The Composite Matrix-Afferent Reset (CMAR) Hypothesis

A Testable Framework Linking Extracellular-Matrix Mechanics, Proprioceptive Force Transduction, Neuromuscular Regulation, and Tissue Mechanical Memory

Hypothesis / Conceptual Article
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All mechanistic and therapeutic claims remain hypotheses requiring experimental validation.

Abstract

This is a conceptual hypothesis paper. The Composite Matrix-Afferent Reset (CMAR) Hypothesis proposes that persistent alterations in extracellular-matrix (ECM) mechanics may modify the mechanical input reaching proprioceptive endings by changing local force transmission and receptor deformation. The strongest anatomical basis is the Golgi tendon organ (GTO), in which Group Ib sensory endings are intertwined with collagen bundles and are mechanically deformed as those bundles are loaded [35,36,56,57]. CMAR therefore asks whether pathological or experimentally altered matrix mechanics can change the mapping between macroscopic muscletendon force and receptor-level deformation. The framework explicitly separates this core mechanical-to-afferent proposition from downstream spinal inhibitory and motor effects, parallel cellular mechanotransduction involving PIEZO-associated mechanosensation and YAP/TAZ-associated remodeling, and a self-reinforcing mechanoepigenetic tissue-memory loop that could, in principle, help maintain an altered mechanical state [1,7,11,38-43]. Muscle architecture, pre-tension or "slack," loading velocity, pathology, age, and chronicity are treated as experimental moderators rather than universal assumptions. The proposed intervention sequence – verified mechanical perturbation followed by standardized eccentric loading, with interferential current therapy (IFC/IFT) considered only as an optional conditioning variable - is framed as a falsifiable perturbation strategy. Validation requires objective mechanical, receptor-specific or carefully qualified neurophysiological, motor, functional, and, where feasible, cellular measurements. No component is presented as an established clinical reset mechanism.
Keywords: Golgi tendon organ; Group Ib afferent; extracellular matrix; mechanotransduction; PIEZO2; YAP/TAZ; mechanical memory; proprioception; eccentric loading; interferential current.

Section I: Introduction

Classical proprioceptive models describe the Golgi tendon organ as a force-sensitive proprioceptor whose Group Ib afferent endings are embedded among collagen bundles at myotendinous and myo-aponeurotic junctions [35,36,56,57]. Loading straightens and tensions the collagenous elements and deforms the sensory endings, providing a direct mechanical basis for force transduction [56,57]. CMAR builds on this established receptor architecture but introduces a narrower, unproven question: can changes in the mechanical properties of the tissue pathway that loads the receptor alter the mapping between macroscopic muscle-tendon force and receptor-level deformation? Skeletal-muscle ECM participates in force transmission and changes substantially with injury, disease, aging, and remodeling [4,44-48]. The

manuscript therefore treats altered ECM-to-receptor mechanical coupling as the central testable proposition, not as an established cause of abnormal proprioception. The proposed sequence is: tissue mechanical state -> local force transmission/receptor deformation -> afferent response -> sensorimotor consequences. Cellular mechanotransduction and longer- term remodeling are secondary extensions that require separate evidence and experiments.

Section II: The Core CMAR Hypothesis

The core CMAR hypothesis is that the mechanical state of the tissue pathway loading a proprioceptive receptor can influence receptor deformation and thereby alter the relationship between external force and afferent output. For the GTO, the anatomical plausibility of a mechanically mediated effect is supported by the intimate relationship between Ib sensory endings and collagen bundles [35,36,56,57]. The additional proposition that pathological ECM remodeling outside or contiguous with the receptor materially changes GTO deformation has not been demonstrated and is the principal mechanistic gap that CMAR is designed to test. The model therefore predicts, rather than assumes, that experimentally measured changes in local stiffness, strain transfer, or tissue architecture will covary with changes in proprioceptive or reflex-related outcomes under controlled loading. Neural state, muscle activation, tendon compliance, receptor anatomy, and central processing remain competing or interacting determinants and must be measured or controlled.

Figure 1. Integrated conceptual model of the Composite Matrix-Afferent Reset (CMAR) Hypothesis (Updated September 2026).

Figure 1. Integrated conceptual architecture of the Composite Matrix-Afferent Reset (CMAR) Hypothesis. The model distinguishes the core mechanical-to-afferent hypothesis (altered ECM mechanics and force transmission -> altered receptor-region deformation -> altered afferent output) from downstream neuromuscular consequences, parallel PIEZO2-associated mechanosensory and YAP/TAZ-associated cellular mechanotransduction pathways, and a proposed longer-term mechano-epigenetic tissue-memory loop. The intervention sequence is presented as an experimental perturbation strategy rather than an established therapeutic mechanism. IFC/IFT is depicted as an optional conditioning variable whose timing and mechanistic contribution require independent testing. All proposed causal relationships remain hypotheses requiring experimental validation.

Section III: Evidentiary Boundaries and Discriminating Predictions

CMAR deliberately distinguishes established background biology from the novel causal links that require testing. Established observations include collagen-coupled GTO architecture and force transduction [35,36,56,57], PIEZO2-dependent proprioceptor mechanotransduction [34], mechanically regulated YAP/TAZ signaling in nonneuronal cells [1-3,11,38-40], and ECM remodeling with loading, aging, injury, and disease [4,10,44-48,59]. None of these observations demonstrates that pathological ECM remodeling changes GTO deformation or Group Ib output in vivo. That ECM-to-GTO coupling is the novel CMAR proposition.

A result supports the core mechanism only when a verified change in local mechanics precedes and predicts a change in receptor-region deformation and/or afferent output under controlled loading. A change in pain, tone, stiffness, EMG, reflex excitability, or function without that mechanical-to-afferent link may still be clinically or physiologically important, but it does not validate the core CMAR mechanism.

Evidence hierarchy for interpretation: Established background - GTO collagen-afferent architecture; PIEZO2 in proprioception; ECM force transmission/remodeling; YAP/TAZ mechanoregulation. CMAR core hypothesis - altered local matrix mechanics change receptor-region strain transfer and afferent output at matched external load. Downstream extensions - spinal inhibitory effects, motor consequences, residual force/torque enhancement, and clinical phenotypes. Longer-term extension - self-reinforcing cellular/matrix mechanical memory, including a possible mechano-epigenetic component. Optional intervention variable - IFC/IFT conditioning, which is neither required by nor evidence for the core mechanism.

Prespecified directional predictions are: (1) at matched external load, measured receptor-region strain and/or afferent output will covary with measured local mechanical state; (2) an intervention-related neurophysiological effect attributed to CMAR will be contingent on a verified preceding mechanical change; (3) architecture, pretension/slack, and loading velocity will moderate the mechanical-to-afferent relationship; and (4) if a tissuememory loop exists, mechanical, cellular, and matrix measures will show a temporally ordered feedback relationship rather than isolated cross-sectional associations.

Section IV: Composite Matrix Mechanism

3.1 Shielding premise. Chronic remodeling could alter the correspondence between macroscopic muscle-tendon force and local GTO deformation, but direct evidence for this specific effect is presently lacking. GTO sensory endings are mechanically coupled to collagen bundles [35,36,56,57], while skeletal-muscle ECM contributes to force transmission and can remodel in disease and aging [4,44-48]. CMAR links these established observations as a testable prediction: at a matched external load, an altered local mechanical environment should produce a measurable difference in receptor-region strain and/or afferent output if the proposed coupling effect is real.

3.2 Mechanical-fluidization premise. Controlled manual or mechanical intervention can acutely change some measured tissue properties in selected experimental settings, including muscle stiffness and microcirculatory variables, but these findings are tissue-, technique-, and time-dependent and do not demonstrate ECM 'fluidization' or GTO resetting [9,49-52]. In CMAR, the intervention is therefore treated only as a controllable perturbation intended to create a measurable change in local mechanics. A valid experiment must verify that a mechanical change actually occurred before attributing any downstream neurophysiological effect to the intervention.

3.3 Transduction premise. If local mechanical resistance is altered before eccentric loading, the same macroscopic load may generate a different local mechanical stimulus at the receptor and surrounding cells. This proposition also provides a possible conceptual connection to residual torque enhancement (rTE), a documented history-dependent property of skeletal muscle. Following active eccentric loading, a muscle may exhibit greater steady-state isometric torque than a muscle activated at the same length without prior stretch [27,28,53-55]. The established phenomenon is relevant because it demonstrates that the mechanical history of a muscle can influence subsequent force production. CMAR does not propose that rTE is caused by altered GTO signaling or that rTE validates the hypothesis. Rather, rTE may provide a measurable

physiological outcome through which the effects of altered tissue mechanics, eccentric loading, and subsequent neuromuscular responsiveness could be investigated [27,28].

3.4 Reprogramming premise. If a mechanically induced change in receptor input is demonstrated, a corresponding change in sensorimotor processing or muscle activation would constitute the next level of evidence [17,20,22,23]. CMAR uses the term 'reset' operationally to mean a reproducible transition from one measured system state to another after a defined perturbation; it does not imply permanent normalization, reversal of pathology, or restoration of a prior anatomical state. The broader recursive-state concept described by Breuillaud [24] is used only as a conceptual analogy and provides no biomedical evidence for CMAR. The model proposes two conceptually distinct but potentially interacting branches:

Branch A: PIEZO-associated mechanosensation.

ECM force transmission
↓
membrane/cellular deformation
↓
PIEZO-associated mechanosensitive signaling
↓
Rapid ionic/electrical cellular response

Branch B: YAP/TAZ-associated Mechanotransduction

ECM force transmission
↓
cytoskeletal/mechanical force transmission
↓
YAP/TAZ regulation
↓
nuclear signaling/transcriptional response
↓
longer-term cellular adaptation and ECM remodelling

The two branches are biologically distinct and should not be presented as a demonstrated linear cascade. PIEZO2 has direct evidence as a major mechanotransduction channel in mammalian proprioceptors, including GTO and muscle-spindle endings [34]. YAP/TAZ, by contrast, are mechanically regulated transcriptional coactivators with strong evidence in fibroblasts and other mechanically responsive cells [1,11,38-40]. CMAR therefore predicts only that the same altered mechanical environment could influence these systems in parallel. Demonstrating a PIEZO2-to-YAP/TAZ causal chain is not required for the core hypothesis and would require dedicated cell- and tissue-specific experiments.

The proposed feedback relationship is:

Altered ECM mechanics
↓
altered force transmission
↓
altered mechanosensory and cellular mechanotransduction
↓
cellular/tissue adaptation
↓
further ECM remodeling
↓
persistent altered ECM mechanics

This feedback loop provides the mechanobiological context in which altered proprioceptive signaling may be maintained [5].

Proposed H1–H5 Cascade

H1: ECM strain, stiffening, viscoelastic change, or architectural remodeling alters local mechanical force transmission [4].

H2: Altered force transmission changes the mechanical coupling between the tendon matrix and proprioceptive structures, including GTOs and potentially muscle spindles [4,5].

H3: Altered receptor deformation changes afferent input and downstream interneuronal regulation [5].

H4: If H1-H3 are demonstrated, persistent changes in sensorimotor regulation could contribute to abnormal tone or movement resistance in selected neurological contexts; this is not required to validate the core CMAR mechanism [15,17,20,58] in selected physiological or pathological contexts, i.e. spasticity [15,17,20].

H1-H3 constitute the core mechanistic hypothesis. H4 is a downstream clinical extension and should be tested only after the mechanical-to-afferent relationship is established.

Proposed Mechanistic Cascade:

H1: ECM Strain/Stiffening

↓

H2: Altered GTO/Spindle Mechanical Coupling

↓

H3: Altered Afferent Input and Interneuronal Regulation

↓

H4: Spasticity & Rigidity

↓

Downstream structural outcomes: outside the core CMAR validation pathway

A parallel cellular branch is proposed at H1/H2:

ECM mechanical alteration

↓

PIEZO-associated rapid mechanosensory signaling & ECM mechanical alteration

↓

YAP/TAZ-associated intracellular mechanotransduction

↓

cellular adaptation / ECM remodeling'

These branches are not asserted to be identical or obligatorily coupled. Their proposed commonality is the ECM derived mechanical input and their potential contribution to a mechanically maintained tissue state [1,2,3,6].

Local ECM dysfunction

↓

altered receptor/cellular mechanical coupling

↓

altered sensory and cellular signaling

↓

altered spinal regulation and tissue adaptation

↓

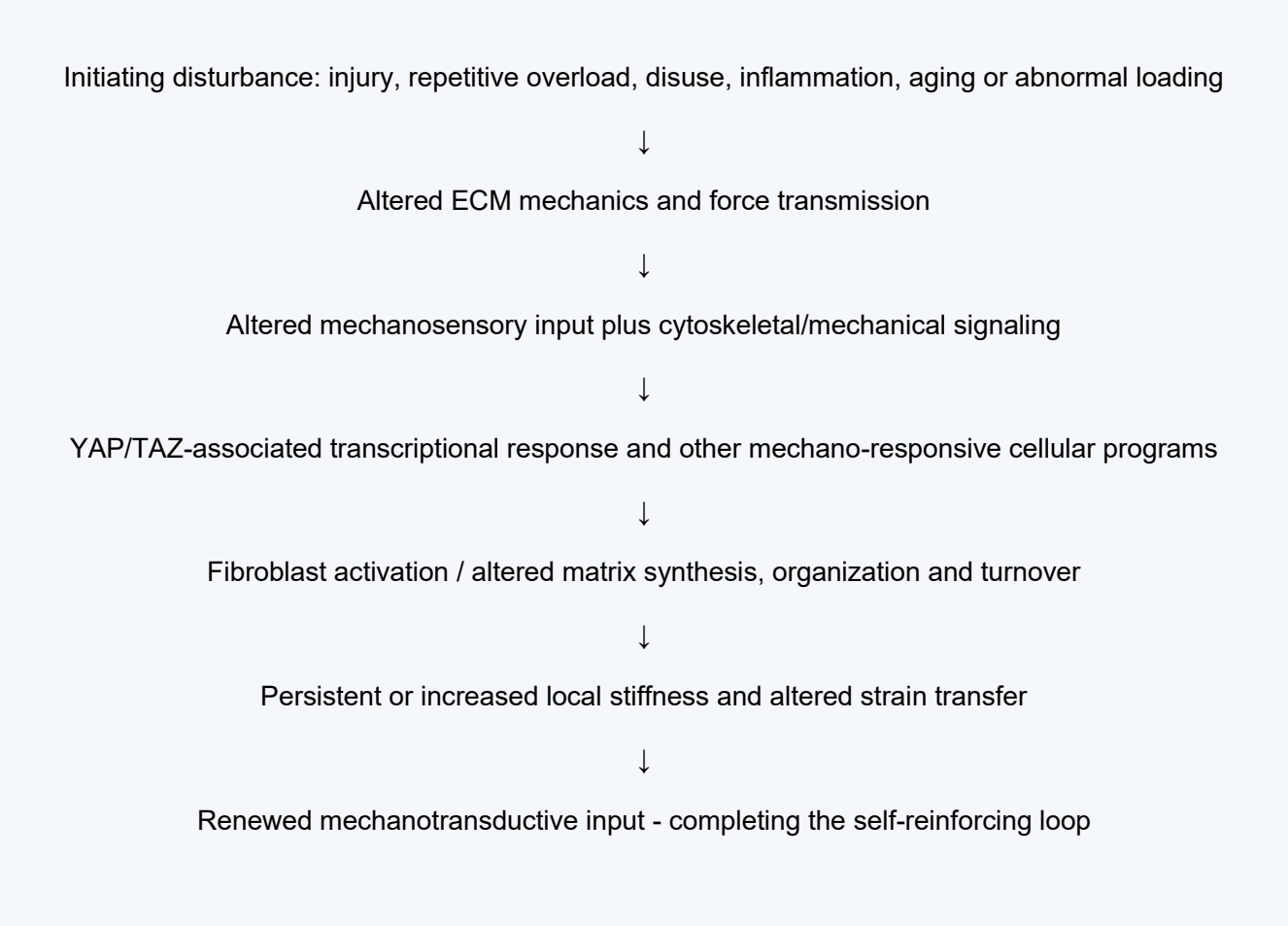
persistent neuromuscular dysfunction [4,5,6].

Cellular Mechanotransduction Extensions

ECM mechanics may influence non-neuronal cells independently of, or in parallel with, receptor-mediated neural signaling. For proprioceptors, PIEZO2 - not PIEZO1 - is the best-supported mechanotransduction channel and is expressed in sensory endings innervating GTOs and muscle spindles [34]. PIEZO1/YAP literature from other cell types can inform general mechanobiological plausibility [25], but it should not be used as direct evidence for GTO signaling. YAP/TAZ-associated responses are therefore treated as a separate tissue-remodeling extension involving mechanically responsive cells such as fibroblasts [1,11,38-40].

Section V: The Self-Reinforcing Mechano-Epigenetic Memory Loop

The self-reinforcing mechano-epigenetic memory loop is a central explanatory extension of the revised CMAR framework because it addresses persistence: why might an altered structural and functional state continue after the initiating injury, overload, inflammatory episode, immobilization, or other disturbance has diminished? Mechanical-memory studies show that cells can retain responses to prior mechanical environments, and fibrotic mechanosignaling can reinforce matrix deposition and stiffness [7,11,41-43]. CMAR applies this literature cautiously to skeletal-muscle/connective-tissue context as a testable extension rather than an established GTO mechanism.



A stronger version of the extension proposes that persistent mechanotransduction may be stabilized through chromatin or epigenetic mechanisms, producing a mechanically maintained cellular phenotype [7,42]. This is the “mechano-epigenetic memory” component. It should be tested independently with time-resolved cellular and matrix measurements. The loop is weakened if mechanical state normalizes while the proposed cellular signature persists unchanged, if the cellular signature changes without any corresponding matrix change, or if disrupting the mechanical environment fails to alter the predicted downstream state.

Section VI: Spinal Inhibitory Circuitry as a Downstream Modulator

The expanded framework considers autogenic inhibition, reciprocal inhibition, and recurrent (Renshaw-cell) inhibition in spasticity. These mechanisms are relevant to CMAR as downstream neural context, but none should be declared the universal or dominant mechanism of spasticity. Spasticity is heterogeneous and can involve altered stretch-reflex excitability, descending control, interneuronal circuitry, motoneuron properties, and secondary muscular/connective-tissue changes [15,17,20,36,37,58].

- **Autogenic/Ib-related pathways:** GTO-derived force feedback is directly relevant to CMAR because the core hypothesis concerns mechanically altered input reaching the GTO. A change in Ib firing could, in principle, modify spinal force-feedback networks, but the sign and functional consequence depend on task, circuitry, pathology, and state [36,37].
- **Reciprocal inhibition:** altered Ia-mediated agonist-antagonist coordination can contribute to abnormal cocontraction. CMAR does not assume that a peripheral mechanical intervention restores reciprocal inhibition; this requires direct neurophysiological testing.
- **Recurrent inhibition:** Renshaw-cell circuits provide negative feedback to motoneuron pools. Their function may be altered in neurological disease, but recurrent inhibition is not a substitute for measuring GTO/Ib signaling.
- **Interpretive rule:** H-reflex, reciprocal-inhibition, recurrent-inhibition, EMG, and clinical tone measures are complementary downstream readouts. None is a direct recording of GTO deformation or Group Ib firing.

SCI-Specific Imbalance Among Spinal Inhibitory Pathways

Following spinal cord injury, inhibitory spinal circuitry should not be conceptualized as undergoing a uniform loss of function. Rather, different inhibitory pathways may be altered in different directions. Human neurophysiological studies have reported increased recurrent inhibition mediated through Renshaw-cell circuitry in some individuals with SCI, whereas presynaptic inhibition of Ia transmission is commonly reduced and reciprocal Ia inhibition may be markedly diminished, absent, or replaced by reciprocal facilitation. These changes can increase effective excitatory transmission to motoneuron pools and impair normal agonist-antagonist coordination.

Ib-related force-feedback pathways are particularly relevant to CMAR but require more cautious interpretation. Nonreciprocal Ib inhibition can be altered after SCI and may exhibit facilitation or state-dependent reorganization rather than a simple universal loss of autogenic inhibition. Evidence that locomotor training can shift reciprocal facilitation toward reciprocal inhibition and Ib facilitation toward Ib inhibition further demonstrates that these spinal circuits retain substantial plasticity after injury.

Thus, SCI may produce an imbalance among inhibitory control systems, rather than generalized disinhibition alone. Increased recurrent inhibition can coexist with reduced presynaptic and reciprocal inhibitory control and altered Ib-mediated force feedback. This distinction is potentially important for CMAR because a mechanically induced change in proprioceptive input would enter a spinal network whose inhibitory organization has already been reorganized by the injury. Consequently, an identical change in peripheral GTO/Ib input need not produce an identical motor response across individuals or stages of SCI.

Chloride homeostasis as a state-dependent constraint on inhibitory efficacy

A further downstream consideration is that the physiological effect of an inhibitory synaptic pathway depends not only on whether inhibitory afferent/interneuronal activity is recruited, but also on the postsynaptic ionic environment. After spinal cord injury, reduced KCC2-mediated chloride extrusion can weaken GABAergic and glycinergic inhibition and contribute to hyperreflexia and spasticity [60-62]. In chronic SCI animal models, pharmacological enhancement of KCC2 activity has reduced electrophysiological correlates of hyperreflexia and stretch-evoked spastic responses, and more recent work has reported improved reflex regulation and locomotor performance without a generalized reduction in motor output [60,61].

This creates an important boundary condition for CMAR. Even if a mechanical intervention alters GTO/Ib input as predicted, the downstream motor consequence may depend on the excitability and chloride-regulatory state of the spinal network receiving that input. CMAR therefore should not assume that successful recruitment of an inhibitory afferent pathway necessarily produces a predictable inhibitory motor response in severe or chronic SCI. KCC2/NKCC1 status, lesion characteristics, residual descending control, medication exposure, and baseline reflex excitability may act as moderators [17,20,60-62].

The supplied therapeutic concept places particular emphasis on restoration of useful load-dependent force feedback through GTO/Ib-related pathways. This is compatible with CMAR as a testable rehabilitation objective, but current evidence does not justify declaring autogenic inhibition universally dominant over reciprocal or recurrent inhibition, nor does it establish that manual therapy or eccentric loading restores autogenic inhibition. The stronger experimental formulation is that a verified change in tissue mechanics and GTO-region loading should be tested for its ability to alter Ib-related force feedback and functional motor control under defined spinal-network conditions.

Section VII: Muscle Architecture, Slack, Pre-Tension and Velocity as Experimental Moderators

Experimental Moderators the mechanical input reaching a GTO is unlikely to be identical across muscles, joint positions, or loading velocities. Muscles differ in fascicle length, pennation, tendon/aponeurosis architecture, baseline passive tension, and the amount of “slack” that must be taken up before force is transmitted efficiently. These factors should be treated as moderators of the CMAR input-output relationship rather than as fixed categories or universal muscle types [4,35,44,47,48,56,57].

• **Slack / low-pre-tension condition:** early movement may first take up compliant tissue before receptor-region tension rises substantially. The predicted afferent response may therefore be delayed or nonlinear. • Pre-tensioned / low-slack condition: changes in length or velocity may be transmitted more rapidly into local force, potentially producing earlier receptor deformation and afferent response.

• **Velocity dependence**: faster loading can change viscoelastic resistance, strain rate, muscle-spindle input, reflex behavior, and motor output. A velocity effect cannot be attributed specifically to GTOs without direct or validated receptor-specific measurements.

• **Muscle-specific architecture:** soleus, gastrocnemius, multifidus/longissimus, and biceps brachii may provide useful contrasting models, but their classification must be based on measured architecture, joint position, passive tension, and strain transfer rather than assumed “slack” labels. This refinement creates a testable prediction: after controlling external load, joint angle, activation, and tendon compliance, the magnitude and timing of receptorregion strain and afferent response should differ systematically with measured pre-tension, architecture, and loading velocity if these variables materially govern the proposed coupling.

Section VIII: Phenomenological and Biophysical Model

The mathematical component is intentionally phenomenological. It is intended to formalize predictions and identify measurable variables, not to claim that the equations represent established physiological laws. Local matrix stress may be represented conceptually as: $\sigma = E\varepsilon + \tau p$

where σ is local stress, E is an effective elastic modulus, ε is local strain, and τp represents additional viscoelastic, fluid, or structural contributions.

A conceptual Group Ib relationship may be written: $fIb = \alpha\sigma e^{(-\beta\Delta E)}$ where fIb represents conceptual afferent output, α is a scaling factor, and βΔE represents a shielding term associated with altered matrix mechanics.

This equation is a hypothesis-generating construct and requires empirical parameterization. Cellular responses can be represented separately: $P = F(\sigma, \varepsilon, \text{membrane deformation})$

$Y = G(\sigma, \text{cytoskeletal force transmission, cellular state})$

where P denotes a PIEZO-associated response and Y denotes a YAP/TAZ-associated response.

The model deliberately does not equate P and Y.

A simplified motor-output relationship can be represented as: $\tau(dVm/dt) = wD\ D + wS\ S - wI\ IIb$ and $M = H(Vm - \theta)$

where D, S, and IIb represent conceptual excitatory/inhibitory inputs, Vm is membrane potential, θ is a threshold, and M is motor output.

These equations provide a framework for testing temporal and directional predictions rather than a validated quantitative model. The distinction between mechanically gated ion-channel signaling and mechanically regulated transcriptional responses is important for CMAR. A change in tissue mechanics may influence rapid electrical or ionic responses, slower cellular adaptation, or both, but these processes should not be treated as interchangeable.

Accordingly, PIEZO-related mechanotransduction and YAP/TAZ-related transcriptional regulation are presented here as potentially interacting but experimentally separable pathways [1,6,25,38-40].

Extracellular-matrix remodeling may also influence cellular behaviour through changes in matrix composition, stiffness, ligand presentation, and cell-matrix interactions. These changes can affect mechanosensitive signaling and cellular adaptation, although the direction and magnitude of the response are context-dependent [4,7,11].

Within CMAR, this literature provides a rationale for investigating whether altered matrix properties could modify the mechanical environment experienced by proprioceptive structures and surrounding cells [4,11,26].

Section IX: Sequential Mechano-Therapy and the Neuromuscular Window

Interferential current therapy (IFC; also termed interferential therapy, IFT) is an optional experimental extension and is not part of the core CMAR mechanism. Existing studies support the possibility of short-term clinical or physiological effects in some pain, stroke, and rehabilitation contexts, but they do not establish direct effects on GTO deformation, PIEZO2, YAP/TAZ, or ECM remodeling [12-15,18-21,29].

Accordingly, IFC should be treated as an independently dosed conditioning factor in a factorial experiment, not as a 'gain-of- function' manipulation or a mechanistically established step in a CMAR reset.

$GIFT = (YCMAR+IFT - YCMAR) / |YCMAR|$ where Y is a predefined outcome.

Device parameters and safety conditions must be determined by appropriately qualified investigators and device-specific protocols. Clinical evidence involving interferential current therapy provides a rationale for investigating whether IFC may produce short-term changes in spasticity, balance, gait, or related functional measures.

Such findings would support the inclusion of IFC as an experimental conditioning intervention, but they would not establish that IFC directly changes Golgi tendon organ signaling, extracellular-matrix mechanics, or the proposed CMAR reset process.

The present hypothesis therefore treats any immediate clinical effect as an observable outcome requiring mechanistic clarification [12- 15,18-21,29].

Section IX.A: Non-Invasive IFT Extension

Interferential current therapy (IFC; also termed interferential therapy, IFT) is an optional experimental extension and is not part of the core CMAR mechanism. Existing studies support the possibility of short-term clinical or physiological effects in some pain, stroke, and rehabilitation contexts, but they do not establish direct effects on GTO deformation, PIEZO2, YAP/TAZ, or ECM remodeling [12-15,18-21,29].

Accordingly, IFC should be treated as an independently dosed conditioning factor in a factorial experiment, not as a 'gain-of- function' manipulation or a mechanistically established step in a CMAR reset. GIFT = (YCMAR+IFT − YCMAR) / |YCMAR| where Y is a predefined outcome. Device parameters and safety conditions must be determined by appropriately qualified investigators and device-specific protocols.

Section IX.B: Evidence Hierarchy vs. Theoretical Superiority

No evidence currently establishes an optimal temporal position for IFC within a CMAR experiment. If IFC is studied, timing should be randomized or otherwise prespecified as an experimental factor rather than assumed to be therapeutically optimal. The core CMAR sequence to be tested is a verified mechanical perturbation followed by a standardized loading challenge and objective measurement.

IFC can be added before or in a separate arm to test conditioning effects. Residual torque enhancement may be included as a history-dependent muscle outcome, but it cannot serve as a surrogate for GTO deformation or afferent resetting [27,28,53-55].

The Multi-Modal ‘Confounding’ Problem

A major methodological consideration arises when IFT/IFC is combined with the CMAR mechanical sequence. A combined intervention may produce a clinically meaningful effect while making it difficult to determine which component, or which interaction among components, is responsible for the observed outcome.

The proposed IFC + CMAR process is inherently multi-modal when electrical preconditioning is combined with targeted manual or mechanical tissue intervention and subsequent eccentric loading. These components may influence different physiological variables and may also interact temporally. Consequently, an observed reduction in abnormal muscle tone, rigidity, or spasticity cannot automatically be attributed to the electrical stimulus, the mechanical intervention, the eccentric loading, or their interaction.

For evidence classification, clinical utility and causal attribution must be separated. The IFC literature is heterogeneous across indications and does not establish the proposed CMAR mechanism [12-15,18- 21,29]. Evidence summary TENS and other somatosensory electrical-stimulation approaches provide a broader comparator literature for neuromodulation, but they do not establish the CMAR mechanism. IFC/IFT alone has limited and heterogeneous evidence in spasticity-specific contexts.

The combined IFC/CMAR sequence remains hypothesis-generating; the independent contributions of electrical stimulation, mechanical intervention, eccentric loading, and their temporal interaction require controlled isolation [12-15,18-21,29].

The important distinction is that formal evidence level and clinical utility are not necessarily equivalent. A multimodal protocol may demonstrate substantial clinical utility while remaining difficult to classify mechanistically because its individual components have not been independently isolated and replicated. Conversely, a modality may possess a larger evidence base when studied independently without demonstrating superiority when incorporated into a specific multi-modal sequence.

IFC differs physically from TENS in waveform generation: two medium-frequency alternating currents interact to produce an amplitude-modulated beat frequency within the treatment field. However, available clinical evidence does not establish selective stimulation of deep paraspinal afferents, muscle spindles, Golgi tendon organs, or dorsal-ramus pathways [12-14,21].

Comparative evidence indicates broadly similar effects of TENS and IFC on pain and function, with substantial heterogeneity in treatment parameters [12]. CMAR therefore has no basis for assuming that IFC is clinically or physiologically superior to TENS. If IFC is studied, it should be justified as a distinct, prespecified experimental perturbation rather than a preferred therapy [12-14,18,21]. In the context of spasticity and neuromodulation, the evidence base should also be described more precisely.

A systematic review of somatosensory electrical stimulation in spasticity identified clinical benefits in some studies but found inconsistent electrophysiological results across spinal and corticospinal measures, including H-reflex and transcranial magnetic stimulation outcomes [15,20,33,55]. Thus, electrical stimulation can plausibly modify sensorimotor function, but the available literature does not establish a uniform neurophysiological mechanism that can be directly mapped onto the CMAR model. This uncertainty reinforces the need to measure the proposed sequence rather than infer it. Accordingly, TENS/somatosensory stimulation should not be treated as a mechanistic surrogate for IFC, and neither should be assumed to directly modify GTO mechanics.

The appropriate question for CMAR is whether a defined electrical preconditioning stimulus produces a reproducible change in the subsequent mechanical, neurophysiological, and functional response. The CMAR hypothesis should not state that IFC reaches or directly activates a GTO, PIEZO-associated channel, or YAP/TAZ pathway. Instead, IFC should be conceptualized as a non-invasive electrical conditioning stimulus whose measurable effects may include altered sensory input, neural excitability, muscle activation, perfusion, or tissuelevel responses.

The critical question is whether any such change is temporally associated with, and experimentally modifies, the response to the subsequent CMAR mechanical intervention. Importantly, the incorporation of interferential current (IFC) into the CMAR framework should not be interpreted as establishing IFC as an intervening step within the primary CMAR sequence.

The fundamental premise of CMAR remains that targeted manual or mechanical therapy is followed by eccentric loading immediately, or as soon as reasonably possible, during the proposed period of altered neuromuscular responsiveness. Introducing IFC between these two components could potentially interrupt or otherwise alter the very sequence that the hypothesis proposes to investigate.

Accordingly, IFC is presently considered a potential adjunctive or preconditioning intervention rather than a defined component of the CMAR sequence. The appropriate timing of IFC whether before manual/mechanical therapy, after mechanical therapy, concurrently with treatment, or at another interval remains an empirical question [12-15,18-21,29].

Because the physiological and mechanical consequences of IFC within the proposed CMAR framework are not yet established, its timing should be determined experimentally rather than incorporated into the core hypothesis a priori. This distinction is important because CMAR does not require IFC to produce its proposed neuromuscular reset. Rather, IFC may represent an additional modality capable of influencing the tissue, sensory, or neuromuscular environment in which the CMAR sequence operates.

Experimental investigation should therefore first determine whether IFC produces a measurable effect and, if so, whether that effect is dependent upon its temporal relationship to the mechanical intervention and subsequent eccentric loading.

Summary of Evidence and Experimental Status

Modality / Combination	Current Evidence Position	Clinical / Experimental Interpretation
TENS / somatosensory electrical stimulation	More extensively studied than IFC in several rehabilitation contexts, including spasticity-related research	Provides a useful comparator for electrical neuromodulation but should not be assumed to establish the mechanism proposed by CMAR.
IFC/IFT alone for spasticity	Limited and heterogeneous SCI-specific evidence	Supports investigation as an independent experimental variable rather than establishing superiority or a specific mechanistic effect.
IFC/IFT + CMAR process	Preliminary / hypothesis-generating	Potentially clinically useful multi-modal sequence, but the independent contribution of electrical stimulation, mechanical intervention, eccentric loading, and their interaction requires controlled investigation.

Section IX.C: Chloride Homeostasis and the Electrical-Conditioning Hypothesis

The proposed use of electrical conditioning before the mechanical-loading sequence raises a specific mechanistic question: can an electrical intervention place the spinal network in a state that permits a more reproducible response to subsequent peripheral mechanical input? Chloride homeostasis provides a biologically plausible reason why baseline spinal state could matter after SCI [60-62]. However, no evidence currently demonstrates that interferential current restores KCC2 expression or activity, normalizes intracellular chloride, or converts depolarizing inhibitory signaling into hyperpolarizing inhibition.

Accordingly, CMAR should not describe IFC/IFT as a method for bypassing a “chloride threshold,” directly restoring KCC2, or selectively driving deep Ia/Ib afferents. Those propositions remain untested. A defensible formulation is to treat IFC/IFT as a non-invasive conditioning variable whose effects on sensory input, reflex excitability, muscle activation, perfusion, or other tissue-level measures can be quantified before the mechanical intervention [12-15,18-21,29]. If SCI populations are studied, KCC2-related chloride dysregulation should be considered a potential state variable or mechanistic confound rather than an assumed target of IFC [60-62].

This distinction also preserves the core CMAR sequence. The primary experimental perturbation remains verified mechanical intervention followed immediately, or as soon as reasonably possible, by standardized eccentric loading. Electrical conditioning may be tested before that sequence, concurrently in a separate experimental arm, or at another prespecified interval. Its value would be supported only if it produces a reproducible interaction with the mechanical-loading sequence beyond the effects of either component alone.

Section X: Experimental Design and Component Isolation

For the IFT-preconditioning extension, electrical stimulation should be treated as an independently dosed experimental factor [12,15,17,20]. The study should record carrier frequency, beat frequency, waveform, electrode configuration, intensity, treatment duration, anatomical placement, and the interval between IFT cessation and the mechanical intervention.

Because IFC and TENS have shown broadly similar effects on pain in the existing comparative literature, this evidence should not be used to infer superiority for spasticity or for the CMAR mechanism. The study should therefore prioritize objective outcomes relevant to the proposed CMAR sequence - such as tissue stiffness, Hreflex or other reflex measures, surface EMG, force/torque, and functional performance rather than analgesia alone [12,15]. Where appropriate, residual torque enhancement could be incorporated as an additional outcome measure.

A standardized eccentric-loading protocol followed by isometric torque measurement could be used to determine whether the preceding intervention changes the magnitude, time course, or persistence of torque enhancement. Such measurements would not directly establish altered GTO deformation or afferent resetting, but could provide a functional readout of the muscle’s response to mechanical history.

To distinguish a mechanical effect from a neural or conditioning effect, torque measurements should be interpreted alongside tissue-stiffness measurements, reflex measures, surface EMG, and other predefined neurophysiological outcomes [27,28,53-55].

A 2025 randomized controlled trial of intramuscular electrical stimulation in chronic low back pain also illustrates that electrical stimulation can be studied against objective measures including muscle tension, perfusion, pressure-pain threshold, ROM, and postural stability, although that study used IMES rather than IFC and therefore should not be interpreted as direct evidence for the CMAR-IFT mechanism [16].

SCI-specific mechanistic measurements

In SCI-focused studies, the experimental battery should characterize the spinal-network state rather than infer it from clinical tone alone. In addition to tissue stiffness, receptor-region strain where feasible, EMG, torque, H-reflex or other validated reflex measures, and functional performance, investigators should record lesion level/completeness, chronicity, antispastic medication exposure, and baseline reflex excitability. Where a translational protocol permits, biomarkers or experimental measures related to chloride homeostasis/KCC2 function may be considered, but these should not be treated as routine clinical proxies for CMAR. The purpose is to test whether baseline inhibitory-network state modifies the relationship between mechanical perturbation, afferent/reflex response, and motor output [60-62].

Experimental Isolation of Multi-Modal Components

To address the multi-modal confounding problem, the experimental design should distinguish the effects of each intervention component from the effect of their combination. At minimum, a factorial or appropriately controlled design should consider:

1. CMAR mechanical intervention alone
2. IFT/IFC alone
3. Eccentric loading alone
4. CMAR mechanical intervention + eccentric loading
5. IFT/IFC + CMAR mechanical intervention + eccentric loading
6. Sham or passive-control condition, where ethically and methodologically appropriate

Such a design would allow investigators to determine whether the combined intervention produces an effect greater than its individual components. It would also permit investigation of potential interaction effects between electrical preconditioning and the subsequent mechanical-loading sequence [12,15,17,20]. The critical comparison is therefore not simply whether the combined protocol improves the outcome.

Rather, investigators should determine whether: Combined effect > effect of individual components and whether any additional benefit is accompanied by the predicted changes in tissue mechanics, reflex excitability, muscle activation, force production, and functional performance [12,15,17,20]. Where feasible, objective neurophysiological measures such as the H-reflex, together with surface EMG, tissue-stiffness measurements, force/torque measurements, and standardized functional measures, should be collected at predefined time points.

This would allow the investigators to distinguish an immediate electrical or neuromodulatory effect from a mechanical response and from a sequence- dependent interaction [15,17,20,22,23,30,31]. The experimental design should therefore prioritize component isolation, temporal control, dose specification, and mechanistic measurement rather than relying solely on the magnitude of clinical improvement.

Because IFC and TENS have shown broadly similar effects on pain in the existing comparative literature, the study should prioritize objective outcomes relevant to the CMAR mechanism - such as tissue stiffness, H-reflex or other reflex measures, EMG, force/torque, and functional performance rather than analgesia alone [12,15].

Section XI: Etiology, Spasticity and Clinical Research Context

A similar clinical phenotype can arise from different etiologies. CMAR should therefore not treat spasticity, rigidity, contracture, chronic hypertonicity, osteoarthritic guarding, pediatric motor disorders, or musculoskeletal stiffness as interchangeable. Central lesions may alter descending and spinal control first, with secondary peripheral remodeling; musculoskeletal disease may begin with local tissue and nociceptive changes; chronic immobilization or contracture may produce substantial structural resistance. The direction of causality can therefore differ across populations [15,17,20,58].

In spinal cord injury specifically, ionic plasticity adds another source of heterogeneity. Experimental evidence indicates that KCC2 downregulation and disturbed chloride homeostasis can weaken postsynaptic inhibition after SCI, while pharmacological enhancement of KCC2 can reduce hyperreflexia and spasticity-related responses in animal models [60-62]. This does not establish a CMAR mechanism, but it means that an identical peripheral afferent input may not produce an identical motor effect across intact, incomplete-SCI, and severe/chronic-SCI states. SCI should therefore be analyzed as a distinct mechanistic population rather than generalized to all forms of spasticity.

Clinical Implications for Chronic Spasticity

A potential clinical implication of the CMAR Hypothesis is that it may help explain a common clinical puzzle: why approaches directed exclusively toward either neurological dysfunction or peripheral mechanical dysfunction may produce incomplete or transient effects in some forms of chronic spasticity.

Chronic spasticity can involve altered descending and spinal regulation together with secondary changes in muscle, connective tissue, extracellular-matrix mechanics, and force transmission. In SCI, this neural component may itself reflect a pathway-specific imbalance, with reduced presynaptic and reciprocal inhibitory control, altered Ib-mediated force-feedback circuitry, and, in some patients, increased recurrent inhibition rather than a uniform loss of spinal inhibition [63-65].

CMAR proposes that these neural and peripheral mechanical components may become functionally coupled through altered proprioceptive mechanical input and downstream sensorimotor regulation. If such coupling exists, targeting either component in isolation may leave other contributors to the persistent neuromuscular state substantially unchanged. This remains a testable clinical implication of the hypothesis rather than an established explanation for treatment failure.

For clinical translation, CMAR is best positioned as a mechanism-oriented stratification framework: identify whether a measurable peripheral mechanical abnormality exists, determine whether it covaries with afferent/reflex or motor measures, and only then test whether changing that mechanical state changes the downstream response. Clinical improvement alone cannot establish the proposed mechanism.

Section XII: Falsification Criteria

CMAR should be treated as a falsifiable hypothesis. The model would be weakened or falsified at specific levels if:

1. The proposed intervention produces no measurable change in tissue mechanics.

2. Tissue mechanics change but no corresponding neurophysiological change occurs under controlled conditions.

3. Neurophysiological changes occur without predicted changes in motor output or function.

4. The sequential intervention is not different from its individual components when timing an dose are controlled. This criterion is particularly important for the multi-modal IFC/CMAR extension. If the combined intervention does not produce an effect that exceeds the effects of its independently tested components under controlled dosing and timing, the proposed synergistic or conditioning contribution of IFC would be weakened. Conversely, a reproducible interaction effect would provide stronger evidence that the sequence represents more than the additive effects of its individual components.

5. Functional improvement occurs without the predicted mechanical and neurophysiological sequence.

6. The proposed cellular branch lacks reproducible relationships between mechanical state and PIEZO- or YAP/TAZ-associated responses.

Divergent timing between PIEZO-associated and YAP/TAZ-associated responses would not necessarily falsify CMAR because the framework predicts that these branches may operate on different timescales.

Section XIII: Tissue Memory Extension - Integration with the Self-Reinforcing Loop

A longer-term extension of CMAR proposes a mechanically maintained tissue-memory loop [1-3,7,11,41-45].

ECM stiffness/mechanical stress → mechanosensation and cytoskeletal force transmission → YAP/TAZassociated nuclear signaling → fibroblast activation and ECM deposition → increased matrix stiffness → renewed mechanotransduction.

This concept does not require a change in DNA sequence. It proposes that persistent mechanical conditions may contribute to stable cellular and matrix states through mechanotransduction and potentially mechano-epigenetic processes. This is a downstream hypothesis and is not required to establish the core CMAR mechanism [7,11,26].

The proposed relationship is:

Increased ECM stiffness / mechanical stress

↓

PIEZO-associated mechanosensory signaling + cytoskeletal tension

↓

YAP/TAZ nuclear localization and transcriptional activation

↓

Fibroblast activation and increased ECM deposition

↓

Further ECM stiffening and altered force transmission

↓

Enhanced mechanotransductive signaling

The proposed sequence is:

Initial injury / abnormal mechanical loading

↓

ECM remodeling and increased tissue stiffness

↓

PIEZO-associated mechanosensation + YAP/TAZ activation

↓

Fibroblast activation

↓

Excessive ECM deposition and reduced matrix turnover

↓

Further tissue stiffening

↓

Persistent mechanotransductive signaling

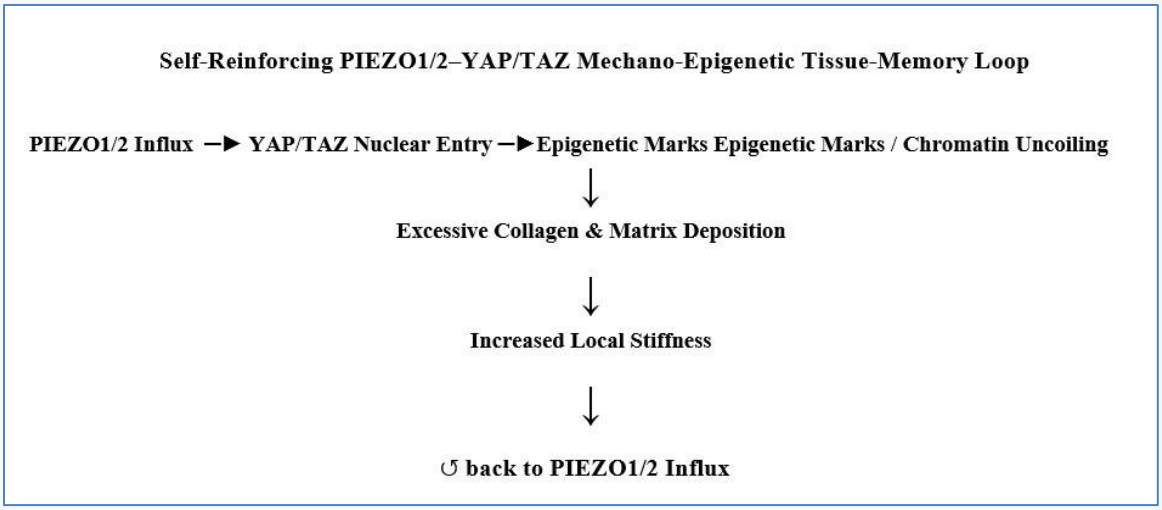
↓

Epigenetic/chromatin stabilization of the pro-fibrotic phenotype

↓

Continued ECM deposition

The proposed memory loop is:



Section XIV: Aging and Other Clinical Extensions

Age-associated changes in collagen organization, cross-linking, tissue compliance, fluid handling, and cellular mechanical responsiveness provide a potential context in which the CMAR framework could be examined [10,4648]. The model does not imply that mechanical therapy is an anti-aging or tissue-rejuvenation treatment. Potential clinical research contexts include chronic hypertonicity, selected forms of spasticity, contracture, fascial or connective-tissue restriction, musculoskeletal dysfunction, functional scoliosis, and aging-associated connectivetissue remodeling. These applications should be regarded as hypotheses for investigation rather than established therapeutic indications.

Section XV: Methodological Precision and Measurement

The original notes emphasize that a mechanobiological hypothesis must convert subjective manual technique into measurable variables. This is essential if the model is to move from conceptual proposal to reproducible science. Mechanical intervention should be described by anatomical location, patient position, direction of applied shear, contact area, duration, estimated force or pressure where measurable, and timing.

Eccentric loading should specify exercise, joint position, intensity, repetitions, velocity, range, and time interval after manual intervention. The distinction between reproducibility and validity is critical. A highly standardized intervention can be reproducible without necessarily producing the hypothesized biological effect.

Conversely, a clinically meaningful intervention may be difficult to standardize if its relevant variable is a force vector or tissuespecific deformation rather than a single scalar force. For this reason, the preferred experimental approach is to measure the tissue response directly and relate that response to the subsequent neurophysiological and functional response. The intervention becomes a controlled perturbation of a measurable mechanical system rather than an unquantified manual procedure.

Section XVI: Clinical and Conceptual Implications

Spasticity is a clinically complex phenomenon in which neural mechanisms coexist with secondary muscular and connective-tissue changes that can contribute to movement resistance [15,17,20,58]. Consequently, a reduction in passive or velocity-dependent resistance after an intervention would not, by itself, demonstrate altered GTO mechanics, ECM force transmission, or proprioceptive afferent signaling. CMAR studies in spasticity must therefore separate neural measures from passive mechanical measures.

Section XVII: Limitations and Boundary Conditions

The decisive limitation is that no study currently demonstrates the complete CMAR causal chain from altered local matrix mechanics to altered GTO deformation, altered Group Ib output, and a subsequent motor effect. Direct receptor-level measurements under experimentally manipulated matrix conditions are therefore the highest-priority test. H-reflex measurements are indirect and are not recordings of GTO/Ib activity. Manual shear is nonspecific and may affect muscle, fascia, tendon, vascular, nociceptive, and other sensory pathways. PIEZO2 is strongly supported in proprioceptor mechanotransduction [34], but its role in any CMAR intervention has not been tested. YAP/TAZ involvement is a separate cellular- remodeling hypothesis, not established GTO biology.

IFC is an optional conditioning variable with no demonstrated CMAR-specific mechanism. Clinical extensions such as spasticity, contracture, aging, or structural deformity must not be used as evidence for the core mechanism.

A further boundary condition concerns chloride-dependent inhibitory efficacy after SCI. The CMAR framework cannot assume that increased inhibitory afferent recruitment will translate directly into motoneuron inhibition when postsynaptic chloride regulation is altered. KCC2 findings support the importance of this state variable in SCI, but they do not demonstrate that CMAR interventions normalize chloride homeostasis [60-62]. Likewise, no current evidence establishes that IFC/IFT restores KCC2 function; this must remain a separate experimental question.

Section XVIII: Future Research Priorities

A publication-grade test of CMAR should proceed as a staged causal program rather than testing the entire multimodal sequence at once.

For SCI-focused translation, an additional staged question should be added: does the baseline inhibitory-network state modify the mechanical-to-afferent-to-motor relationship? Studies could stratify or characterize participants by lesion features, chronicity, medication status, and reflex phenotype, while preclinical work can directly examine KCC2/chloride-related mechanisms. Electrical conditioning should be tested independently for whether it changes these downstream state measures before any claim is made that it facilitates the CMAR sequence [60-62].

Aging represents a particularly relevant population in which to test the CMAR framework. Age-associated ECM remodeling and increased tissue stiffness may alter local force transmission even when contractile tissue remains present. Future studies should determine whether measured age-related changes in ECM mechanics are associated with altered receptor-region strain transfer, proprioceptive or reflex responses, motor-unit recruitment, and force production, and whether experimentally modifying the mechanical state changes these relationships. Such findings would be required before CMAR could be considered a preventive or maintenance-oriented strategy for age-related neuromuscular decline.

A related longitudinal question is whether an experimentally induced change in tissue mechanics persists or progressively returns toward the pre-intervention state. CMAR predicts that, if a self-reinforcing mechanical-memory process contributes to chronic ECM remodeling, repeated measurements of stiffness, strain transfer, afferent/reflex responses, and motor output should reveal whether a measurable “stiffness drift” occurs over time. Only if such recurrence is demonstrated should the frequency or potential value of repeated mechanical intervention be investigated.

Stage 1: Should determine whether controlled changes in local tissue mechanics alter strain transfer in the GTO/tendon region at matched external load.

Stage 2: Should test whether those verified mechanical changes alter proprioceptive afferent activity or the closest validated neurophysiological proxy.

Stage 3: Should test whether the afferent change predicts motor output under controlled activation.

Only after those steps should investigators test manual/mechanical interventions, eccentric-loading sequence effects, IFC conditioning, or longer-term cellular remodeling. This ordering prevents a clinical response from being mistaken for validation of the proposed mechanism. Such findings would be informative even if they did not support the full CMAR mechanism, because they could distinguish a measurable change in muscle force production from the more specific proposed relationship between ECM mechanics, mechanosensory signaling, and motor regulation [27,28].

The critical objective is not simply to demonstrate that a treatment works. It is to determine whether the predicted chain of mechanical → neurophysiological → motor → cellular events occurs in the proposed order. The broader neuroscience literature also emphasizes that neuronal structure and function can change in response to activity and environmental conditions. Such activity-dependent plasticity provides a conceptual precedent for considering whether sustained changes in mechanical input, sensory feedback, or neuromuscular activity could contribute to longer-term alterations in system responsiveness.

Within CMAR, however, this remains a proposed analogy and does not establish that the specific intervention sequence produces structural or functional resetting [22,23,30,31,33]. These findings further support the need to distinguish an immediate mechanical or electrophysiological response from a longer- term adaptive response. CMAR may involve both timescales: an acute change in tissue or neuromuscular responsiveness followed, potentially, by activity-dependent adaptation. The proposed model therefore requires measurements taken immediately after intervention as well as at later time points to determine whether any observed change is transient, persistent, or absent [22,23,33].

The existence of an ongoing registered clinical investigation into peripheral modulation of muscle stiffness and spasticity provides a relevant translational context for CMAR. The registry has no posted efficacy results and does not validate the proposed mechanism, but it illustrates that peripheral interventions aimed at modifying muscle stiffness and tone can be examined experimentally. CMAR could extend this line of inquiry by incorporating objective measurements of tissue mechanics, reflex excitability, EMG, torque, and functional performance rather than relying exclusively on clinical impressions of tone or movement resistance [15,17,20,29,32].

Conclusion

The Composite Matrix-Afferent Reset Hypothesis is best regarded as a focused mechanical-to-afferent hypothesis with optional downstream extensions. Its central prediction is that a measured change in the mechanical pathway loading a proprioceptive receptor particularly the collagen-coupled GTO can alter receptor region deformation and afferent output at a matched external load.

GTO collagen-afferent architecture and PIEZO2-dependent proprioceptor mechanotransduction provide biological plausibility [34-36,56,57], while skeletal-muscle ECM remodeling provides a plausible source of altered force transmission [4,44-48]. None of these observations demonstrates the CMAR link itself.

The hypothesis will be strengthened only if mechanical change precedes and predicts afferent change under controlled conditions; it will be weakened if receptor-region mechanics or afferent output remain unchanged despite the proposed perturbation.

Manual therapy, eccentric loading, IFC, YAP/TAZ signaling, tissue memory, and clinical applications should therefore be treated as separable experimental extensions rather than evidence that the core mechanism already exists.

Declarations

1. Competing Interests
The authors declare that they have no competing financial or commercial interests relevant to the preparation or publication of this manuscript.

2. Funding
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3. Ethics Approval and Consent to Participate
Not applicable. This manuscript presents a conceptual and theoretical hypothesis and does not report original research involving human participants or animals.

4. Consent for Publication
Not applicable. This manuscript does not contain identifiable personal information or individual participant data requiring consent for publication.

5. Availability of Data and Materials
No original experimental datasets were generated or analyzed in the preparation of this manuscript. The manuscript presents a theoretical hypothesis supported by previously published scientific literature.

6. Author Contributions
Herbert Miller developed the original hypothesis and its underlying scientific and conceptual framework. He contributed to the development, preparation, and critical revision of the manuscript.

Todd Miller contributed to the scientific development, literature review, preparation, and critical revision of the manuscript.

Both authors reviewed and approved the final manuscript and accept responsibility for its scientific content, accuracy, and integrity.

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References

1. Dupont S, Morsut L, Aragona M, Enzo E, Giulitti S, Cordenonsi M, et al. Role of YAP/TAZ in mechanotransduction. Nature. 2011;474(7350):179-183. doi:10.1038/nature10137.
2. Cai X, Wang KC, Meng Z. Mechanoregulation of YAP and TAZ in cellular homeostasis and disease progression. Front Cell Dev Biol. 2021;9:673599. doi:10.3389/fcell.2021.673599.
3. Martino F, Perestrelo AR, Vinarsky V, Pagliari S, Forte G. Cellular mechanotransduction: From tension to function. Front Physiol. 2018;9:824. doi:10.3389/fphys.2018.00824.
4. Gillies AR, Lieber RL. Structure and function of the skeletal muscle extracellular matrix. Muscle Nerve. 2011;44(3):318-331. doi:10.1002/mus.22094.
5. de Nooij JC. MS and GTO proprioceptor subtypes in the molecular genetic era: Opportunities for new advances and perspectives. Curr Opin Neurobiol. 2022;76:102597. doi:10.1016/j.conb.2022.102597.
6. Wang Y, Xiao B. The mechanosensitive Piezo1 channel: Structural features and molecular bases underlying its ion permeation and mechanotransduction. J Physiol. 2018;596(6):969-978. doi:10.1113/JP274404.
7. Li CX, Talele NP, Boo S, Koehler A, Knee-Walden E, Balestrini JL, et al. MicroRNA-21 preserves the fibrotic mechanical memory of mesenchymal stem cells. Nat Mater. 2017;16(3):379-389. doi:10.1038/nmat4780.
8. Kisilewicz A, Madeleine P, Ignasiak Z, Ciszek B, Kawczynski A, Larsen RG. Eccentric exercise reduces upper trapezius muscle stiffness assessed by shear wave elastography and myotonometry. Front Bioeng Biotechnol. 2020;8:928. doi:10.3389/fbioe.2020.00928.
9. Brandl A, Keiner M, Wilke J, Egner C, Schleip R, Schmidt T. Effects of a manual treatment on lumbar microcirculation and tissue stiffness following submaximal eccentric trunk extensor exercise: A randomized controlled trial. J Sports Sci Med. 2024;23:581-592. doi:10.52082/jssm.2024.581.
10. Kragstrup TW, Kjaer M, Mackey AL. Structural, biochemical, cellular, and functional changes in skeletal muscle extracellular matrix with aging. Scand J Med Sci Sports. 2011;21(6):749-757. doi:10.1111/j.1600-0838.2011.01377.x.
11. Liu F, Lagares D, Choi KM, Stopfer L, Marinkovic A, Vrbanac V, et al. Mechanosignaling through YAP and TAZ drives fibroblast activation and fibrosis. Am J Physiol Lung Cell Mol Physiol. 2015;308(4):L344-L357. doi:10.1152/ajplung.00300.2014.
12. de Almeida CC, da Silva VZM, Cipriano Junior G, Liebano RE, Durigan JLQ. Transcutaneous electrical nerve stimulation and interferential current demonstrate similar effects in relieving acute and chronic pain: A systematic review with meta-analysis. Braz J Phys Ther. 2018;22(5):347-354. doi:10.1016/j.bjpt.2017.12.005.
13. Fuentes JP, Armijo Olivo S, Magee DJ, Gross DP. Effectiveness of interferential current therapy in the management of musculoskeletal pain: A systematic review and meta-analysis. Phys Ther. 2010;90(9):1219-1238. doi:10.2522/ptj.20090335.
14. Hussein HM, Alshammari RS, Al-Barak SS, Alshammari ND, Alajlan SN, Althomali OW. A systematic review and meta-analysis investigating the pain-relieving effect of interferential current on musculoskeletal pain. Am J Phys Med Rehabil. 2022;101(7):624-633. doi:10.1097/PHM.0000000000001870.
15. Garcia MAC, Vargas CD. Is somatosensory electrical stimulation effective in relieving spasticity? A systematic review. J Musculoskelet Neuronal Interact. 2019;19(3):317-325. PMID:31475939.
16. Kuzdzal A, Olaniszyn G, Clemente FM, et al. Impact of intramuscular electrical stimulation on multifidus muscle function in chronic low back pain: A randomized controlled trial. Med Sci Monit. 2025;31:e949677. doi:10.12659/MSM.949677.
17. Hsieh JTC, Wolfe DL, Connolly S, Townson AF, Curt A, Blackmer J, et al. Spasticity after spinal cord injury: An evidence-based review of current interventions. Top Spinal Cord Inj Rehabil. 2007;13(1):81-97. doi:10.1310/sci1301-81.
18. Rampazo EP, Luz Junior MA, Correa JB, de Oliveira NTB, Dos Santos I, Liebano RE, Costa LOP. Effectiveness of interferential current in patients with chronic non-specific low back pain: A systematic review with meta-analysis. Braz J Phys Ther. 2023;27(5):100549. doi:10.1016/j.bjpt.2023.100549.
19. Eslamian F, Farhoudi M, Jahanjoo F, Sadeghi-Hokmabadi E, Darabi P. Electrical interferential current stimulation versus electrical acupuncture in management of hemiplegic shoulder pain and disability following ischemic stroke: A randomized clinical trial. Arch Physiother. 2020;10:2. doi:10.1186/s40945-019-0071-6.
20. Massey S, Vanhoestenberghe A, Duffell L. Neurophysiological and clinical outcome measures of the impact of electrical stimulation on spasticity in spinal cord injury: Systematic review and meta-analysis. Front Rehabil Sci. 2022;3:1058663. doi:10.3389/fresc.2022.1058663.
21. Rampazo EP, Liebano RE. Analgesic effects of interferential current therapy: A narrative review. Medicina (Kaunas). 2022;58(1):141. doi:10.3390/medicina58010141.
22. Wolpaw JR, Tennissen AM. Activity-dependent spinal cord plasticity in health and disease. Annu Rev Neurosci. 2001;24:807-843. doi:10.1146/annurev.neuro.24.1.807.
23. Tahayori B, Koceja DM. Activity-dependent plasticity of spinal circuits in the developing and mature spinal cord. Neural Plast. 2012;2012:964843. doi:10.1155/2012/964843.
24. Breuillaud N. The Reset Operator: A Minimal Structural Hypothesis for Recursive Transitions in Complex Systems. SSRN. 2026. doi:10.2139/ssrn.6767700. Preprint/working paper; not peer reviewed.
25. Wen R, Wang H, Pan W, Yan Z, Wang S. The Piezo1/YAP mechanotransduction axis: From mechanistic insights to therapeutic perspectives in disease. Biochem Pharmacol. 2026;253(Pt 1):118290. doi:10.1016/j.bcp.2026.118290.

26. Ley AWY, Bersie-Larson LM, Adhikari S, Provenzano PP, Dorfman KD, Barocas VH. Cell-extracellular matrix feedback results in spontaneous cell polarization and heterogeneous remodeling in 3D isotropic and aligned discrete-fiber models of cell-mediated remodeling. Cell Mol Bioeng. 2026;19(3):407-426. doi:10.1007/s12195-026-00922-0.
27. Jakobi JM, Kuzyk SL, McNeil CJ, Dalton BH, Power GA. Motor unit contributions to activation reduction and torque steadiness following active lengthening: A study of residual torque enhancement. J Neurophysiol. 2020;123(6):2209-2216. doi:10.1152/jn.00394.2019.
28. de Campos D, Orssatto LBR, Trajano GS, Herzog W, Fontana HB. Residual force enhancement in human skeletal muscles: A systematic review and meta-analysis. J Sport Health Sci. 2022;11(1):94-103. doi:10.1016/j.jshs.2021.05.006.
29. Suh HR, Han HC, Cho HY. Immediate therapeutic effect of interferential current therapy on spasticity, balance, and gait function in chronic stroke patients: A randomized control trial. Clin Rehabil. 2014;28(9):885-891. doi:10.1177/0269215514523798.
30. Balaguer JM, Prat-Ortega G, Ostrowski J, Borda L, Verma N, Yadav P, et al. Neural mechanisms underlying the recovery of voluntary control of motoneurons after paralysis with spinal cord stimulation. Neuron. 2025;113(22):3846-3862.e6. doi:10.1016/j.neuron.2025.08.023.
31. Seanez I, Capogrosso M, Minassian K, Wagner FB. Spinal cord stimulation to enable leg motor control and walking in people with spinal cord injury. In: Reinkensmeyer DJ, Marchal-Crespo L, Dietz V, eds. Neurorehabilitation Technology. 3rd ed. Springer; 2022:369-400. doi:10.1007/978-3-031-08995-4_18.
32. Johns Hopkins University. Peripheral Modulation of Muscle Stiffness and Spasticity. ClinicalTrials.gov identifier NCT03306615. Updated June 30, 2026. No results posted as of September 10, 2026.
33. Hogan MK, Hamilton GF, Horner PJ. Neural stimulation and molecular mechanisms of plasticity and regeneration: A review. Front Cell Neurosci. 2020;14:271. doi:10.3389/fncel.2020.00271.
34. Woo SH, Lukacs V, de Nooij JC, Zaytseva D, Criddle CR, Francisco A, et al. Piezo2 is the principal mechanotransduction channel for proprioception. Nat Neurosci. 2015;18(12):1756-1762. doi:10.1038/nn.4162.
35. Mileusnic MP, Loeb GE. Mathematical models of proprioceptors. II. Structure and function of the Golgi tendon organ. J Neurophysiol. 2006;96(4):1789-1802. doi:10.1152/jn.00869.2005.
36. Windhorst U. Muscle proprioceptive feedback and spinal networks. Brain Res Bull. 2007;73(4-6):155-202. doi:10.1016/j.brainresbull.2007.03.010.
37. Nichols TR. Distributed force feedback in the spinal cord and the regulation of limb mechanics. J Neurophysiol. 2018;119(3):1186-1200. doi:10.1152/jn.00216.2017.
38. Dupont S. Role of YAP/TAZ in cell-matrix adhesion-mediated signaling and mechanotransduction. Exp Cell Res. 2016;343(1):42-53. doi:10.1016/j.yexcr.2015.10.034.
39. Fischer M, Rikeit P, Knaus P, Coirault C. YAP-mediated mechanotransduction in skeletal muscle. Front Physiol. 2016;7:41. doi:10.3389/fphys.2016.00041.
40. Dupont S. Regulation of YAP/TAZ activity by mechanical cues: An experimental overview. Methods Mol Biol. 2019;1893:183-202. doi:10.1007/978-1-4939-8910-2_15.
41. Yang C, Tibbitt MW, Basta L, Anseth KS. Mechanical memory and dosing influence stem cell fate. Nat Mater. 2014;13(6):645-652. doi:10.1038/nmat3889.
42. Heo SJ, Thorpe SD, Driscoll TP, Duncan RL, Lee DA, Mauck RL. Biophysical regulation of chromatin architecture instills a mechanical memory in mesenchymal stem cells. Sci Rep. 2015;5:16895. doi:10.1038/srep16895.
43. Hinz B. The extracellular matrix and transforming growth factor-beta1: Tale of a strained relationship. Matrix Biol. 2015;47:54-65. doi:10.1016/j.matbio.2015.05.006.
44. Csapo R, Gumpenberger M, Wessner B. Skeletal muscle extracellular matrix - What do we know about its composition, regulation, and physiological roles? A narrative review. Front Physiol. 2020;11:253. doi:10.3389/fphys.2020.00253.
45. Smith LR, Barton ER. A glitch in the matrix: The pivotal role for extracellular matrix remodeling during muscle hypertrophy. Am J Physiol Cell Physiol. 2022;323(3):C763-C777. doi:10.1152/ajpcell.00137.2022.
46. Gumpenberger M, Wessner B, Graf A, Narici MV, Fink C, Braun S, et al. Remodeling the skeletal muscle extracellular matrix in older age-effects of acute exercise stimuli on gene expression. Int J Mol Sci. 2020;21(19):7089. doi:10.3390/ijms21197089.
47. Pavan P, Monti E, Bondi M, Fan C, Stecco C, Narici M, Reggiani C, Marcucci L. Alignment, cross linking, and beyond: A collagen architect's guide to the skeletal muscle extracellular matrix. Am J Physiol Cell Physiol. 2023;325(4):C1017-C1038. doi:10.1152/ajpcell.00126.2023.
48. Kjaer M, Langberg H, Heinemeier K, Bayer ML, Hansen M, Holm L, et al. From mechanical loading to collagen synthesis, structural changes and function in human tendon. Scand J Med Sci Sports. 2009;19(4):500-510. doi:10.1111/j.1600-0838.2009.00986.x.
49. Eriksson Crommert M, Lacourpaille L, Heales LJ, Tucker K, Hug F. Massage induces an immediate, albeit short-term, reduction in muscle stiffness. Scand J Med Sci Sports. 2015;25(5):e490-e496. doi:10.1111/sms.12341.
50. Brandl A, Egner C, Schleip R. Effects of a myofascial technique on the stiffness and thickness of the thoracolumbar fascia and lumbar erector spinae muscles in adults with chronic low back pain: A randomized before-and-after experimental study. Life (Basel). 2023;13(3):699. doi:10.3390/life13030699.
51. Morales-Osorio MA, Mejia-Mejia E, et al. Assessment of the effects of direct myofascial release in the lateral gastrocnemius muscle of tennis athletes using ShearWave elastography. J Bodyw Mov Ther. 2025;41:233-239. doi:10.1016/j.jbmt.2024.07.011.
52. Herzog W, Schappacher G, DuVall M, Leonard TR, Herzog JA. Residual force enhancement following eccentric contractions: A new mechanism involving titin. Physiology (Bethesda). 2016;31(4):300-312. doi:10.1152/physiol.00049.2014.

53. Fukutani A, Herzog W. Current understanding of residual force enhancement: Cross-bridge component and non-cross-bridge component. Int J Mol Sci. 2019;20(21):5479. doi:10.3390/ijms20215479.
54. Power GA, Makrakos DP, Rice CL, Vandervoort AA. Residual force enhancement following eccentric induced muscle damage. J Biomech. 2012;45(10):1835-1841. doi:10.1016/j.jbiomech.2012.04.006.
55. Gordon T, English AW. Strategies to promote peripheral nerve regeneration: Electrical stimulation and/or exercise. Eur J Neurosci. 2016;43(3):336-350. doi:10.1111/ejn.13005.
56. Swett JE, Schoultz TW. Mechanical transduction in the Golgi tendon organ: a hypothesis. Arch Ital Biol. 1975;113(4):374-382. PMID:1230097.
57. Jami L. Functional properties of Golgi tendon organs. Arch Int Physiol Biochim. 1988;96(4):A363-A378. PMID:2463816.
58. Raghavan P. Muscle physiology in spasticity and muscle stiffness. Toxicon. 2025. doi:10.1016/j.toxicon.2025.108350. PMID:40216366.
59. Ge X, Jin Y, He J, Jia Z, Lu Y, Xu Y, et al. Extracellular matrix in skeletal muscle injury and atrophy: mechanisms and therapeutic implications. J Orthop Transl. 2025;52:404-418. doi:10.1016/j.jot.2025.03.004.
60. Bilchak JN, Yeakle K, Caron G, Malloy D, Cote MP. Enhancing KCC2 activity decreases hyperreflexia and spasticity after chronic spinal cord injury. Exp Neurol. 2021;338:113605. doi:10.1016/j.expneurol.2021.113605.
61. Bilchak JN, Danner SM, Caron G, Cote MP. KCC2 enhancers normalize reflex responses and improve locomotor function after chronic spinal cord injury. J Physiol. 2025;603(19):5701-5721. doi:10.1113/JP287774.
62. Talifu Z, Pan Y, Gong H, Xu X, Zhang C, Yang D, Gao F, Yu Y, Du L, Li J. The role of KCC2 and NKCC1 in spinal cord injury: From physiology to pathology. Front Physiol. 2022;13:1045520. doi:10.3389/fphys.2022.1045520.
63. Shefner JM, Berman SA, Sarkarati M, Young RR. Recurrent inhibition is increased in patients with spinal cord injury. Neurology. 1992;42(11):2162–2168. doi:10.1212/WNL.42.11.2162. PMID:1436529.
64. Mirbagheri MM, Duffell LD, Kotsapouikis D, Rogers LM. Reciprocal inhibition becomes facilitation aft er spinal cord injury: Clinical application of a system identification approach. Annu Int Conf IEEE Eng Med Biol Soc. 2014;2014:4395–4398. doi:10.1109/EMBC.2014.6944598. PMID:25570966.
65. Knikou M, Smith AC, Mummidisetty CK. Locomotor training improves reciprocal and nonreciprocal inhibitory control of soleus motoneurons in human spinal cord injury. J Neurophysiol. 2015;113(7):2447–2460. doi:10.1152/jn.00872.2014. PMID:25609110.