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Review

Excitation–Inhibition Imbalance as a Framework for the rTMS Mechanism of Action in Depression

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neurostimulation therapy with established evidence in the treatment of depression. Despite its clinical use, the mechanism(s) underlying the therapeutic effects of rTMS for depression is not yet understood. The excitation–inhibition (E–I) imbalance framework suggests that disruptions in the balance between excitatory and inhibitory neural activity contribute to the pathophysiology of several neuropsychiatric disorders, and it proposes a candidate explanation for how rTMS exerts its antidepressant effect. Understanding the mechanism of action of rTMS enables the refinement of rTMS protocols for better efficacy and positions rTMS as an intervention in disorders where excitation/inhibition imbalance contributes to the underlying etiology. In this narrative review, we review evidence for E–I imbalance in depression, describe the effects of rTMS on excitatory and inhibitory systems at the molecular, cellular, and cortical levels, and integrate these findings to evaluate whether the restoration of E–I balance is a plausible mechanism of action. While findings are mixed and adequately powered, longitudinal, controlled studies are needed, the available evidence is broadly consistent with an E–I model of rTMS in depression. This review and our proposed model can serve as a foundation for future mechanistic work in this field.

Keywords: neuromodulation; GABA; glutamate; DLPFC

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation modality for stimulating neurons in superficial cortical regions of the brain. rTMS induces electrical currents by applying repetitive magnetic pulses to a target region in the brain [1]. This results in depolarization of the neurons and initiation of action potentials, which activates post-synaptic neurons [2].

The stimulation of neural circuits in this manner has promising clinical applications that are under investigation. Some areas of interest for rTMS include pain, movement disorders, multiple sclerosis, substance use disorders, and mood disorders [3]. Of these areas, rTMS has demonstrated strong evidence in the treatment of depression, neuropathic pain, and motor recovery after stroke [3].

rTMS is an effective treatment for major depressive disorder (MDD), with a reported remission rate of approximately 35% in treatment-resistant depression [4]. Modern rTMS protocols involve stimulation to the dorsolateral prefrontal cortex (DLPFC)—a region known to be dysfunctional in depression. While it is known that targeting this region

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ameliorates depressive symptoms, the neurophysiological mechanism behind these improvements is unclear. Knowledge of the underlying mechanism would provide insight as to what makes a patient a responder, which improves patient selection and treatment efficacy. The aim of this review is therefore to propose a mechanistic framework, grounded in existing evidence, for the antidepressant effect of rTMS.

2. Methods

This narrative review aimed to synthesize the available literature on excitation–inhibition balance in depression before and after receiving rTMS therapy. The literature search was performed using PubMed in June 2026. Only papers published in English were reviewed. The following search terms were used: (transcranial magnetic stimulation OR rtms) AND (gamma aminobutyric OR gamma aminobutyric acid OR GABA OR gamma aminobutyric OR glutamates OR glutamic acid OR excitability OR excitable OR excitation OR excitations OR excite OR excited OR excites OR inhibit OR inhibitable OR inhibit OR inhibited OR inhibits OR inhibiting OR inhibition OR inhibitive) AND (depressed OR depression OR depressive disorder OR depressive OR depressive OR depressiveness OR depressives). We also identified additional articles by reference list/hand searching. Study eligibility was broad to compensate for the limited existing research, particularly the lack of randomized control trials. Preclinical and clinical studies on depression (including unipolar and bipolar depression) were included to broaden the search. There was no limit on the publication period. Microsoft Word Copilot was used for language editing (Microsoft® Word for Microsoft 365 MSO (Version 2610 Build 16.0.20527.20150) 64-bit).

3. Results

3.1. Excitation–Inhibition Imbalance Framework

The excitation–inhibition (E–I) imbalance is a conceptual framework proposing that disruptions in the balance between excitatory and inhibitory processes contribute to dysfunctional neural circuits in neuropsychiatric disorders. This theory was first proposed in 2003 when Rubenstein and Mezenich hypothesized that some forms of autism might be caused by disproportionately high levels of excitation (or weak inhibition) in neural circuits that mediate language and social behaviors [5]. E–I imbalance has since been explored as a framework for numerous other disorders, including Alzheimer's disease [6], schizophrenia [7], and major depressive disorder [8]. E–I balance is maintained by the interplay of systems operating at the molecular, cellular, and cortical levels. We consider each in turn before examining how each is altered in depression. In this review, E–I balance refers to a multiscale conceptual framework rather than a simple measurable biological ratio. It describes how excitatory and inhibitory processes interact within a defined spatial, temporal, and methodological context. Accordingly, molecular concentrations, cellular markers, cortical physiological responses, and network activity provide complementary but non-equivalent information about E–I regulation. Available methods indirectly assess specific E–I-related processes (Figure 1).

3.1.1. Molecular Level

At the molecular level, γ-aminobutyric acid (GABA) and glutamate are the principal inhibitory and excitatory neurotransmitters, respectively. Glutamic acid decarboxylase (GAD) is the enzyme responsible for GABA synthesis from glutamate. GAD is expressed in GABAergic neurons and is considered a marker for GABAergic activity. GAD67, an isoform of GAD, produces over 90% of the brain's basal GABA and is critical for neuronal function [9]. The inhibitory effect of GABA on nerve cells is achieved by stimulating the $GABA_A$ receptor, which is the drug target for benzodiazepines [10]. Reduced GAD

expression results in lower GABA synthesis and, together with reductions in GABA receptor expression or function, may contribute to impaired inhibitory neurotransmission. Glutamate is generated by the tricarboxylic acid cycle, which requires the carboxylation of pyruvate by pyruvate carboxylase to eventually form glutamine, which is converted to glutamate in the neuron [11]. The excitatory effect of glutamate is achieved by binding to receptors: ionotropic receptors such as N-methyl-D-aspartate receptors (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA), and metabotropic receptors (mGlu) [11]. Five high-affinity glutamate transporters are known: excitatory amino acid transporters (EAATs) 1 to 5, which are primarily responsible for glutamate uptake in the brain [11]. Alterations in pyruvate carboxylase, glutamate receptors, or transporter function would each be expected to affect cortical excitation.

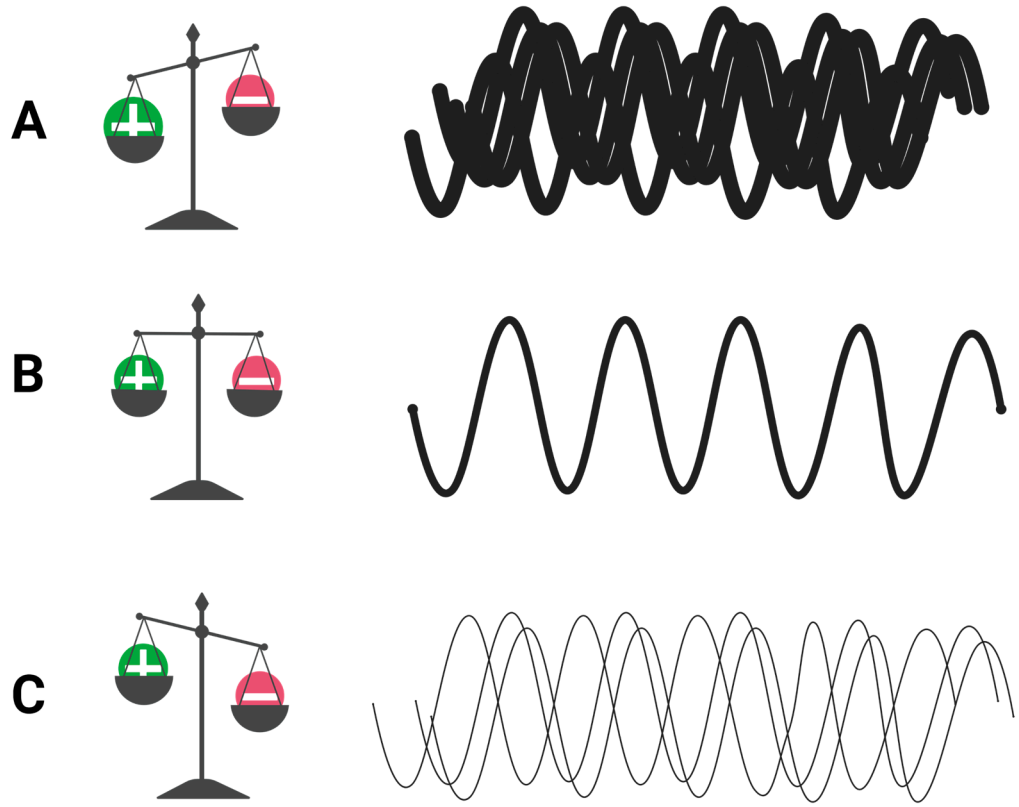


Figure 1. This conceptual diagram depicts the signal-to-noise ratio, with overlapping waveforms depicting noise and wavelength thickness depicting signal strength. (**A**) The noise ratio is elevated relative to signal. Increased excitation or decreased inhibition creates a hyperexcitable circuit with reduced efficacy of signal transmission. (**B**) The signal-to-noise ratio is balanced. Excitatory and inhibitory activity are balanced, and signal transmission is optimal. (**C**) The ratio of signal is low relative to noise. Decreased excitation or increased inhibition causes decreased efficacy of signal transmission. Created with BioRender.com.

3.1.2. Cellular Level

In the cerebral cortex, roughly 80% of the neurons are excitatory glutamatergic neurons and 20% are inhibitory GABAergic neurons [5]. The balance of excitation to inhibition in the cortex is controlled by the density and organization of synapses and relative numbers and activities of these glutamatergic and GABAergic neurons. According to Rubenstein and colleagues, these activity levels are regulated by extrinsic excitatory (glutamatergic thalamic afferents), mixed excitatory/inhibitory (serotonin, norepinephrine, dopamine and acetylcholine afferents from the hindbrain, midbrain, and basal forebrain, respectively), and exclusively inhibitory (from the zona incerta) inputs to the cortex [5].

3.1.3. Cortical and Network Level

Sohal and Rubenstein propose that E–I imbalance causes "noisy" circuits with less efficient information processing. "Noise" in this case indicates input that is not meaningful. If inhibition is too high, there is a reduced signal output relative to the noise. If excitatory activity is elevated, then noise is increased relative to the signal output. Therefore, both noise levels and signal strength need to be optimal for effective neural communication. E–I balance exists on a single-neuron level based on the numbers of inhibitory and excitatory synapses, as well as large-scale cortical circuits based on the relative numbers of inhibitory and excitatory cortical neurons. E–I balance is thus dynamic, in that the E–I ratio may vary between neurons and cortical regions while attempting to maintain overall cortical homeostasis [12]. E–I balance is not limited to a single neural network but involves the interplay of the activity of the entire brain. Inhibition in one area of the brain can result in excitation in another to maintain homeostasis of the overall system.

Interestingly, antidepressant therapy targets like serotonin and norepinephrine may produce their clinical effects through upstream alterations of GABA and glutamate, which may explain the delayed onset of clinical benefit [13]. GABA and glutamate may reflect potential endpoints where changes affect the depressive phenotype and could account for the clinical effects of rTMS, electroconvulsive therapy (ECT), and antidepressant therapy, which all interact with GABA and glutamate balance.

3.2. E–I Imbalance in Depression

Studies have found various alterations to GABAergic and glutamatergic systems at the molecular, cellular, circuit, and network levels in depression.

3.2.1. Molecular Level

In depression, studies of gene expression of GABAergic and glutamatergic components for neural circuitry suggest deficits in the GABA system, particularly the somatostatin (SST) GABA neurons, which regulate signal input [14]. Human post-mortem studies have reported decreased SST gene expression in the DLPFC, pregenual anterior cingulate cortex (PACC), and amygdala of MDD patients as compared with healthy controls [15–18].

GABA is an essential neurotransmitter for intercellular communication and is primarily derived from glutamate and GAD67. A preclinical study shows GAD67 gene removal is associated with substantial deficits in GABAergic transmission to pyramidal neurons in the prefrontal cortex and results in hyperexcitability, suggesting that levels of GAD67 directly affect the balance of excitatory and inhibitory activity in the brain [9]. Studies have found that GAD67 in the DLPFC is significantly decreased in patients with depression compared with matched controls [19]. Decreased density of GAD65 and GAD67 was also reported in the hypothalamic paraventricular nucleus and orbitofrontal cortex [20,21]. Other preclinical studies found decreased GAD67 in the medial prefrontal cortex and nucleus accumbens with an induced depression protocol [22,23]. These changes suggest impaired GABA synthesis and decreased inhibition at the affected brain regions (Figure 2).

In depression, there is impaired function of both $GABA_A$ and $GABA_B$ receptors, resulting in decreased inhibitory activity [24,25]. These changes are evidenced by deficits in short- and long-interval cortical inhibition (SICI, LICI), which are measured by transcranial magnetic stimulation (TMS) evoked electromyogram (EMG) potentials in the motor cortex and electroencephalogram (EEG) potentials in other cortical areas. SICI and LICI are indicators of $GABA_A$ and $GABA_B$ receptor inhibition, respectively.

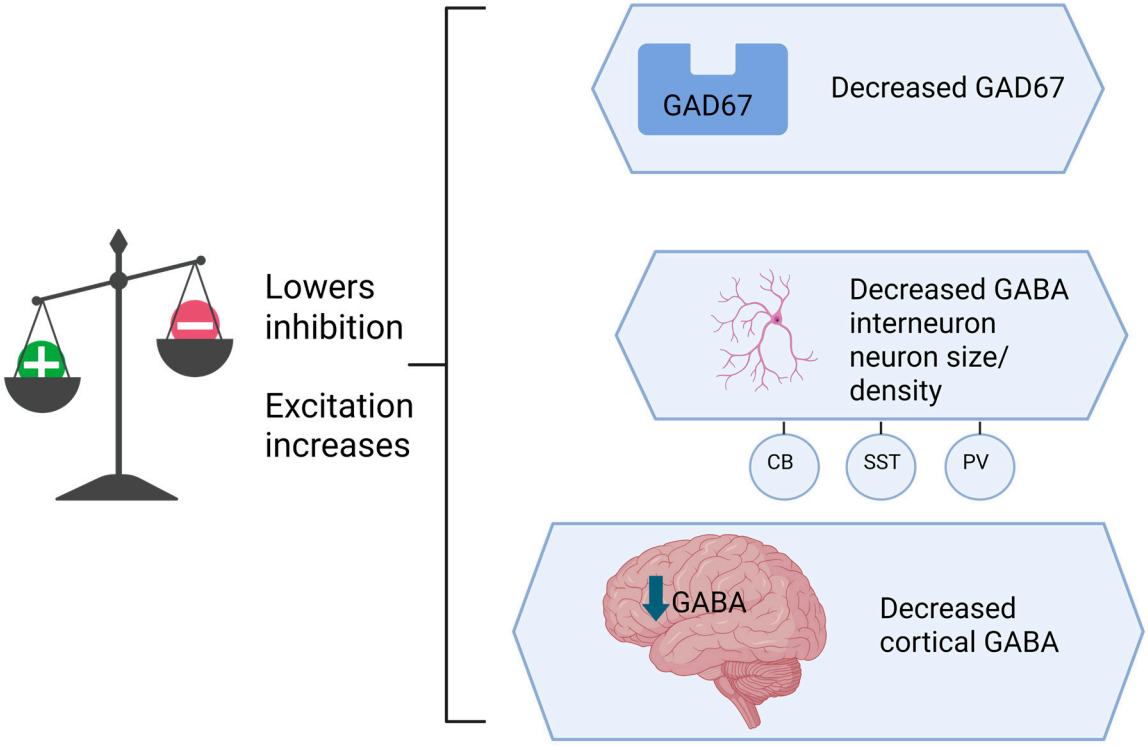


Figure 2. This conceptual diagram depicts decreased Glutamic acid decarboxylase (GAD) levels, decreased neuronal size and density, and decreased cortical inhibition, which may contribute to a hyperexcitable state. Created with BioRender.com.

3.2.2. Cellular Level

Neuronal size and density are indicators of neuronal activity, with decreased size and density corresponding to decreased activity levels. Several studies in patients with MDD have indicated a reduction in neuronal size in layers 5 and 6 of the anterior cingulate cortex (ACC), the DLPFC, and layers 2 and 3 of the orbitofrontal cortex (OFC) compared to healthy controls [26,27]. Another study found reduced neuronal soma size in MDD was present in all layers deep to layer 2 in the prefrontal cortex, with more marked reductions in layer 5 [28]. Cortical layers with a greater number of pyramidal neurons had greater reductions in size and density in MDD, suggesting that pyramidal neurons are particularly vulnerable [28] (Figure 3).

Reported neuronal density in patients with MDD varies based on brain region and cortical layer. In the ACC, neuronal density was increased in layer 5 [26,28] but decreased in layer 6 [26]. Glial densities were reduced in the DLPFC and OFC [27] and increased in the amygdala [29]. In a study by Cobb and colleagues, neuronal density in the hippocampus was not significantly different between patients with MDD and controls, but became significantly increased with the duration of illness [30].

In a post-mortem study, reductions were found in the average density and size of GABAergic cortical neurons in DLPFC in patients with MDD compared to controls [31].

3.2.3. Circuit and Network Levels

Patients with MDD exhibit altered cortical brain activity and neurochemistry compared with healthy controls. Specifically, decreased GABAergic activity is a well-replicated finding in depression. Numerous studies have also documented reduced GABA concentrations in the cerebrospinal fluid (CSF) [32–34] and plasma [35] of depressed patients. In vivo magnetic resonance spectroscopy (MRS) has more recently demonstrated region-specific reduction of GABA levels in the occipital cortex (OC) [36–39] in treated and untreated

depressed patients [36,40] and in the prefrontal cortex (PFC) [41,42] and ACC [37,42–44] of depressed patients. These studies demonstrate reduced GABA levels in the OC, PFC, and ACC of depressed patients, which could represent a net reduction in cortical inhibition in these areas and contribute to the depressive phenotype.

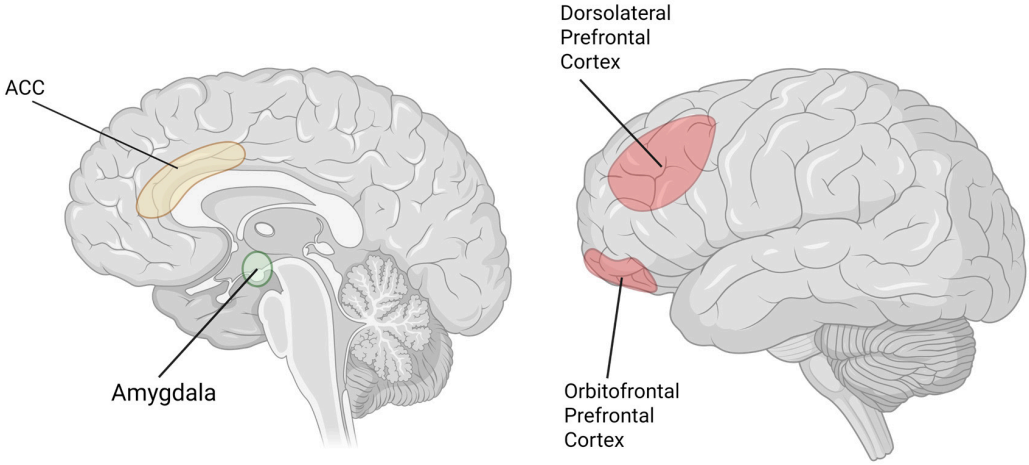


Figure 3. This diagram shows areas of altered neuronal size and density in patients with Major Depressive Disorder (MDD). dorsolateral prefrontal cortex (DLPFC) and orbitofrontal prefrontal cortex (OFPFC) have decreased neuronal size and density in layers 2 and 3, while the amygdala has increased neuronal density. The Anterior Cingulate Cortex (ACC) exhibited decreased neuronal density in layer 6 but increased in layer 5, with reductions in neuron size in both layers 5 and 6. Created with BioRender.com.

Interestingly, one study noted that GABAergic abnormalities were dependent on the depressive subtype [36]. According to that study, the largest and most consistent GABA reductions were reported in patients with melancholic features, whereas GABA concentrations were normal or near-normal in most patients with atypical depression [36] A few small studies support stratified GABA abnormalities by subtype. In a study by Roy and colleagues, there was a significant difference in CSF GABA concentrations in depressed and control subjects, but only when they limited the analysis to melancholic patients against controls [36]. A study by Petty and colleagues reported that the lowest concentrations of GABA appeared in subjects with melancholic depression [45]. These findings suggest that different depressive phenotypes may have different underlying neurophysiological imbalances, and may require targeted interventions for each subtype (Figure 4).

While studies in GABAergic changes in depression have been consistent in their direction across brain regions, glutamatergic changes vary by brain area and are less consistent. Several studies have suggested that plasma glutamate levels are elevated in depressed patients compared with healthy controls [46–48]. Similar to GABA, there is some evidence that the differences between these groups can be corrected with antidepressant therapy [49,50]. In the ACC, studies found decreased glutamate levels [51–54], which were reversed with ECT treatment [51]. In the CSF, results have been mixed [55,56]. Decreased levels are also present in the DLPFC of depressed patients [42,57,58] and animals [59] but are elevated in the OC [36]. In contrast, one post-mortem study found increased glutamate levels in the frontal cortex of unipolar and bipolar patients compared with controls; however, patients were not necessarily depressed at the time of death [60]. A meta-analysis found a significant decrease in glutamate in the frontal lobe of depressed adults [61] (Figure 5).

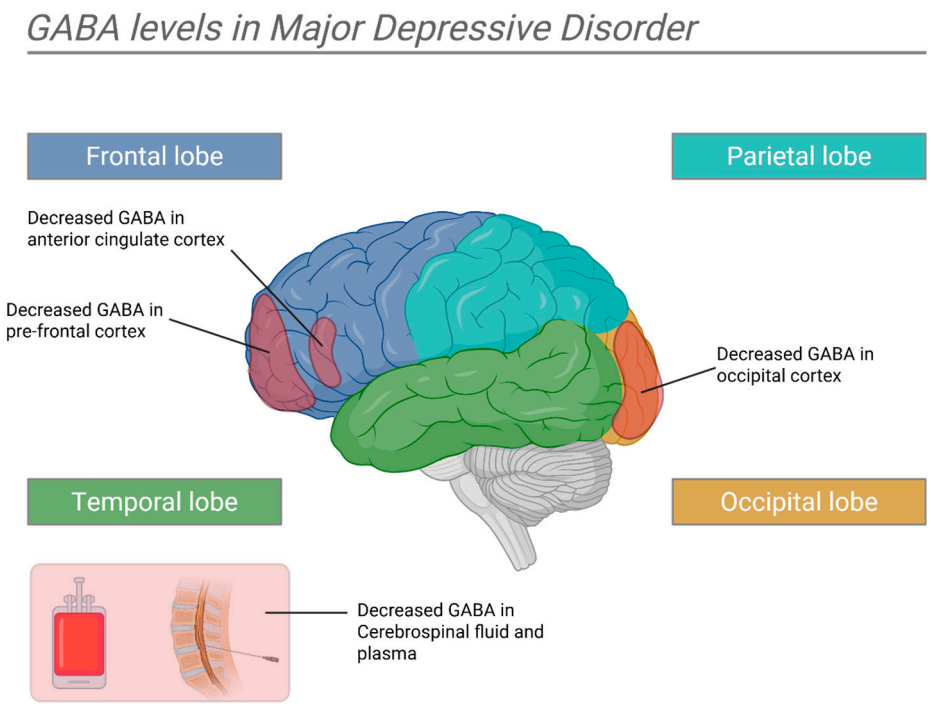


Figure 4. This diagram summarizes GABA level changes in depression. GABA levels are decreased in the frontal and occipital cortices and Cerebrospinal fluid (CSF) in Major Depressive Disorder (MDD). Created with BioRender.com.

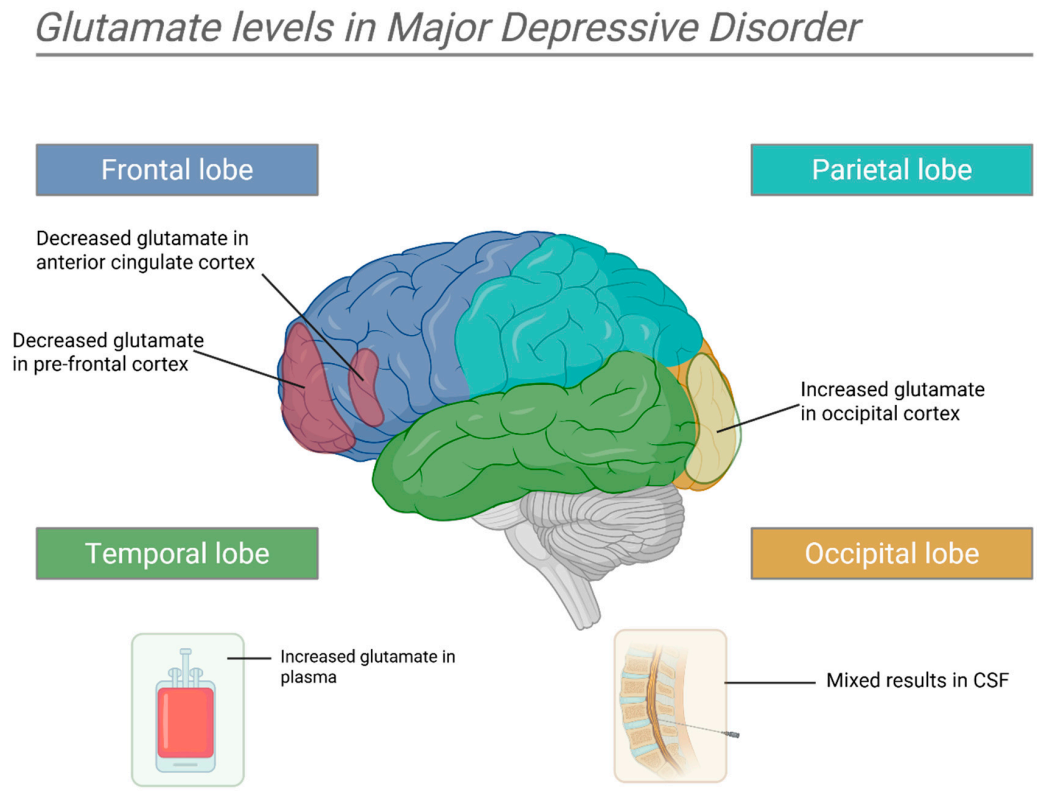


Figure 5. This diagram summarizes glutamate level changes in depression. Glutamate levels are decreased in the Anterior Cingulate Cortex (ACC) and Prefrontal Cortex (PFC) and increased in the Occipital Cortex (OCC) and plasma. Created with BioRender.com.

In summary, there is evidence that patients with depression have decreased plasma and cortical GABA levels, including in the DLPFC, ACC, and OC. Glutamate levels are increased in the plasma and OC and decreased in the ACC and DLPFC, although evidence is less consistent. Both imbalances have shown some evidence of reversal through antidepressant therapy and ECT.

3.3. Effect of rTMS on E–I Imbalance in Depression

rTMS has notable effects on the balance of excitatory and inhibitory activity at the molecular, cellular, and cortical levels. Adjusting this balance may optimize the signal-to-noise ratio in synaptic transmission. If rTMS can restore a favorable signal-to-noise ratio in neural communication by altering the E–I balance in individuals with depression, with clinical response to rTMS, it would support the hypothesis that the mechanism for clinical improvement in rTMS is mediated by correcting E–I imbalance.

Studies indicate that low-frequency rTMS (≤1 Hz) increases inhibition in the stimulated cortex [62] whereas high-frequency rTMS (>1 Hz) increases excitation [63]. One proposed mechanism of action for the therapeutic effects of rTMS in depression is the restoration of the balance between excitatory and inhibitory neural circuits. By applying rTMS to stimulate inhibitory or excitatory activity in these areas of the brain, it is hypothesized that the favorable E–I balance may optimize the signal-to-noise ratio of synaptic transmission, thus improving clinical symptoms (Tables 1 and 2).

3.3.1. Gene Expression

In a study on mice, rTMS altered the expression of genes encoding neurotransmitter transporters for glutamate, GABA, and glycine [64]. rTMS-treated mice showed upregulation of these transporters, which may alter the balance of excitatory and inhibitory activity. Another small animal study found that genes such as *Metrn* and *Map1b*, which are associated with neurogenesis, were enriched by repetitive sessions of low-frequency rTMS [65].

3.3.2. Molecular Markers

An animal study from Zorzo and colleagues found that cytochrome c oxidase activity, a marker of metabolic activity, and c-Fos, a marker of neuronal activity, were increased in limbic areas of the brain three days post-rTMS [66].

Brain-derived neurotrophic factor (BDNF) is a marker of synaptic plasticity known for its functions in neurogenesis, migration and differentiation of neurons, the growth of dendrites and axons, and synapse formation [67]. rTMS has been found to increase BDNF levels in depressed patients, indicating changes in neuronal architecture [68].

3.3.3. Enzyme Regulation

Evidence that rTMS alters GAD expression is mixed and appears to be protocol-dependent. Some evidence suggests that rTMS alters GAD67 and GAD65 expressions. One animal study reported that intermittent theta-burst stimulation (iTBS), continuous theta-burst stimulation (cTBS), and low-frequency rTMS each produced an acute decrease in frontal-cortex GAD67 followed by a strong and sustained increase lasting up to seven days; changes in GAD65 depended on the protocol, with low-frequency stimulation producing steady increases while iTBS- and cTBS-induced changes reversed within a day [68]. GAD67 upregulation post-rTMS has also been reported in other regions, including the globus pallidus [69]. Some studies have found evidence of reduced GAD67 expression post-rTMS.

One study found that iTBS in rats led to reduced GAD67 expression, while cTBS was associated with the upregulation of GAD65. Interestingly, this study found that learning a tactile task during iTBS weakened the decrease in GAD67 in rats, indicating sensory activity

interfered with the iTBS effect. Other studies corroborate findings of decreased GAD67 expression post-rTMS [70–73].

Transient reductions in GAD67 expression may facilitate excitatory plasticity before homeostatic mechanisms restore inhibitory function. Overall, these studies suggest rTMS may alter GAD67 expression and GABAergic inhibition.

3.3.4. Cellular Level

Animal studies in rats have found an increase in synaptic density in the hippocampus post-rTMS and increased synaptophysin (SYN) levels—a biomarker associated with increased synaptic density [74].

An animal study found that rTMS after subacute cerebral ischemia increased Bcl-2-expressing cells, which are known to decrease apoptosis, and decreased Bax-expressing cells, which are known to increase apoptosis, in the peri-ischemic area compared to controls [75].

Parvalbumin (PV) and calbindin (CB)-expressing interneurons are involved in the feedback inhibition of pyramidal cells. Studies have found a general hypoactivity and reduced number of PV- and CB-expressing interneurons post-iTBS, leading to lower basal inhibitory activity caused by decreased excitatory inputs to these interneurons [70–73].

3.3.5. Receptor Number and Function

GABA and NMDA receptors play a role in long-term potentiation (LTP) and long-term depression (LTD)—long-term increases or decreases in neuronal signal strength. These changes are thought to be key mechanisms in changes in post-neural stimulation. Binding glutamate to NMDA receptors induces a cascade of changes resulting in increased glutamate sensitivity and upregulation of glutamate receptors, leading to LTP. rTMS has been found to decrease both $GABA_A$ and $GABA_B$ receptor activity and increase NMDA receptor activity.

rTMS increases the expression of neuronal NMDA receptors in the ventromedial thalamus [76]. High-frequency stimulation leads to upregulation of the AMPA receptors consistent with long-term potentiation [77]. rTMS also reduced 5-HT2 receptors, similar to antidepressant therapy [78].

Neurophysiological markers of GABA receptor-mediated inhibition, N45 and N100, are altered post-rTMS. N45 and N100 refer to negative transcranial magnetic stimulation evoked potentials (TEPs) recorded on EEG, which peak at 45 and 100 msec, respectively, and have been hypothesized to reflect GABA receptor activation based on animal studies. N45, associated with $GABA_A$ receptor activation, decreased in patients post-rTMS. N100, which is associated with $GABA_B$ receptor activation, decreased concordantly with depressive symptoms. These changes were not induced by sham treatment [79]. These markers are, however, sensitive to artifacts generated by the TMS equipment. Noise, physical sensation, and cranial muscle activation from the rTMS coil contaminate these signals and may limit interpretation. In patients with spinal cord injuries, it was found that GABA receptors were upregulated post-rTMS [80]. In rats, isolation induced upregulation of GABA(A) receptors in the hippocampus, which was reversed by rTMS [81]. In a study of patients with unipolar or bipolar depression, no significant changes were found in $GABA_A$ receptor availability post iTBS [82].

3.3.6. Cortical Level

The neurophysiological effects of rTMS are an ongoing area of research. There are two methods available to investigate the neurochemical changes in the brain evoked by rTMS. The first is proton magnetic resonance spectroscopy (MRS). MRS is a non-invasive technique based on nuclear magnetic resonance (NMR) that can measure in vivo biochemical or metabolite concentrations in localized areas [83]. The second method is using transcranial

magnetic stimulation combined with electromyography (EMG) or electroencephalography (EEG). Cortical inhibition by GABA inhibitory neurons can be measured by delivering a paired-pulse TMS to the target cortical region and measuring the suppression of motor evoked potentials via EMG or resulting TEP waveforms on EEG. While TMS–EMG is limited to the motor cortex, TMS–EEG can measure inhibition in other cortical areas. Different TMS paradigms, such as long interval cortical inhibition (LICI) or cortical silent period (CSP), are thought to reflect $GABA_B$ receptor inhibitory neurotransmission, while short interval cortical inhibition (SICI) reflects inhibition through $GABA_A$ receptors [84]. Applying these tools to different brain regions in individuals pre- and post-rTMS allows us to monitor GABAergic and glutamatergic changes.

GABA

MRS studies have been conducted in various brain regions and patient samples. These studies are limited by their small sample sizes, but in summation, they can provide clues about the neurochemical changes occurring with rTMS. Various areas of the prefrontal cortex have been studied. The medial prefrontal cortex (mPFC) shows an increase in GABA levels post-rTMS in both unipolar and bipolar depression [85,86]. In patients with treatment-resistant depression, GABA levels in the left DLPFC did not change post-rTMS [87], while another study found an insignificant increase [88]. In the right DLPFC, GABA decreases in response to rTMS were insignificant. GABA levels in the ACC have not shown a significant decrease post-rTMS [88]. In the basolateral amygdala of mice which underwent a protocol to mimic posttraumatic stress disorder (PTSD) symptoms, GABA levels increased post-rTMS treatment [89]. In a group of healthy males who underwent rTMS, GABA levels were elevated post-rTMS in the primary motor cortex [90], but the changes were not significant in a study conducted in healthy mice [91]. Two other animal studies examined hippocampal changes post-rTMS—one finding increased GABA levels and the other finding a decrease [92,93]. In addition, one of these studies found decreased GABA levels in the hypothalamus, no change in the midbrain, and increased levels in the striatum [93].

Bourla and colleagues showed that an increase in resting motor threshold during rTMS therapy may predict response to treatment [94]. This is relevant because an increase in resting motor threshold has been attributed to improvement in GABAergic activity in the brain [95] (Figure 6).

Glutamate

Similar to GABA, changes in the concentration of glutamate in various brain regions have been explored with MRS. These studies face similar limitations due to small sample sizes. Glutamate is an excitatory neurotransmitter in the brain, and in these studies, changes are typically expressed as either glutamate alone or Glx (glutamate + glutamine). While glutamine is an inactive metabolite rather than an excitatory neurotransmitter, the acid hydrolysis generally used in the sequencing of amino acids converts glutamine into glutamate. Therefore, labs are unable to determine the original molecule, and they are measured together. Glutamine and glutamate also exhibit similar radio frequencies, making them difficult to separate on MRI and are instead grouped together. As a result, changes in Glx may not accurately reflect changes in glutamate and should be interpreted cautiously.

In the mPFC, one study reported no change in glutamate levels in response to rTMS [85]. In adults with depression, a study found that lower pre-rTMS glutamate concentrations in the left DLPFC predicted response to treatment. Moreover, rTMS resulted in an increase in DLPFC glutamate in responders [96]. An additional study of adults with treatment-resistant depression found a decrease in Glx levels in the ACC post-rTMS, but these results were not significant [88]. Several studies examined the change in the left DLPFC post-

rTMS. One study found Glx levels significantly increased in the left DLPFC post-rTMS in patients with treatment-resistant depression; however, this increase did not correlate with treatment response [97]. Two studies found a non-significant increase in Glx post-treatment [87,88]. In the right DLPFC, one study found an insignificant increase [88]. A study of mice under a protocol to induce PTSD symptoms, rTMS, led to decreased glutamate in the amygdala [89]. In the hippocampus, two studies found rTMS in rats led to significantly elevated glutamate [92,93]. In the sensorimotor cortex, two studies found no significant changes in Glx post-rTMS [90,91]. One of these studies did find that glutamine levels increased significantly, but the effects were transient and returned to baseline after 2 weeks [91]. In the striatum, a study of rats found a significant increase in glutamate post-rTMS [93]. The same study found no changes in glutamate levels in the midbrain, but a significant decrease in the hypothalamus. A 2024 meta-analysis of rTMS and MRS studies showed rTMS in clinical responders increased glutamatergic metabolites [98]. A meta-analysis of MRS studies across depression treatment modalities, including pharmacotherapy, ketamine, rTMS, and ECT, found significantly increased prefrontal Glx levels after treatment among responders [99].

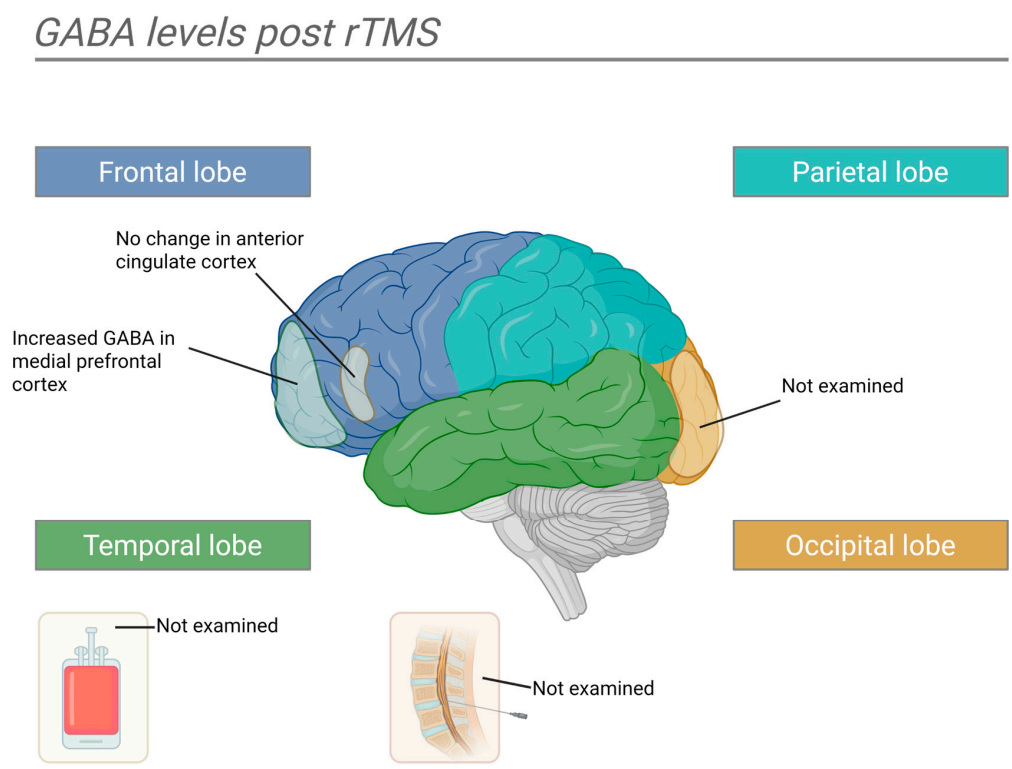


Figure 6. This diagram summarizes GABA level changes after rTMS therapy. GABA levels increase in the medial prefrontal cortex post-rTMS, while changes in the Dorsolateral Prefrontal Cortex (DLPFC) were mixed or non-significant. Created with BioRender.com.

Table 1. Summary of pre-clinical studies examining changes in excitatory and inhibitory neural systems post-rTMS. Studies are listed in chronological order of publication.

Study	Population	Sample Size	Control	Stimulation Protocol	Brain Region	Measurement Method	Assessment Timing	Principal Findings
Ben Schacher D. et al. (1999) [78]	Adult male rats	40	Sham rTMS	15 Hz for 3.5 s daily for 10 days	Whole brain	High-performance liquid chromatography analysis	4 h post rTMS	β-adrenergic receptors upregulated in the frontal cortex. 5HT2 receptors down-regulated in the frontal cortex
Kole et al. (1999) [76]	Adult female rats	11	Sham rTMS	20 Hz for 3 s	Parietal area	Scintillation proximity radioimmunoassay	24 h after stimulation	Increased density of 5HT1A binding sites in frontal cortex, ACC, and anterior olfactory nucleus compared to sham. Increased NMDA binding sites in ventromedial hypothalamus
Stagg C.J. et al. (2009) [90]	Healthy adult males	16	Sham rTMS	One cTBS session—for 600 pulses	Left primary motor cortex (M1)	MRS	20 min post-TBS	Increased GABA post-rTMS compared to control, no change in Glx
Trippe J. et al. (2009) [68]	Adult male rat	18	Sham rTMS	iTBS (3000 pulses), cTBS (3000 pulses), or 1 Hz stimulation (3600 pulses)	Interhemispheric cleft 8 mm above the rat's occipital cortex	Immunohistochemical analysis	1, 3, or 7 days following rTMS	All protocols increased the expression of GAD65 and GAT-1 in frontal, motor, somatosensory, and visual cortex. GAD67 had an initial decrease, which reversed after 1 day, leading to a strong increase in GAD67
Yue L., Xiao-lin H., and Tao S. (2009) [93]	Adult rats	16	Sham rTMS	500 pulses of 0.5 Hz rTMS for 15 days	Whole brain	High-performance liquid chromatography	Immediately after last rTMS treatment	Increase in glutamate and GABA in hippocampus and striatum after chronic rTMS, but decreased in the hypothalamus
Benali A. et al. (2011) [70]	Adult male rats	68	Sham rTMS	One low-frequency rTMS protocol (1 Hz, 3600 pulses) and two high-frequency theta-burst protocols (iTBS and cTBS, 3000 pulses)	8 mm above the occipital pole of the rat's brain	Immunohistochemistry, western blot, PCR	2 h as well as 1, 3, and 7 days post rTMS	iTBS reduced PV expression in fast-spiking interneurons; cTBS reduced CB expression

Table 1. *Cont.*

Study	Population	Sample Size	Control	Stimulation Protocol	Brain Region	Measurement Method	Assessment Timing	Principal Findings
Yoon K.J., Lee Y.T., and Han T.R. (2011) [75]	Adult male rats with an induced transient focal infarction at the MCA	20	Sham rTMS	rTMS starting 4 days post-ischemia for 10 sessions over 2-week period. 10 Hz, 3500 total pulses	Motor cortex	Immunohistochemistry and Western blot	Post-op day 18 (from induced occlusion)	Increased antiapoptotic Bcl-2 and fewer Bax cells in rTMS group
Vlachos et al. (2012) [77]	3–4-week-old mouse organotypic entorhino-hippocampal slice cultures (mature hippocampal CA1 pyramidal neurons)	23	Non-stimulated control	Nine trains of 100 pulses at 10 Hz	1 cm below coil	Immunostaining, time-lapse imaging, whole-cell patch-clamp recordings	20 min post rTMS	Enlargement of dendritic spines of pyramidal neurons in stratum radiatum. Increased AMPA subunit GluA1
Hoppenrath K. and Funke K. (2013) [71]	Adult male rats	42	Sham rTMS	iTBS (number of pulses not reported)	10 mm above the head with the handle oriented at a right-angle to the head–body axis	Immunohistochemical analysis	10, 20, 40, 870, or 160 min after iTBS	Early phase (20 min) upregulation of c-Fos and GAD65, followed by subsequent (40 min) decrease in GAD67, CB, and PV. GAD65 and c-Fos then decreased at 160 min
Volz L.J. et al. (2013) [72]	Adult male rats	36	Sham rTMS	cTBS or iTBS with 600, 1200, 1800, or 2400 pulses.	Coil was centered 10 mm above the interhemispheric cleft of the occipital forebrain	Immunohistochemistry, western blot	60 min post rTMS	Both iTBS and cTBS caused a significant increase in GAD65, while GAD67 and calcium-binding proteins, pavalbumin, calbindin, and c-fos, progressively decreased
Gao W. et al. (2015) [80]	Adult male rats	50	Normal control	10 Hz starting 8 or 15 days post SCI. 1000 pulse stimulations 5 days per week for 4 weeks	Center of cranium	Western blot, PCR	4 weeks post rTMS treatment	GABAa and GABAb receptors were downregulated in SCI. GABAa and GABAb receptors were upregulated in the spine, cerebral cortex, hippocampus, and cerebellum of the rTMS group
Thimm A. and Funk K. (2015) [73]	Adult male rats	32	Sham rTMS	cTBS or iTBS, 3000 pulses	Corpus callosum	Immunohistochemical analysis	3.5 h post rTMS	Enhanced c-fos expression but reduced PV and GAD67 expression only after iTBS

Table 1. *Cont.*

Study	Population	Sample Size	Control	Stimulation Protocol	Brain Region	Measurement Method	Assessment Timing	Principal Findings
Tan T. et al. (2018) [81]	Adult male rats	4 groups with 10–20 per group	Sham rTMS	LF-rTMS, 1 Hz, 1500 pulses daily for 2 weeks	Placed over the intersection of the midline and interocular line	Western blot, electrophysiology study, behavioral tests	4 days post rTMS treatment	Rats subjected to neonatal isolation displayed autistic-like behaviors and had increased GABAa receptors and VGAT1. GABAa receptors and VGAT1 were effectively downregulated by rTMS, and the behaviors resolved
Ikeda T. (2019) [64]	Male mice	50	Sham rTMS	20 Hz for 2 s, 20 times per day	Whole brain	Gene expression analysis by RT-PCR	1, 20, 30, or 50 days of rTMS, then analyzed 1, 4, 12, and 24 h after	Upregulation of EAAT4, GLAST, GLT-1, GAT2, GAT4, GLYT1, and GLYT2
Li Y., Li L., and Pan W. (2019) [74]	Adult male rats	16	Sham rTMS	Daily rTMS for 15 days, consisting of 500 pulses per day at 0.5 Hz	Tangential to the parietal bone and parallel to the midline	qRT-PCR and transmission electron microscopy	Immediately after the last rTMS treatment	rTMS group had increased synaptic density and SYN expression compared to sham
Seewoo B.J. et al. (2019) [91]	Adult rats	18	None	Daily rTMS at 10 Hz or 1 Hz for 15 days	Between right eye and ear	MRS, fMRI	Baseline and days 7 and 14 of daily stimulation	Increase in Glx and GABA, which returned to baseline in the 10 Hz group after 14 days, while 1 Hz stimulation group had a sustained decrease in cortical Glx, Glu, and Gln at 14 days
Zorzo C. et al. (2019) [66]	Male young rats	28	Sham rTMS	10 min trains of 100 Hz lasting 30 s each with 30 s intertrain intervals for 3 consecutive days	Upper skull midline (5.04 mm and bregma −3.94 mm)	Quantitative Cox histochemistry	90 min after last stimulation session	Enhanced metabolic activity after rTMS in the retrosplenial and parietal cortex and CA1 and CA3 subfields of the hippocampus as well as elevated c-Fos levels
Xu X. et al. (2021) [92]	Male mice, 3 groups—control, hindlimb unloading (simulates microgravity for space flights), hindlimb unloading + rTMS	25	Sham rTMS	Daily rTMS for 14 days, 300 pulses at 15 Hz	Parallel to parietal bone	Western blot, behavioral tests	After behavioral tests, 14 days post-rTMS	Glutamate was decreased, and GABA was increased by HU. rTMS reversed these changes, increasing glutamate and decreasing GABA, GAD67, and GABA receptors in the hippocampus

Table 1. *Cont.*

Study	Population	Sample Size	Control	Stimulation Protocol	Brain Region	Measurement Method	Assessment Timing	Principal Findings
Hwang W. et al. (2022) [65]	Adult male rats	8	Sham rTMS	Single session or 5 consecutive days of left unilateral rTMS at 1 Hz	Left hemisphere	Microarray analysis	5 min after single session or 60 min after repeated session	Positive regulation of axonal extension, axonogenesis, intracellular transport, and synaptic plasticity were among the overrepresented gene ontology categories following repeated sessions of low-frequency rTMS
Wang N. et al. (2023) [69]	Pregnant rats	48 rats	Sham rTMS	High-frequency rTMS (10 Hz, 960 pulses) for 7 days	Coil was placed horizontally above each head, in close proximity to the scalp	Rotarod test, western blotting, and immunohistochemical staining	Analyzed 14 days after rTMS and 28 days postnatally	rTMS mitigated the negative effects of bilirubin on the general health of kernicterus-model rats and improved their growth and development. Increased the expression of GABAergic neuronal marker GAD67 in the globus pallidus
Claverie D. et al. (2024) [89]	Adult male mice. Half randomized to conditioning to induce PTSD like symptoms	58	Healthy control	5 sessions from day 8–12 with 24 h between sessions. 12 Hz, 750 pulses per session for 3750 total pulses	rTMS coil was positioned tangential to the skull and centered on the interhemispheric line, at Bregma +2 mm,	PCR	Day 23	Lowered mRNA-related glutamate neurotransmission and increased GABA neurotransmission in the basolateral amygdala

Table 2. Summary of clinical studies examining changes in excitatory and inhibitory neural systems post-rTMS. Studies are listed in chronological order of publication.

Study	Population	Sample Size	Control	Stimulation Protocol	Brain Region	Measurement Method	Assessment Timing	Principal Findings
Dubin M.J. (2016) [85]	Patients with depression	23	None	25 daily sessions of rTMS at 10 Hz, 3000 pulses	Left DLPFC	H MRS, HAMD24	Baseline and 5 weeks following rTMS	GABA in mPFC increased. No effect on Glx
Baeken C., Lefaucher J.P., and Van Schuerbeek P. (2017) [88]	Patients with unipolar treatment-resistant depression	18	Sham rTMS	High-frequency accelerated rTMS. 20 Hz, 5 sessions/day for 4 days. 1560 pulses per session	Left DLPFC	MRS	Baseline, end of first week, end of second week	TRD patients had decreased baseline glutamate compared to controls in the left DLPFC. rTMS did not significantly change neurochemical concentrations, but clinical improvement was related to increased GABA in the left DLPFC.

Table 2. *Cont.*

Study	Population	Sample Size	Control	Stimulation Protocol	Brain Region	Measurement Method	Assessment Timing	Principal Findings
Bhattacharyya P. et al. (2021) [87]	Patients with MDD and inadequate response to at least one antidepressant	12	None	10 Hz 5 times per week for 6 weeks for 3000 pulses daily	Left DLPFC	MRI	1 week prior to rTMS and 1 week after 6-week treatment.	No significant changes in Glx/tCr or GABA/tCr were observed as a result of rTMS therapy
Diedrichs C. et al. (2021) [86]	Adults with bipolar I or II in a depressive episode with failed first-line treatment on a stable mood stabilizer dose	18	Sham rTMS	One session of iTBS, 600 pulses per session	Left DLPFC	3T MRS, MADRS, HAMD, SHAPS	Baseline and 4 weeks post-treatment	Increased GABA in mPFC in iTBS but not in the sham group, but was not associated with an antidepressant effect
Godfrey et al. (2021) [97]	Patients in a treatment-resistant unipolar or bipolar depressive episode	31	None	Weekday rTMS for 4 weeks. 10 Hz, 4000 pulses per day	Left DLPFC	MRS	Baseline and after rTMS treatment	Glx increased following rTMS. No difference in GABA observed
Voineskos D. et al. (2021) [79]	Patients with treatment-resistant depression	30	Sham rTMS	Sequential bilateral or HFL-rTMS for 6 weeks, 5 days per week	Left motor cortex and DLPFC	TMS EEG	1 week prior to treatment and 48 h after last session	N45 and N100 decreased after rTMS, but not sham. TEP amplitudes decreased after rTMS in left and right DLPFC, but not sham
Bourla A. et al. (2023) [94]	Adult patients receiving rTMS for TRD (failure of 2 antidepressants)	30	None	10 HZ 3000 pulses on Left DLPFC; 1 Hz 1500 pulses on right DLPFC; theta burst was 1800 pulses on left DLPFC on weekdays for 6 weeks	Left or right DLPFC	GAD7, PHQ9, MT	PHQ/GAD at baseline and end of treatment, MT weekly	Symptoms improved in all groups, but greater in the high frequency and theta burst group. MT increased over the course of treatment, but was only statistically significant in the remission group
Steinholtz L. et al. (2025) [82]	Patients with unipolar or bipolar depression	42	Sham rTMS	Theta-burst stimulation twice daily for 10–15 consecutive weekdays (2400 pulses daily)	Dorsomedial prefrontal cortex	MRS, PET, MADRS-S	One weekday before the treatment onset and again four weeks later	No significant changes in neurotransmitter levels or GABAA-receptor availability post-iTBS. However, changes in MADRS-S scores after active iTBS were positively correlated with changes in GABA levels in the dACC and baseline GABAA-receptor availability in the nucleus accumbens

4. Discussion

This study examines E–I balance as a model for the neurophysiologic mechanism underlying rTMS in the treatment of depression. Current literature suggests dysregulation of excitatory and inhibitory balance in depression, with an overall decrease in inhibitory activity and a hyperactive state. This is reflected by changes in GABA, such as decreased levels of GAD67, the enzyme responsible for GABA synthesis; impaired GABA receptor function; decreased cortical GABA, particularly in the ACC, PFC, and OC. Overall neuronal size and density are also decreased in depressed patients.

E–I-related processes may contribute to rTMS effects, but whether normalization causally mediates these effects remains unclear. Several rTMS-induced changes are consistent with a reversal of this hyperexcitable state, most directly the increases in cortical GABA observed across multiple regions on MRS, alongside increased synaptic density and elevated markers of neuroplasticity such as BDNF. At the same time, the mechanistic picture is not uniform. Some molecular and receptor-level findings in animal studies—including protocol-dependent reductions in GAD67, reduced PV/CB interneuron activity after iTBS, and decreased $GABA_A$ and $GABA_B$ receptor activity—point in the opposite direction, and standard high-frequency rTMS to the left DLPFC is itself an excitatory protocol. These apparent contradictions may reflect genuine regional and protocol-specific heterogeneity in how rTMS reshapes E–I balance, differences between local and network-level effects, and varied models and time points across studies. An adequate mechanistic account will need to reconcile increased cortical GABA with the co-occurring reductions in some inhibitory markers, rather than treating the evidence as uniformly supporting increased inhibition.

Applying the E–I balance model to rTMS highlights potential markers for identifying patients who stand to benefit from rTMS and a means of monitoring their response. If rTMS improves depressive symptoms by restoring E–I balance, then patients with depressive symptoms who do not have this underlying imbalance may be less likely to benefit. On the contrary, it could be hypothesized that patients with a profound imbalance may be more likely to have a meaningful response. This hypothesis invites the development of well-designed clinical studies assessing the change in depressive symptoms post-rTMS in depressed patients with and without evidence of altered excitatory or inhibitory activity to investigate the relationship between E–I balance and the depressive phenotype. TMS EEG measures such as SICI, LICI, and CSP, as well as neurophysiological changes identified on MRS such as cortical GABA, GAD enzymes, and GABA receptors, offer objective markers that may provide the means to identify and monitor E–I imbalance. Other antidepressant therapies such as ECT, pharmacotherapy, and even psychotherapy show evidence of interacting with E–I balance, and characterizing how rTMS interacts with this system may offer insights into tailoring other interventions.

The proposed E–I framework generates some testable predictions. First, if restoring E–I balance contributes to the antidepressant mechanism of rTMS, changes in E–I balance should precede improvement in depressive symptoms. Randomized controlled trials studies assessing E–I-related measures at baseline, during treatment, and following treatment could help clarify whether changes in these measures contribute to the antidepressant effects of rTMS. Improvement in depressive symptoms without changes in E–I-related measures, or changes in these measures without clinical improvement, would challenge the hypothesis that modulation of E–I-related processes mediates the antidepressant effects of rTMS. E–I-related changes should also be significantly greater in the treatment group than in the sham group. Second, early changes in E–I-related measures should be associated with and may predict subsequent clinical response to rTMS therapy.

Several limitations impact the ability to draw conclusions regarding E–I balance in rTMS. First, a major limitation of the current evidence is that E–I-related abnormalities in

depression and changes in E–I measures after rTMS do not show that these changes mediate clinical improvement. Most studies rely on within-group changes, symptom correlations, or responder subgroup analyses, none of which can establish causality. Moreover, the studies are limited in number, sample size, and methodological rigor. Larger samples with longitudinal randomized controlled trials examining markers of E–I balance before and after rTMS in patients with depression in both responders and non-responders would better evaluate the role of E–I imbalance restoration in the treatment of depression with rTMS, but without sham-controlled longitudinal designs, temporal precedence, and formal mediation analyses. Future studies should aim to characterize changes to the glutamatergic and GABAergic systems in depression and perform systematic assessments of GABA and glutamate changes before, during, and after rTMS. Following these changes over time would determine if these changes were sustained. While patterns of GABA dysregulation in depression may be indicated, the pattern of other key neurotransmitters like glutamate needs more investigation. Studies of E–I imbalance in depression vary widely, so their findings should be interpreted in light of each method's limitations. MRS estimates regional brain concentrations of GABA and glutamate but cannot distinguish between intracellular and extracellular levels. Moreover, MRS does not directly measure synaptic release, receptor-mediated inhibition, or a functional E–I ratio. Similarly, TMS–EEG measures such as N45/N100 and TMS–EMG measures such as SICI/LICI are associated with GABA receptor function but do not directly measure it. One potential limitation to future studies is the impact of other antidepressant treatments, such as pharmacotherapy, confounding changes in the E–I balance.

While findings are mixed and adequately powered, longitudinal, controlled studies are required; the available evidence is broadly consistent with an E–I model of rTMS in depression.

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