

Baseline Synaptic Configuration and Post-Stimulation Retention Under Homeostatic Scaling: A Reduced Model Motivated by Repetitive Transcranial Magnetic Stimulation

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ABSTRACT

Patients respond to a course of repetitive transcranial magnetic stimulation (rTMS) for depression in very different ways, and much of this variability is unexplained. Homeostatic synaptic scaling, which in cultured and rodent neurons adjusts excitatory synaptic strengths over hours to days to return activity toward a set point, could affect how long a stimulation-induced change lasts. Computational work has already linked rTMS to homeostatic changes in synapse number. This paper asks a narrower question about existing synapses: when scaling restores a neuron's activity after a stimulation-induced change, does what remains of that change depend on the starting synaptic configuration, even when starting activity is the same? I address it in a reduced theoretical model built from published findings; no new data were collected. Uniform scaling multiplies every excitatory synaptic strength by one factor, so it preserves their ratios and cannot undo a change that altered them. If activity is also linear in synaptic strength and exactly restored, two configurations with equal baseline activity that receive the same change are rescaled by the same factor, and their difference survives in proportion. In a worked example, one configuration keeps an illustrative target property after restoration and the other loses it, although the one that loses it keeps the larger residual change. A repeated-update control shows the limits of the result. With identical changes and full restoration in every round, the configurations converge, so this version of the model predicts different times of reaching the target rather than lasting nonresponse. I outline observations that could separate this mechanism from weak initial induction and from changes in synapse number. Whether intermittent clinical rTMS recruits synaptic scaling in human cortex is unknown; the model generates hypotheses and does not account for treatment response.

Keywords: homeostatic synaptic scaling, repetitive transcranial magnetic stimulation, treatment-resistant depression, synaptic normalization, response trajectory, theoretical model

I. INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation method in which a coil held over the scalp produces brief, rapidly changing magnetic fields that induce electric currents in the underlying cortex. Delivered in repeated sessions, usually once a day over several weeks to the left dorsolateral prefrontal cortex, it is used to treat major depression that has not improved with antidepressant medication (Carpenter et al., 2012; Blumberger et al., 2018). Repetition is central to the treatment. In human motor cortex, a single session of theta-burst stimulation, a patterned form of rTMS delivered in brief, rapid bursts, can change excitability for a period that outlasts the stimulation (Huang et al., 2005). A clinical course is meant to build a lasting change from many such sessions. Deep brain stimulation (DBS), in which implanted electrodes deliver electrical stimulation to selected targets, is a second, invasive form of clinical neuromodulation. Here, neuromodulation means these stimulation treatments, not the action of neuromodulatory transmitters such as dopamine, which is the sense used in some computational work cited below. The main case throughout is rTMS for depression; DBS appears only as a comparison (Section V.E).

Patients respond to a course of rTMS in very different ways. In a large randomized trial comparing two rTMS protocols for treatment-resistant depression, roughly half of patients responded under either protocol (Blumberger et al., 2018). In naturalistic clinical practice, response ranged from about 42% to 58% depending on who rated it and which scale was used (Carpenter et al., 2012). The course of improvement over the sessions, called the response trajectory, also differs. Group-based trajectory modeling of the first trial identified four trajectories: rapid response, two linear-response patterns that differed mainly in baseline severity, and nonresponse (Kaster et al., 2019). In a naturalistic sample treated with an extended course of up to 51 sessions, four trajectories were again identified, and only one of them showed considerable further improvement with additional sessions (Chen et al., 2024). At the group level, a meta-analysis of trials comparing real with sham (placebo) stimulation found that improvement rose over the first weeks, tapered around weeks three to four, and was maintained to week 16 (Hsu et al., 2024). Response rates depend on protocol, sample, and outcome measure, but differences between patients appear consistently.

Several explanations for this variability have been proposed. Baseline symptom severity is associated with trajectory membership (Kaster et al., 2019; Chen et al., 2024), and the average trajectory differs between stimulation protocols (Hsu et al., 2024). State-dependent accounts stress that the brain's state at the time of stimulation shapes what a given session does (Miniussi and Bortoletto, 2025). In human motor cortex, for example, the excitability state defined by the ongoing electroencephalogram (EEG) at the moment of stimulation changed how much plasticity a TMS protocol induced (Zrenner et al., 2018). Homeostatic regulation is part of this literature too. Miniussi and Bortoletto (2025) discuss neural variability in relation to excitability, plasticity, and homeostatic regulation, and non-invasive stimulation studies have probed homeostatic control of cortical plasticity in the intact human brain for over a decade (Karabanov et al., 2015). Homeostatic responses to rTMS have also been modeled directly. In a recurrent

network model, rTMS triggered homeostatic structural plasticity, the formation and removal of excitatory synapses, and the outcome depended on stimulation frequency, intensity, and duration (Anil et al., 2023). That model concerns the number of synapses. A different homeostatic process changes the strength of synapses that already exist. Neurons are not passive. They monitor their own firing rate through intracellular calcium and adjust synaptic properties to maintain a target level, a family of mechanisms called homeostatic plasticity (Turrigiano, 2012; Turrigiano and Nelson, 2004). In one of its best-studied forms, synaptic scaling, a neuron adjusts the strengths of its excitatory synapses over hours to days, in the classic description by a common factor (Section II). If repeated stimulation held activity in stimulated cortex away from its set point for long enough, the calcium sensor that stabilizes circuits under ordinary conditions could begin to work against the change the treatment is trying to build. A neuron in that position would be like a thermostat set to 70 degrees while someone holds a heat source near the sensor: the system generates corrective force against the very change being imposed.

This paper asks a question narrow enough to answer within a reduced model. When uniform synaptic scaling returns a neuron's activity to its set point after a stimulation-induced change, does the part of that change that remains depend on the neuron's starting synaptic configuration, even when starting activity is the same? The claim is deliberately narrower than saying that the brain adapts to stimulation, which few would dispute. It concerns one well-characterized adjustment and whether it could treat two similar neurons differently. I apply a simple normalization model to that question, state its assumptions, and work out what follows from them. The purpose is mechanistic. The paper proposes no diagnostic tool or change to treatment, and it does not explain clinical trajectories. Its contribution is to connect a known property of multiplicative scaling to the question of what survives stimulation, and to show where that connection stops. The central uncertainty is whether intermittent clinical rTMS produces enough sustained calcium displacement in human cortical neurons to recruit synaptic scaling at all.

Section II summarizes the evidence the model draws on. Section III describes how the model was built and states its assumptions. Section IV gives the results, including a worked example and a repeated-update control. Section V compares the model with existing work and discusses how it could be tested, and Section VI sets out its limitations.

II. BACKGROUND: ESTABLISHED EVIDENCE ON HOMEOSTATIC SYNAPTIC SCALING

This section summarizes the evidence the model draws on. Each result is stated with the preparation in which it was obtained, because most of it comes from cultured neurons or rodent cortex, and none of it from the human prefrontal cortex that rTMS targets.

A. The Instability Problem in Hebbian Plasticity

A central tension runs through systems neuroscience. Neural circuits must be plastic enough to encode information and change in response to experience, yet stable enough to sustain coherent activity over time. These two demands are not easily reconciled. Stable neural function requires active regulation. Long-term potentiation (LTP) strengthens synapses participating in postsynaptic firing (Bliss and Collingridge, 1993; Malenka and Bear, 2004), raising the probability of further firing and further potentiation. Left unchecked, this positive feedback could drive activity toward saturation or silence, and theoretical work has argued that Hebbian plasticity on its own is unstable and requires additional stabilizing mechanisms (Abbott and Nelson, 2000). Homeostatic regulation is not ancillary. Plastic nervous systems need compensatory mechanisms that prevent runaway excitation or quiescence (Turrigiano and Nelson, 2004), and chronic changes in activity can lead neurons to change the strength of all their synapses together, in the direction that counters the imposed change (Burrone and Murthy, 2003).

B. The Scaling Mechanism: Evidence and Core Properties

Turrigiano et al. (1998) characterized synaptic scaling in cultured rat neocortical neurons. They measured synaptic strength as the amplitude of miniature excitatory postsynaptic currents (mEPSCs), the small currents produced when single packets of the transmitter glutamate are released spontaneously at individual synapses. Chronic activity suppression increased mEPSC amplitude; chronic elevation decreased it. Two properties stood out. It was compensatory, opposing rather than following the perturbation. It also appeared multiplicative: the change at each synapse was proportional to its initial strength, which preserves relative weight differences while adjusting overall gain. Later work added a third property. Scaling can be driven by a neuron's own firing, since blocking firing in individual neurons was enough to induce it (Ibata et al., 2008). The multiplicative property matters because relative synaptic weights encode experience-dependent information. Multiplicative scaling restores firing rate without erasing that information. Turrigiano (2017) describes this as regulating overall activity while preserving the relative information stored in synaptic weights. Just as important is what synaptic scaling does not do. Because it is triggered by a neuron's overall firing rather than by activity at particular synapses (Ibata et al., 2008), it carries no information about which inputs caused a deviation.

These properties have limits that matter for the model. Experience-dependent scaling has been demonstrated in intact rodent visual cortex, with layer-specific developmental critical periods (Desai et al., 2002), and firing-rate homeostasis has been recorded in freely behaving rodents (Hengen et al., 2013; Torrado Pacheco et al., 2021). Most of this evidence, however, comes from cultured neurons and young animals, and adult cortex differs. In layer 2/3 of adult mouse visual cortex, experience-dependent homeostatic plasticity persisted but was no longer multiplicative (Goel and Lee, 2007), and after enucleation (removal of one eye) only a subset of excitatory neurons recovered their activity, a recovery helped by reduced synaptic inhibition (Barnes et al., 2015). Scaling is also not always uniform across a neuron's synapses, even in culture. Re-analysis of miniature-current data from cultured mouse cortical neurons found a scaling factor that was close to 1 for the smallest synapses and increased with synapse

size, and the authors argue that such divergent scaling is common in published data (Koesters et al., 2024). Local mechanisms can also adjust synapses independently of cell-wide scaling (Turrigiano, 2012). Global multiplicative scaling is therefore best treated as an idealization, which is how the model in Section IV uses it.

C. The Calcium Sensor, Molecular Effectors, and Timescale

The best-characterized sensor for scaling is intracellular calcium. Somatic influx during action potentials makes average calcium a proxy for time-averaged firing rate (Turrigiano, 2012). When postsynaptic firing is blocked in cultured cortical neurons, the resulting drop in somatic calcium influx reduces activation of the kinase CaMKIV and increases transcription, producing upward scaling (Ibata et al., 2008). Scaling changes synaptic strength mainly by changing the number of AMPA receptors, the glutamate receptors that carry most fast excitatory current at these synapses (Turrigiano, 2012). Scaling up in cultured cortical neurons requires AMPA receptors containing the GluA2 subunit (Gainey et al., 2009). Downward scaling during elevated activity uses different effectors. In cultured hippocampal neurons, the activity-inducible kinase Plk2, which targets the synaptic scaffold protein SPAR for degradation (Pak and Sheng, 2003), is required for scaling during elevated activity, and CDK5 acts as a priming kinase for this step (Seeburg et al., 2008). The immediate-early gene product Arc provides a parallel route through a selective AMPA receptor endocytic pathway (Shepherd et al., 2006). For the model, the individual molecules matter less than the overall pattern, which is that both scaling up and scaling down are driven by signals reporting the neuron's own recent activity.

Scaling develops on a slower timescale than the after-effects of a single stimulation session. It has been detected within a few hours of firing blockade in culture (Ibata et al., 2008), and in the original culture experiments, compensation for raised activity developed over about 48 hours (Turrigiano et al., 1998). In freely behaving juvenile rats, monocular deprivation (closing one eye) suppressed firing in visual cortex for about two days, after which firing returned to baseline over the next two to three days despite continued deprivation, accompanied by bidirectional changes in mEPSC amplitude (Hengen et al., 2013). Downward firing-rate homeostasis in freely behaving rodents depends strongly on sleep (Torrado Pacheco et al., 2021). All of these timescales come from manipulations that lasted continuously for hours or days. Whether brief stimulation sessions separated by a day produce an equivalent homeostatic signal has not been tested.

D. Repeated Stimulation, Cultures, and Course-Level Trajectories

In human motor cortex, theta-burst stimulation changes excitability for a period that outlasts the stimulation, with intermittent and continuous patterns producing opposite effects (Huang et al., 2005), and several human plasticity protocols share this property (Ziemann et al., 2008). Culture studies bring stimulation closer to the synapse. In mouse organotypic slice cultures, an iTBS protocol produced persistent structural and functional plasticity (Lu et al., 2025b). A preprint that has not yet been peer reviewed followed CA1 pyramidal neurons in mouse entorhino-hippocampal slice cultures through ten daily iTBS sessions (d'Errico et al., 2026). Two to four hours after the last session, mEPSC frequency and

dendritic spine density were lower, while mEPSC amplitude had not changed significantly. The response depended on microglia; without them, mEPSC amplitude, spine size, and spine density increased instead. This supports homeostatic structural remodeling after repeated stimulation. One amplitude measurement at one time point cannot rule out scaling of existing synaptic strengths, so the study neither shows nor excludes it. Whether after-effects in human prefrontal cortex accumulate from session to session is not established. Two things are established. Clinical improvement follows different paths in different patients (Kaster et al., 2019; Chen et al., 2024), and at the group level it rises over the first weeks and then tapers (Hsu et al., 2024).

E. Similar Activity From Different Configurations

Neurons producing identical firing patterns do not necessarily share identical underlying conductance configurations. This is degeneracy: structurally different elements producing the same or similar function (Edelman and Gally, 2001). Neurons of the same type show variable ion-channel conductance densities while producing similar activity (Goaillard and Marder, 2021), and in a model of the crustacean pyloric network, virtually indistinguishable activity arose from widely different combinations of synaptic strengths and intrinsic properties (Prinz et al., 2004). None of these studies measures the excitatory synaptic configuration of human prefrontal neurons. They motivate the possibility, used in Section IV, that neurons with the same activity differ in how their excitatory synaptic strengths are distributed.

III. METHODS: CONCEPTUAL FRAMEWORK DEVELOPMENT

A. Literature Basis

No new human or animal data were collected, no experiments were performed, and no parameters were fitted to data. The paper builds a reduced model from published findings. The motivation was the variability in patients' responses to repeated rTMS for depression (Section II.D). The model studies one mechanism that might contribute to it. I then assembled results on homeostatic synaptic scaling from cellular and animal studies (Sections II.A to II.C), recording for each the preparation, species, and developmental stage in which it was obtained. Sources were identified in three ways. Two papers were read with the research mentor at the start of the project (Turrigiano, 2012; Miniussi and Bortoletto, 2025), the studies they cite were followed up, and targeted searches covered the homeostatic plasticity, neuronal variability, and rTMS literatures, including existing models of homeostasis under rTMS. This was not a systematic review. Throughout, the aim was to avoid stretching evidence from cultured neurons or computational models to human patients without marking the gap. For this revision, each cited source was re-checked against the sentence it supports, using the full text where it was accessible and otherwise the abstract together with independent published descriptions of the study.

B. Model Construction

I selected a minimal set of these results and stated them as assumptions (Section III.C), labeling any extension beyond the preparation in which a result was established. The assumptions were represented in

a reduced geometric model in which the strengths of a neuron's excitatory synapses form a point in a multidimensional space. This representation follows computational work on degeneracy and homeostasis. Prinz et al. (2004) used a model of a crustacean stomatogastric network, and Fyon and Drion (2026) used conductance-based models of stomatogastric and dopaminergic neurons in which calcium homeostasis adjusts intrinsic ion-channel conductances while neuromodulatory signals reshape firing. In their model, the interaction between the two processes depends critically on whether their targets intersect in conductance space, which motivated the intersection conditions in Section IV.B. Because that work concerns intrinsic conductances and neuromodulatory transmitters, it is a methodological precedent here and provides no evidence for the mechanism proposed. Unlike network models of homeostatic structural plasticity (Anil et al., 2023), the present model represents only the strengths of one neuron's existing excitatory synapses. Results were derived analytically. The worked example and the repeated-update control were computed with exact fractions, and their values are arbitrary, dimensionless quantities chosen for illustration.

C. Model Assumptions

The general model rests on five assumptions (Figure 1).

A1. Activity displacement. Repeated rTMS changes activity in stimulated cortex for periods that outlast each session. This is established for single sessions in human motor cortex (Huang et al., 2005) and assumed for prefrontal cortex across a clinical course.

A2. Homeostatic recruitment. If sufficiently sustained, this displacement produces a calcium error signal that recruits synaptic scaling in the stimulated neurons. This has not been tested in humans and is the assumption on which the framework most depends (Figure 1, dashed box).

A3. Idealized uniform multiplicative scaling. Scaling multiplies all of a neuron's excitatory synaptic strengths by a common positive factor α . This idealizes findings in cultured neurons (Turrigiano et al., 1998); real scaling is not always uniform, and in adult cortex it may not be multiplicative (Section II.B).

A4. Bounded scaling. The factor α is restricted to a finite range, $\alpha_{\min} \leq \alpha \leq \alpha_{\max}$, with $0 < \alpha_{\min} < 1 < \alpha_{\max}$, because synaptic strength cannot be scaled without limit. The bounds are introduced for the model and are not estimated.

A5. Isolation of the scaling component. Hebbian plasticity, homeostatic regulation of inhibitory synapses and of intrinsic excitability, structural plasticity, and network interactions are not modeled. The model isolates the contribution of excitatory synaptic scaling and does not claim that scaling acts alone.

I write $\alpha(t)$ for the scaling factor at time t and assume only that it depends on the recent history of calcium displacement from its set point, decreasing after sustained elevation and increasing after sustained reduction. Its functional form is not specified. The retention analysis in Sections IV.C and IV.D adds three assumptions. They are illustrative simplifications, chosen so that the analysis can be carried out exactly.

A6. Linear activity. Activity is a linear function of excitatory synaptic strengths, $\Phi(g) = w \cdot g$, with fixed positive weights w and with inhibition and input statistics held fixed. Synaptic strengths are nonnegative and baseline activity is positive ($C = w \cdot g_0 > 0$). A change δ is admissible only if $g' = g_0 + \delta$ has no negative component and $C + w \cdot \delta > 0$.

A7. Exact restoration. Scaling returns activity exactly to the set point with a single factor inside the bounds of A4. This is a limiting case; the model does not describe how, or how fast, it would be reached.

A8. Identical repeated rounds. In the repeated-update control, each round adds the same change δ , which has no negative component and satisfies $w \cdot \delta > 0$, so repeated application keeps every configuration admissible. Each round ends with exact restoration by a factor inside the bounds of A4. A round has no assigned clinical duration.

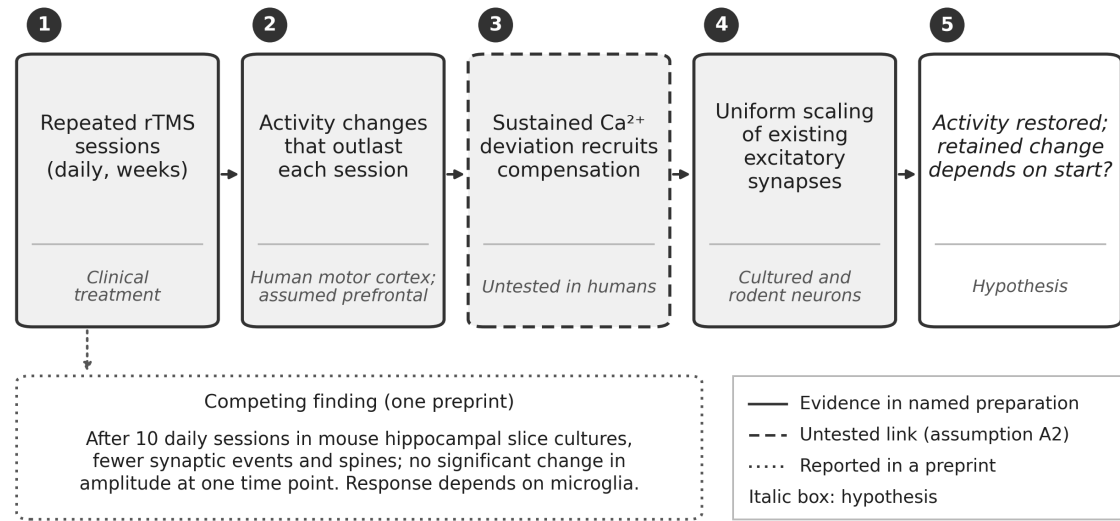


Figure 1. Proposed pathway and a competing finding. The figure is original and conceptual and contains no data. Numbered boxes show the proposed sequence, and the lower line in each box names the kind of evidence for that step. Solid borders mark steps with evidence in the named preparation, the dashed border marks the untested link (assumption A2), and the italic box is the hypothesis. The dotted box summarizes one preprint in mouse hippocampal slice cultures (d'Errico et al., 2026). It is linked to repeated stimulation rather than to the calcium step, because that study did not examine the calcium pathway, and its results support structural remodeling without excluding scaling of existing synaptic strengths.

D. Model Variables

Table 1 defines each quantity and states its status. None has been measured in patients. The general model is static: it describes which configurations scaling could reach, not how a neuron moves through them over time, and its activity function Φ contains no stimulation term. The repeated-update control in Section

IV.D adds a discrete update rule whose rounds have no assigned duration; it is not a continuous-time model.

Table 1. Model quantities, their interpretation, and their status.

Symbol	Definition in the model	Biological interpretation	Status
$g = (g_1, \dots, g_n)$	Strengths of a model neuron's n excitatory synapses (a configuration)	AMPA-receptor-mediated synaptic strengths; not intrinsic Na^+ , K^+ or Ca^{2+} channel conductances	Model abstraction; latent, not measured in patients
g_0	Configuration before stimulation	Baseline synaptic configuration	Latent starting state
δ ; $g' = g_0 + \delta$	Stimulation-induced change and the resulting configuration	Net synaptic change left by stimulation	Unspecified in general; fixed in the worked example
g_I	Inhibitory synaptic strengths	Inhibitory input onto the neuron	Held fixed (A5)
$\Phi(g, g_I)$	Steady-state firing rate under fixed input statistics	Time-averaged activity, the quantity homeostasis regulates	Modeling abstraction; linear in Sections IV.C and IV.D (A6)
F_{set} ; H	Set-point firing rate; configurations with $\Phi = F_{\text{set}}$ (Eq. 3)	Homeostatic set point, reflected in average intracellular calcium	Established concept in cultured and rodent neurons
$\alpha(t)$; α_{min} , α_{max}	Common positive scaling factor and its bounds	Net effect of cell-wide synaptic scaling	Phenomenological (A3, A4); bounds not estimated
$R(g)$	Configurations reachable from g by scaling alone (Eq. 1)	Idealized scaling path	Consequence of A3 and A4
T	Configurations with a property the intervention is assumed	Illustrative target; not a clinical or symptom measure	I define this construct

	to favor		
α^*, g^*	Factor that exactly restores set-point activity, and the restored configuration (Eq. 6)	Endpoint of complete compensation	Limiting case (A6, A7)

IV. RESULTS

Sections IV.A to IV.D work out what follows from the assumptions, and their results are properties of the model; none of them is an empirical finding. Sections IV.E and IV.F then state the clinical hypothesis and the tests it suggests, which go beyond the model.

Put simply, the results make four points. Uniform scaling can make all of a neuron's synapses stronger or weaker together, but it cannot change their proportions (Section IV.A). Being able to reach a target is not the same as keeping it once activity has been restored (Section IV.B). Two neurons that start with the same activity can end up in different places after the same change and the same compensation (Section IV.C). And when the same change is repeated, those differences shrink rather than grow (Section IV.D).

A. What Uniform Scaling Preserves

Under A3 and A4, scaling multiplies every component of a configuration g by the same positive factor. From g , scaling alone can therefore reach only

$$R(g) = \{ \alpha g : \alpha_{\min} \leq \alpha \leq \alpha_{\max} \}. \quad (1)$$

Geometrically, $R(g)$ is a segment of the ray from the origin through g , so under the idealization scaling moves a configuration along a single line. One degree of freedom. In an n -dimensional space, that is a severe constraint. It also leaves the ratios between synaptic strengths unchanged:

$$(\alpha g)_i / (\alpha g)_j = g_i / g_j \quad \text{for all } i, j \text{ with } g_j > 0 \text{ and every } \alpha > 0. \quad (2)$$

Uniform scaling can therefore change the overall magnitude of the synaptic-strength vector but not the relative synaptic strengths, and it cannot return a neuron to its original configuration after a change that altered those ratios. The property belongs to multiplicative scaling itself (Turrigiano, 2017); what the model adds is its use in the retention question below. If stimulation strengthens some synapses more than others, as synapse-specific Hebbian mechanisms would (Bliss and Collingridge, 1993), later scaling acts

along the ray through the changed configuration g' , not along the ray through g_0 . The path available to compensation is set by the configuration at the start of each scaling episode.

An everyday comparison helps here. Resizing a photograph makes the whole image larger or smaller, but it never changes the proportions of what is in it. Uniform scaling works the same way on a neuron's synapses. It changes how strong they are overall, not how that strength is shared among them.

B. Reaching a Target Versus Retaining It

To ask what survives restoration, the model needs a target and a set point. I define T as the set of configurations that have a property the intervention is assumed to favor, such as sufficiently strong drive through one input. T is not a clinical measure, and nothing in the model links it to symptoms. The set-point surface H contains the configurations whose activity equals the set point:

$$H = \{ g : \Phi(g, gI) = F_{\text{set}} \}. \quad (3)$$

One could ask whether scaling can reach T from a post-stimulation configuration g' :

$$R(g') \cap T \neq \emptyset. \quad (4)$$

This reachability condition says little about retention. Because $\alpha = 1$ lies inside the allowed range, g' itself belongs to $R(g')$. If stimulation has already placed g' inside T , condition (4) holds automatically, even when compensation then moves the configuration out of T . Reachability cannot separate a change that survives restoration from one that is lost, and it implies no convergence, equilibrium, or stability. The distinction matters for the argument developed in this paper, because the clinical question is whether an induced change survives compensation. Target retention needs both constraints at once. A post-stimulation configuration can keep the target property after restoration only if some configuration reachable by scaling has set-point activity and lies in T :

$$R(g') \cap H \cap T \neq \emptyset. \quad (5)$$

Condition (5) is still an existence statement. It shows that a restored configuration with the target property is available. Whether any biological process reaches that configuration is a separate question. In simpler terms, a scaling path that passes through the target on its way is not enough. What matters for retention is where the path ends once activity is back at the set point.

C. Configuration-Dependent Retention

With the illustrative assumptions A6 and A7, condition (5) can be evaluated exactly. Let a baseline configuration g_0 have set-point activity, $w \cdot g_0 = C$, and let stimulation add a change δ , so that $g' = g_0 + \delta$. Exact restoration requires

$$\alpha^* = C / (C + w \cdot \delta), \quad g^* = \alpha^*(g_0 + \delta), \quad (6)$$

provided $\alpha_{\min} \leq \alpha^* \leq \alpha_{\max}$; if the required factor lies outside the bounds, exact restoration is not possible within the model. I call $g^* - g_0$, the part of the stimulation-induced change left after restoration, the residual change. It equals $g^* - g_0 = [C\delta - (w \cdot \delta)g_0] / (C + w \cdot \delta)$. If the stimulation-induced change is proportional to the existing configuration ($\delta = \beta g_0$), this is zero, and compensation returns the neuron exactly to where it started. A change that is not proportional generally leaves a residual change in relative synaptic strengths.

The result that matters here concerns two starting configurations. Suppose A and B have the same baseline activity C and receive the same change δ . Both then have the same activity after stimulation, so both are rescaled by the same factor α^* , and

$$g^*_A - g^*_B = \alpha^*(g_{0,A} - g_{0,B}). \quad (7)$$

The difference between the configurations survives restoration in proportion. Same change, different ending. Equal baseline activity and an equal perturbation therefore determine neither the residual change nor whether a target defined by individual synaptic strengths is still met.

A worked example with two inputs makes this concrete (Table 2; Figure 2A). Let $\Phi(g) = g_1 + g_2$, $C = 2$, $\delta = (0.6, 0)$, $\alpha_{\min} = 0.5$, $\alpha_{\max} = 1.5$ and $T = \{g : g_1 \geq 1.3\}$. All values are arbitrary, dimensionless model quantities, and T represents an assumed property of one input with no link to symptom severity. Neither configuration lies in T at baseline, and both enter it after the change, so condition (4) holds for both. Restoration requires $\alpha^* = 10/13$, which lies within the bounds. Afterwards B still satisfies $g_1 \geq 1.3$ and A does not, so condition (5) holds for B only. The contrast holds for every threshold θ with $1.2 < \theta \leq 18/13$ (about 1.385), so it does not depend on the choice of 1.3. The example establishes a possibility under explicit assumptions. It says nothing about whether such differences exist in human cortex, or how common they would be.

Two outcomes need to be kept apart. Target retention means that g^* still lies in T; the residual change is $g^* - g_0$. In the example they point in opposite directions. A keeps the larger residual change: its first input ends 18/65 (about 0.277) above its own baseline, against 12/65 (about 0.185) for B, and in both configurations the second input falls by the same amount because total activity is restored. B stays in T only because it started closer to the threshold. Target retention is therefore not evidence that more of the induced change was preserved.

Table 2. Worked example of one round (A6, A7). Coordinates are (g_1, g_2) ; $T = \{ g : g_1 \geq 1.3 \}$.

Stage	Configuration A	Configuration B
Baseline	(0.8, 1.2); activity 2; outside T	(1.2, 0.8); activity 2; outside T
After the change $\delta = (0.6, 0)$	(1.4, 1.2); activity 2.6; inside T	(1.8, 0.8); activity 2.6; inside T
After restoration, $\alpha^* = 10/13$	$(14/13, 12/13) \approx (1.077, 0.923)$; activity 2; outside T	$(18/13, 8/13) \approx (1.385, 0.615)$; activity 2; inside T
Residual change $g^* - g_0$	$(18/65, -18/65) \approx (0.277, -0.277)$	$(12/65, -12/65) \approx (0.185, -0.185)$

D. A Repeated-Update Control

A treatment course repeats stimulation many times, so one round cannot establish anything about a course. As a control, I repeat exactly the same change and restore activity fully after each round (A8). With $d = w \cdot \delta > 0$, $q = C/(C + d)$ and $\alpha_{\min} \leq q$, the update and its exact solution are

$$g_{k+1} = q(g_k + \delta), \quad g_k = qkg_0 + (1 - qk)(C/d)\delta, \quad (8)$$

which gives, for two configurations,

$$g_{k,A} - g_{k,B} = qk(g_{0,A} - g_{0,B}), \quad 0 < q < 1. \quad (9)$$

Under these assumptions the difference between configurations shrinks every round, and both approach the same limit, $(C/d)\delta$, which is (2, 0) in the worked example. B crosses the illustrative threshold after the first round and A after the third (Table 3; Figure 2B). This control yields different times of crossing the threshold, with neither lasting nonresponse in A nor growing differences between configurations. The conclusion is specific to the control. It does not show that every model containing uniform scaling behaves this way; changes that vary between rounds, incomplete restoration, or other update rules could behave differently. Each step from one restored state to the next also becomes smaller, so a shrinking increment per round can coexist with convergence. In the example the second input declines toward zero, which would not be plausible over many rounds; the control tests the reasoning and is not a model of a treatment course.

Does repeating the same change make the gap between A and B grow? In this control it does the opposite. A plain way to picture it is two people walking toward the same spot from different starting points. Each

round covers part of the remaining distance, the one who starts closer arrives first, and the gap between them keeps shrinking.

If lasting differences between patients are part of what needs explaining, something beyond uniform scaling is required. Candidates include stimulation-induced changes that differ between individuals, incomplete recovery between sessions, induction that depends on previous stimulation, and set points that differ between individuals, and each would bring assumptions of its own that need justifying.

Table 3. Repeated-update control (A6 to A8): first component g_1 after each round of the same change followed by full restoration.

Round	A: g_1	B: g_1	In T ($\theta = 1.3$)
0	0.8000	1.2000	Neither
1	1.0769	1.3846	B only
2	1.2899	1.5266	B only
3	1.4538	1.6359	Both
Limit	2	2	Both

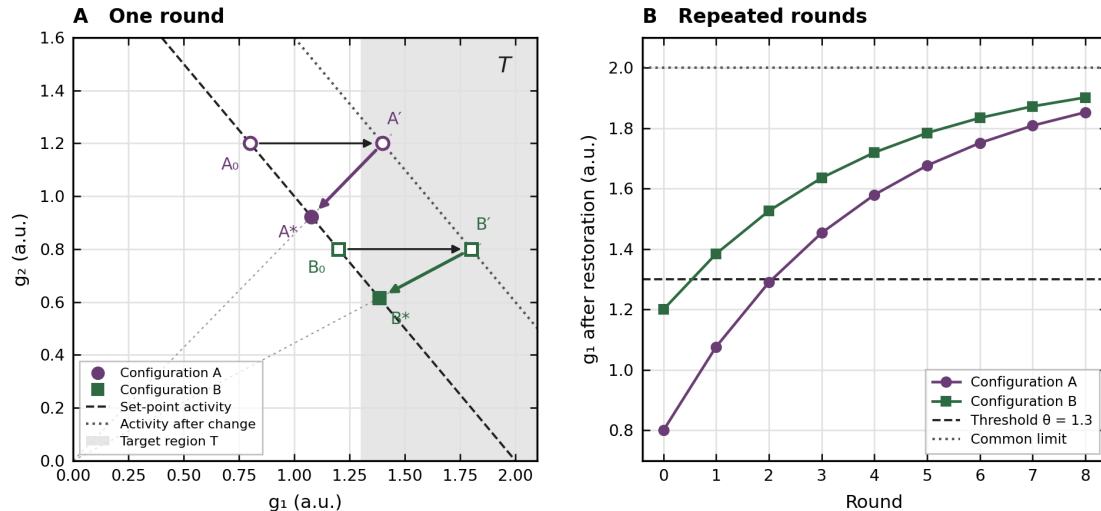


Figure 2. Worked example and repeated-update control. Values are arbitrary model quantities in arbitrary units (a.u.), not data or clinical sessions. (A) One round. Circles show configuration A and squares configuration B. Open markers at A_0 and B_0 are the baseline configurations, which have the same activity (dashed line). Black arrows show the same change $\delta = (0.6, 0)$, which places both inside the illustrative target region T (shaded). The dotted line through A' and B' marks their common activity after

the change. Colored arrows along the faint rays from the origin show restoration by the common factor $\alpha^* = 10/13$, ending at A^* and B^* (filled markers). Relative synaptic strengths remain changed in both. B^* stays in T and A^* does not, although A keeps the larger residual change (Table 2). (B) Repeated rounds of the same change, each followed by full restoration. B crosses the threshold after round 1 and A after round 3, and both approach the same limit.

E. From Model to Clinical Hypothesis

Sections IV.A to IV.D describe properties of a reduced model. The paper's clinical claim is a separate hypothesis that goes beyond them:

If repeated rTMS recruits synaptic scaling in stimulated cortex (A2), then how much of each session's change survives compensation may depend on how that change is distributed across synapses relative to the existing configuration, and this could contribute to differences in when patients' improvement appears.

Testing this would require a model of the perturbation, the compensation, and the relevant activity, which the present framework supplies only in reduced form, and its simplest version predicts only differences in timing (Section IV.D). Here is the key difference from state-dependency models. State-dependency says each session's outcome depends on how excitable the circuit is at that moment. The present hypothesis concerns what survives compensation between sessions, and it depends on a configuration that changes slowly, if at all, compared with momentary brain state. The contrast is drawn here for clarity; state-dependent accounts themselves already discuss plasticity and homeostatic regulation (Miniussi and Bortoletto, 2025). The two accounts are not mutually exclusive: session-level state-dependency and cumulative homeostatic resistance may both contribute to variability through distinct biology on different timescales.

F. Proposed Tests and Their Limits

The tests below follow from the clinical hypothesis together with additional assumptions stated for each. They are not derived from the static model alone, and none would identify synaptic scaling on its own.

P1. Added value of treatment history. Does a patient's course so far, such as the change in symptoms or in a neural measure over previous sessions, improve prediction of later response beyond baseline severity and measured pre-session state? Added value would fit a slow cumulative process without identifying scaling, and pre-session measures may themselves partly reflect its consequences. No added value in adequately powered data would weaken the case for a slow cumulative contribution.

P2. Persistence between sessions. Three quantities need separating: the state before each session, the immediate response to it, and how much of that response persists until the next session. The hypothesis concerns persistence. Where retention differs between patients, the difference should show up there, and it need not show up in the immediate response. Any measure used must first be shown to detect

session-induced changes, because EEG measures can miss plasticity that motor-evoked potentials detect (Desideri et al., 2018).

P3. Session spacing. The static model has no time variable, so it predicts no spacing effect by itself; one would need a recovery rule describing how compensation develops between sessions. Given such a rule, the interval between sessions could interact with a baseline measure named in advance, for example a baseline TMS-evoked EEG response, in predicting trajectory. The link between that measure and the latent configuration is an extra assumption, and accelerated and standard schedules also differ in dose and protocol. Because downward firing-rate homeostasis in rodents depends strongly on sleep (Torrado Pacheco et al., 2021), the number of sleep periods between sessions may matter as much as elapsed time. A comparison of accelerated and standard protocols found no association between protocol and trajectory membership after adjusting for baseline severity (Kaster et al., 2020), which constrains, but does not test, an interaction of this kind.

P4. State-controlled stimulation. Timing stimulation to the brain's momentary state changes its effect (Zrenner et al., 2018). Comparing state-controlled with conventional stimulation could help weigh session-level variability against slower attenuation, but it cannot settle the question, because controlling state may itself change the activity displacement that recruits compensation.

The most informative design would follow an induced change across repeated exposure and measure its persistence separately from the immediate response, in a preparation where synaptic strength and synapse number can both be measured (Section V.D). A compatible result would justify further work. Identifying synaptic scaling would take more.

V. DISCUSSION

This section compares the model with existing work, sets out what the analytical result does and does not imply, and discusses how the mechanism could be separated from alternatives.

A. Relation to Existing Models and Evidence

Homeostatic responses to rTMS have been modeled and measured before. In the network model of Anil et al. (2023), rTMS changed connectivity through homeostatic structural plasticity, and feedback inhibition shaped the outcome. Lu et al. (2025a) combined experiments and modeling to study how synaptic scaling and homeostatic structural plasticity interact to maintain network firing rates, and in hippocampal slice cultures repeated daily stimulation produced a microglia-dependent reduction in synaptic events and spines (d'Errico et al., 2026). The present model is narrower. It represents only the strengths of one neuron's existing excitatory synapses and asks what uniform scaling of those strengths preserves. Changes in synapse number, in inhibition, and in the thresholds for inducing plasticity are separate mechanisms that can produce overlapping observations.

State-dependent accounts ask why the same protocol can have different effects on different occasions

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(Miniussi and Bortoletto, 2025; Zrenner et al., 2018). Studies of homeostatic plasticity with non-invasive stimulation have also discussed evidence that abnormal homeostatic plasticity may be associated with several neuropsychiatric disorders (Karabanov et al., 2015).

B. What Compensation Removes and What It Keeps

The analytical result runs against a simple picture of homeostasis as an obstacle to treatment. The scaling mechanism is driven by a calcium error signal with no representation of the therapeutic goal. In the model, it removes a change proportional to the existing configuration and keeps a change in relative synaptic strengths, so whether homeostasis works against a treatment-induced change depends on how that change is distributed across synapses as well as on its size. The resulting variability is structured rather than random, because it follows from where each configuration starts. This agrees with the long-standing view that multiplicative scaling regulates overall activity while preserving relative synaptic information (Turrigiano, 2017). Under the repeated-update control's own assumptions, configurations converge when the change is identical and restoration is complete, so that version of the model produces no lasting nonresponse, growing differences between patients, or spacing effects. Other update rules, including those listed in Section IV.D, would be needed to test whether scaling could produce them.

C. Evidence, Inference, and Assumption

The components of the proposal differ in their support. Several are established in the stated preparations. Synaptic scaling exists, is compensatory, and is approximately multiplicative in cultured neurons (Turrigiano et al., 1998), and it can be driven by a neuron's own firing through calcium-dependent signaling (Ibata et al., 2008). Firing-rate homeostasis operates over days in freely behaving rodents (Hengen et al., 2013). A preprint reports that repeated daily magnetic stimulation can recruit a structural homeostatic response in hippocampal slice cultures (d'Errico et al., 2026), and rTMS outcomes follow different trajectories (Kaster et al., 2019; Chen et al., 2024). Two points rest on the model alone: uniform scaling preserves synaptic ratios, and under A6 and A7 what is retained depends on the starting configuration. Still assumed or untested: that intermittent clinical rTMS recruits scaling in human cortex (A2), that scaling is uniform and multiplicative there (A3), and that any target region corresponds to clinically relevant activity. The weakest link is A2.

D. Separating the Mechanism From Alternatives

Course-level differences between patients have many possible sources. Baseline severity is associated with trajectory membership (Kaster et al., 2019; Chen et al., 2024), and differences in stimulation targeting, illness biology, expectancy, and the measurement properties of rating scales could also shape trajectories. Microglial and neuroimmune state is another candidate, proposed by the authors of the culture study discussed above (d'Errico et al., 2026). Three kinds of observation would help separate loss of a change through scaling from these alternatives. Measuring before stimulation, soon after it, and after a defined recovery interval, repeatedly across a course, separates weak initial induction from loss of a change that was initially present. In preclinical preparations, measuring synaptic strength together with

synapse or spine number and event frequency separates scaling of existing synapses from structural remodeling; a change in average strength or in an amplitude distribution alone does not show that every synapse changed by one common factor (Koesters et al., 2024). Comparing repeated stimulation with sham, together with an intervention that affects the candidate scaling pathway, could test whether that pathway causes the loss of an induced change, although no available manipulation is perfectly selective, and one that also alters induction cannot isolate delayed compensation.

There are three measurement levels in clinical neuromodulation research, and the mechanism proposed here lives at the one current instruments reach least directly. Level 1 is clinical outcomes: depression rating scales, symptom inventories. Direct therapeutic relevance; no mechanistic resolution between causes of non-response. Level 2 is neural proxies: EEG excitability, individual alpha frequency, resting-state connectivity, motor-evoked potential amplitudes. Level 2 provides predictive value for stimulation outcomes (Miniussi and Bortoletto, 2025; Zrenner et al., 2018) but remains several synaptic steps removed from the conductance dynamics at issue. Level 3 is the mechanistic level: synaptic scaling activity, AMPA receptor surface expression, intracellular calcium dynamics, conductance trajectory under sustained perturbation. Part of Level 3 has become measurable. A PET tracer for AMPA receptors allows receptor density to be imaged in the living human brain, and in patients with epilepsy its uptake tracked AMPA receptor protein measured in resected tissue (Miyazaki et al., 2020). The question this model raises, whether the synapses of an individual human neuron are scaled by a common factor, is still out of reach. Imaging of this kind reports receptor density across a region, not the distribution of strengths across one neuron's synapses. Closed-loop approaches to psychiatric DBS adjust stimulation using physiological or behavioral read-outs of target engagement (Widge, 2024); in my reading, this reflects the same gap. In patients, repeated AMPA-receptor PET could show whether regional receptor density in the stimulated area changes across a course. TMS-evoked EEG responses and magnetic resonance spectroscopy of glutamate plus glutamine (Glx) and of the inhibitory transmitter GABA can track related changes. None of these identifies scaling or the latent configuration; each is, at best, a correlate. A null result from such a measure is informative only if its sensitivity to session-induced change has been established.

E. Deep Brain Stimulation as a Comparison

DBS differs from rTMS in ways that matter for the model. It is invasive, it is usually delivered for months to years rather than in brief daily sessions, and it affects fibers of passage and local circuit elements. If the relevant variable is time-integrated calcium displacement, stimulation that disrupts pathological oscillations without raising average activity might recruit less scaling than stimulation intended to shift average excitability. This has not been tested, and I do not assert it as an established mechanistic distinction.

F. Possible Clinical Relevance

If the hypothesis were supported, it could eventually bear on whether session spacing should differ between patients and whether adaptive protocols should account for slow compensation as well as

momentary state. These are directions for future work. The framework does not justify any change to treatment.

VI. LIMITATIONS

The limitations are listed in order of importance.

First, recruitment of scaling by clinical rTMS is unknown. Scaling is slow. It takes hours to begin, days to fully express. That timescale mismatch with rTMS sessions lasting minutes is the first reason skeptics will doubt this framework, and they may be right, because whether intermittent stimulation produces calcium integration equivalent to the continuous manipulations used to characterize scaling has never been tested in human cortical tissue. In a culture study of repeated daily stimulation, the measured response was structural and microglia-dependent, and mEPSC amplitude did not change significantly at the one time point tested (d'Errico et al., 2026); that result neither shows nor excludes scaling. The proposed chain from repeated rTMS to homeostatic engagement rests on an untested assumption about calcium integration that constitutes the most important empirical gap for the framework.

Second, the analysis is reduced. Linear activity, exact restoration, and identical repeated changes (A6 to A8) were chosen because they make the result exact, not because they describe neurons. The model has no stimulation input and no continuous time course, and the repeated-update control uses discrete rounds of unspecified length. The worked example and the control are possibility results; neither predicts a clinical trajectory.

Third, uniform multiplicative scaling is an idealization, and the evidence for it comes from other preparations. Scaling is not always uniform across synapses (Koesters et al., 2024), local homeostatic mechanisms exist (Turrigiano, 2012), and in adult mouse visual cortex homeostatic plasticity persisted but was no longer multiplicative (Goel and Lee, 2007). Adult cortex may also rely on different mechanisms (Barnes et al., 2015), and scaling in visual cortex has layer-specific developmental critical periods (Desai et al., 2002). With non-uniform scaling, Eq. 2 need not hold, and the reachable set is no longer a segment of a ray.

Fourth, the target region is arbitrary. T represents an assumed property of one input. Nothing in the model specifies which synaptic configurations correspond to antidepressant benefit, and depression is not a property of single neurons.

Fifth, the model describes a single neuron. The framework assumes single-neuron conductance dynamics meaningfully constrain circuit-level behavioral outcomes. This is not directly established. Recurrent connectivity, diverse interneuron populations, and network dynamics may buffer or amplify single-neuron homeostatic responses in ways the present account does not model.

Sixth, other homeostatic mechanisms are omitted. In cultured visual cortical neurons, activity deprivation reduces inhibitory synaptic strength while increasing excitatory strength (Kilman et al., 2002). Different forms of visual deprivation engage different mechanisms, including changes in intrinsic excitability (Maffei and Turrigiano, 2008), and homeostatic structural plasticity changes synapse number (Anil et al., 2023; Lu et al., 2025a). Any of them could alter what a neuron retains.

Seventh, the set point is assumed to be stable. Set point plasticity in adult human cortex is not well characterized. A set point that moved during a course would change what counts as restored activity. I treat set point stability as a null hypothesis to be falsified rather than as an established fact.

Finally, clinical stimulation produces effects far more complex than single-neuron conductance changes. Repetitive TMS produces spatially heterogeneous electric fields, recruits excitatory and inhibitory neurons, and engages axons as well as somata. Dopaminergic and serotonergic modulation of plasticity thresholds, disease-related receptor expression changes, and pharmacological interactions with concurrent medications are additional contributors not addressed here. The proposed mechanism should be understood as a hypothesis about one class of cellular responses, potentially accounting for a subset of variability.

VII. CONCLUSION

Within a reduced model, uniform synaptic scaling preserves the ratios between a neuron's excitatory synaptic strengths, so it cannot undo a stimulation-induced change that altered them. With linear activity and exact restoration, two configurations that start with the same activity and receive the same change keep their difference after restoration. An illustrative target property can then be retained by one and lost by the other, and target retention need not follow the size of the residual change. In a control that repeats the same change with full restoration, configurations converge, so this simplest version predicts differences in when a target is reached, not lasting nonresponse. All of this follows from stated assumptions. The assumption everything else depends on, that clinical rTMS recruits synaptic scaling in human cortex, has not been tested, and the model does not explain clinical trajectories. The most useful next step is preclinical. An induced change should be followed across repeated stimulation, with its persistence measured separately from the immediate response, and with synaptic strength and synapse number tracked together. Repeated neuromodulation should be modeled as a perturbation applied to an actively regulated system. The reduced model shows one specific way in which that regulation could make the outcome depend on where a neuron starts.

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DATA AVAILABILITY

No data were collected or analyzed in this study. All values in the worked example and the repeated-update control follow from Eqs. 6 to 9 and can be reproduced by hand from the values given in Section IV.C.

COMPETING INTERESTS

I declare no competing interests.

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