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Posted Date: 11 August 2026

doi: 10.20944/preprints202507.2002.v4

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Hypothesis

An Etiological, Pathophysiological, and Rehabilitative Framework for Focal Task-Specific Dystonia: An M1-Centered Motor Synergy Hypothesis

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Abstract

Focal task-specific dystonia (FTSD) is an isolated dystonia in which abnormal muscle contractions occur only during a particular motor task while most other movements remain relatively spared. In this Hypothesis article, we propose that FTSD arises within a task-specific motor synergy (TSMS) in primary motor cortex (M1), a local excitatory-inhibitory ensemble supporting a specific movement component of the affected task. We hypothesize that excitatory synapses within the affected TSMS become disproportionately strong relative to parvalbumin (PV)-centered inhibitory circuitry, creating a hyperexcitable dystonic synergy recruited when attempted task intensity exceeds the capacity of the residual functional synergy. A change in movement coordination is proposed to reduce the capacity of a previously established TSMS, producing task-specific true weakness at higher intensities. Repeated overreaching beyond this reduced capacity may then favor excitatory over inhibitory strengthening, consolidate the dystonic synergy, and generate the symptom-threshold phenomenon. A spiking neural network provides a conditional proof of concept that specified functional and E/I-imbalanced conditions can exhibit an input-dependent crossover in relative population firing. Finally, we propose below- or at-threshold retraining (BATR), in which symptom-free practice may promote inhibitory rebalancing and raise the symptom-threshold. This framework offers an experimentally testable M1-centered account of FTSD.

Keywords: focal dystonia; musician's dystonia; rehabilitation; neuroplasticity; motor retraining; computational modeling

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Introduction

Background and Rationale

Focal task-specific dystonia (FTSD) is an isolated dystonia in which abnormal muscle contractions are elicited during a particular motor activity or task while most other movements remain relatively spared (Albanese et al., 2025; Frucht, 2014; Stahl & Frucht, 2017). Because symptoms may remain restricted to one task or task condition, FTSD provides a useful model for investigating maladaptive sensorimotor plasticity (Quartarone et al., 2006). Neurophysiological studies have repeatedly reported reduced short-interval intracortical inhibition (SICI) and evidence consistent with primary motor cortex (M1) hyperexcitability in FTSD (Furuya et al., 2018; Ridding et al., 1995; Siebner et al., 1999). These findings support a disturbance of rapid intracortical inhibitory control, but they do not by themselves identify the initiating anatomical site, the responsible interneuron class, or the causal sequence through which FTSD develops.

Basal ganglia-, cerebellar-, and network-centered accounts have each organized important aspects of the dystonia literature. Basal ganglia models emphasize altered direct- and indirect-pathway signaling in dystonia (Simonyan et al., 2017). Cerebellar accounts emphasize abnormal

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motor calibration and cerebello-cortical plasticity (Teo et al., 2009), whereas distributed-network models emphasize abnormal interactions among cortical, basal ganglia, thalamic, cerebellar, sensory, and spinal components of the motor system. These perspectives are compatible with a substantial body of neuroimaging and neurophysiological evidence. Nevertheless, the conjunction of marked task specificity, relative preservation of other movements, and intensity-dependent symptom expression remains only partially explained at the level of a specific motor-generating circuit.

In this Hypothesis article, we advance an M1-centered account in which the relevant unit of dysfunction is a task-specific motor synergy (TSMS): a local excitatory-inhibitory ensemble in M1 that supports a particular unidirectional movement component within an affected task. We hypothesize that excitatory synaptic strength within the affected TSMS becomes disproportionately strong relative to rapid inhibitory control centered on parvalbumin-expressing (PV) interneurons. This proposed imbalance would create a hyperexcitable dystonic synergy that becomes preferentially recruited when task demands exceed the capacity of the residual functional synergy. Reduced SICI and disturbed surround inhibition are consistent with impaired rapid cortical inhibition, but current human TMS methods do not provide cell-type- or synapse-specific resolution. PV involvement is therefore treated here as a mechanistic inference and experimentally testable hypothesis rather than as a directly established cellular lesion.

We further propose a candidate etiological pathway in which a substantial change in the spatiotemporal coordination of a previously learned movement reduces the effective excitatory and inhibitory capacity of the corresponding TSMS. Repeated attempts to perform above this reduced capacity are hypothesized to generate fragmented or poorly coordinated cortical activity that strengthens excitatory connections without equivalent strengthening of inhibitory circuitry. Over time, this asymmetric plasticity may consolidate a dystonic synergy and produce the characteristic symptom-threshold phenomenon. Predisposing biological factors may influence susceptibility to this process. For example, altered cortical inhibition in non-manifesting DYT1 carriers indicates that abnormal excitability can exist without overt dystonia, consistent with the possibility that physiological predisposition may be insufficient by itself for clinical expression (Edwards et al., 2003).

FTSD is also associated with abnormalities outside M1, including altered basal ganglia signaling, cerebellar connectivity and modulation, somatosensory processing, and spinal inhibition (Elbert et al., 1998; Kita et al., 2021; Simonyan et al., 2017; Tinazzi et al., 2003). The existence of these abnormalities is not disputed, but their temporal and causal relationship to cortical dysfunction remains unresolved. The present framework hypothesizes that at least some extra-M1 findings arise or become reinforced through repeated activation of an abnormal M1 synergy. A companion Hypothesis article, *Focal Task-Specific Dystonia Beyond M1: Network Adaptations and a Synergy-Based Taxonomy of Dystonia*, develops these proposed extra-M1 network adaptations in greater detail. The proposed causal ordering should be understood as a testable prediction rather than as an established conclusion.

Current treatments for FTSD include botulinum toxin injections, oral medications, task modification, rehabilitative interventions, and, in selected severe cases, surgical treatment (Stahl & Frucht, 2017; Grigoriu et al., 2015). These approaches can provide meaningful symptomatic benefit, but they are not specifically designed to test or reverse the TSMS-level synaptic imbalance proposed here. Interest in motor retraining has grown from the broader view that dystonia involves maladaptive plasticity (Quartarone & Hallett, 2013). Reports of slow-down exercise and related sensorimotor retraining have described substantial improvement, including near-complete recovery in individual cases, although the evidence remains limited and the responsible neurophysiological mechanisms have not been established (Sakai, 2006; van Vugt et al., 2014; Yoshie et al., 2015). Building on this work, we formulate below- or at-threshold retraining (BATR) as a mechanism-informed rehabilitation hypothesis in which symptom-free practice is predicted to promote rebalancing of excitatory and inhibitory synaptic efficacy within the affected TSMS, thereby strengthening rapid inhibitory control relative to excitation.

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Threshold Phenomenon and Key Terminology

Many FTSD phenotypes exhibit a symptom-threshold phenomenon in which the affected task can be performed without overt dystonic symptoms at lower movement intensities or under specific symptom-sparing task conditions, whereas dystonic contractions emerge once task demands exceed a particular level (Ehrlich et al., 2023; Haslinger et al., 2005; Sakai, 2006; Yoshie et al., 2015). We use symptom-threshold to denote the highest task intensity, under a specified performance condition, at which overt dystonic symptoms remain absent. The symptom-threshold is a behavioral construct whose defining movement parameters are task-specific and may consist of a single dominant variable, such as speed or force, or a multidimensional combination of movement demands.

This term is distinct from spike threshold, or firing threshold, which denotes the membrane-potential level at which an individual neuron generates an action potential. We therefore hyphenate symptom-threshold when referring to the behavioral phenomenon and use spike threshold when referring to neuronal firing. The computational crossover introduced later is defined separately and is treated as a proposed qualitative analogue of the behavioral symptom-threshold rather than as a directly calibrated equivalent.

Scope and Objectives

This Hypothesis article synthesizes published evidence; it presents no original human-participant or animal data and does not report a clinical case. It has four principal aims: first, to propose an M1-centered mechanism in which FTSD arises from an imbalance between excitatory pyramidal circuitry and PV-centered inhibitory control within an affected TSMS; second, to outline a candidate etiological sequence linking altered movement coordination and repeated overreaching to formation of an excitatory-dominant dystonic synergy; third, to formulate BATR as a testable rehabilitation hypothesis; and fourth, to use a spiking neural network model to test whether an imposed excitation-inhibition (E/I) difference can generate an input-dependent crossover between specified functional and E/I-imbalanced model conditions. The model addresses only this restricted network-level proposition and does not establish M1 localization, PV specificity, the proposed etiological sequence, or BATR efficacy. The framework is intended to generate falsifiable predictions that can be compared with basal ganglia-primary, cerebellar-primary, and distributed-network alternatives.

The Proposed M1-Centered TSMS Framework

Core Pathophysiological Hypothesis: PV-Centered E/I Imbalance within an M1 TSMS

Definition and Proposed Organization of a TSMS

Motor synergies are commonly described at a macro level as coordinated patterns of muscle activation that support a movement or motor subtask (Safavynia et al., 2011). Here, we use the term task-specific motor synergy (TSMS) in a narrower, hypothesis-level sense to denote a task-dependent ensemble of pyramidal neurons and local inhibitory interneurons within the relevant M1 representation that contributes to a particular unidirectional movement component of an effector. At the muscular level, that component may be generated by several prime movers; for example, a finger-flexion TSMS may recruit both intrinsic hand and extrinsic forearm muscles that routinely act together to flex the relevant digit. Proximal stabilizers and muscles that influence posture without directly generating the specified movement direction are treated as interacting with, but not constituting the primary output of, the TSMS.

A muscle may participate in more than one TSMS when it contributes to several movement directions, and individual cortical neurons may participate in multiple, partially overlapping TSMSs. The TSMS is therefore proposed as a task-dependent functional microcircuit rather than a discrete anatomical module or a one-to-one mapping among neurons, muscles, and movements. Its organization is hypothesized to emerge through repeated co-recruitment of excitatory and inhibitory elements during performance of a learned movement component, making it the circuit-level unit in which the proposed FTSD-related E/I imbalance is instantiated.

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PV-Centered Inhibitory Control in a Functional TSMS

Across the neocortex, including M1, nearly all GABAergic interneurons fall within three non-overlapping molecular families: parvalbumin-positive (PV), somatostatin-positive (SST), and ionotropic serotonin receptor 5HT3a-expressing (5HT3aR) interneurons (Rudy et al., 2011). We focus on PV fast-spiking interneurons because their rapid, predominantly $GABA_A$-mediated perisomatic inhibition is well positioned to regulate the timing, gain, and spatial specificity of pyramidal population activity (Tian & Izumi, 2022). SST and 5HT3aR interneurons may also contribute to TSMS function and are considered separately below.

Within a functional TSMS, increasing pyramidal activity is expected to recruit matched local inhibitory circuitry. Excitatory input onto inhibitory neurons (E→I) drives rapid feedback inhibition, while inhibitory output onto pyramidal neurons (I→E) limits excessive or spatially diffuse firing. This recurrent interaction is conceptually analogous to pyramidal-interneuron network gamma, or PING-like, coupling, although the TSMS hypothesis does not require a particular gamma-oscillatory regime (Keeley et al., 2017).

Motor-skill learning is accompanied by experience-dependent remodeling of excitatory and inhibitory circuitry in M1, including strengthening of horizontal intracortical connections, LTP-like modification and occlusion, subtype-specific reorganization of inhibitory contacts, and phase-dependent changes in glutamatergic and GABAergic transmission (Chen et al., 2015; Kida et al., 2016; Rioult-Pedotti et al., 1998, 2000). Coordinated plasticity across excitatory and inhibitory inputs can also regulate the local E/I relationship in other cortical preparations (D'Amour & Froemke, 2015; Field et al., 2020). On this basis, we propose that E-E, E→I, and I→E motifs within a functional TSMS become jointly adapted during skill acquisition, allowing output to scale while rapid inhibitory control and movement specificity are preserved. Existing evidence supports experience-dependent E/I remodeling but does not directly establish proportional co-strengthening of these motifs within a human TSMS. At the systems level, such organization would be compatible with normal SICI and an appropriate balance between intracortical inhibition and facilitation. However, SICI and intracortical facilitation are indirect population-level measures and do not by themselves reveal synapse-specific strengths or identify the interneuron class responsible for inhibition within an individual TSMS.

Neurophysiological Evidence and Cell-Type Inference

In FTSD, we hypothesize that recurrent excitation and rapid local inhibition become mismatched within the affected TSMS. Specifically, E-E connectivity is proposed to become disproportionately strong relative to the E→I and/or I→E motifs that recruit and deliver fast inhibitory control. This constitutes a relative circuit imbalance rather than a complete loss of inhibition: PV-centered circuitry may remain functional but fail to scale adequately as excitatory drive and task demand increase. The imbalance could therefore reflect insufficient recruitment of PV interneurons, reduced efficacy of their inhibitory output, or both.

A substantial TMS literature in FTSD and related focal dystonias reports reduced SICI (e.g., Furuya et al., 2018; Huang et al., 2010; McDonnell et al., 2007; Ridding et al., 1995; Siebner et al., 1999; Stinear & Byblow, 2004). Because SICI is strongly influenced by rapid $GABA_A$ receptor-mediated intracortical inhibition, these findings are consistent with deficient fast inhibitory control in M1 (Di Lazzaro et al., 2006). They do not directly measure E→I or I→E strength within a TSMS or uniquely identify PV interneurons. The PV-centered account therefore rests on the convergence of the SICI phenotype, the rapid time course of the inhibitory abnormality, and the fast-spiking, perisomatic role of PV interneurons, making it a biologically motivated cellular hypothesis rather than a cell-type-specific finding established in humans.

Findings for long-interval intracortical inhibition (LICI) are more heterogeneous: LICI has been reported as normal in some cohorts (Furuya et al., 2018; Meunier et al., 2012), reduced in others (Chen et al., 1997; Espay et al., 2006), and occasionally increased (Caux-Dedeystère et al., 2021). This contrast with the more frequently reported reduction in SICI suggests that rapid and slower inhibitory processes are not affected uniformly across FTSD phenotypes. It does not exclude SST or 5HT3aR

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involvement, but it motivates the comparison below between deficient rapid perisomatic inhibition and disturbances of slower dendritic or disinhibitory pathways.

Alternative Interneuron Classes and Phenomenological Predictions

A useful qualitative comparison can be drawn between the predicted consequences of disturbances in rapid perisomatic inhibition and those of disturbances in slower dendritic or disinhibitory pathways. Shao and Burkhalter (1999) demonstrated that slow $GABA_B$ receptor-mediated inhibition can constrain late polysynaptic activity: blocking this inhibition in rat visual cortex unveiled reverberant excitatory responses following an initial stimulus. Because dendrite-targeting SST/Martinotti-cell motifs recur across neocortical areas, including M1, these findings motivate the possibility that a predominant reduction of slower dendritic inhibition in a motor circuit would prolong or destabilize recurrent excitation after an initial motor command (Jiang et al., 2015).

In an idealized TSMS, such a disturbance might be expected to favor delayed, reverberant, or temporally fragmented activity rather than solely increasing the immediate gain of the initial pyramidal response. This prediction differs qualitatively from many FTSD presentations, in which the affected task elicits sustained or patterned co-contraction once the symptom-threshold is crossed. The comparison is nevertheless inferential rather than diagnostic. The relevant evidence was obtained outside human M1, $GABA_B$-mediated inhibition cannot be assigned uniquely to one interneuron population, and FTSD itself can include mixtures of tonic, phasic, and tremulous features. Clinical phenomenology therefore cannot exclude SST involvement or establish interneuron identity by itself.

By contrast, a predominant reduction of rapid PV-centered perisomatic inhibition, with slower dendritic inhibitory mechanisms remaining relatively preserved, would be expected to increase the probability and spatial extent of the initial pyramidal population response. Continued recurrent excitation could then sustain an elevated output state while slower inhibitory processes limit late reverberation. This configuration provides a plausible qualitative account of a task-bound contraction that emerges when input exceeds a particular intensity and remains present during continued performance. It does not demonstrate that PV dysfunction is sufficient to cause biological FTSD, but it identifies a network phenotype that is consistent with the proposed PV-centered mechanism.

A similar qualification applies to 5HT3aR interneurons, including vasoactive-intestinal-peptide-positive (VIP) populations that frequently inhibit SST interneurons and thereby regulate dendritic disinhibition. Reduced VIP output could enhance SST-mediated inhibition and decrease pyramidal gain, whereas excessive VIP recruitment could reduce dendritic inhibition and facilitate recurrent excitation. These effects are strongly state- and circuit-dependent, however, and cannot be mapped uniquely onto a particular clinical movement phenotype. The present framework therefore does not require SST or VIP circuitry to be entirely normal. Rather, it proposes that deficient rapid PV-centered inhibitory control is the dominant abnormality responsible for the core threshold-dependent motor output, while SST- and 5HT3aR-related pathways may modify its expression.

This comparison generates a testable prediction. Selective weakening of PV-centered inhibition within an experimentally defined motor ensemble should reproduce threshold-dependent excessive and sustained output more consistently than comparable disruption of SST- or VIP-centered pathways. Conversely, selective restoration of PV recruitment or output should increase the input level at which abnormal activity emerges. Direct cell-type-specific manipulation and recording will be required to evaluate these predictions.

Surround Inhibition and Motor-Output Consequences

Within the proposed framework, dystonic output can be recruited through direct or indirect routes. In the direct case, the affected TSMS itself is driven above its symptom-threshold. At lower attempted intensities, residual rapid inhibition may remain sufficient to constrain pyramidal output; as attempted intensity increases, excitatory recruitment is hypothesized to outpace the available inhibitory control, pushing the TSMS into a hyperexcitable regime that produces involuntary contraction, posturing, or other dystonic output.

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In the indirect case, strong activation of a neighboring TSMS generates excitatory activity that spreads toward the affected representation. Surround inhibition would normally suppress this competing output, but a deficient inhibitory boundary may allow the spillover to recruit the affected TSMS into its dystonic regime. Direct symptom expression therefore reflects insufficient control when the affected TSMS itself is strongly recruited, whereas surround-inhibition failure reflects inadequate suppression of that TSMS during recruitment of a neighboring representation.

This indirect route offers a candidate explanation for the disturbed surround inhibition reported in focal hand dystonia (Beck & Hallett, 2011; Beck et al., 2009; Sohn & Hallett, 2004). Rapid local inhibition is well positioned to suppress competing cortical outputs, and deficient PV-centered control could facilitate spillover into an affected TSMS. Human surround inhibition is nevertheless an emergent systems-level phenomenon that may involve several cortical and subcortical processes; its proposed dependence on PV-centered synaptic weakness is therefore a prediction of the framework rather than an established cellular explanation.

More generally, at the synaptic level, the proposed TSMS E/I imbalance could arise through reduced excitatory recruitment of inhibitory neurons (E→I), reduced inhibitory efficacy onto pyramidal neurons (I→E), or both. Reduced SICI is compatible with diminished net $GABA_A$-mediated inhibition but does not distinguish these loci. Experimental disruption of local $GABA_A$-mediated inhibition nevertheless demonstrates that cortical disinhibition can degrade motor selectivity. In nonhuman primates, focal bicuculline application to motor or premotor cortex produced abnormal motor output, including inappropriate agonist-antagonist co-contraction (Matsumura et al., 1991). In humans with focal dystonia, peripheral afferent input that normally suppresses motor cortical output has instead been reported to facilitate it, supporting abnormal inhibitory gating of sensorimotor input (Abbruzzese et al., 2001). These observations support a contribution of insufficient rapid inhibition in M1 without identifying a particular interneuron class or synaptic locus.

I-wave studies provide an additional, indirect probe of this circuitry. In healthy M1, a subthreshold conditioning pulse can suppress later I-wave components more strongly than the earliest I1 component, indicating differential intracortical regulation of the indirect volleys contributing to corticospinal output (Hanajima et al., 1998). Current direction also biases recruitment of partly distinct cortical circuits: posterior-anterior stimulation commonly favors earlier I-wave recruitment, whereas anterior-posterior stimulation can place greater weight on later indirect-wave circuitry (Di Lazzaro et al., 2001).

In focal hand dystonia, Hanajima et al. (2008) reported reduced SICI under one current orientation while inhibition under another was comparatively preserved. This pattern indicates that intracortical inhibition is altered in a circuit- and orientation-dependent manner rather than uniformly absent. Similarly, the greater conditioning-pulse intensity sometimes required to elicit SICI suggests reduced recruitability or an altered operating state of the inhibitory network (Stinear & Byblow, 2004). These findings are compatible with insufficient E→I recruitment of rapid inhibitory circuitry, although altered interneuron excitability, differences in the excitatory populations sampled by TMS, and broader network-state changes remain possible.

Taken together, the evidence supports three relatively secure conclusions: rapid intracortical inhibition is frequently altered in FTSD; surround inhibition and sensorimotor gating are disturbed in at least some phenotypes; and experimentally reducing local $GABA_A$-mediated inhibition in motor cortex can produce abnormal co-contraction and loss of motor selectivity. The more specific claim advanced here is that these findings arise from insufficiently strengthened PV-centered E→I and/or I→E circuitry relative to E-E connectivity within an affected TSMS. That claim remains a mechanistic hypothesis. If correct, cell-type-specific measures should reveal deficient PV recruitment or output within the affected motor ensemble, and restoration of that inhibitory control should expand the range of task intensity over which normal motor output is maintained.

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Proposed Etiological Pathway: From Altered Movement Coordination to Dystonic Synergy

Reorganization of a Previously Learned TSMS

The sequence developed below proposes how FTSD could arise following a substantial alteration in the spatiotemporal coordination of a previously learned movement. Such alterations may result from a deliberate technique change or from another change in how an established task is executed. We do not propose that altered coordination ordinarily produces dystonia; rather, under particular conditions, it may reduce the effective capacity of an established TSMS and create a state in which subsequent overreaching becomes maladaptive.

When a learned task is executed with a substantially different coordination pattern, the new movement is unlikely to recruit a wholly separate population of M1 neurons. Motor cortical populations are broadly tuned to movement direction, muscle combinations, and other movement features, and individual neurons can contribute to multiple, partially overlapping ensembles (Economo et al., 2024 and references therein; Shinotsuka et al., 2023). The prior and altered coordination patterns are therefore expected to share some neuronal and synaptic components while differing in others.

At the movement level, this overlap may reflect shared directional, muscular, or joint-related features. Two methods of producing the same piano keystroke, for example, may differ in global hand posture, force distribution, and interdigit coordination while preserving flexion of a particular digit or stabilization of neighboring fingers. Cortical populations contributing to these shared components may continue to be recruited, whereas populations and temporal relationships supporting features unique to the prior pattern may be recruited differently.

At the microcircuit level, the overlap is hypothesized to include E-E connectivity together with associated E→I and I→E motifs. Because pyramidal neurons and inhibitory interneurons may participate in multiple task-dependent ensembles, some previously strengthened connections may remain appropriate for the altered movement and continue to be recruited. The prior and altered TSMSs should therefore be understood as partially overlapping functional configurations rather than anatomically separate networks dedicated to an “old” and a “new” technique. Connections whose recruitment and timing remain compatible with the altered coordination may retain or further strengthen their efficacy, whereas connections optimized for relationships no longer present may become susceptible to weakening.

Plasticity during Altered Movement Coordination

A central premise of the proposed pathway is that learned synaptic efficacy is instantiated at particular connections and activity relationships rather than being freely transferable between motor patterns. Long-term changes in excitatory efficacy can involve postsynaptic receptor trafficking and presynaptic modification, while motor training in M1 is accompanied by the formation and selective stabilization of dendritic spines (Beattie et al., 2000; Kida et al., 2016; Xu et al., 2009). An altered coordination pattern therefore cannot automatically inherit all of the efficacy accumulated during practice of the prior pattern. Connections newly required for the altered movement must acquire or stabilize efficacy through their own activity, whereas previously strengthened connections that no longer match the new coordination may become susceptible to weakening.

We propose that this weakening can reflect active interference rather than passive loss through disuse alone. Altered coordination changes the correlation, firing-rate, and timing relationships experienced by neurons within the partially overlapping ensemble. The direction and magnitude of synaptic plasticity depend jointly on relative spike timing, repetition rate, initial synaptic state, and cooperativity among inputs, and LTD can be expressed through AMPA-receptor endocytosis (Beattie et al., 2000; Bi & Poo, 1998; Sjöström et al., 2001). Connections that remain appropriately aligned with postsynaptic firing may therefore undergo Hebbian maintenance or potentiation, whereas those repeatedly recruited under decorrelated or systematically altered timing conditions may weaken or fail to retain previously stabilized efficacy. Applying these principles to an altered human TSMS remains a mechanistic extrapolation.

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The same timing-based interference may affect the inhibitory motifs coupled to the excitatory ensemble. Plasticity at excitatory synapses onto inhibitory interneurons varies according to interneuron type, and inhibitory synapses onto pyramidal neurons can undergo timing-dependent potentiation or depression (D'Amour & Froemke, 2015; Lu et al., 2007; Vickers et al., 2018). Altered coordination could therefore change E-E, E→I, and I→E efficacy differently. Previously useful E-E connections may weaken when their activity no longer predicts postsynaptic firing; altered pyramidal-interneuron timing may reduce the subsequent recruitment of inhibitory cells; and inhibitory output may become less effectively aligned with its pyramidal targets. The framework does not require a universal direction of plasticity at every inhibitory synapse, but proposes that reorganization of the relevant timing relationships can partially destabilize the matched excitatory and inhibitory architecture of the prior TSMS.

Several additional forms of plasticity may reinforce this redistribution. Heterosynaptic plasticity can coordinate changes across paired and unpaired excitatory and inhibitory inputs and influence the local E/I set point (Field et al., 2020). Recent activity can alter the threshold or direction of subsequent plasticity through metaplastic mechanisms, including changes associated with NMDA-receptor function (Philpot et al., 2003). Synaptic tagging and capture allows transiently tagged excitatory synapses to use plasticity-related products generated by stronger activity elsewhere in the same neuron (Frey & Morris, 1997), while motor learning can rapidly reorganize excitatory spines and interneuron boutons in M1 and selectively stabilize a subset of newly formed structures (Chen et al., 2015; Xu et al., 2009). Together, these processes could favor stabilization of connections repeatedly aligned with the altered movement while allowing poorly aligned connections to weaken or fail to reconsolidate. Whether analogous tagging-and-capture mechanisms stabilize E→I or I→E motifs within an M1 TSMS remains unknown.

This account does not require a fixed, circuit-wide supply of potentiation that must be divided between the prior and altered patterns. Efficacy is instead proposed to be redistributed through changes in activity statistics, synapse-specific competition, and selective consolidation. Some elements of the prior TSMS remain appropriate and are preserved, whereas others weaken and newly relevant motifs remain incompletely strengthened.

We use the term partial baseline shift to describe the resulting reduction in the functional capacity of the altered TSMS. The shift is partial because overlap with the prior coordination preserves sufficient circuitry for lower-demand performance rather than eliminating the movement entirely. At higher task demands, however, the preserved and newly recruited excitatory and inhibitory motifs may not yet possess the efficacy or coordination required to reproduce the performance capacity of the previously consolidated movement.

Movement Intensity and Functional TSMS Capacity

Within this framework, movement intensity denotes the level of task demand placed on a TSMS. Its behavioral expression is task-specific and may involve speed, force, movement amplitude, pressure, vocal intensity, or a combination of these variables. Piano performance may vary in keystroke speed and force, writing in speed and pen pressure, and phonation in loudness and articulatory demand. Movement intensity therefore does not correspond to one universal physical variable across all FTSD phenotypes.

At the neural level, increasing intensity is hypothesized to involve changes in the magnitude and temporal organization of population activity, including recruitment of additional pyramidal neurons, increases in mean firing rate, and changes in population timing or synchrony. This activity is shaped by premotor and supplementary motor regions, basal ganglia-thalamo-cortical circuits, cerebellar pathways, and sensory feedback. The present framework represents the final cortical expression of this broader network command in simplified form as the net drive delivered through the relevant TSMS.

Attempted intensity denotes the speed, force, loudness, or other task demand that the individual intends to produce, whereas realized output denotes the movement that is actually produced. Under

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normal conditions, the two remain appropriately matched throughout the functional range of the task.

We define the functional capacity of a TSMS as the highest task demand that its current excitatory and inhibitory architecture can implement with the intended movement pattern and without either task-specific underproduction or dystonic output. Excitatory efficacy influences how strongly incoming activity recruits and depolarizes the pyramidal population, allowing a motor command to produce larger and more reliable corticospinal output. If excitatory efficacy is reduced, further increases in attempted intensity may produce smaller-than-intended increases in descending output and lower the maximum speed or force that can be implemented normally.

Inhibitory efficacy determines whether that output remains appropriately timed, scaled, and spatially selective. E→I connections influence how effectively increasing pyramidal activity recruits rapid inhibitory interneurons, while I→E connections determine how strongly those interneurons constrain pyramidal output. When these motifs scale appropriately with excitation, task demand can increase without uncontrolled firing or recruitment of competing representations. If rapid inhibitory control is disproportionately weak, the same increase in attempted intensity may instead produce excessive, spatially diffuse, or poorly regulated activity.

The operating state of a TSMS can therefore be described through the relationship between excitatory output capacity and inhibitory control capacity. When both are sufficiently strong and proportionate, attempted intensity is translated into the intended movement throughout the normal range. When both are reduced but remain approximately proportionate, controlled performance may be preserved at lower intensities while higher-intensity output becomes insufficient. When excitation becomes excessive relative to inhibition, increasing attempted intensity may recruit a hyperexcitable regime and produce involuntary output. These latter states form the basis of the proposed true-weakness and dystonic conditions.

Proposed True-Weakness State

We use the term true weakness to denote a proposed task-specific state in which an attempted increase in movement intensity fails to produce the corresponding increase in speed, force, or other relevant output, despite preserved lower-intensity performance and relative preservation of strength and dexterity outside the affected task. Unlike overt dystonia, true weakness is characterized by insufficient production of the intended movement rather than excessive or involuntary output.

Within the proposed etiological sequence, true weakness follows a partial baseline shift that has reduced the functional capacity of the relevant TSMS. The altered movement can still be executed normally within a lower-demand range because sufficient excitatory and inhibitory circuitry remains preserved or has become newly stabilized. At higher attempted intensities, however, the residual functional synergy lacks the effective gain required to generate the intended descending output.

The partial baseline shift is hypothesized to reduce both excitatory and inhibitory capacity while leaving them approximately proportionate. Excitatory output is limited, but inhibitory control has not yet become disproportionately weak relative to excitation. The circuit therefore remains broadly balanced while operating at a lower maximum capacity. This distinguishes true weakness from the later dystonic state, in which excitation has become excessive relative to rapid inhibitory control.

At the neural level, reduced excitatory efficacy limits recruitment and firing of the pyramidal population during a strong motor command. Corticospinal output consequently fails to recruit the motoneuron activity required for the intended high-intensity movement. Behaviorally, increasing effort produces a smaller-than-intended increase in realized output, so that the movement remains slower, weaker, or otherwise less intense than intended.

We define the true-weakness threshold as the highest task intensity at which attempted intensity can still be translated faithfully into realized output by the residual functional synergy. At or below this threshold, output scales appropriately with task demand. Above it, further increases in attempted intensity generate disproportionate effort with inadequate increases in realized output. In a three-state intensity landscape, the true-weakness range lies above the normal functional range but below the intensity at which an established dystonic synergy becomes dominant.

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True weakness is introduced as a testable behavioral and mechanistic construct rather than a validated clinical category. Prospective studies will need to determine whether such an intensity range can be measured reproducibly and distinguished from fatigue, pain, anxiety, peripheral neuromuscular weakness, biomechanical constraint, and compensatory movement.

Overreaching and Excitatory-Biased Plasticity

We use the term overreaching to denote repeated recruitment of a TSMS beyond the level of activity that its current excitatory and inhibitory architecture can implement normally. Overreaching may occur directly when the affected TSMS is intentionally driven above its reduced functional capacity, or indirectly when strong activation of a neighboring TSMS generates excitatory spillover that exceeds the surround-inhibitory capacity required to keep the affected representation suppressed.

In either case, the motor command is strong enough to recruit portions of the relevant excitatory ensemble but the weakened circuit cannot generate or regulate the complete population pattern required for the intended motor state. Activity may therefore become fragmented, weakly synchronized, temporally inconsistent, or insufficiently constrained. During direct overreaching, this produces an incomplete attempt to generate the intended high-intensity movement; during indirect overreaching, it produces partial or inappropriate recruitment of a TSMS that should have remained suppressed.

The central hypothesis is that repeated activity in this fragmented regime biases plasticity toward recurrent excitation. The relevant activity need not eliminate inhibitory recruitment. Rather, it must be sufficient to strengthen at least a subset of E-E connections while being less favorable for matched strengthening of E→I and I→E circuitry.

Several properties of cortical plasticity make such an asymmetry plausible. First, induction rules differ across synapse classes. Plasticity at excitatory cortical synapses depends jointly on spike timing, repetition rate, initial strength, and cooperativity, whereas E→I plasticity varies according to the postsynaptic interneuron type (Bi & Poo, 1998; Lu et al., 2007; Sjöström et al., 2001). A fragmented activity pattern could therefore affect E-E connections and excitatory recruitment of inhibitory neurons differently.

Second, rapid feed-forward and somatic inhibition narrows the temporal integration window of pyramidal neurons and improves spike-time fidelity (Gabernet et al., 2005; Pouille & Scanziani, 2001). Weakly synchronized or temporally dispersed excitatory packets may consequently recruit rapid inhibitory control less consistently than coherent population activity. The framework predicts that such activity can remain sufficient for incremental E-E strengthening while failing to produce equally reliable E→I adaptation.

Third, I→E synapses are themselves plastic. Timing-dependent changes have been demonstrated at cortical inhibitory synapses, including PV-interneuron output synapses, although their direction and induction requirements depend on timing, circuit context, and the pre-existing E/I state (D'Amour & Froemke, 2015; Vickers et al., 2018). Irregular interneuron recruitment during overreaching may therefore fail to generate the temporal relationships needed for strengthening of inhibitory output onto the active pyramidal population.

Finally, consolidation mechanisms could amplify an initially small asymmetry. Synaptic tagging and capture allows transiently potentiated excitatory inputs to use plasticity-related products generated by stronger activity elsewhere in the same neuron (Frey & Morris, 1997). Active E-E connections may therefore be tagged and stabilized more consistently than inhibitory motifs that are recruited weakly or irregularly. The extension of this mechanism to differential stabilization of E-E, E→I, and I→E circuitry in an M1 TSMS remains speculative.

These mechanisms are not mutually exclusive, and the proposed sequence has not been demonstrated directly in FTSD. Together, they define a testable plasticity hypothesis: repeated overreaching generates an activity regime that strengthens a recurrent excitatory subnetwork without producing proportionate strengthening of its rapid inhibitory control.

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Formation of the Dystonic Synergy and the Symptom-Threshold

Under the proposed pathway, repeated excitatory-biased plasticity may gradually produce a functionally differentiated subnetwork in which recurrent excitation has strengthened beyond the capacity of its matched rapid inhibitory control. We refer to this excitatory-dominant configuration as a dystonic synergy. It is not assumed to be anatomically separate from the residual functional synergy; instead, the two configurations may contain partially overlapping neurons and synapses while differing in their effective connectivity, recruitment conditions, and predominant operating ranges.

During its early formation, the dystonic synergy may function as a high-intensity extension of the residual functional synergy. At lower attempted intensities, the functional configuration remains dominant because its excitatory and inhibitory circuitry can still implement the movement normally. Above its reduced capacity, however, fragmented recruitment is hypothesized to strengthen an excitatory subset without proportionate strengthening of the associated inhibitory motifs. Continued overreaching increases the probability that this subset will recruit itself through recurrent excitation.

Once task-related input enters a range in which the excitatory-dominant configuration is more readily recruited than the residual functional configuration, the dystonic synergy is hypothesized to become dominant. Its inadequate inhibitory control then permits excessive, spatially inappropriate, or poorly regulated pyramidal activity, producing involuntary contraction, abnormal posturing, or recruitment of competing motor output.

Within this framework, the behavioral symptom-threshold represents the task demand at which the relative dominance of the two configurations changes. At or below the symptom-threshold, the residual functional synergy retains sufficient control to produce voluntary, symptom-free movement. Above it, the dystonic configuration is preferentially recruited and overt symptoms emerge. The symptom-threshold therefore reflects a network crossover between functional states rather than the complete absence of dystonia-related circuitry at lower intensities.

The functional and dystonic configurations are expected to overlap most strongly when dystonia first emerges. Some pyramidal neurons and inhibitory elements may participate in both lower-intensity voluntary movement and the higher-intensity dystonic state. Repeated activation in the higher-intensity range could then selectively stabilize the synaptic relationships supporting the dystonic configuration while the residual functional synergy continues to govern lower-demand performance.

Metaplasticity, synaptic consolidation, and structural remodeling may progressively make the dystonic configuration more reproducible. Prior activity can alter the threshold or direction of subsequent plasticity (Philpot et al., 2003), synaptic tagging and capture can stabilize selected excitatory inputs (Frey & Morris, 1997), and motor learning in M1 can generate and preserve new dendritic spines associated with enduring motor memory (Xu et al., 2009). By analogy, repeated high-demand recruitment could preferentially stabilize E-E connections within the emerging dystonic configuration, while less consistently recruited E→I and I→E motifs undergo weaker consolidation. This would allow the dystonic synergy to develop from a transient high-intensity extension of the residual circuit into a stable, threshold-dependent network state.

This progression has not been observed directly at the circuit level. It provides a candidate explanation for the coexistence of normal lower-intensity performance and abnormal higher-intensity output and generates a specific prediction: experimentally increasing inhibitory control relative to recurrent excitation should raise the symptom-threshold, whereas weakening that control should lower it.

Persistence and a Three-State Intensity Landscape

Once repeatedly consolidated, a dystonic configuration may become relatively stable, although it is not assumed to be anatomically independent of the residual functional synergy or immune to subsequent plasticity. Its persistence may arise partly from differences in the operating ranges and activation histories of the two configurations. The functional synergy remains repeatedly active during lower-intensity, symptom-free performance, whereas the dystonic synergy is recruited

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primarily at higher intensities and may subsequently be activated less often if symptom-provoking movements are avoided.

This difference in use may make the residual functional synergy more susceptible to further changes in movement coordination. A new coordination pattern practiced within the symptom-free range repeatedly engages and reshapes the functional configuration. By contrast, the higher-intensity dystonic configuration may be less strongly affected if the new pattern is practiced below the symptom-threshold and therefore does not recruit it extensively. Its relative preservation would reflect a different activation and consolidation history rather than complete separation from the functional circuitry.

Saturation or occlusion of excitatory connections may also contribute to persistence without requiring indefinite progression. Motor-skill learning can strengthen horizontal connections in M1 and reduce the amount of additional experimentally inducible LTP, indicating that prior learning alters the remaining range of synaptic modification (Rioult-Pedotti et al., 1998, 2000). If repeated overreaching brings a substantial portion of the dystonic configuration's E-E connectivity toward a local potentiation ceiling, subsequent activation may produce diminishing additional strengthening. This provides one possible explanation for why a dystonic pattern can remain stable rather than continually increasing in severity.

If the residual functional synergy undergoes a further reduction in capacity while an established dystonic configuration remains expressed at a higher intensity, the framework predicts a possible three-state intensity landscape. At lower intensities, at or below the true-weakness threshold, attempted and realized output remain appropriately matched. At intermediate intensities, task demand exceeds the reduced capacity of the functional synergy but remains below recruitment of the established dystonic configuration, producing a true-weakness range in which greater effort yields inadequate output. At higher intensities, above the symptom-threshold, the dystonic configuration becomes preferentially recruited and overt symptoms emerge.

This three-state organization is predicted only when residual functional capacity has fallen sufficiently to create a measurable interval between the true-weakness threshold and the symptom-threshold. Repeated changes in movement coordination without adequate consolidation constitute one possible route to such a state. These intensity boundaries also define the operating range targeted by the rehabilitation hypothesis described next.

Rehabilitative Hypothesis: Below- or At-Threshold Retraining

Definition and Relationship to Existing Retraining Approaches

Within the present framework, the central rehabilitative prediction is that repeated practice confined to a symptom-free and functionally intact range may progressively rebalance activity within the affected TSMS. We refer to this principle as below- or at-threshold retraining (BATR). BATR is defined as systematic practice of the affected movement at or below the highest task intensity at which it can be executed accurately and without overt dystonic symptoms.

In a proposed three-state intensity landscape that also includes true weakness, the relevant training limit is the lower of the symptom-threshold and the true-weakness threshold. Practice above the true-weakness threshold, even if it remains below the symptom-threshold, would exceed the current capacity of the residual functional synergy and could reproduce the fragmented activity regime hypothesized to promote maladaptive plasticity. BATR therefore confines practice to a range in which attempted intensity and realized output remain appropriately matched.

The variable defining this range is task-specific and need not be movement speed alone. Depending on the FTSD phenotype, the relevant demand may include force, movement amplitude, pressure, vocal intensity, intereffector coordination, or a multidimensional combination of variables. Practice should recruit the intended movement reliably while remaining within the current functional capacity of the TSMS. The optimal location within this range, the required number of repetitions, and the most effective progression schedule remain empirical questions.

BATR is conceptually related to the slow-down exercise described by Sakai (2006) and subsequently examined by Yoshie et al. (2015), as well as to related sensorimotor retraining

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approaches evaluated in musicians with dystonia (van Vugt et al., 2014). These reports provide clinical precedent for the possibility that carefully constrained, symptom-sparing practice can improve task performance, but they do not establish a universal treatment protocol or demonstrate that improvement occurs through PV-mediated synaptic strengthening.

The principal contribution of BATR is therefore not simply a recommendation to perform the task slowly. It defines practice relative to an individualized symptom-threshold and, where applicable, a true-weakness threshold; allows the controlling task variable to differ across FTSD phenotypes; and links symptom-free performance to a specific, testable hypothesis of TSMS-level E/I rebalancing.

Proposed Neurophysiological Mechanism of BATR

The proposed mechanism of BATR follows from the contrast between activity within and beyond the functional capacity of a TSMS. During overreaching, pyramidal activity is hypothesized to become fragmented, weakly coordinated, or insufficiently constrained, favoring recurrent excitatory strengthening without proportionate adaptation of rapid inhibitory control. During BATR, by contrast, practice remains within a range that the residual functional synergy can implement normally. Pyramidal activity is therefore predicted to be more coherent and to recruit matched inhibitory circuitry more reliably.

Repeated high-fidelity performance within this range may promote coordinated adaptation across E-E, E→I, and I→E motifs. Motor learning in M1 remodels both excitatory and inhibitory circuitry, although these changes are phase- and subtype-specific rather than a simple monotonic increase in inhibition. Learning has been associated with increased PV-related perisomatic boutons, reduced SST-related distal boutons, and dynamic changes in glutamatergic and GABAergic transmission (Chen et al., 2015; Kida et al., 2016). In other cortical preparations, coordinated homosynaptic and heterosynaptic plasticity across excitatory and inhibitory inputs can adjust the local E/I relationship (D'Amour & Froemke, 2015; Field et al., 2020). On this basis, we hypothesize that symptom-free practice produces activity patterns that recruit rapid inhibitory circuitry more consistently and support more proportionate adaptation of excitatory and inhibitory motifs than above-capacity practice.

The framework further proposes that the functional and dystonic configurations are only partially segregated. They may share pyramidal neurons, inhibitory interneurons, and local inhibitory projections. If PV interneurons recruited during functional movement also receive input from, or project onto, pyramidal neurons participating in the dystonic configuration, repeated symptom-free practice could strengthen inhibitory control across both states.

Under this shared-circuit hypothesis, recruitment of the functional synergy repeatedly drives E→I input onto overlapping inhibitory neurons and delivers I→E output to a broader local pyramidal population. Such activity could strengthen inhibitory recruitment within the functional configuration while also stabilizing inhibition onto pyramidal neurons that participate preferentially in the dystonic configuration. BATR could therefore improve control of the dystonic synergy without repeatedly driving its excitatory-dominant state into overt expression.

The dystonic excitatory configuration need not be completely silent during below-threshold movement because some pyramidal neurons may participate in both configurations. The critical distinction is which network state organizes the population activity. During BATR, the residual functional configuration is predicted to remain dominant and to recruit inhibition effectively, rather than allowing the excitatory pattern associated with above-threshold dystonic output to assume control. The resulting plasticity would therefore be expected to favor balanced circuit stabilization rather than further consolidation of the dystonic state.

Several cellular processes could support this adaptation. Plasticity at E→I synapses depends on interneuron target type, and PV-interneuron output synapses can undergo timing-dependent changes in efficacy (Lu et al., 2007; Vickers et al., 2018). Activity-dependent modification of postsynaptic inhibitory strength can also involve changes in $GABA_A$-receptor organization, including gephyrin-dependent receptor immobilization during inhibitory LTP in non-M1 preparations (Petrini

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et al., 2014). These mechanisms provide plausible routes through which repeated, appropriately timed activity could improve excitatory recruitment of inhibitory neurons and their output onto pyramidal cells. Synaptic tagging and capture may additionally support consolidation, although its extension from excitatory LTP to stabilization of E→I or I→E motifs during BATR remains uncertain.

As rapid inhibitory control strengthens relative to the recurrent excitation of the dystonic configuration, progressively greater task-related input should be required to recruit the hyperexcitable state. The principal behavioral prediction is therefore an upward shift of the symptom-threshold: intensities that previously produced dystonic output increasingly remain under functional control. In a three-state landscape, strengthening of the residual functional synergy could also raise the true-weakness threshold by expanding the range over which attempted intensity is translated accurately into realized output.

This recovery process does not require immediate erasure of the excitatory connections supporting the dystonic configuration. Functional rebalancing may occur once inhibitory recruitment and output become sufficient to constrain those connections across the required range of task demand. Longer-term practice could also remodel maladaptive excitatory relationships, but that additional process is not necessary for the primary inhibitory-rebalancing hypothesis.

If BATR operates through the proposed mechanism, behavioral improvement should covary with recovery of rapid intracortical inhibition, surround inhibition, and related physiological measures of motor selectivity. Normalization of SICI would support recovery of fast inhibitory control but would not by itself prove PV-specific synaptic strengthening. Conversely, substantial improvement without corresponding change in these inhibitory measures would challenge the proposed mechanism and favor alternative explanations involving sensory learning, attention, compensation, or broader network reorganization.

BATR should therefore be regarded as a hypothesis-driven rehabilitation strategy rather than an established curative treatment. The framework predicts that precise and sustained symptom-free practice may raise the symptom-threshold, reduce dystonic recruitment, and permit substantial functional recovery in at least some patients. Its efficacy, safety, durability, optimal dosage, and generalizability require prospective clinical evaluation.

Materials and Methods

Computational modeling was used as a complementary proof-of-concept approach to examine a restricted network-level implication of the proposed TSMS framework. Specifically, we asked whether a simplified spiking neural network containing functional and excitation-inhibition (E/I)-imbalanced components could exhibit an input-dependent crossover in relative population firing. The model was not designed to reproduce the complete proposed etiological sequence from altered movement coordination through true weakness, overreaching, and formation of a dystonic synergy. It also does not simulate muscular output, clinical symptoms, or recovery through BATR.

Instead, the simulation examines the conditional behavior of a specified network architecture in which the functional and E/I-imbalanced states are represented directly. Because the relevant imbalance is imposed within the model, the results address the internal computational plausibility and network-level consequences of that assumption rather than independently verifying its biological origin or establishing it as the mechanism of human FTSD.

Network Model

We simulated a simplified spiking neural network composed of interconnected excitatory and inhibitory components. The network contained N_{ex} excitatory neurons and N_{inh} inhibitory neurons governed by a leaky integrate-and-fire (LIF) model with synaptic interactions. The model was deliberately reduced to isolate the relationship among E/I organization, external drive, and population firing. It does not reproduce the full cellular diversity, laminar organization, long-range connectivity, sensory feedback, or descending motor-output pathways of an M1 TSMS. Although the biological hypothesis emphasizes PV-centered inhibitory control, the inhibitory units in the

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simulation are generic model neurons and should not be interpreted as a cell-type-specific representation of PV interneurons.

The neurons evolved according to the following membrane potential equation:

$$\tau_m dV/dt = (V_{rest} - V) + I_{syn}$$

where V is the membrane potential, V_{rest} is the resting potential, τ_m is the membrane time constant, and I_{syn} represents synaptic input.

Spiking events were generated when V exceeded a threshold V_{th}, after which the membrane potential was reset to V_{reset}.

Synaptic Connectivity

Synaptic interactions were implemented with conductance-based synapses, where synaptic current was given by:

$$I_{syn} = g_I(V - E_E) + g_E(V - E_I)$$

where g_{syn} is the synaptic conductance, and E_{syn} is the reversal potential of the synapse. Excitatory-to-inhibitory (E→I) and inhibitory-to-excitatory (I→E) connections were defined with a probability of connection p. Upon a synaptic input, the strength of the communication is increased by s.

The modeled connection patterns and synaptic strengths represent specified network conditions. They are not intended to reproduce all synaptic motifs of a biological M1 microcircuit or to identify a particular synaptic abnormality in patients with FTSD.

Input Drive and External Stimuli

External input was applied to the neurons through a Poisson-distributed spike train representing an abstract combination of background activity and task-related drive. Input amplitude to the excitatory populations was varied systematically to characterize how the modeled populations responded as drive increased. Within the conceptual interpretation of the model, increasing drive corresponds qualitatively to increasing task demand. It is not, however, calibrated directly to movement speed, force, loudness, or any other behavioral or clinical measure.

The external drive followed:

$$I_{ext} = A \times Poisson(r)$$

where A denotes the input amplitude and r denotes the baseline firing rate of the Poisson process.

Representation of Functional and E/I-Imbalanced Synergies

To represent the two modeled network configurations, we specified two model populations: a functional-synergy population (FS) and a dystonic-synergy population (DS). The FS population was assigned balanced excitatory and inhibitory drive, represented by E_F and I_F, whereas the DS population was assigned relatively increased excitatory strength without a corresponding increase in inhibitory strength, represented by E_D and I_D. FS and DS are model constructs rather than directly recorded biological populations.

The E/I imbalance was imposed rather than generated through simulated movement reorganization, overreaching, or synaptic plasticity. Systematically increasing model drive therefore tests how the FS and DS populations respond under their respective E/I conditions as model demand increases. It should not be interpreted as a simulation of the biological formation of dystonia or as evidence that overreaching produces the imposed synaptic imbalance in human FTSD.

Firing Rate Analysis

Network activity was summarized using the population-averaged firing rates of the FS and DS populations. Firing rate was calculated as:

$$r = \frac{total\ spikes}{number\ of\ neurons \times simulation\ time}.$$

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For each tested input-strength value, the population-averaged firing rates of the FS and DS populations were calculated and plotted against input strength.

Simulation and Implementation

All simulations were implemented in Python using custom-built neuron models. Differential equations were integrated using the Euler method with a time step of dt = 0.1 ms. Simulations were run with different seeds to account for variability. The network was simulated for T = 2000 ms, and simulation outputs were processed and summarized descriptively using Pandas and visualized with Matplotlib. In Table 1, we show parameters implemented in the simulation code, covering single-neuron dynamics, synaptic properties, network structure, external drive, and numerical integration. Values correspond to the PYR class defaults and network/simulation parameter block used to generate the reported results.

Table 1. Single-neuron, synaptic, network, and simulation parameters used in the reported computational analyses.

Category	Symbol	Description	Value	Units
Single-Neuron (LIF)	C_m	Membrane capacitance	200	pF
Single-Neuron (LIF)	g_L	Leak conductance	10	nS
Single-Neuron (LIF)	E_L	Resting (leak) potential	–65	mV
Single-Neuron (LIF)	V_{th}	Spike threshold	–50	mV
Single-Neuron (LIF)	V_{reset}	Post-spike reset potential	–60	mV
Single-Neuron (LIF)	τ_{ref}	Absolute refractory period	2.0	ms
Synaptic	E_E (E)	Excitatory reversal potential	0	mV
Synaptic	E_I (I)	Inhibitory reversal potential	−75	mV
Synaptic	τ_{syn}	Synaptic conductance decay time constant	6	ms
Synaptic	g_E – Pop.1 E cells	Fixed excitatory synaptic weight	2	nS
Synaptic	g_I – Pop.1 I cells	Inhibitory synaptic weight; scales with input strength s	6 × s	nS
Synaptic	g_E – Pop.2 E cells	Excitatory synaptic weight; scales with input strength s	4 × s	nS
Synaptic	delay	Axonal conduction delay	1.5	ms
Network Structure	N_{ex}	Excitatory neurons per population	20	—
Network Structure	N_{inh}	Inhibitory (interneuron) count, Population 1 only	5	—
Network Structure	N_{neuron}	Total size of Population 1 (Nex + Ninh)	25	—
Connection probability	p	The same connection probability is used for all neurons in the network.	1	—
External Input / Drive	r	Baseline external Poisson input rate, both populations	8	Hz
Simulation / Integration	dt	Integration time step	0.1	ms

The source code and associated analysis materials are available at https://github.com/normanklu/Dystonia.

Results

The simulations characterized the firing behavior of the FS and DS model populations. We first examined activity under the functional-reference condition, then considered alternative input-output

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behavior under different E/I conditions, and finally compared the relative firing rates of the FS and DS populations. These conditions should be understood as illustrative network states rather than as successive stages in the biological development of dystonia.

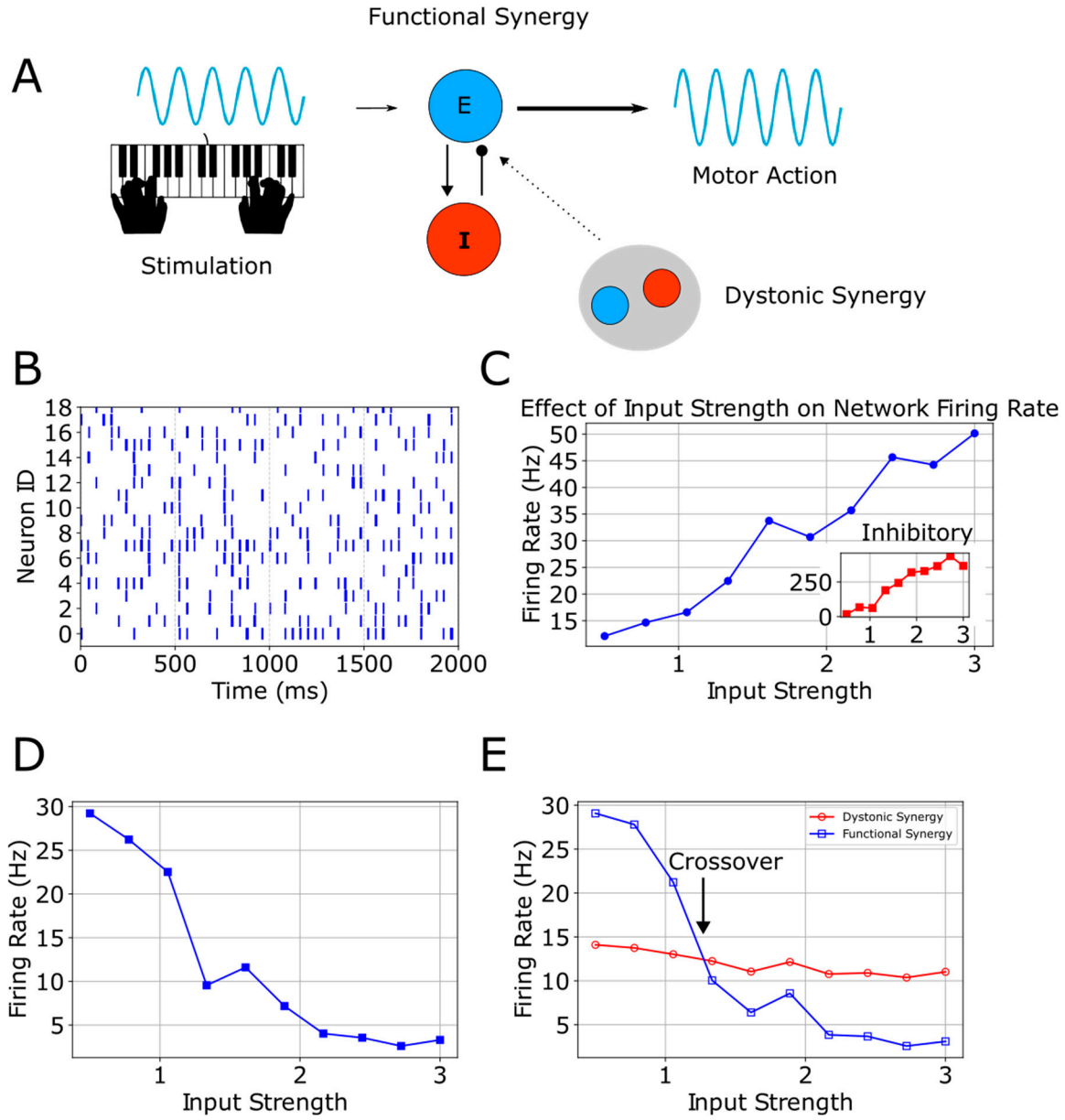
Figure 1B presents a representative raster plot from the functional-reference condition. Under the selected parameterization, the network displayed stable spiking activity over the simulated interval.

Figure 1C shows the relationship between input synaptic strength and population firing rate in the same model condition. Across the tested range, firing rate increased as input synaptic strength increased. The inset shows the corresponding activity of the inhibitory model units.

The relationship between increasing external drive and population firing was not identical across all specified network conditions. In a E/I network, stronger external input can increase excitatory firing while simultaneously recruiting greater inhibitory feedback through the network's connectivity. Depending on the imposed relationship between excitation and inhibition, this feedback may limit, stabilize, or reduce the net population response as input increases.

Figure 1D illustrates an alternative input-output pattern in which firing rate decreases across increasing input strength under the selected model parameters.

Together, Figures 1C and 1D demonstrate that the simplified model can produce qualitatively different input-output relationships under different specified E/I conditions.



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Figure 1. A. Conceptual schematic of the model framework. The piano keyboard represents abstract task-related stimulation, and the functional and dystonic synergy labels denote model constructs rather than directly measured biological circuits. The depicted "motor action" is conceptual and is not explicitly simulated. **B.** Representative raster plot from the functional-reference condition. Each row represents a model neuron, and each tick mark indicates a spike. **C.** Relationship between input strength and network firing rate in the functional-reference condition. The inset shows activity of the generic inhibitory model units. **D.** Alternative model response in which firing rate decreases as input strength increases under a different imposed E/I configuration. **E.** Comparison of population-averaged firing rates of the FS and DS populations across increasing input strength. The marked crossover denotes the model-level point at which the relative firing-rate ordering changes. Input strength is an abstract model quantity and is not directly calibrated to clinical movement intensity.

Figure 1E compares the population-averaged firing rates of the FS and DS populations across increasing input strength. At lower values, DS firing remained below FS firing. Above the model-level crossover, this ordering reversed and DS exhibited the higher firing rate. The imposed difference in E/I organization therefore produced an input-dependent crossover between the two firing-rate curves.

This result supports a restricted conditional proposition: under the specified architecture and parameterization, different E/I configurations can change their relative population firing as model drive increases. The crossover is interpreted as an abstract network-level analogue of threshold-dependent recruitment; it does not independently establish biological competition between motor synergies or simulate involuntary contraction, muscular output, maladaptive plasticity, or clinical FTSD.

Finally, we performed a local, one-at-a-time (OAT) sensitivity analysis to characterize how selected parameters influenced population-averaged firing under the specified baseline model conditions. We chose one specific case from our seeds, and there, each of eight parameters was perturbed by ±20% from its baseline value while all other parameters were held fixed. The network was re-simulated at the highest tested input strength, $s = 3.0$, using a fixed random seed across runs so that differences in output primarily reflected the parameter perturbation rather than a different realization of the Poisson drive.

At baseline, the FS population remained essentially quiescent at this drive level, with a population-averaged firing rate of 0.00 Hz, whereas the DS population fired at 1.80 Hz. Sensitivity was therefore summarized as the absolute change in firing rate, in Hz, for the FS population and as the percentage change in firing rate for the DS population. Within this local analysis, spike threshold and the excitatory synaptic weight assigned to the DS population produced the largest changes in DS firing, followed by the synaptic time constant, membrane capacitance, external-drive rate, and leak conductance. The synaptic weights assigned to the FS population had comparatively little effect on either population at the selected drive level.

These findings describe local parameter dependence around one specified model state. They should not be interpreted as identifying the biological determinants of FTSD, establishing the causal importance of the corresponding cellular properties in patients, or providing a global analysis of all possible model configurations. Parameter interactions and behavior outside the selected operating point were not evaluated by this OAT analysis.

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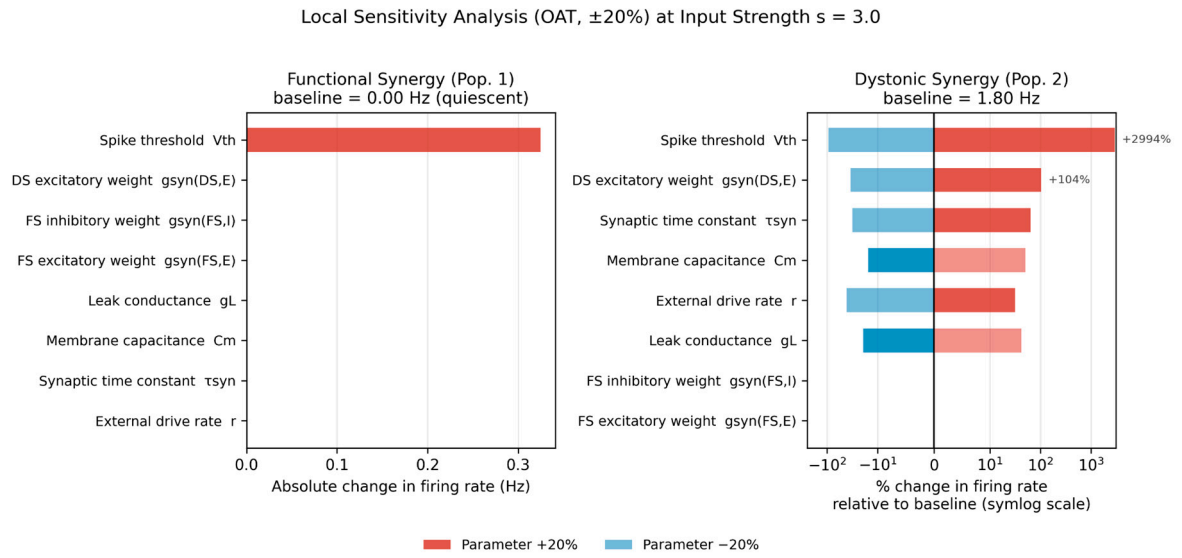


Figure 2. Local sensitivity analysis of population firing rates. Tornado plots show the changes in population-averaged firing produced by independently perturbing each selected model parameter by +20% (red) or −20% (blue) relative to its baseline value, with all other parameters held fixed at $s = 3.0$. Left: FS (Population 1), shown as absolute change in firing rate (Hz) from a quiescent baseline (0.00 Hz). Right: DS (Population 2), shown as percent change in firing rate from baseline (1.80 Hz); the x-axis uses a symmetric-log scale to accommodate the large dynamic range driven by the spike-threshold parameter. Parameters are ordered by the magnitude of their effect on the DS. r, external Poisson drive rate; τ_{syn}, synaptic conductance decay time constant; C_m, membrane capacitance; g_L, leak conductance; V_{th}, spike threshold; $g_{syn}(FS,E)/g_{syn}(FS,I)$, excitatory/inhibitory synaptic weights of the FS population; $g_{syn}(DS,E)$, excitatory synaptic weight of the DS population.

Discussion

Relation to Existing Models and Literature

A central question is how the M1-centered TSMS hypothesis relates to basal ganglia-, cerebellar-, and distributed-network accounts of FTSD. Basal ganglia models emphasize the contribution of cortico-striato-pallido-thalamo-cortical pathways to facilitation of intended movements and suppression of competing output. Altered direct- and indirect-pathway signaling may disinhibit thalamocortical activity and contribute to abnormal motor cortical excitability (Alexander & Crutcher, 1990; Berman et al., 2013; Calabresi et al., 2014; Gerfen, 1992; Perlmutter et al., 1997; Simonyan et al., 2017; Wichmann & DeLong, 1996). Cerebellar accounts emphasize abnormal motor calibration, sensorimotor integration, and cerebello-cortical plasticity (Bologna & Berardelli, 2017; Hubsch et al., 2013; Morigaki et al., 2021), whereas distributed-network models conceptualize FTSD as emerging from abnormal interactions among cortical, basal ganglia, thalamic, cerebellar, and sensory systems without assigning exclusive causal primacy to one node (Fuertinger & Simonyan, 2018; Jinnah et al., 2017; Schirinzi et al., 2018).

These perspectives operate at partly different explanatory levels and need not be mutually exclusive. The distinctive claim of the TSMS framework concerns the proposed initiating locus and causal ordering: the decisive E/I imbalance is hypothesized to arise within an M1 ensemble that directly contributes to the affected movement component, while abnormalities elsewhere in the motor network shape, reinforce, or adapt to its expression.

Locating the initiating imbalance within a task-specific motor-generating ensemble offers a direct account of both task specificity and intensity-dependent symptom expression. Symptoms remain restricted because the maladaptive plasticity is concentrated within the ensemble recruited by the affected movement rather than distributed uniformly across the motor system. At lower task demands, the residual functional configuration retains control; above the symptom-threshold, the excitatory-dominant dystonic configuration becomes preferentially recruited.

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This explanatory economy does not establish M1 primacy. Basal ganglia, cerebellar, premotor, and broader network processes can also be organized somatotopically and according to task context. A distributed or subcortical-primary model could therefore accommodate narrowly expressed symptoms if the affected network channel were sufficiently task-specific. The TSMS proposal should be evaluated not simply by whether it can explain task specificity, but by whether its predictions concerning causal timing, cell-type-specific physiology, and threshold-dependent recruitment are supported more strongly than those of competing accounts.

The reported responsiveness of some FTSD cases to slow-down exercise and related sensorimotor retraining is compatible with a plasticity-based mechanism but is not uniquely diagnostic of an M1 TSMS abnormality (Sakai, 2006; van Vugt et al., 2014; Yoshie et al., 2015). Improvement could arise through changes in M1, sensory processing, cerebellar error processing, compensatory recruitment of other motor representations, or broader network reorganization. Behavioral recovery therefore supports the potential reversibility of FTSD but does not by itself establish the anatomical or cellular mechanism of that recovery.

The framework further predicts that repeated activation of a hyperexcitable M1 synergy can induce or reinforce changes throughout the motor hierarchy, including altered basal ganglia signaling, cerebellar adaptation, somatosensory reorganization, and diminished spinal inhibition. These proposed network adaptations are developed in greater detail in the companion Hypothesis article. Alternative causal sequences remain viable: basal ganglia or cerebellar dysfunction could precede and induce M1 disinhibition, abnormalities could arise concurrently across several nodes, or causal ordering could differ among FTSD phenotypes. Longitudinal measurements and temporally resolved interventions will be required to distinguish these possibilities.

The TSMS framework is therefore not intended to deny the distributed organization of FTSD. It proposes a hierarchy within that distributed system in which a task-specific cortical ensemble contains the initiating E/I imbalance, while the broader motor network contributes to its expression, adaptation, and persistence. Its value will depend on whether it produces discriminating predictions rather than merely accommodating findings that can be explained equally well by competing models.

Evidentiary Status and Limitations

The present framework is mechanistic and integrative, but several of its central constructs remain unobserved directly. The TSMS is defined as a task-dependent M1 ensemble supporting a particular unidirectional movement component. Although partially overlapping motor cortical populations are consistent with contemporary accounts of M1 organization (Arbuckle et al., 2020; Ejaz et al., 2015), an FTSD-specific TSMS has not been isolated anatomically or followed longitudinally during the proposed transition from normal function to dystonia. It should therefore be understood as a functional circuit hypothesis rather than an established discrete cortical module.

The proposed predominance of PV-centered inhibitory dysfunction is likewise inferential. Reduced SICI, disturbed surround inhibition, and abnormal cortical excitability support dysfunction of rapid intracortical inhibition, but human TMS cannot identify the responsible interneuron class or distinguish directly between E→I and I→E synaptic abnormalities. SST- and 5HT3aR-related pathways may also contribute, and clinical phenomenology cannot establish cellular identity. Testing the PV-centered account will require recording or manipulation of identified interneuron populations within task-relevant motor ensembles.

The etiological sequence from altered movement coordination through partial baseline shift, true weakness, overreaching, excitatory-biased plasticity, and formation of a dystonic synergy has not been observed longitudinally at the circuit level. Its component mechanisms are drawn from broader studies of motor learning, excitatory and inhibitory plasticity, metaplasticity, and synaptic consolidation. Their proposed combination and direction within an M1 TSMS remain to be demonstrated. True weakness is similarly introduced as a testable behavioral and mechanistic construct rather than a validated clinical category. Prospective studies must determine whether the predicted intensity range can be measured reproducibly and distinguished from fatigue, pain, anxiety, peripheral weakness, biomechanical constraint, and compensatory movement.

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The causal primacy assigned to M1 also remains unresolved. Basal ganglia, cerebellar, sensory, and spinal abnormalities are well documented in dystonia, but existing cross-sectional evidence generally cannot determine whether they are causes, consequences, compensations, or interacting components of the same pathological process. The framework predicts that at least some of these abnormalities develop secondarily to repeated abnormal M1 output; consistent evidence that extra-M1 abnormalities precede cortical disinhibition or independently predict symptom emergence would instead favor an upstream or distributed causal account.

The clinical evidence supporting symptom-sparing retraining is promising but limited. Existing reports include individual cases and relatively small cohorts and do not establish the efficacy, optimal dose, durability, safety, or generalizability of BATR (Sakai, 2006; van Vugt et al., 2014; Yoshie et al., 2015). Improvement would also not establish PV-mediated rebalancing by itself, because sensory learning, altered attention, compensatory strategies, and broader network reorganization could contribute. The proposed BATR mechanism therefore requires both controlled clinical evaluation and longitudinal physiological testing.

The computational model addresses only the restricted proposition that specified FS and DS conditions can exhibit an input-dependent crossover in relative population firing. Because the E/I configurations and network architecture are imposed, the simulation does not establish that the modeled conditions exist biologically, arise through the proposed etiological sequence, or are reversed through BATR. Its role is to clarify one conditional network consequence of the framework and generate quantities that can guide subsequent experimental tests.

Finally, FTSD is clinically and physiologically heterogeneous. Symptom-thresholds may depend on several interacting task variables, differ across individuals and phenotypes, and appear as gradual or context-dependent transitions rather than a single abrupt boundary. The relative contributions of M1, other motor-network nodes, genetic susceptibility, sensory processing, and behavioral history may likewise vary. The framework should therefore be evaluated as a candidate causal account whose applicability may differ among FTSD phenotypes rather than as a universal mechanism established for every case.

These limitations define the observations needed to adjudicate the hypothesis. The framework will be strengthened by prospective findings that are not merely compatible with it, but that distinguish its proposed causal sequence and cellular mechanism from viable basal ganglia-primary, cerebellar-primary, and distributed-network alternatives.

Testable Predictions and Falsification Criteria

The central predictions of the TSMS framework can be evaluated through human longitudinal studies and experimental models. Because measures such as SICI are indirect and reflect several circuit processes, an isolated negative result would not necessarily reject the complete framework. Repeated failure of its central predictions across appropriately designed studies would, however, challenge the corresponding components of the hypothesis.

Human Longitudinal Tests of the Symptom-Threshold and BATR

The most immediate human prediction is that successful BATR will expand the range of task intensity over which voluntary movement remains symptom-free. Prospective studies should therefore quantify the symptom-threshold before, during, and after training using task-specific measures such as movement speed, force, pressure, amplitude, vocal intensity, or a prespecified combination of these variables. Repeated trials incorporating standardized video assessment, kinematic analysis, surface electromyography, and task-performance measures could determine whether increasing attempted intensity produces normal output, true weakness, or overt dystonia.

If BATR operates through recovery of rapid inhibitory control, an upward shift of the symptom-threshold should covary with normalization of SICI, surround inhibition, and related physiological measures of motor selectivity (Beck et al., 2009; Furuya et al., 2018; Ridding et al., 1995; Stinear & Byblow, 2004). Such covariation would support recovery of fast cortical inhibition but would not by itself establish PV-specific synaptic strengthening. Conversely, substantial behavioral improvement

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without corresponding recovery of these inhibitory measures would challenge the proposed PV-centered mechanism, although it would not necessarily invalidate BATR as a rehabilitation strategy. Alternative mechanisms could include sensory learning, altered attention, compensatory recruitment, or broader network reorganization.

The proposed true-weakness state can be tested by varying task intensity systematically while measuring attempted and realized output independently. The framework predicts that at least some individuals will display an interval in which increasing effort fails to produce the intended increase in output before overt dystonic activity becomes dominant. Failure to identify such an interval across carefully characterized cohorts would limit the generality of true weakness and suggest that it applies only to a subset of FTSD phenotypes or etiological pathways.

Testing Causal Ordering across the Motor Network

The hypothesis that M1 contains the initiating maladaptation generates specific predictions about temporal ordering. Longitudinal studies should combine M1 physiology with task-related measures of basal ganglia function, cerebello-cortical connectivity, somatosensory processing, and spinal inhibition before and during symptom change. The central prediction is that changes in the affected TSMS and its rapid inhibitory physiology will precede or closely track normalization elsewhere in the motor network.

Evidence that basal ganglia, cerebellar, sensory, or spinal abnormalities consistently precede cortical disinhibition and predict later symptom development would favor an upstream or distributed causal sequence. Earlier or independent normalization of extra-M1 measures during recovery would likewise weaken a strictly downstream interpretation, whereas simultaneous changes across several nodes could indicate that the initiating pathology cannot be localized to a single component of the network.

The timing of intervention-related changes may be especially informative. If BATR first alters M1 inhibitory physiology and later produces normalization of extra-M1 measures, that sequence would support the proposed hierarchy. If the earliest changes occur consistently in cerebellar, basal ganglia, sensory, or compensatory networks, the causal account would require revision. Temporal ordering alone would not prove causality, but it would substantially constrain the range of viable models.

Cell-Type-Specific and Etiological Tests in Experimental Models

Experimental models are required to test the proposed predominance of PV-centered dysfunction. In a well-learned forelimb task, cell-type-specific recording and manipulation could compare the behavioral consequences of reducing PV-, SST-, or VIP-centered inhibitory control within a defined motor cortical ensemble. The framework predicts that selective disruption of rapid PV-centered inhibition will be especially likely to produce excessive, spatially diffuse, and threshold-dependent output while preserving lower-demand performance.

Failure of PV manipulation to produce this phenotype would challenge the proposed cellular mechanism. The claim of PV predominance would also require modification if disruption of SST- or VIP-centered circuitry reproduced the same threshold-dependent and sustained abnormal output as consistently as PV disruption. Conversely, selective restoration of PV recruitment or inhibitory output should increase the task demand required to elicit abnormal motor activity.

A separate experimental design should test the proposed etiological sequence. Animals could first be trained to stable performance on a skilled motor task and then exposed to an altered coordination requirement that reduces effective task capacity. One group would practice only within its retained functional range, whereas another would be repeatedly driven above that range. Longitudinal recordings of pyramidal and identified inhibitory populations could determine whether altered coordination first reduces task capacity and whether subsequent overreaching produces progressive divergence between excitatory and inhibitory circuit efficacy.

The framework predicts that overreaching, rather than altered coordination alone, is required for formation of a threshold-dependent hyperexcitable configuration. Equivalent abnormalities in

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both groups would argue against overreaching as the decisive factor, while development of abnormal output without a preceding reduction in functional capacity would challenge the proposed sequence from partial baseline shift through true weakness to dystonia.

A subsequent BATR-like phase could test reversibility. Animals would practice within the intact performance range while behavioral thresholds and excitatory and inhibitory physiology are tracked longitudinally. The strongest support for the framework would consist of a linked sequence in which altered coordination reduces capacity, overreaching produces excitatory-dominant activity, a behavioral symptom-threshold emerges, and symptom-free retraining restores inhibitory control while raising that threshold. Partial or divergent results would identify which elements of the etiological and rehabilitation hypotheses require modification.

Translational Implications and Proposed Clinical Evaluation of BATR

BATR is presented as a rehabilitation hypothesis rather than a validated treatment protocol. Its operational principle is that practice should remain within a range in which the intended movement is produced accurately and without overt dystonia or true weakness. Clinical development will therefore require standardized procedures for threshold assessment, training dosage, progression, monitoring, and safety.

The first requirement is reliable identification of the relevant performance boundary. Because task intensity is phenotype-specific, assessment should determine which variable or combination of variables most strongly governs symptom expression. These may include keystroke speed or force, writing speed or pressure, phonatory intensity, movement amplitude, or intereffector coordination. The symptom-threshold should be estimated through repeated measurements rather than a single subjective judgment, and potentially state-dependent influences such as fatigue, stress, pain, and recent practice should be documented.

A manualized protocol would then define a training range at or below the measured symptom-threshold and, in individuals displaying true weakness, below the intensity at which attempted and realized output begin to diverge. Training intensity should be increased only when repeated assessment indicates that the relevant threshold has shifted upward, consistent with an expansion of the intact functional range. If a higher attempted intensity produces dystonic activity or task-specific underproduction, that intensity should be regarded as exceeding the current symptom-threshold or true-weakness threshold, and practice should return to the highest intensity that remains accurate and symptom-free. We further hypothesize that threshold gains may be non-linear over time, with periods of relatively stable performance between detectable improvements; this proposed trajectory should be evaluated prospectively.

The framework does not yet justify fixed prescriptions concerning daily practice duration, uninterrupted session length, repetition count, rest intervals, or rate of progression. Dose-finding studies should therefore compare shorter and longer sessions, distributed and concentrated practice, different rest schedules, and clinician-supervised versus partially self-directed formats.

Initial clinical studies should emphasize feasibility and protocol refinement. They should determine whether thresholds can be measured reliably, whether participants can remain within the prescribed range, how often symptoms are inadvertently provoked, and which task-performance outcomes are most responsive. Fatigue, pain, compensatory movement, deterioration in other tasks, treatment burden, and other adverse events should be recorded systematically.

Subsequent controlled trials could compare manualized BATR with usual care, an active motor-training control, or BATR combined with established symptomatic treatment. Outcomes should include blinded clinical ratings, quantitative task kinematics, patient-reported function, symptom-threshold measurements, durability of previously achieved gains after training is reduced or discontinued, and whether further improvement plateaus in the absence of continued practice. The framework predicts that reducing or discontinuing BATR would primarily slow or halt further improvement rather than immediately reverse previously consolidated gains, although this prediction requires prospective testing. Mechanistic measures such as SICI, surround inhibition,

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sensory processing, and network-level imaging could determine whether clinical improvement follows the physiological route predicted by the framework.

Reports of slow-down exercise and related sensorimotor retraining provide a rationale for this development pathway but do not establish the efficacy of BATR as presently formulated (Sakai, 2006; van Vugt et al., 2014; Yoshie et al., 2015). Demonstrating efficacy will require improvement beyond natural fluctuation, expectancy effects, nonspecific practice, and compensatory task modification. Formal clinical integration should be considered only after efficacy, safety, dosage, and durability have been established.

Conclusions

FTSD is hypothesized here to arise within an M1 TSMS in which excitation becomes disproportionately strong relative to rapid PV-centered inhibitory control. In the proposed etiological sequence, altered movement coordination reduces the capacity of a previously consolidated functional synergy, creating a task-specific true-weakness range. Repeated overreaching beyond that capacity then biases plasticity toward excitation, consolidates a dystonic synergy, and produces a symptom-threshold at which the dystonic configuration becomes preferentially recruited.

BATR follows directly from this proposed mechanism. Practice confined to the intact, symptom-free range is predicted to preserve coherent functional-synergy recruitment, strengthen rapid inhibitory control, and progressively raise the symptom-threshold. The reduced spiking model supports the conditional plausibility of an input-dependent crossover between specified functional and E/I-imbalanced conditions, but it does not establish the biological origin of the imbalance, M1 or PV specificity, or BATR efficacy.

The TSMS framework is intended as a falsifiable causal hypothesis. Its central claims can be tested through longitudinal measurement of task thresholds and inhibitory physiology, cell-type-specific manipulation of motor cortical circuits, experimental comparison of within-capacity practice and overreaching, temporal analysis of M1 and extra-M1 changes, and controlled evaluation of BATR. These tests should determine which components of the proposed sequence are supported, which require revision, and whether the framework can distinguish initiating abnormalities from downstream adaptations in FTSD.

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