to apply, quantify, and observe behaviorally, TMS application to the M1 allows for a simple way to examine the locality of and interaction between the various cortical pathways involved in motor processing and movement initiation. When coupled with electromyography (EMG), TMS can provide valuable information about the excitability and integrity of many of the ascending and descending intracortical pathways in the M1 region. As the utility of non-invasive neurostimulation grows, the applicability of these techniques in clinical medicine and pharmacology continues to expand.

Medications affecting the central nervous system are typically categorized based on their physiological mechanism of action. For instance, benzodiazepines are minor tranquilizers prescribed for their anxiolytic and sedative effects. Benzodiazepines have antagonizing effects on certain GABA receptors involved in inhibitory intracortical circuits. The understanding of the physiological effects of drug-induced excitability differences and specific mechanisms of neurochemical transmission can be broadened by the use of TMS, which provides a method to recruit inhibitory and excitatory circuits and characterize their performance by the administration of

CNS active drugs^{1,2}. Investigating the variations in cortical excitability induced by pharmaceutical agents could aid in differentiating between cortical pathways and may also assist in further clarifying the specific mechanism of action these substances³. Similarly, drugs with well-described mechanisms of action can be employed in conjunction with TMS techniques to assess the integrity of interacting neuronal circuitry.

Studying the systemic mechanisms behind the pharmaceutical application of various drugs would contribute to the development of more specific drugs. This will help in enhancing the therapeutic effect and minimizing side effects. Similarly, if the specific synaptic transmission effects of CNS active drugs are known, clinicians would have a more comprehensive physiological drug profile to aide their choice of medication.

An array of defined TMS measures may be used to study the pattern of effects of a drug with unknown or multiple modes of action. Acute drug effects may be rather different from chronic drug effects. These differences can be studied using TMS measures. It is possible to recruit specific neuronal circuits of the human brain and to evaluate in vivo the effects of drugs on several neurotransmitter systems that influence these circuits².

The aim of this review is to provide a general understanding of TMS-induced cortical excitability measures and show that TMS is an invaluable tool when combined with the administration of CNS active drugs.

Measurements of Cortical Plasticity

Motor Threshold

Motor threshold (MT) is the most basic parameter of cortico-motor excitability⁴. Simply defined as the minimum stimulus intensity necessary to elicit a small motor evoked potential in a target muscle, MT can be determined by a single-pulse TMS technique^{4,5}. The Resting Motor Threshold (RMT) is the motor evoked potential threshold for a muscle at rest. The RMT is typically modulated by glutamatergic intracortical synaptic transmission. The Active Motor Threshold (AMT) is the threshold magnitude of an active muscle and is mainly dependent on voltage-gated cation channels, as the AMT is regulated by axonal excitability^{5,6}. The dependence the motor threshold has on the axonal fibers that terminate in the motor cortex render MT measurements

particularly susceptible to fluctuations in cation channel activity. Thus, pharmacological agents that block cation channels or glutamatergic activity will usually have a notably heightening effect on motor threshold levels. However, because the motor threshold is independent of any known inhibitory cortical and spinal circuits, agents that exert GABAergic actions will usually not impact MT magnitude.

Motor Evoked Potential Amplitude

When TMS is applied to the motor cortex at a stimulus intensity at or above threshold, a motor evoked potential (MEP) can be recorded in the EMG of the target muscle. The amplitude of MEP is representative of the quality of both excitatory and inhibitory neuronal pathways throughout the cortex that terminate in the motor region⁶. The resulting MEP amplitude positively correlates with stimulus intensity and depends on both TMS intensity and corticospinal excitability⁴. The neuronal pathways responsible for MEP amplitude are, in turn, transynaptically mediated by both excitatory and inhibitory inputs⁶. Therefore, drugs modulating cation channels, inhibitory channels, or both excitatory and inhibitory mechanisms have an effect on MEP amplitude. Though both MEP and MT are direct measurements of cortical facilitation, changes in MEP amplitude can occur without changes in MT magnitude, proving that the two measurements are modulated by different mechanisms⁷.

Cortical Silent Period

The cortical silent period (CSP) is a biphasic, TMS-induced interruption in voluntary muscle activity^{6,7}. The early phase of the CSP is mediated by spinal inhibitory mechanisms, while the late phase is mediated by supraspinal inhibitory mechanisms⁸. The exact mechanism of CSP is still unknown, but it has been hypothesized that the silent period is modulated by inhibitory mechanisms pertaining specifically to the GABA_B receptor subtype. However, this assumption is often discredited because of some pharmacological agents, such as baclofen, a specific GABA_B receptor agonist, have no significant effect on CSP duration. Furthermore, CSP was shown to lengthen after the administration of benzodiazepines, which have GABA_A receptor subtype modes of action. Thus, it might also be asserted that CSP can be affected by variations in motor attention resulting from the significant sedative effect many GABAergic agents exert^{1,8}. Notably,

some studies have found that low TMS intensities produce a CSP resulting from GABA_A activation and high-intensity TMS trigger a GABA_B activated CSP. Therefore, changes in CSP can be manipulated by the actions of non-specific GABAergic drugs⁹. While further investigation of the specific mechanisms of CSP modulation is necessary, it is indisputable that CSP duration is not affected by pharmaceuticals that modify facilitatory mechanisms.

Short-Interval Intracortical Inhibition

The application of a paired-pulse TMS technique composed of a subthreshold conditioning pulse, a short interstimulus interval of 2-5 milliseconds, and a suprathreshold test pulse, results in short intracortical inhibition (SICI)⁷. The initial conditioning, low-intensity TMS pulse activates GABA_A inhibitory interneuronal circuits, the mechanisms of which modulate SICI^{2,3,10,11}. Specifically, the $\alpha 1$ and $\alpha 2$ subunits of the GABA_A receptor subtypes are thought to mediate SICI mechanisms⁶. Benzodiazepines and other GABAergic agents that act on GABA_A receptors have been shown to enhance the duration of SICI^{6,7}. Drugs that interfere with membrane excitability and block voltage-gated channels do not have an effect on SICI length¹².

Long Intracortical Inhibition

Like SICI, long-interval intracortical inhibition also results from a paired-pulse TMS technique. However, long intercortical inhibition (LICI) occurs after the administration of two suprathreshold pulses of equal intensity that are separated by a long interstimulus interval of 50-200 milliseconds^{7,9}. LICI duration is proposed to be mediated by the GABA_B receptor subtype^{3,6,7,10}. Activation of GABA_B receptors leads to a decrease in the amplitude of the second MEP elicited by the paired-pulse technique. This decrease in MEP amplitude results in an increased duration of intracortical inhibition⁶. LICI can thus be modulated by the administration of GABAergic agents but not by channel blocking drugs. Although the general consensus is that GABA_B receptors play a direct role in LICI duration, the specific mechanisms of LICI should be further tested to examine this assertion⁷.

Intracortical Facilitation

Employing a prolonged interval of 7-20 milliseconds between TMS stimuli produces a period of intracortical facilitation (ICF)⁷. The ICF is a measure of the efficacy of excitatory

neuronal circuits in the motor cortex and how these circuits are affected by slight variations in intervening trans-synaptic inhibitory pathways⁷. ICF is modulated by both excitatory and inhibitory mechanisms and can be manipulated by either NMDA or GABAergic transmission. Although ICF modulation involves facilitation, it does not require any alteration in membrane excitability and therefore remains unaffected by channel-blocking drugs⁴. GABAergic drugs, specifically those with GABA_A activity, have been found to produce a reduction in ICF duration^{6-8,13} (Table I).

Long-Term Synaptic Potentiation (LTP) and Long-Term Synaptic Depression (LTD) Trains of Repetitive TMS (rTMS) to assess induction of LTP/LTD and Modulate Cortical Activity

This approach of "off-line" rTMS with modulation of cortical activity, both locally and along functional neural networks, can be extremely useful to study brain-behavior relations, but in addition, offers the possibility of therapeutic applications of TMS in neurological and psychiatric disorders. The mechanisms of cortical excitability modulation beyond rTMS train duration are still unclear. Long-term synaptic potentiation and depression have been suggested as mechanisms to explain the effect of high- and low-frequency rTMS, respectively. Endogenous neurotransmitters such as GABA and glutamate, and neuromodulators (DA, NE, 5-HT, ACh) play a fundamental role in the regulation of the neuronal activity in the cerebral cortex^{7,8}. Many neurological and psychiatric disorders are caused by abnormal neuronal network activity as a consequence of altered neurotransmitter or neuromodulator systems.

Dopamine has been shown to enhance long-term potentiation (LTP) in a task-dependent manner^{9,10} not only in the hippocampus, but also in the cerebral cortex^{6,8} and striatum⁴.

The GABA_A agonists enhance Short-interval intracortical inhibition (SICI) Di^{11,12}. DA agonists and NE antagonists (guanfacine) increase SICI, while DA antagonists (haloperidol) and NE agonists decrease SICI.

The effects of neuromodulators on rTMS measures may depend on genetic polymorphisms of the receptors and transporters involved, and this may explain some of the variability of findings reported. One first study to support this notion demonstrates that the selective serotonin re-up-

Table I. The TMS-induced effects of drugs on cortico-motor excitability.

Class	Drug	Mechanism of action	Measurement						Reference
			MT	MEP	CSP	SICI	LICI	ICF	
GA-BAergic	Lorazepam	GABAAR	◦	◦↓	↑	↑	↑	↓	(1,4,5,11,14)
	Diazepam	GABAAR	◦	↓	◦↓	↑	◦	↓	(1,4,5,10,11,14,15)
	Zolpidem	GABA α 1	◦	◦↓	↑	◦↑	↑	↓	(1-3,5,14)
	Baclofen	GABABR	◦	◦	◦↑	◦↓	↑	↓	(1,7,26,29,30)
	Vigabatrin	GABAAR	◦	◦	↑	◦	↑◦	↓	(5,30)
Chan-nel blockers	Losigamone	Unknown, Ca ²⁺ channel blocker	↑	◦	◦	◦	◦	◦	(5,8)
	Gabapentin	Ca ²⁺ channel blocker	◦	◦	↑	↑	◦	↓	(12,17)
	Carbamazepine	Na ⁺ channel blocker	↑	↑	↑	◦	◦	◦	(5,8)
	Lamotrigine	Na ⁺ channel blocker	↑	◦	◦	◦	◦	◦	(1,4,5,8)
	Valproate	Na ⁺ channel blocker	↑	◦	↑	◦	◦	◦	(5-8)
5-HT	Fluoxetine	SSRI	◦	↑	◦	◦	◦	◦	(22)
	Citalopram	SSRI	↑	◦	↑	↑	◦	◦	(4,5,31)
	Sertraline	SSRI	◦	↑	◦	◦	◦	◦	(5,23)
	Paroxetine	SSRI	◦	↑	◦	◦	◦	◦	(32)

◦ - no effect ↑ - increase ↓ - decrease; * More than one symbol represents inter-study differences.

take inhibitor citalopram increases SICI, but only in those subjects who are homozygotic for the long variant of the 5-HT transporter gene¹³. This is explained by the fact that homozygosity for the long variant is associated with two times more efficient 5-HT re-uptake compared to the short variant. A reasonable way to account for these potential problems in drug dosing is the inclusion of different or incremental doses into the study design. Another critical issue is the timing of TMS measurements. While most studies chose timing according to the pharmacokinetics, i.e., the course of the plasma level of the drug under study, this may be inappropriate for drugs, which produce their effect through complex pharmacodynamic action. An example is the antiepileptic drug vigabatrin. Its effect is exerted via irreversible inhibition of the GABA-degrading enzyme GABA-transaminase, which has a much slower and longer time course than the vigabatrin plasma concentration¹⁴. GABA concentration in the brain peaks 24 hours after intake of a single dose of vigabatrin⁹, while vigabatrin concentration in the plasma peaks after one hour and the plasma half-life is 6 to 8 hours⁹. Accordingly, a significant vigabatrin-induced decrease in ICF was only observed 24 hours after intake, and not after 6 hours¹⁵ (Table I).

Channel Blockers

Sodium Channel Blockers

Voltage-gated sodium channels play a crucial role in axonal excitability by allowing for alterations in cell membrane potential necessary to generate an action potential. The blockage of these channels decreases the repeated firing of axons and thus, the frequency of signal propagation, by preventing neuronal Na⁺ influx at excitatory synaptic sites⁷. The predominant mechanism of most antiepileptic drugs (AEDs) is the manipulation of axonal Na⁺ channels to suppress epileptogenic activity by increasing motor threshold⁸. In certain situations, an increase in motor evoked potential threshold may also occur, as MEP is a measure that depends on both excitatory and inhibitory input. Drugs that are antagonists of Na⁺ channels do not, however, affect intracortical facilitation or inhibition, as these measures are altered only by manipulation at inhibitory synapses specifically.

Administration of t+ channel blockers Carbamazepine, Lamotrigine, and Valproate all result in a significant increase in motor threshold^{11,7,8,16}. While the effects of Lamotrigine on cortical plasticity are limited only to increasing motor threshold, both Carbamazepine and Valproate seem to amplify cortical silent period as well¹⁶.

However, because GABA receptors and cortical inhibitory circuits largely modulate cortical silent period, these Na⁺ channel-blocking drugs may also potentially have calcium channel blocking abilities at GABAergic presynaptic terminals. Carbamazepine has also been shown to increase MEP amplitude, as MEP is a measurement that can be altered by changes to either excitatory or inhibitory cortical mechanisms^{8,16}.

Calcium Channel Blockers

Voltage-gated calcium channels, like Na⁺ channels, are also found at excitatory synapses. The involvement of calcium channels in membrane excitability substantiates the effect voltage-gated calcium channel blockers have on increasing motor threshold. Along with regulating axonal excitability, certain Ca²⁺ channel subtypes are also critical in neurotransmitter release at presynaptic terminals.

Both Losigamone and Gabapentin are categorized as AEDs and calcium channel blockers but differ in their modulatory effects of cortical plasticity^{5,8}. While the specific mechanisms of action of Gabapentin are unknown, there is strong evidence to establish Gabapentin's role in promoting the synthesis of the inhibitory neurotransmitter GABA. Gabapentin tends to prolong the cortical silent period and short intracortical inhibition while shortening intracortical facilitation¹⁷. Although a Ca²⁺ channel antagonist, Gabapentin seems to have no substantial effects on motor threshold, proving that the Ca²⁺ channel subtype that Gabapentin blocks must play a role in neurotransmitter release but not in the modulation of membrane excitability^{5,8,12,17}.

Losigamone has been shown to increase motor threshold through specific mechanisms not yet well understood. It is predicted that this AED works not only by blocking voltage-gated calcium channels but possibly voltage-gated potassium channels as well. Because the administration of Losigamone increases the motor threshold without having any significant effects on other cortical plasticity measures, it can be assumed that the calcium ion channel subtype Losigamone effects is present within axonal membranes and not at presynaptic terminals.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) are pharmacological agents prescribed for the treatment of depression and other mood disor-

ders. SSRIs act to enhance synaptic serotonin (5-HT) and norepinephrine concentrations by inhibiting 5-HT reuptake inhibitors¹⁸. Although considerable research has been conducted with SSRIs and cortico-motor significance in animal models, studies conducted with TMS examining the effects of SSRI administration on human motor cortical plasticity remain sparse¹⁹⁻²¹. From the research that has investigated the role of serotonin in motor function and reorganization, it seems as though the effects of SSRIs are widespread and vary on a drug-to-drug basis⁶.

Fluoxetine, paroxetine, and sertraline all exert upregulation of $\alpha 1$ and downregulation of $\alpha 2$ receptors on norepinephrine, acetylcholine, and dopamine reuptake mechanisms and share similar excitability characteristics by increasing MEP amplitude²¹⁻²³.

Citalopram affects cortico-motor excitability in ways the aforementioned SSRIs do not. Being an extremely selective 5-HT reuptake inhibitor, citalopram produces effects that suggest that an enhancement of GABAergic interneuronal activity may be involved in its physiological basis because of increased SICI and CSP duration post-administration²⁴. Additionally, citalopram produces an elevation in motor threshold, suggesting that administration of this SSRI might be involved with cortical facilitation and membrane excitability. However, MT can also increase with increased drowsiness, a common side effect of SSRI administration²³. Thus, changes in MT levels may or may not be due to the therapeutic effect of the drug itself.

GABAergic Agents

Gamma-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system. It plays a crucial role in monitoring and determining the efficacy and integrity of most, if not all, of the inhibitory pathways throughout the cortex. Transcortical inhibitory circuits involve the actions of GABA receptors, of which the two main subtypes are GABA_A and GABA_B. GABA_B receptor subtypes are metabotropic and mediate pre and postsynaptic inhibition by reducing calcium currents and activating potassium currents^{1,25}. Likewise, GABA_A receptors are ionotropic chloride transporters, leading to hyperpolarization when activated. These two receptor subtypes can be categorized further past their subunit composition, which is usually a combination of α , β , and γ subunits¹. Pharmacological GABAergic agents are effective

because they have been manufactured to have a certain affinity for specific subunits of each receptor subtype.

Benzodiazepines

Medications that fall into the behavioral-clinical class of minor tranquilizers can be chemically classified as benzodiazepines. Benzodiazepines are clinically prescribed because of their powerful sedative-hypnotic, anticonvulsant, and anxiolytic properties and are involved in the positive allosteric modulation of the GABA_A receptor subtype^(1,5,26). Recalling the properties of GABA_A receptors, it can be concluded that benzodiazepines manipulate the frequency of the chloride ion transmission of various cortical inhibitory circuits, thereby increasing intracortical inhibition^{26,27}.

Diazepam is a classical benzodiazepine agent that binds non-selectively to all four of GABA_A α subunits^{1,11,14}. However, it has been postulated that diazepam may have more of an affinity to $\alpha 2$ GABA_A receptors, a subunit that mediates the anxiolytic action of benzodiazepine receptor sites¹¹.

Similar to diazepam, lorazepam is another commonly administered benzodiazepine with an unknown subunit specificity². However, due to the likeness of its effects to those of diazepam, lorazepam is thought to also share an affinity to $\alpha 2$ receptors while maintaining its reputation as a non-selective GABA_A agent^{3,11,14}.

Zolpidem is yet another benzodiazepine. However, unlike lorazepam and diazepam, zolpidem has a ten-fold greater affinity for $\alpha 1$ GABA_A receptor subunits than any other GABA_A subunits^{1,3,11,14}. Though still present in M1, $\alpha 1$ subunits, which are known to mediate sedation, are most dense in the cerebellum than in other brain regions^{1,28}.

When physiologically tested in conjunction with TMS, all three benzodiazepines have similar effects on MEP and ICF. However, the effects on cortical silent period following benzodiazepine administration do not seem to follow any logical trend. Again, CSP has complicated physiological mechanisms that remain to be more thoroughly examined, so the differing effects of benzodiazepines on this measure of excitability will be better interpreted following the establishment of the physiological basis of CSP⁷. The SICI is yet another excitability measurement that has different effects among the benzodiazepines; diazepam and lorazepam both have similar enhancing ef-

fects on SICI across several studies while zolpidem did not. It can, therefore, be asserted that modulatory effects of SICI are not the responsibility of $\alpha 1$ GABA_A receptors¹¹.

Other GABAergic Agents

Baclofen is an antispastic drug that has been shown to have antiepileptic effects in animal models and is thought to have antagonistic actions at GABA_B receptors prevalent in CNS inhibitory circuits^{7,10,29}. Baclofen administration seems to have similar effects to benzodiazepines with subtle differences. Notably, baclofen has been shown to have significant lengthening effects on LICI, establishing the involvement of GABA_B receptors in this specific measurement of motor excitability²⁹ (Table II).

Vigabatrin is, unlike the aforementioned benzodiazepines or baclofen, an enzyme inhibitor. Vigabatrin is a commonly prescribed AED and exerts its effects by irreversibly binding to and inhibiting the GABA-degrading enzyme, GABA-transaminase^{7,8,30}. Because vigabatrin is not directly involved with the potentiation of ion or metabotropic mechanisms, administration of this enzyme-inhibitor does not significantly affect intracortical inhibition⁸. However, vigabatrin increases endogenous GABA levels and, as a result, decreases intracortical facilitation^{8,30}.

Conclusions

For nearly three decades now, TMS has been implemented in various clinical and research settings to provide a valuable method for examining cortical interactions in a non-invasive and painless way. The use of TMS in conjunction with pharmacological agents allows for an elegant technique to both elaborate on specific drug physiologies while also testing the integrity of cortico-motor circuits in the constantly adapting brain. Studies that have thus far examined systemic drug mechanisms have been immensely significant in all aspects of pharmacology and have been able to help differentiate between AEDs, benzodiazepines, SSRIs, and show the various actions of these drug classes on cortical plasticity. Although great advances have been made in the ability to provide a more comprehensive pharmacological profile of CNS active drugs, many modifications can be suggested to make future studies more clinically pertinent.

Table II. Typical uses and side effects of CNS-active agents.

Class	Drug	Uses	Severe side effects
GABAergic	Lorazepam	Anxiety, Epilepsy, Insomnia	Fever, Dyspnea, Yellowing skin/eyes, Arrhythmia, Shuffling walk, tremor
	Diazepam	Anxiety, Epilepsy, Muscle spasms	Fever, Dyspnea, Yellowing skin/eyes, Arrhythmia, Shuffling Walk, Tremor
	Zolpidem	Insomnia	Urticaria, Itching, Swelling of the lips, eyes, tongue, throat, Dyspnea, Nausea and vomiting, Chest pain, Vision problems
	Baclofen	Muscle spasms	Seizures, Dyspnea
	Vigabatrin	Seizures	Cognitive symptoms, Fatigue, Irregular heartbeat, Urticaria, Pallor
Channel blockers	Losigamone	Seizures epilepsy, Postherpetic neuralgia, Restless Leg Syndrome	Currently undergoing clinical trials
	Gabapentin		Urticaria, Swelling of the face, lips, tongue, Seizures, Dyspnea, Dysphagia
	Carbamazepine	Seizures	Cognitive effects, Chest pain, Yellowing skin/eyes, Vision problems
	Lamotrigine	Seizures, Mania	Sensitivity to light, Chest pain, Swollen extremities, Syncope, Headache
5-HT	Valproate	Seizures, Mania	Purple marks on skin, Blisters, Urticaria, Swollen glands, Depression, Weakness, Suicidal thoughts, Fever
	Fluoxetine	Depression, OCD, Panic attacks	Urticaria, Joint pain, Swelling of extremities and face, Dyspnea, Fever, Arrhythmia, Hallucinations, Seizures
	Citalopram	Depression	Dyspnea, Urticaria, Seizures, Cognitive effects, Coma, Excessive sweating, Fever, Fainting, Dizziness, Hallucinations
	Sertraline	Depression, OCD, Panic attacks, PTSD, Social anxiety disorder	Seizures, Abnormal bleeding/bruising, Hallucinations, Vision problems,
	Paroxetine	Depression, Panic attacks, Social anxiety disorder	Fever, Irregular heartbeat, Cognitive effects Abnormal vomit that looks like coffee grounds, Abnormal stool, Bloody stool, Painful urination, Blisters, Red spots on skin, Abnormal bleeding/bruising, Blurred vision, Hallucinations, Irregular and painful heartbeat

It is essential to accurately administer the correct drug dose, as drug potency and effectiveness appear to vary on a subject-to-subject and dose-to-dose basis⁷. Many studies have used identical doses used in previous studies. However, subject variability is too great of an inconsistency and can be eliminated by obtaining pharmacodynamic and pharmacokinetic data for each drug being administered for each individual subject. Another option is to administer a drug based on weight, scaled to a subject's individual body mass. However, when a drug has more than one mechanism of action, neither dose-response curves nor scaling doses will eliminate non-therapeutic side effects from resulting. Thus, drugs with only specific or known mechanisms of action should be selected to study cortical plasticity.

Many studies are conducted as acute, single-dose trials when the drugs being investigated take several days or several-doses to have

any measurable effects in the cortex, although plasma levels may peak after just a few hours. It is suggested that drugs thought to possess longer mechanisms of actions be administered in a non-acute manner. Routes of administration should also be taken into consideration when comparing inter-study differences. Understanding and modifying TMS-pharmaceutical testing methods will create valuable advances in the fields of psychiatry, pharmacology, neurology, and research.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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