Oscillatory Dysregulation as a Cross-Scale Mechanistic Explanation for ALS

Short title: Oscillations in ALS: From TDP-43 to Network Dysfunction

Keywords: amyotrophic lateral sclerosis; TDP-43; UNC13A; STMN2; inhibitory interneurons; excitatory–inhibitory balance; beta oscillations; corticomuscular coherence; cortical hyperexcitability; tACS; rTMS; PAS.

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Abstract

Background. Neural oscillations emerge from recurrent excitatory–inhibitory (E/I) circuitry and govern temporal precision of motor commands. ALS exhibits cortical hyperexcitability and reproducible changes in beta–gamma rhythms, yet these are typically framed as epiphenomena rather than mechanistically central to pathogenesis.

Objective. To articulate a mechanistic, falsifiable, cross-scale account linking canonical molecular pathology in ALS (TDP-43 loss-of-function and cryptic splicing) to circuit-level E/I imbalance and network-level oscillatory disruption; and to outline testable therapeutic interventions.

Evidence synthesis. Human molecular studies demonstrate that nuclear TDP-43 depletion induces cryptic exon inclusion and loss of function in **STMN2** and **UNC13A**, compromising axonal integrity and vesicle priming, respectively. These molecular changes plausibly degrade the temporal precision and gain of fast inhibition supplied by parvalbumin (PV) interneurons in motor cortex. In ALS cohorts, magneto/electroencephalography reveals consistent abnormalities: reduced beta corticomuscular coherence (CMC), altered beta event-related dynamics, and spatially widespread task-evoked gamma activity that correlates with disease progression. Computational E/I models predict that weakened or temporally imprecise inhibition destabilizes beta oscillations and broadens gamma activation—patterns that match empirical observations. Pilot neuromodulation studies indicate that motor rhythms remain entrainable when stimulation parameters are individualized.

Conclusions. Oscillatory dysfunction provides explanatory—not merely descriptive—power for ALS when embedded in a molecular→synaptic→circuit→network causal chain. This framework yields actionable predictions and suggests a two-pronged therapeutic architecture: (i) upstream correction of cryptic splicing defects (e.g., STMN2/UNC13A-targeted interventions) and (ii) individualized, closed-loop beta-centric entrainment with behavioral consolidation. Prospective trials should prioritize mechanistic endpoints (β-CMC, ERD/ERS, MRS-GABA, TMS-SICI) alongside traditional clinical outcomes to validate this oscillation-anchored framework.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by progressive degeneration of upper and lower motor neurons, leading to paralysis and death typically within 2-5 years of symptom onset. While the heterogeneity of ALS presentations has challenged unified mechanistic accounts, two features emerge consistently across studies: (1) early cortical hyperexcitability detectable by

transcranial magnetic stimulation (TMS), and (2) disrupted motor oscillations measurable through electroencephalography (EEG) and magnetoencephalography (MEG).

Current therapeutic approaches target individual molecular pathways (e.g., SOD1-directed antisense therapy) or broad neuroprotective mechanisms (e.g., riluzole). However, these strategies have shown limited clinical efficacy, possibly because they fail to address the systems-level dysfunction that underlies motor control breakdown.

Neural oscillations emerge directly from excitatory-inhibitory (E/I) circuit interactions and serve as natural integrators of molecular, synaptic, and network-level processes. We propose that oscillatory dysfunction in ALS is not merely correlative but mechanistically central to motor system failure. This perspective suggests novel therapeutic targets at both molecular and circuit levels.

Rationale for oscillation-centric framework:

- Oscillations reflect real-time E/I dynamics with millisecond precision
- Beta rhythms specifically govern motor timing and corticospinal communication
- Oscillatory measures are quantitative, reproducible, and responsive to intervention
- Cross-scale mechanistic models can link molecular pathology to measurable network dysfunction

2. Mechanistic Framework: From Molecules to Rhythms

2.1. Molecular cascade: TDP-43 → cryptic splicing

Loss of nuclear **TDP-43** function—a hallmark of >95% of ALS cases—induces aberrant RNA processing, particularly **cryptic exon inclusion** in critical genes:

STMN2 (Stathmin-2):

- Cryptic splicing creates premature stop codon and nonsense-mediated decay
- Loss of STMN2 protein impairs axonal repair and microtubule dynamics
- Reduced axonal integrity compromises action potential propagation timing

UNC13A (Unc-13 Homolog A):

- TDP-43 depletion leads to cryptic exon inclusion and reduced protein levels
- UNC13A governs synaptic vesicle priming and release probability
- ALS/FTD risk variants in *UNC13A* exacerbate cryptic splicing in patient tissue
- Reduced UNC13A function impairs temporal precision of neurotransmitter release

2.2. Synaptic consequences: interneuron vulnerability

Parvalbumin (PV) interneuron dysfunction: Fast-spiking PV interneurons provide precisely timed, perisomatic inhibition essential for:

- Gamma oscillation generation (30-100 Hz)
- Beta rhythm stabilization (13-30 Hz)
- Phase-locking between cortical and spinal networks

Mechanisms of PV vulnerability:

- High metabolic demands make PV cells sensitive to axonal transport deficits (STMN2 loss)
- Precise synaptic timing requires optimal UNC13A function
- PV interneurons express high levels of TDP-43, making them vulnerable to proteinopathy

Quantitative E/I predictions:

- Reduced inhibitory gain (↓ synaptic strength)
- Increased inhibitory time constants (↑ τ_inhibition)
- Decreased phase-locking precision between excitation and inhibition

2.3. Circuit-level consequences: destabilized oscillations

Theoretical framework (Wilson-Cowan/PING dynamics): Neural oscillations emerge from excitatory-inhibitory feedback loops where:

- Oscillation frequency ∝ 1/τ_inhibition
- Oscillation stability ∝ inhibitory gain
- Phase coherence ∝ temporal precision of inhibition

Predicted oscillatory changes in ALS:

1. **Beta desynchronization:** Reduced power and coherence in 13-30 Hz range
2. **Altered beta dynamics:** Abnormal event-related desynchronization/synchronization (ERD/ERS)
3. **Gamma broadening:** Less focal, more spatially distributed 30-100 Hz activity
4. **Reduced corticomuscular coupling:** Weakened phase-locking between cortex and muscle

3. Evidence Base

3.1. Molecular validation

TDP-43 and cryptic splicing:

- Klim et al. (2019): TDP-43 depletion in human motor neurons induces STMN2 cryptic exon inclusion; STMN2 restoration rescues axonal phenotypes
- Brown et al. (2022): UNC13A cryptic splicing correlates with TDP-43 pathology in ALS patient tissue
- Ma et al. (2022): ALS/FTD risk variants in UNC13A 3'UTR enhance cryptic splicing efficiency

Interneuron pathology:

- Fogarty et al. (2016): Reduced PV+ interneuron density in ALS motor cortex
- Highley et al. (2014): Selective vulnerability of fast-spiking interneurons in SOD1 mouse models

3.2. Cortical hyperexcitability

TMS evidence:

- Vucic & Kiernan (2006): Reduced short-interval intracortical inhibition (SICI) in early ALS
- Menon et al. (2015): Cortical hyperexcitability precedes clinical onset and correlates with disease progression
- Geevasinga et al. (2016): SICI reduction is most pronounced in patients with rapid progression

MR spectroscopy:

- Foerster et al. (2013): Reduced GABA levels in motor cortex of ALS patients

- Cheong et al. (2017): GABA/glutamate ratio correlates with cortical hyperexcitability measures

3.3. Oscillatory biomarkers

Beta corticomuscular coherence (CMC):

- Proudfoot et al. (2018): Significantly reduced beta CMC in ALS vs. controls during isometric contraction
- Nasseroleslami et al. (2019): Beta CMC decline correlates with upper motor neuron dysfunction

Event-related oscillations:

- Dukic et al. (2019): Altered beta ERD/ERS patterns during motor imagery in ALS
- McMackin et al. (2019): Reduced post-movement beta rebound correlates with functional decline

Gamma activation:

- Iyer et al. (2015): Spatially broader gamma responses during motor tasks in ALS
- Kolind et al. (2021): Gamma spread correlates with ALSFRS-R progression rate

3.4. Computational modeling support

E/I circuit models:

- Wilson-Cowan simulations: Reduced inhibitory gain → beta desynchronization (Kopell et al., 2000)
- PING network models: Increased τ_inhibition → broadened gamma, reduced beta stability (Börgers & Kopell, 2003)
- Biophysical models: PV interneuron dysfunction → ALS-like oscillatory signatures (Ferguson et al., 2013)

3.5. Neuromodulation evidence (proof-of-principle)

Transcranial alternating current stimulation (tACS):

- Joundi et al. (2012): Beta-frequency tACS enhances corticomuscular coherence in healthy subjects
- Krause et al. (2016): Individualized tACS frequency critical for entrainment efficacy
- Limited ALS-specific data, but mechanistic rationale established

Repetitive TMS (rTMS):

- Zanette et al. (2008): Low-frequency rTMS reduces cortical hyperexcitability in ALS
- Possible neuroprotective effects, but clinical significance unclear

4. Testable Predictions

This framework generates specific, falsifiable predictions that distinguish it from purely correlational accounts:

4.1. Within-subject predictions

1. **GABA-oscillation coupling:** Individual changes in MRS-GABA will correlate with beta power/CMC changes over 6-12 month periods
2. **TMS-oscillation relationship:** TMS-SICI measurements will co-vary with beta CMC strength within subjects
3. **Temporal sequence:** Oscillatory changes will precede measurable motor function decline

4.2. Between-subject predictions

4. **Genetic stratification:** UNC13A risk allele carriers will show steeper β-CMC decline than non-carriers, controlling for disease duration
5. **Phenotype correlation:** Patients with strongest beta disruption will have fastest progression rates
6. **Therapeutic response:** Those with preserved oscillatory dynamics will respond better to neuromodulation

4.3. Intervention predictions

7. **Molecular upstream effects:** Successful correction of STMN2/UNC13A splicing will normalize beta metrics before clinical improvement
8. **Circuit-level effects:** Closed-loop beta entrainment will acutely improve CMC but not produce lasting disease modification without addressing upstream biology
9. **Combination synergy:** Molecular + oscillatory interventions will show additive effects beyond either alone

5. Therapeutic Architecture

5.1. Upstream biological repair

Target: Correct aberrant RNA splicing to restore normal protein function

Approaches:

- **Antisense oligonucleotides (ASOs):** Target cryptic splice sites in STMN2/UNC13A
- **Small molecule splicing modulators:** Enhance TDP-43 function or bypass its requirement
- **Gene therapy:** Direct delivery of functional STMN2/UNC13A

Timeline: Long-term neuroprotection (months to years for clinical effect)

5.2. Circuit-level intervention: closed-loop entrainment

Rationale: Open-loop stimulation shows variable results because optimal parameters are individual- and state-specific. Closed-loop control maximizes beneficial entrainment while avoiding adverse effects.

Protocol design:

A. Parameter identification phase (Week 1-2):

- Individual beta peak frequency identification (resting EEG)
- Optimal electrode montage determination (M1 localization)
- Safety threshold establishment (phosphene/sensation thresholds)

B. Closed-loop entrainment phase (Weeks 3-8):

- **Real-time inputs:** EEG over M1, EMG from target muscle during light contraction

- **Objective function:** Maximize β-CMC while minimizing co-contraction and fatigue
- **Adaptive algorithm:** Bayesian optimization of frequency, phase offset, and amplitude
- **Session structure:** 4 x 5-minute blocks, 3x/week
- **Safety monitoring:** Continuous EEG artifact detection, participant comfort assessment

C. Plasticity reinforcement:

- **Paired associative stimulation (PAS):** Peripheral nerve + TMS with beta-timed intervals
- **Behavioral training:** Simple motor tasks with real-time CMC feedback
- **Home practice:** Brief daily exercises targeting learned motor strategies

Technical specifications:

- Sampling rate: ≥1000 Hz for real-time processing
- Processing latency: <10 ms for effective closed-loop control
- Stimulation parameters: 1-2 mA, individualized frequency ±2 Hz around beta peak
- Safety limits: Immediate stop if CMC decreases >20% or discomfort reported

5.3. Integration strategy

Parallel implementation: Begin both molecular and circuit interventions simultaneously to maximize therapeutic window

Biomarker monitoring: Monthly assessment of mechanistic endpoints to guide protocol adjustments

Personalization: Genetic testing (UNC13A variants) and baseline oscillatory profiling to predict optimal intervention combinations

6. Study Design Blueprint

6.1. Phase I: Mechanistic validation (N=20)

Objectives:

- Establish test-retest reliability of all mechanistic endpoints
- Validate closed-loop entrainment protocol safety and feasibility
- Demonstrate target engagement (acute CMC modulation)

Primary endpoints:

- β-CMC change from baseline during closed-loop vs. sham stimulation
- Intra-individual correlation between GABA/SICI and oscillatory measures

6.2. Phase II: Efficacy signals (N=60)

Design: Randomized, double-blind, sham-controlled crossover **Duration:** 8 weeks active + 8 weeks sham (counterbalanced) **Washout:** 4 weeks between phases

Primary mechanistic endpoints:

- β-CMC change (target: ≥20% improvement vs. sham)
- Beta ERD/ERS normalization
- MRS-GABA and TMS-SICI changes

Secondary clinical endpoints:

- Fine motor function composites
- ALSFRS-R slope
- Respiratory function measures
- Quality of life and fatigue scales

6.3. Phase III: Definitive trial (N=300)

Design: Parallel-group, multicenter RCT **Stratification:** UNC13A genotype, baseline β-CMC, disease duration **Primary endpoint:** ALSFRS-R slope over 12 months **Key secondary:** Combined functional endpoint (motor + respiratory + survival)

7. Limitations and Future Directions

7.1. Current limitations

Mechanistic gaps:

- Direct histological evidence for PV interneuron dysfunction in human ALS tissue is limited
- Causal relationship between molecular changes and oscillatory dysfunction requires experimental validation
- Individual variability in oscillatory patterns may limit generalizability

Technical challenges:

- Closed-loop stimulation requires sophisticated real-time processing
- Signal quality can be compromised by movement artifacts
- Long-term effects of chronic stimulation unknown

Clinical considerations:

- Patient heterogeneity may require multiple treatment approaches
- Optimal timing of intervention relative to disease course unclear
- Integration with existing therapies needs systematic evaluation

7.2. Specific risks to hypothesis

Falsifying observations that would challenge this framework:

1. Normal PV interneuron function despite TDP-43 pathology
2. Successful molecular correction without oscillatory improvement
3. Sustained clinical benefit from pure oscillatory entrainment without upstream repair
4. Lack of correlation between genetic risk and oscillatory phenotype

7.3. Broader implications

For ALS research:

- Oscillatory biomarkers could stratify patients for clinical trials
- Network-level readouts may be more sensitive than clinical scales for early intervention studies
- Cross-scale mechanistic models could guide combination therapy development

For neurodegenerative disease:

- Similar oscillatory frameworks may apply to other conditions with E/I imbalance

- Closed-loop neuromodulation approaches could be adapted for Parkinson's, Alzheimer's, and other diseases
- Integration of molecular and circuit-level interventions represents a new therapeutic paradigm

8. Conclusions

Neural oscillations in ALS represent more than epiphenomena—they provide a mechanistic bridge linking molecular pathology to systems-level dysfunction. The TDP-43 → cryptic splicing → interneuron dysfunction → oscillatory disruption cascade offers a falsifiable account that integrates established findings while predicting novel therapeutic targets.

The proposed two-pronged approach—upstream molecular repair plus individualized oscillatory entrainment—exemplifies precision medicine applied to neurodegeneration. By targeting both the biological driver and the functional consequences, this strategy may overcome the limitations of purely molecular or purely symptomatic treatments.

Critical next steps include rigorous validation of mechanistic predictions, optimization of closed-loop entrainment protocols, and systematic testing in appropriately powered clinical trials. Success would establish oscillatory dysfunction as a central feature of ALS pathophysiology and provide a new framework for therapeutic development across neurodegenerative diseases.

The ultimate test of this framework will be its ability to produce sustained clinical benefit—not just acute oscillatory changes, but meaningful preservation of motor function and quality of life for people living with ALS. This ambitious goal requires continued collaboration between molecular biologists, systems neuroscientists, bioengineers, and clinicians to transform mechanistic insights into therapeutic reality.

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[Note: This represents a selection of key references. A complete bibliography would include 100+ citations]

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