Transcutaneous Spinal Cord Stimulation

in Spinal Muscular Atrophy (SMA)

A Summary of Current Research Evidence

Executive Summary

Spinal Muscular Atrophy (SMA) is a rare, inherited neuromuscular disease characterized by progressive degeneration of spinal alpha motor neurons, leading to muscle weakness and atrophy. According to the State of SMA 2025 Report (Cure SMA), an estimated 9,000-9,500 individuals are currently living with SMA in the United States alone, with 64% being adults — a figure that reflects the dramatic drop in mortality (nearly 60% in 10 years) made possible by five FDA-approved disease-modifying therapies (DMTs). However, pharmacological treatment alone does not fully restore motor function, and rehabilitation remains a critical component of comprehensive care.

Spinal cord stimulation (SCS) — both transcutaneous non-invasive (tSCS) and epidural — is emerging as a highly relevant rehabilitation tool for SMA. The evidence base now includes: two studies of tSCS in SMA patients on DMT (Moshonkina et al., 2023 and 2024), and the landmark first-in-human study of epidural SCS in ambulatory SMA patients, published in Nature Medicine in February 2025 (Prat-Ortega et al.). Crucially, recent neurophysiological research has identified a specific sensory-motor circuit impairment in SMA that makes spinal cord stimulation mechanistically well-suited to this condition — beyond its established benefits in spinal cord injury.

Key findings across the published evidence include: statistically significant gains in motor function scales (HFMSE, RULM), improved forced vital capacity (FVC), reduction of joint contractures, meaningful improvements in walking distance (6MWT) and fatigability, and no adverse events reported across all participants. These results position spinal cord stimulation as a valuable adjunct rehabilitation strategy for SMA patients, for those already stabilized on DMT.

1. Background: Spinal Muscular Atrophy

1.1 Disease Overview

SMA is a genetic disease caused by deletion or mutation of the SMN1 (Survival of Motor Neuron 1) gene, located on chromosome 5q. This gene is essential for the survival and function of spinal alpha motor neurons. The paralogous SMN2 gene produces a small amount of functional SMN protein, and the number of SMN2 copies a patient carries is the main determinant of disease severity.

SMA is classified into four main types based on age of onset and maximum motor milestone achieved:

- Type 1 (Werdnig-Hoffmann): Onset in the first 6 months of life. Maximum milestone: sitting with support. Most severe form, historically fatal without intervention.
- Type 2 (Dubowitz): Onset between 6-18 months. Patients can sit independently but cannot walk. Progressive scoliosis and respiratory compromise are common.
- Type 3 (Kugelberg-Welander): Onset after 18 months. Patients achieve independent ambulation but may lose this ability over time.
- Type 4: Adult onset, generally milder course.

1.2 Disease-Modifying Therapies (DMTs)

As of 2026, five DMTs have received FDA approval for SMA, each targeting SMN protein production via different mechanisms. This represents a rapidly expanding therapeutic landscape — three therapies were approved between 2016-2021, and two additional approvals followed in 2025-2026:

- **Nusinersen (Spinraza®, Biogen) — Low Dose:** An antisense oligonucleotide administered intrathecally that corrects SMN2 pre-mRNA splicing. Approved December 2016. All ages, all SMA types. Standard of care in most SMA centers worldwide.
- **Onasemnogene Abeparvovec (Zolgensma®, Novartis) — IV:** AAV9-based gene therapy delivering a functional SMN1 copy. Single intravenous infusion. Approved May 2019. For individuals under 2 years old.
- **Risdiplam (Evrysdi®, Roche) — oral solution:** An oral small molecule that corrects SMN2 splicing. Approved August 2020. All ages, all SMA types.
- **Risdiplam (Evrysdi®, Roche) — tablet formulation:** Tablet form of risdiplam for individuals ≥18 years. FDA approved February 2025.
- **Intrathecal Onasemnogene Abeparvovec (ITVISMA®, Novartis):** Intrathecal (IT) route gene therapy for individuals ≥18 years old. FDA approved November 2025.
- **Nusinersen High Dose Regimen (Spinraza®, Biogen):** A higher-dose regimen of nusinersen (50 mg loading, 28 mg maintenance) for all ages. FDA approved March 2026.

According to the State of SMA 2025 Report (Cure SMA), approximately 77% of individuals with SMA in the U.S. were utilizing an FDA-approved treatment in Q4 2025 — 96% of children, 90% of teens, and 78% of adults. Approximately 34% of individuals have received two or more SMA treatments, either sequentially or in combination.

Despite these extraordinary therapeutic advances, significant unmet needs persist. The most commonly reported unmet needs by adults on treatment are gaining muscle strength (84-93% across SMA Types 2 and 3) and reducing fatigue (66-73%) — the very functional domains

where spinal cord stimulation shows the most promise as a complement to pharmacological therapy. Additionally, 52% of adults who do not currently receive physical therapy report feeling they would benefit from it, while 55% have difficulty finding a therapist knowledgeable about SMA.

Clinical trials and real-world studies demonstrate that nusinersen treatment produces measurable increases in motor unit numbers in children with SMA — confirmed by MUNE (Motor Unit Number Estimation) electrophysiology in a prospective cohort study (Veerapandiyan et al., PMC 2021). Similarly, 10 months of risdiplam treatment increases CMAP amplitudes — a marker of the active motor unit pool — in adult patients with SMA Type 2 and 3 (Stahl et al., PMC 2024). This neurological restoration creates an important window of opportunity: newly available motor neurons may be activated and strengthened through targeted rehabilitation.

Despite these advances, DMTs alone are insufficient to fully restore motor function lost prior to treatment, and ongoing rehabilitation remains essential. Studies confirm that disease duration and age at treatment initiation are negatively correlated with motor outcome — in a retrospective study of 52 children with SMA Types 1, 2, and 3, both longer disease duration ($r = -0.567$, $p = 0.043$) and older age at initiation ($r = -0.771$, $p = 0.002$) were significantly associated with worse HFMSE gains under nusinersen treatment (Wu et al., Frontiers in Neurology 2024), highlighting the need for early and comprehensive intervention.

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2. Transcutaneous Spinal Cord Stimulation: Mechanism and Technique

2.1 Mechanism of Action

Transcutaneous spinal cord stimulation (tSCS) is a non-invasive form of neuromodulation delivered through electrodes placed on the skin over the spine. The technique modulates spinal neuronal networks without requiring surgical implantation, making it suitable for pediatric populations.

The SMA-Specific Sensory-Motor Circuit Impairment

A critical insight that makes spinal cord stimulation particularly well-suited to SMA — beyond its established use in spinal cord injury — is the discovery of a specific sensory-motor circuit impairment in SMA that precedes motor neuron death itself. Research by Mentis et al. (2011) in SMA mouse models demonstrated that Ia afferent fibers — the proprioceptive sensory neurons that carry feedback from muscles to the spinal cord — have diminished excitatory input. This impairs their synaptic connection with motoneurons, resulting in a diminished ability to excite motor neurons. Crucially, this sensory-motor circuit impairment occurs **before** motor neuron loss — meaning it is a primary driver of motor dysfunction, not just a consequence of it.

This finding has now been confirmed in humans. Simon et al. (2025) demonstrated that individuals with SMA show impaired proprioception, diminished H-reflex (a measure of sensory-motor circuit integrity), and reduced proprioceptive synapses and Kv2.1 ion channels compared to healthy controls. The SMA sensory-motor loop shows a reduced H/M ratio — evidence of a functionally compromised circuit even in individuals with preserved motor neurons.

This is where spinal cord stimulation (SCS) becomes mechanistically specific to SMA: SCS artificially increases Ia-afferent input to motoneurons — precisely the signal that is deficient in SMA. The dual effect of SCS in this context is:

- **Assistive effect (immediate):** Immediate increase in motoneuron firing rates during stimulation, enabling motor activation that the compromised sensory circuit cannot achieve alone.
- **Therapeutic effect (long-term):** Long-term reversion of motoneuron dysfunction through repeated stimulation-driven circuit activation — a neuroplastic effect that persists beyond the stimulation period.

General Mechanism in the SMA Context

In the context of SMA, the proposed mechanism of tSCS involves:

- Direct activation of spinal motor neurons — both those that remained intact and those that have been functionally restored through DMT treatment.
- Restoration of Ia-afferent input to motoneurons, compensating for the sensory-motor circuit impairment that is intrinsic to SMA pathophysiology.
- Modulation of spinal interneuronal networks involved in locomotion and posture control.
- Enhancement of synaptic efficacy through repeated stimulation, potentially supporting motor learning and skill acquisition.
- Recruitment of the expanded motor unit pool created by nusinersen and risdiplam, which may otherwise remain functionally dormant without targeted activation.

This stands in contrast to tSCS use in conditions such as spinal cord injury, where the motor neurons themselves are intact but descending brain-to-muscle signals are disrupted. In SMA, the challenge is both at the motor neuron level and in the sensory-motor feedback loop — making SCS uniquely positioned to address the core pathophysiology of the disease.

An important historical distinction: tSCS must not be confused with conventional peripheral therapeutic electrical stimulation (TES), which applies low-intensity current directly to muscles rather than to the spinal cord. A randomized controlled trial by Fehlings et al. (2002, PubMed) evaluated low-intensity nighttime TES applied directly to the deltoid and biceps muscles in 13 children with SMA Types 2 and 3 over 6 months. No statistically significant improvement in muscle strength, excitable muscle mass (M-wave amplitudes), or function was found in the treated arm compared to the placebo-stimulated control arm. This negative result is mechanistically expected: peripheral muscle stimulation bypasses the spinal sensory-motor circuit entirely, directly contracting muscle fibers without engaging the Ia-afferent pathway or the spinal motor neuron networks that are impaired in SMA. tSCS, by contrast, targets the spinal

cord itself — specifically the dorsal root afferents and the motor neuron pools — addressing the root neurological deficit rather than the downstream muscle.

3. Key Research Studies

3.1 Study 1 — First Use of tSCS in Children with SMA (Moshonkina et al., 2023)

Published in: Life (MDPI), 2023

Study Design & Population
• Design: Case series (pilot / proof-of-concept)
• Participants: 5 children, ages 6-13 years
• Diagnoses: SMA Type II (n=3) and Type III (n=2)
• DMT: All treated with nusinersen for approximately 2 years prior to tSCS
• Protocol: tSCS combined with physical therapy, 30-40 min/day, 10-14 days

Primary Outcomes

Outcome Measure	Findings
Tolerability	All participants tolerated stimulation well; no adverse events observed
Joint contractures (goniometry)	Reduction of ≥5 degrees in 4/5 participants; one participant showed 16 and 27 degree reduction in knee contractures
Upper limb motor function (RULM)	Increased by ~1-2 points in treated participants
Functional ability (HFMSE)	Increased by ~1-2 points
Forced Vital Capacity (FVC)	Increased by 1-7% predicted in 3 out of 5 participants
Motor skills	All 5 participants expanded range of active movement and/or acquired new motor skills

Significance: This was the first published report applying tSCS to SMA patients. Although limited by small sample size (n=5), it established proof-of-concept for feasibility and safety, and generated the hypothesis that tSCS can activate DMT-restored motor neurons in SMA.

3.2 Study 2 — Expanded Cohort with Orphan Drug-Treated Patients (Moshonkina et al., 2024)

Published in: Biomedicines (MDPI), May 2024

Study Design & Population
• Design: Prospective cohort study
• Participants: 37 children and adults, age range 3-42 years
• Diagnoses: SMA Type 2 (majority) and Type 3
• DMT: 30 on nusinersen, 6 on risdiplam, 1 on onasemnogene abeparvovec
• Median DMT duration: >20 months at time of tSCS
• Protocol: tSCS combined with physical therapy, 20-40 min/day, ~12 days (6 days/week)

Primary Outcomes

Outcome Measure	Findings
Safety	No adverse events in any of the 37 participants (ages 3-42); confirmed safety across both pediatric and adult populations
Motor function scales	Statistically significant improvements in HFMSE and RULM scores in both Type 2 and Type 3 groups
Respiratory function (FVC)	Significant improvement in forced vital capacity across the cohort
Joint contractures	Significant reduction of knee joint contractures in both Type 2 and Type 3 participants
Age correlation	Magnitude of functional changes was not associated with participant age — older patients benefited as much as younger ones
DMT type	Beneficial effects observed regardless of whether participants were on nusinersen, risdiplam, or gene therapy

Significance: This larger study confirmed and extended the pilot findings. Statistical significance was achieved across multiple outcome domains. Crucially, the finding that age did not predict response suggests that tSCS may be beneficial across the lifespan for SMA patients on DMT, not only in pediatric populations. The inclusion of risdiplam and onasemnogene abeparvovec patients extends clinical relevance beyond nusinersen.

3.3 Study 3 — First-in-Human Epidural Spinal Cord Stimulation in SMA (Prat-Ortega et al., 2025)

Published in: Nature Medicine, February 2025 | Columbia University Irving Medical Center & University of Pittsburgh

Study Design & Population

- Design: First-in-human prospective interventional study
- Participants: 3 ambulatory adults with SMA Type 3
- Stimulation type: Epidural SCS (surgically implanted leads at T10-L1)
- Protocol: SCS combined with strength and walking training, 4 weeks
- Primary outcome measures: HFMSE, 6-Minute Walk Test (6MWT), Fatigability Index
- Follow-up: >50 days post-explantation

Primary Outcomes

Outcome Measure	Findings
6-Minute Walk Test (6MWT)	All 3 participants improved walking distance: +33m (SMA01), +20m (SMA02), +24m (SMA03) — exceeding the Minimal Detectable Change (MDC) for SMA Type 3
HFMSE motor scale	SMA01: +1 point; SMA02: stable (40); SMA03: stable (49) — functional gains were reflected more in walking performance than scale scores
Fatigability Index	Substantial reductions in fatigability: -11% (SMA01), -30% (SMA02), -10% (SMA03) — indicating patients could sustain effort better and more consistently across the 6MWT
Walking speed consistency	Participants walked faster and maintained more consistent speed throughout the 6MWT — a qualitative improvement in walking endurance
Gait kinematics	Improvements achieved through restored access to selectively impaired proximal musculature, NOT through compensatory maladaptive strategies — hip flexor and knee extensor recruitment improved
Safety	No serious adverse events related to stimulation; procedure well tolerated

Significance: This is the most clinically significant SCS study in SMA to date. Published in Nature Medicine — one of the highest-impact medical journals — it represents the first demonstration that spinal cord stimulation directly addresses walking performance and fatigability in ambulatory SMA patients. The gait analysis component is especially important: it showed that walking improvements resulted from restored access to proximal muscles (hip flexors and knee extensors) that are selectively impaired in SMA — not from compensatory strategies that mask underlying weakness. This aligns precisely with the Ia-afferent circuit impairment mechanism identified by Mentis et al. (2011): SCS restores the sensory input that normally drives these motor pools, enabling functional movement that exercise alone cannot achieve.

4. Summary of Observed Outcomes Across Studies

4.1 Motor Function

All three published studies document consistent improvements in standardized SMA motor scales. In the 2023 tSCS case series, HFMSE and RULM scores each increased by 1-2 points following a 10-14 day course. In the 2024 expanded tSCS cohort, statistically significant gains were confirmed in both SMA Type 2 and Type 3 groups. In the 2025 epidural SCS study (Prat-Ortega), HFMSE remained stable while walking performance improved substantially — suggesting that functional gains may manifest in real-world tasks before they register on standardized scales.

All five children in the 2023 pilot study expanded their range of active movements and/or learned new motor skills, including activities that had previously been outside their functional capacity. This qualitative shift — not just measurable scale improvement — is clinically meaningful for families and practitioners.

4.2 Respiratory Function

Respiratory compromise is one of the most serious and life-limiting aspects of SMA, particularly in Type 1 and Type 2. In the pilot study (2023), predicted FVC increased by 1-7% in 3 of 5 participants. The 2024 expanded cohort confirmed statistically significant improvement in FVC across both SMA types.

This is particularly noteworthy because the primary respiratory muscles are innervated from cervical and thoracic spinal levels — the diaphragm from C3-C5 via the phrenic nerve, and the intercostal muscles from T1-T12 — levels where tSCS electrode placements can directly modulate motor centers. The parallel improvement in respiratory and limb function suggests a comprehensive effect on spinal motor networks.

Contextually, systematic reviews on nusinersen's respiratory effects show a general trend toward FVC stabilization rather than consistent improvement, particularly in older and more advanced patients. The additional respiratory gains seen with tSCS+PT may therefore represent a clinically important supplement to pharmacological management.

4.3 Joint Contractures

Contracture development is a significant complication in SMA, impairing both function and quality of life. In the 2023 pilot, contracture reduction of 5 degrees or more was observed in 4 of 5 participants, with one child showing reductions of 16-27 degrees in the knee joints. The 2024 cohort confirmed significant reduction of knee contractures in both SMA types.

This effect likely reflects the combination of active mobilization during physical therapy and enhanced muscle activation via tSCS. The consistent findings across both the 2023 and 2024 studies — in different patient populations and with different treatment durations — suggest a reliable effect on joint mobility that warrants further investigation in controlled trials.

4.4 Fatigability and Exercise Intolerance

Fatigability — the measurable decline in performance during a continuous task — is one of the most disabling and least addressed symptoms in SMA. It is distinct from perceived fatigue (a subjective experience) and is directly linked to the pathophysiology of the disease. Research presented at Columbia University Irving Medical Center (Magun et al., 2025) confirms that SMN repletion therapies, regardless of mode of delivery, do not fully rescue exercise intolerance and fatigability — due to persistent mitochondrial dysfunction, fatty infiltration of muscle, and NMJ and sensorimotor circuit dysfunction that DMTs do not address.

This is a critical finding from a real-world outcomes perspective. According to the State of SMA 2025 Report (Cure SMA), 'reduce fatigue' is the second most common unmet need reported by adults with SMA Type 2 (66%) and Type 3 (73%) — second only to 'gain muscle strength.' Fatigue levels in SMA adults are consistently rated in the 'severe' category across all SMA types on the Fatigue Severity Scale, with 'fatigue interferes with my physical functioning' being among the top-rated items.

The 2025 epidural SCS study (Prat-Ortega et al.) is the first to demonstrate that spinal cord stimulation directly reduces fatigability in SMA — with Fatigability Index reductions of 10-30% across all three participants. This occurred alongside improvements in walking distance and consistency of walking speed. This is mechanistically consistent with the Ia-afferent restoration hypothesis: by improving the sensory-motor circuit, SCS reduces the compensatory effort required to sustain movement, thereby reducing the rate of fatigability during continuous tasks.

4.5 Safety Profile

Safety is consistently reported across all published studies of tSCS in SMA specifically, and across the broader tSCS literature in pediatric and adult populations with motor neuron and spinal cord conditions. The evidence base supports a favorable safety profile characterized by an absence of serious adverse events and mild, transient side effects where they occur at all.

Safety in SMA-Specific Studies

Across all three published studies of spinal cord stimulation in SMA:

- **Moshonkina et al. (2023)** (Life, MDPI): 5 children with SMA Type 2 and 3, aged 6-13 years. Zero adverse events reported across all participants and all sessions.
- **Moshonkina et al. (2024)** (Biomedicines, MDPI): 37 participants with SMA Type 2 and 3, aged 3-42 years. Zero adverse events reported across the entire cohort, spanning both pediatric and adult participants.
- **Prat-Ortega et al. (2025)** (Nature Medicine): 3 adults with SMA Type 3, epidural SCS (surgically implanted). No serious adverse events related to stimulation. Procedure well tolerated.

Notably, the 2024 tSCS study (Moshonkina et al.) included participants as young as 3 years old — the youngest population studied to date with spinal cord stimulation in any condition — with

no adverse events reported. This is particularly relevant given the concern that young children with SMA may have fragile respiratory and autonomic function.

Safety of tSCS in Pediatric Populations with Motor Neuron and Spinal Conditions

Transcutaneous spinal cord stimulation uses the same underlying technology and delivery method regardless of the underlying diagnosis — surface electrodes placed over the spine, electrical current delivered to the spinal cord, parameters individualized per patient. Safety data generated in other pediatric populations with spinal and motor neuron conditions therefore characterizes the safety of the technique itself, not just its application to a specific disease. The following studies establish the safety profile of tSCS in pediatric populations — consistent with, and contextualizing, the zero adverse event findings reported in the SMA-specific studies above.

A review published in Top Spinal Cord Injury Rehabilitation (2023) — specifically examining tSCS safety from adults to children — confirms that continuous tSCS sessions of 5-20 minutes do not adversely affect hemodynamic parameters in children.

A pilot study evaluating cumulative tSCS with locomotor training in children with spinal cord injury (Amirova et al., Children 2025) systematically tracked adverse events across 130 intervention sessions in three children. 88.5% of sessions were entirely free from any adverse effects. Where adverse events occurred, they included mild skin redness at electrode sites (4.6% of sessions) and headaches (1.5%). No significant impact on fatigue or hemodynamic parameters was observed.

A study establishing safety and feasibility of cervical tSCS in children with spinal cord injury, published in Neuromodulation (2023), confirmed that all seven pediatric participants tolerated cervical tSCS across 21 experiment sessions without any serious adverse events. Three of seven participants perceived mild, transient sensitivity during stimulation — rated as acceptable and not causing discontinuation.

Safety in the Broader tSCS Adult Literature

A systematic review of tSCS for lower limb rehabilitation in spinal cord injury (ResearchGate, 2026) covering 14 studies and 183 participants found: no serious adverse events were directly attributed to tSCS across all studies. The most commonly reported effects were mild and transient — skin irritation and tingling. The GRADE assessment rated the evidence for safety as **moderate certainty** — the highest certainty level among all assessed outcomes in the review, and higher than certainty for clinical efficacy outcomes.

A PLOS One methodological review of tSCS across 25 studies (Minassian et al., 2021) found that four studies reported complete absence of adverse events with continuous vital sign monitoring. Where adverse events were recorded across other studies, they included: modest transient increase in tone post-treatment, mild skin redness, and discomfort at high intensities. No burns, seizures, or other serious complications were reported in any study.

Summary of Reported Adverse Events Across tSCS Literature

Outcome Measure	Findings
Skin redness at electrode sites	Mild, transient. Resolves after session. Prevented by correct electrode placement and adequate conductivity gel.
Tingling / paraesthesia during stimulation	Common sensation, not harmful. Usually well tolerated and expected with electrical stimulation.
Discomfort at high intensities	Managed by titrating intensity to individual tolerance threshold. Does not occur at therapeutic intensities.
Headaches	Reported rarely (1.5% of sessions in one pediatric study). Mild and transient.
Serious adverse events	None reported in any published tSCS study in SMA or in the broader pediatric tSCS literature.
Burns, seizures, cardiac events	Not reported in any tSCS study across all published literature.

Key Safety Statement for Clinical Reference
• Zero serious adverse events have been reported across all three published studies of spinal cord stimulation in SMA (n=45 total participants, ages 3-42 years).
• The broader tSCS literature across pediatric and adult populations with spinal and motor neuron conditions consistently demonstrates a favorable safety profile with only mild, transient effects.
• tSCS is non-invasive — surface electrodes only, no anesthesia, no surgery — and can be discontinued immediately if any discomfort occurs.
• The technique does not involve ionizing radiation, implanted hardware, or pharmacological agents.
• Safety evidence in the tSCS literature has been rated as moderate certainty by GRADE assessment — the highest certainty level among all assessed outcomes.

5. Clinical Considerations and Integration with DMT

5.1 Rationale for Combining tSCS with DMT

The synergy between DMT and tSCS rests on a key biological insight: disease-modifying drugs work by restoring motor neurons (increasing their number and viability), but pharmacological restoration alone does not guarantee functional activation of those neurons. Physical use and neural activation are required to strengthen neuromuscular connections.

tSCS serves as a targeted activator of the expanded motor neuron pool created by DMT. When delivered simultaneously with individualized physical therapy, it appears to enable patients to access functional capacity that would otherwise remain latent. This positions tSCS not as an alternative to pharmacological treatment, but as a rehabilitation strategy that may maximize the functional gains made possible by DMT.

5.2 Limitations of Current Evidence

While the early results are encouraging, several important limitations must be acknowledged:

- All published studies originate from a single research group (Moshonkina et al., Russia). Independent replication is lacking.
- No randomized controlled trials (RCTs) have been published specifically in SMA with tSCS. This limits the strength of causal inference.
- The mechanism by which tSCS produces improvements in SMA is not yet fully understood. Authors note this as a critical gap requiring further investigation.
- Long-term follow-up data beyond the immediate post-treatment period are not yet available.
- **SMA Type 1 — absence of published studies does not imply contraindication:** Published tSCS studies in SMA have enrolled Type 2 and Type 3 patients exclusively. However, the absence of published data on Type 1 should not be interpreted as a contraindication. The core mechanism of tSCS — restoration of Ia-afferent input to spinal motor neurons and activation of partially preserved motor neuron pools — is relevant in any SMA phenotype where motor neurons remain present, including Type 1 patients treated with disease-modifying therapy. Gene therapy (onasemnogene abeparvovec) in particular creates a biologically plausible window for tSCS benefit in Type 1, as it increases SMN protein availability in motor neurons that may otherwise be functionally silent. Formal research on tSCS in SMA Type 1 is an identified gap in the published literature and an important direction for future study.
- Sample sizes remain small (n=5 and n=37 in tSCS studies; n=3 in the epidural SCS study). Larger, multi-center trials are needed.

6. Why tSCS — and Not Just Exercise: The Mechanistic Case for Spinal Stimulation

The previous sections established that disease-modifying therapies (nusinersen, risdiplam, onasemnogene abeparvovec) restore motor neurons to a recoverable state, and that active rehabilitation is required to activate them. A critical question follows: if exercise already activates motor neurons, what does tSCS add? This section addresses that question directly, building the case for tSCS as a distinct and superior tool — not a replacement for exercise, but a mechanism that enables what exercise alone cannot achieve in SMA.

6.1 The Fundamental Problem: Voluntary Effort Cannot Reach Silent Neurons

In SMA, the core barrier to functional recovery is not motivation or effort — it is neurological access. Motor neurons affected by SMA have elevated activation thresholds: they require more input to fire than healthy motor neurons. Many neurons partially recovered by disease-modifying therapy remain below the threshold for voluntary recruitment even during maximal effort. The patient tries to move — but the signal is not strong enough to reach and activate those neurons.

This is fundamentally different from simple muscle weakness, where stronger effort can improve recruitment. In SMA, the limiting factor is the motor neuron itself: its excitability is reduced, its connections to neuromuscular junctions are incomplete or newly formed, and its response to descending voluntary drive is insufficient. Exercise can strengthen what is already active — but it cannot reliably recruit what is neurologically silent.

A clinical trial protocol evaluating motor neuron stimulation in SMA (NCT06977269, ClinicalTrials.gov) states this directly: while exercise is beneficial in SMA, regular exercise is very challenging — not only due to physical limitations but psychological ones too. The protocol authors propose that electrical stimulation may replicate some of the neurological effects of physical exercise at the level of the lower motor neuron, while offering several additional advantages: the possibility to activate motor neurons in non-collaborative infants, minimization of the motivational barrier in adults, and — most importantly — the ability to involve very weak muscle groups that voluntary effort alone cannot reach.

6.2 What tSCS Does That Exercise Cannot

Transcutaneous spinal cord stimulation works by applying electrical current through surface electrodes placed over the spine, directly activating the posterior roots of the spinal cord. This bypasses the need for a complete voluntary drive signal from the brain — instead, it recruits motor neurons from below, through the spinal circuitry itself. Research on the neural substrates of tSCS (Tashiro et al., PMC 2022) confirms that dorsal root fiber recruitment leads to activation of motor neurons through monosynaptic and polysynaptic proprioceptive circuits, increasing the overall excitability of the spinal cord and allowing greater responsiveness to both descending signals and sensory feedback.

The key distinction from exercise is the mechanism of motor neuron recruitment:

Exercise vs. tSCS: How Motor Neurons Are Recruited
• Exercise (top-down): Voluntary effort sends a descending signal from the brain → through the corticospinal tract → to spinal motor neurons. In SMA, this signal is often insufficient to reach neurons with elevated thresholds or incomplete neuromuscular junctions.
• tSCS (bottom-up): Electrical stimulation activates large-diameter sensory afferents (dorsal roots) → which drive motor neurons through monosynaptic and polysynaptic

spinal reflexes. This route bypasses the weakened descending drive and can recruit motor neurons that voluntary effort cannot reach.
• Combined (synergistic): When tSCS is applied simultaneously with voluntary movement, the two inputs converge at the motor neuron level, producing summation. The combined input crosses the activation threshold that neither input could cross alone — enabling activation of neurons that are silent during either tSCS or exercise independently.

This synergistic effect is well documented in spinal cord injury research. A scoping review published in the Journal of Neurophysiology (2023) concluded that paired activity-based training and spinal cord stimulation produces outcomes described as "greater than the sum of its parts" — with improvements in voluntary motor recovery and walking indices that persist long after stimulation is discontinued, indicating durable neuroplastic changes rather than only acute facilitation.

6.3 tSCS Raises the Excitability of the Entire Spinal Motor System

Beyond recruiting individual neurons, tSCS has a broader neuromodulatory effect: it raises the overall excitability of spinal circuits, making the motor system more responsive to all inputs — both electrical and voluntary. In practical terms, when tSCS is applied during a physical therapy session, the same voluntary movements the patient was already attempting now have a better chance of activating motor neurons — because the threshold for activation has been temporarily lowered across the relevant spinal segments. The patient's own effort becomes more effective. Muscles that could not be activated during unassisted exercise can now be recruited and trained.

A study on tSCS programming for upper extremity rehabilitation (Neuromodulation, 2024) articulates this mechanism precisely: tSCS is not meant to drive specific muscle group functions, but to enhance basal excitability to enable voluntary activation of preserved neuronal substrates. This is exactly the role tSCS plays in SMA — it does not replace voluntary effort, it makes voluntary effort capable of reaching neurons it could not previously access.

Supporting this, a study on subthreshold tSCS at the cervical cord (PMC 2025) demonstrated that even subthreshold tSCS transiently facilitates motor unit firing via recruitment of sensory afferents, resulting in enhanced muscle output, grip strength, and task-specific muscle activation patterns — including in individuals with significant motor impairment.

6.4 Multi-Level Stimulation: Reaching All Relevant Motor Centers Simultaneously

A further advantage specific to tSCS over exercise is the ability to stimulate multiple spinal levels simultaneously. In the SMA studies by Moshonkina et al. (2024), electrodes were placed at cervical (C3-C5), thoracolumbar (T11-T12), and lumbosacral (L1-L2) levels — corresponding to the motor centers for upper limb, respiratory, and lower limb function respectively.

Exercise, by definition, is task-specific: arm exercises recruit cervical motor neurons; leg exercises recruit lumbar ones. Respiratory exercises target intercostal and diaphragmatic circuits. Each must be trained separately, and the patient must have enough voluntary capacity to perform each task. In severely affected SMA patients, some of these tasks may be physically impossible without external support.

The observed improvements in FVC (forced vital capacity) in the SMA studies are consistent with direct modulation of spinal respiratory motor centers — an effect that supports the rationale for combining tSCS with respiratory-focused physical therapy in SMA management.

6.5 The Synergistic Model: Why tSCS and Exercise Together Outperform Either Alone

The evidence strongly supports a model in which tSCS and physical therapy are not alternatives but partners. A review on spinal neuromodulation advances (PMC 2023) articulates the foundational principle: Hebbian theory reminds us that inactivity leads to the pruning of neural reorganization, while a return to activity strengthens synaptic connections — and that neuromodulation approaches are only effective when combined with intensive, task-specific rehabilitation.

- **Physical therapy provides:** task-specific, functionally relevant movement patterns; sensory feedback from real motor tasks; progressive loading and skill acquisition; use-dependent neuroplasticity through repetition.
- **tSCS provides:** lowered activation threshold for motor neurons, enabling recruitment of neurons that voluntary effort cannot reach; simultaneous activation of multiple spinal motor levels; sustained excitability enhancement throughout the session; access to very weak or newly recovered motor units that physical therapy alone cannot engage.

When combined, the two inputs converge at the spinal motor neuron: tSCS provides the electrical "boost" that brings latent neurons within reach of voluntary drive, while physical therapy provides the meaningful, task-specific context in which those newly accessible neurons are trained and consolidated. The result is use-dependent neuroplasticity — lasting synaptic changes — in neurons that would otherwise remain permanently inactive. This is supported by findings from paired stimulation studies (PMC 2022) showing that when neuromodulation is combined with locomotor training, sensory-input driven networks recover the most — and that motor neuron output increases reflect changes sustained beyond the stimulation period.

Summary: What tSCS Adds That Exercise Alone Cannot Provide in SMA
• Recruits motor neurons with elevated activation thresholds that voluntary effort cannot reach — including newly restored neurons from disease-modifying therapy
• Activates motor circuits via the dorsal root / sensory afferent pathway, bypassing insufficient descending voluntary drive
• Raises overall spinal excitability, making the patient's own voluntary movements more effective during the session

• Simultaneously targets multiple spinal levels (cervical, thoracic, lumbar) — including respiratory motor centers difficult to reach with exercise
• Enables activation of very weak muscle groups in patients whose physical limitations prevent meaningful voluntary effort
• Produces durable neuroplastic changes when combined with task-specific exercise — outcomes sustained beyond the stimulation period

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