The Composite Matrix-Afferent Reset (CMAR) Hypothesis

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

From Mechanical Disturbance → Altered Receptor Deformation → Altered Afferent Output → Tissue Adaptation, Retention/Memory … and How to Test and Potentially Reset It.

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KEY CONCEPTS

Extracellular Matrix (ECM)
- Stiffness / viscoelasticity
- Collagen architecture
- Hydration and cross-linking
- Force transmission
- Changes with injury, aging, disease

Golgi Tendon Organ (GTO)
- Group Ib afferent endings
- Interwoven with collagen
- Force transmission via ECM
- Receptor deformation

PIEZO2 Mechanosensor
- Mechanosensitive ion channel
- Rapid ionic/electrical response
- Present in proprioceptors and other mechanosensitive cells

YAP/TAZ Mechanotransduction
- Mechanically regulated transcriptional co-activators
- Involved in tissue adaptation and ECM remodeling

Intervention (Hypothesis)
- Verified mechanical perturbation
- Standardized loading challenge (e.g., eccentric)
- Optional IFC/IFT (conditioning variable)
- Controlled experimental testing required
- Not an established clinical sequence

Mechanical Moderators (Experimental Considerations)
- Muscle architecture (pennation)
- Pre-tension / tissue slack
- Loading velocity / strain rate
- Tendon compliance
- Joint position and baseline activation state

CMAR Test Phase (Experimental, not established)
- Modify local ECM mechanics
- Alter viscoelastic behaviour
- Prepare tissue environment

I. CORE CMAR HYPOTHESIS (PRIMARY MECHANISTIC PATHWAY)

Altered tissue mechanics → altered receptor deformation → altered afferent output → altered neuromuscular function

1 Altered ECM Mechanics Force Transmission
- Pathological or adaptive changes in ECM stiffness, viscoelasticity, or architecture
- Altered collagen organization
- Modified local force transmission to the GTO
- Influenced by injury, aging, disease, and loading conditions

2 Altered Receptor-Region Deformation (GTO-Focused)
- Changed mechanical input and deformation of GTO endings
- Group Ib afferents interwoven with collagen bundles
- Altered relationship between external force and receptor strain
- Influenced by mechanical moderators (architecture, slack, velocity, etc.)

3 Altered Afferent Output and Sensorimotor Processing
- Modified Group Ib firing patterns
- Changes in spinal interneurons
- Altered sensorimotor processing
- May affect tone, reflex excitability, and motor control

4 Neuromuscular Consequences (Downstream Extension)
- Changes in reflex excitability
- Altered muscle activation and control
- Impaired motor function
- Context dependent (e.g., spasticity, pain)
- Must not be used as evidence for the core mechanism

MODEL CONTEXT

The CMAR hypothesis builds on established anatomy and physics, but proposes that altered ECM mechanics and GTO deformation can influence afferent signalling, downstream neuromuscular outcomes, and a self-reinforcing tissue-memory loop.

All components are hypotheses requiring experimental validation.

Not an established clinical mechanism.

II. PARALLEL AND DOWNSTREAM MECHANISMS (EXPERIMENTAL EXTENSIONS)

Biologically distinct but potentially interacting processes within a common ECM environment

A PIEZO2-Associated Mechanosensation (Proprioceptive / Neuronal)
- ECM force transmission → membrane/cellular deformation
- PIEZO2-associated mechanosensitive signalling
- Rapid ionic/electrical cellular response
- Primary role in acute mechanosensation
- Functions independently of YAP/TAZ

B YAP/TAZ-Associated Mechanotransduction (Cellular / Non-neuronal)
- ECM force transmission → cytoskeletal/mechanical force
- YAP/TAZ regulation → nuclear signalling / transcription
- Longer-term cellular adaptation and ECM remodeling
- Mechanically regulated in fibroblasts, tenocytes, myocytes
- Functions independently of PIEZO2

C SCM/ECM Remodeling & Tissue Adaptation (Longer-Term Extenstion)
- Changes in ECM composition and structure
- Altered collagen organization and cross-linking
- Viscoelastic changes and altered mechanics
- Contributes from PIEZO2- and/or YAP/TAZ pathways
- Represents a potential tissue "memory" mechanism
- Requires separate experimental validation

Spinal Inhibitory Circuitry (Downstream Extension)
- Altered Ib-mediated force feedback
- Reduced reciprocal (Ia) inhibition (in some SCI/pathological states)
- Reduced presynaptic inhibition of Ia transmission (context dependent)
- Increased recurrent inhibition (Renshaw cell circuitry) in some SCI
- Pathway-specific changes in sensorimotor regulation

Chloride Homeostasis (Neural State Modifier)
- KCC2 / NKCC1 regulation may influence inhibitory efficacy and motor response to altered afferent input.
- Downstream modifier – not an established target of CMAR or IFC/IFT.
- Must be considered in interpretation of neuromuscular outcomes.

III. THE SELF-REINFORCING MECHANO-EPIGENETIC TISSUE-MEMORY LOOP

How initial mechanical disturbance can lead to persistent dysfunction

INITIATING FACTORS
- Injury (acute or repetitive)
- Overuse / abnormal loading
- Poor biomechanical / posture
- Aging and degenerative changes
- Inflammation / disuse
- Systemic or metabolic factors

Once established, this loop can maintain an abnormal tissue state, sustain aberrant input, and contribute to ongoing neuromuscular dysfunction even after the initial insult has resolved.

1. Altered ECM Mechanics (stiffness, cross-linking, organization)
2. Changed GTO Deformation (altered mechanical input)
3. Altered Afferent Signalling (modified Group Ib output)
4. Cellular Adaptation & Proposed Epigenetic Memory (YAP/TAZ signalling, transcriptional response, fibroblast activity, ECM remodeling)
5. Persistent Tissue Changes (stiffer matrix, altered mechanics)

SELF-REINFORCING MECHANO-EPIGENETIC TISSUE-MEMORY LOOP
Maintains the cycle of structural and functional impairment

POTENTIAL CONSEQUENCES (Hypothesized)
- Persistent increases in ECM stiffness
- Sustained altered GTO input
- Maladaptive reflex and motor patterns
- Tissue hypo/hyperexcitability
- Chronic pain and dysfunction
- Difficulty to reverse without addressing mechanical and/or neural contributors

CLINICAL IMPLICATION (Hypothesis)
Persistent neuromuscular dysfunction may involve interacting central neural and peripheral mechanical abnormalities. Addressing either component in isolation may leave other contributors unchanged.

IV. PROPOSED EXPERIMENTAL INTERVENTION SEQUENCE (TO TEST THE CMAR HYPOTHESIS)

Hypothesized sequence. Timing and role of IFC/IFT have not been established and should be tested as an independent variable.

1 Verified Mechanical Perturbation (Manual therapy)
- Targeted intervention to modify
- local tissue mechanics / ECM state
- e.g., joint/tissue mobilization

2 Standardized Loading Challenge (Eccentric or Controlled Loading)
- Defined mechanical stimulus
- Increases GTO mechanical loading
- Enhances Group Ib afferent activity
- Provides directional stimulus for testing

3 Optional Conditioning Variable (Interferential Current Therapy – IFC/IFT)
- Tested as an adjunct (pre, during, or post loading – timing not established)
- May augment mechanosensory signalling
- Requires independent evaluation

Core Mechanistic Validation: Verified mechanical change → altered receptor-region deformation and/or afferent output under controlled loading.
Clinical or functional improvement alone does not validate the core CMAR mechanism.

OVERALL GOAL (Hypothesis)
Test whether targeted mechanical perturbation and standardized loading can modify ECM-to-receptor force transmission, alter afferent signalling, and promote more adaptive neuromuscular function.

PREDICTED OUTCOMES (TESTABLE ACROSS MULTIPLE LEVELS)

Tissue Mechanics
- ↓ Stiffness (where applicable)
- ↑ Viscoelasticity
- More normal collagen organization

Neurophysiology
- Normalized reflex excitability
- Improved sensorimotor integration

Muscle Function
- Improved muscle length
- Reduced hypertonicity
- Enhanced strength and motor control

Clinical Outcomes
- Reduced pain
- Improved function
- Better movement quality
- Enhanced quality of life

LEGEND
- Hypothesized pathway
- Potential interaction
- Optional / not established
- Core CMAR pathway (testable)
- Secondary/extension pathway
- Cellular process

All mechanistic and therapeutic claims remain hypotheses.

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

"Start with the mechanics. Test the pathway. Restore the function."