Progress of Anodal Transcranial Direct Current Stimulation Combined with Neuromuscular Training in Rehabilitation across Neurological and Musculoskeletal Disorders

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Abstract: Anodal transcranial direct current stimulation (tDCS) is a non-invasive brain neuromodulation technique capable of reshaping cortical excitability and inducing neural neuroplasticity. With the advantages of easy operation, low cost, and a favorable safety profile, combining it with standardized neuromuscular training has emerged as a research focus in the rehabilitation of motor dysfunction. This review synthesizes evidence from animal experiments, clinical trials, and meta-analyses, summarizing the current status of this combined intervention across six conditions: stroke, Parkinson's disease, multiple sclerosis, spinal cord injury, knee osteoarthritis, and chronic low back pain. A cross-disease comparison is conducted across three dimensions: pathological rationale, clinical efficacy, and evidence quality. Existing studies indicate that stroke-related mechanistic research is the most systematic, yet conclusions from multicenter trials exhibit heterogeneity. Patients with knee osteoarthritis and chronic low back pain can achieve demonstrable synergistic benefits from combined central and peripheral intervention. Parkinson's disease trials have been increasing annually, but meta-analysis findings remain divergent. Research on multiple sclerosis and spinal cord injury remains in the exploratory phase, with promising potential that justifies further investigation. The heterogeneity in treatment responses across diseases stems from multiple factors, including pathological characteristics, neuroplasticity reserve, and the lack of standardized protocols. Future efforts should promote cross-disease comparative studies, establish standardized intervention protocols, identify predictive biomarkers, distinguish optimal patient populations, and facilitate the translation of this intervention model to individualized clinical rehabilitation.

Keywords: Anodal Transcranial Direct Current Stimulation; Neuromuscular Training; Neurological and Musculoskeletal Disorders; Cross-Disease Rehabilitation

1. Introduction

Motor dysfunction is a common clinical manifestation of neurological and musculoskeletal disorders, directly compromising patients ‘mobility and severely affecting daily activities and quality of life. Stroke and Parkinson’s disease result from brain tissue damage or progressive dopaminergic neuron degeneration, and disrupt motor regulatory circuits. Knee osteoarthritis and chronic low back pain are primarily characterized by persistent pain induced by local tissue injury, along with central pain sensitization and abnormal movement compensation patterns. Although conventional rehabilitation training can improve function to some extent, persistent challenges — such as rehabilitation plateau, limited training benefits, and insufficient individualization — have long constrained clinical outcomes. Identifying adjunctive approaches that enhance neuroplasticity and improve rehabilitation efficacy remains an ongoing research priority in rehabilitation medicine.

In recent years, the clinical translation of non-invasive brain modulation technologies has been accelerating. Transcranial direct current stimulation (tDCS) has gained widespread application in neurorehabilitation due to its favorable safety profile, portability, and low cost [1]. This technique modulates neuronal membrane potential through weak direct current, and bidirectionally regulates cortical excitability and further influences synaptic plasticity, brain network connectivity, and motor learning processes. The functional improvement achieved with tDCS alone is relatively limited. Neuromuscular training, which focuses on optimizing neuromuscular coordination and sensorimotor integration through task-oriented exercises, gait training, and motor control exercises, can be combined with tDCS to amplify rehabilitation effects through dual mechanisms of central facilitation and peripheral reinforcement.

The neural facilitation hypothesis provides the theoretical foundation for this combined approach. Preconditioning with tDCS to upregulate cortical excitability in the target region can lower the threshold for synaptic activation, creating a favorable central environment for subsequent training-induced long-term plasticity and continuously amplifying the functional gains from neural reorganization [2,3]. This model not only compensates for the lack of task-specific training in standalone brain stimulation but also addresses the deficiency in central motor drive in conventional rehabilitation, and possesses both strong theoretical rationale and clinical value. Although numerous trials have applied this combined intervention across various motor disorders, differences in injury location and plasticity potential across diseases, together with the lack of standardized protocols for stimulation parameters, training regimens, and outcome measures, hinder the extraction of consistent clinical conclusions. This review therefore synthesizes research progress across six disease categories, compares evidence quality and efficacy differences, analyzes sources of heterogeneity, and outlines future directions to inform clinical decision-making and research design.

2. Synergistic Mechanisms of tDCS Combined with Neuromuscular Training

The complete synergistic pathways of tDCS and neuromuscular training have not yet been fully elucidated, but existing electrophysiological, molecular, brain imaging, and neuromuscular studies have established a multi-level theoretical framework. The synergistic effects can be conceptualized within four major dimensions.

Anodal stimulation drives membrane depolarization, lowering the firing threshold and upregulating cortical excitability in the target region [2]. This modulatory effect is polarity-specific: anodal stimulation over M1 increases excitability, whereas cathodal stimulation suppresses it. However, current intensity, stimulation duration, and individual brain anatomy can modulate regional responses. Modulating M1, the dorsolateral prefrontal cortex, and the premotor areas can enhance motor command generation and conduction, providing sufficient central drive for subsequent rehabilitative training [2]. Neuroplasticity is a key mechanism underlying functional recovery. tDCS can amplify training-induced LTP-like synaptic enhancement and suppress LTD, thereby improving neural network stability [3]. The plasticity gains exhibit clear time-dependent and dose-dependent characteristics, with the timing of stimulation and training directly affecting final outcomes [3]. Animal studies have shown that concurrent tDCS and rehabilitation training upregulated GAP-43 and MAP-2 expression in the peri-infarct zone of ischemic rats. These proteins are involved in axonal growth, synaptic formation, and microtubule stabilization, which are key markers of neural repair. Additionally, tDCS increases BDNF expression, thereby facilitating motor learning and functional recovery through this critical factor [3-5].

Both stroke and Parkinson's disease involve brain network disruption and hemispheric imbalance. tDCS can modulate cross-regional connectivity within motor networks and promote reorganization of damaged circuitry. Using fNIRS, Hou et al. reported that tDCS enhanced bilateral cortical functional connectivity in stroke patients, improved task-related cortical activation patterns, and facilitated a stable network foundation for functional recovery, while also modulating pain and sensory integration systems to improve motor performance multidimensionally [6]. The modulatory effects of tDCS can also propagate along the corticospinal tract to influence spinal motor neurons, enhancing neural drive to muscles and motor unit recruitment efficiency. Surface electromyography has revealed increased activation of affected muscles, reduced compensatory movements, and improved motor control precision and stability. Collectively, this combined intervention, operating through multi-level pathways of cortical facilitation, synaptic remodeling, network reorganization, and peripheral muscle strengthening, has the potential to achieve superior and more stable rehabilitation outcomes compared to single-modality approaches, and provides theoretical support for multi-disease applications.

3. Clinical Application of tDCS Combined

with Neuromuscular Training across Disorders

3.1 Stroke

Stroke is the most extensively studied condition in this field. The lesion reduces cortical excitability on the affected side, leads to contralesional overactivation, and results in hemispheric imbalance and motor network disruption, all of which can be specifically targeted by tDCS. Animal studies have shown that the combined intervention upregulated plasticity-related proteins and accelerated peri-infarct neural circuit remodeling [4,5]. Multiple lines of evidence support the value of this approach in improving upper limb function. Zheng et al., in a network meta-analysis of 74 RCTs, reported that tDCS-combined task-oriented training produced significantly greater improvements in FMA-UE and WMFT than rehabilitation alone [7]. Tang et al. further suggested anodal M1 stimulation as the optimal protocol [8]. Zeng et al. reported that HD-tDCS, which enables more precise focal targeting compared to conventional electrode configurations, yielded superior improvements in fine motor control [9]. Using fNIRS, Hou et al. provided imaging evidence of network reorganization following combined intervention [6]. However, the large-scale multicenter NETS trial yielded negative results, with no significant advantage over sham stimulation, suggesting that stroke stage, baseline function, and stimulation parameters contribute to heterogeneous outcomes [10]. Overall, while the mechanistic framework for stroke is well-established, clinical protocols still require individualization.

3.2 Parkinson's Disease

The core pathology of Parkinson's disease is progressive loss of nigrostriatal dopaminergic neurons, and basal ganglia-cortical loop dysfunction reduces motor cortical plasticity—which makes it a rational target for tDCS. Lee et al., in a meta-analysis of 16 RCTs, reported that the combined intervention acutely improved gait speed, stride length, and overall motor function, with greater benefits in patients with shorter disease duration and in female patients, but these gains were not sustained at the long-term follow-up [11]. A gait-specific meta-analysis suggested improvements in gait parameters but found no significant change in Unified Parkinson‘s Disease Rating Scale Part III (UPDRS-III) motor scores [12]. Domínguez-Pera et al. reported no statistically significant difference between active stimulation and sham stimulation [13]. These discrepancies likely stem from heterogeneity in stimulation targets, current intensity, intervention duration, disease stage, and medication status. Although the number of trials has been increasing, the evidence base remains inconclusive, and standardized long-term RCTs are still needed.

3.3 Multiple Sclerosis

Multiple sclerosis is a chronic inflammatory demyelinating disorder of the central nervous system. Patients typically exhibit cortical excitability disturbances and insufficient central motor drive, making this condition pathologically suitable for combined tDCS-rehabilitation approaches. A review by Santos suggested that tDCS combined with lower limb training can improve balance and gait. Cinbaz et al., in a double-blind sham-controlled trial, reported that the tDCS combined with robot-assisted gait training optimized gait parameters and alleviated fatigue [14]. Nombela-Cabrera et al., in a meta-analysis, also found evidence supporting the benefits of tDCS for balance and gait [15]. Existing trials in this area are generally limited by small sample sizes and heterogeneous protocols, and the evidence remains preliminary, without unified clinical guideline recommendations.

3.4 Spinal Cord Injury

Spinal cord injury disrupts corticospinal pathways. Beyond local conduction deficits, patients also experience central changes, including reduced cortical excitability and muscle denervation. tDCS can upregulate cortical activity and enhance descending motor drive. Motor evoked potentials (MEPs) can objectively assess corticospinal pathway integrity, and existing reviews have confirmed their value in the localization and prognostic assessment of spinal cord injury [16]. Sarraj et al. reported in an RCT that tDCS combined with neuromuscular training improved lower limb motor function in chronic incomplete spinal cord injury [17]. Chen et al. showed that HD-cathodal tDCS preconditioning combined with mirror therapy improved both walking function and cortical electrophysiological parameters [18]. Home-based long-term tDCS also appears to be safe. Research in this area remains preliminary but shows promising clinical potential.

3.5 Knee Osteoarthritis

Knee osteoarthritis is characterized by joint pain, mobility limitation, and central pain sensitization. Traditional rehabilitation focuses on peripheral interventions and lacks central modulatory components. tDCS can suppress abnormal activity in pain-related cortical regions and act synergistically with training. Luo et al., in a long-term follow-up trial with 6 weeks of tDCS combined with TENS and 19 weeks of follow-up, reported greater pain relief and Timed Up-and-Go (TUG) improvement in the combined group, with longer-lasting effects [19]. Zhang et al. reported that this combined approach reduces pain and improves obstacle-crossing gait stability in older adults [20]. Kaboodi et al., in a double-blind RCT, reported that anodal tDCS combined with aquatic neuromuscular training was superior to sham in terms of analgesia, functional improvement, kinesiophobia reduction, and quality of life enhancement [21]. The consistent findings across multiple independent trials suggest that knee osteoarthritis may be a promising indication for this combined approach.

3.6 Chronic Low Back Pain

Chronic low back pain involves lumbar muscle control dysfunction, motor cortex remodeling, and impaired endogenous pain inhibitory pathways. tDCS can modulate the cortical representation of lumbar muscles, thereby optimizing motor control and pain perception. Sornkaew et al., in a 6-week RCT of 22 participants, reported that tDCS combined with motor control training significantly modulated cortical topography, reduced pain, and improved daily function [22]. Xia et al., in a meta-analysis, suggested superior analgesic effects of the combined intervention over rehabilitation alone [23]. Current consensus regards central pain modulation and neuromuscular control optimization as the two core pathways through which this intervention improves chronic low back pain.

3.7 Applications to Other Conditions

Beyond these six core conditions, this intervention model has shown additional applications. For children with cerebral palsy, combined training has been shown to improve motor control and independence. For sarcopenia, tDCS can enhance the muscle-strengthening effects of resistance training. Pilot studies have also suggested that tDCS combined with neuromuscular training may confer adjunctive benefits in post-stroke aphasia, cognitive decline, and depressive comorbidity.

4. Comparative Analysis of Efficacy Heterogeneity across Diseases

Clear gradients exist across diseases in the rehabilitation gains from combined tDCS-neuromuscular training, driven by four interacting factors. Pathological differences are fundamental: stroke presents a focal cortical lesion with a clear target for neuromodulation; Parkinson's disease is a progressive neurodegenerative condition with continuously declining plasticity; multiple sclerosis involves widespread demyelination with complex repair mechanisms; spinal cord injury involves structural disconnection of conduction pathways; knee osteoarthritis and chronic low back pain have peripheral origins but can be addressed through both central analgesic and motor control pathways. Neuroplasticity reserve also importantly influences outcomes: the highest plasticity occurs in the acute and subacute phases of stroke, whereas degenerative and chronic conditions have substantially reduced plasticity reserves, limiting both the magnitude of improvement and long-term stability. Substantial heterogeneity in intervention protocols exists, with no unified standards for stimulation targets, current parameters, training types, or stimulation-training intervals, thereby reducing cross-study comparability. The outcome measure diversity further amplifies inconsistencies, with some studies using subjective functional scales and others relying on objective gait, imaging, or electrophysiological parameters, complicating data synthesis. In summary, the evidence base is strongest for stroke, moderate for knee osteoarthritis and chronic low back pain, conflicting for Parkinson's disease, and preliminary for multiple sclerosis and spinal cord injury.

5. Overall Limitations and Future Directions

The existing body of literature reveals multiple shortcomings that point to clear directions for future investigation. First, a standardized intervention framework is lacking. Key parameters for brain stimulation and rehabilitative training lack universal specifications, and this excessive protocol variability undermines the reliability of meta-analytic syntheses [2,7,21]. Second, study design quality is limited. Most trials are single-center and small in sample size, and many lack double-blind sham-controlled designs, which introduces high risk of bias; long-term follow-up data are scarce, which precludes assessment of sustained efficacy and safety [10,11,13]. Third, cross-disease comparative studies are lacking. Most trials focus on single conditions, and the absence of head-to-head comparisons under unified protocols prevents objective identification of optimal patient populations [15,18]. Fourth, predictive models for individualized therapy remain underdeveloped. The role of disease duration, BDNF genotype, and baseline function have not been systematically integrated into assessment frameworks, which hinders stratified precision intervention [6,21]. Fifth, the underlying mechanisms remain incompletely resolved. The molecular and network-level dynamics of synergistic effects require further multimodal investigation [3,14]. Sixth, research is unbalanced across diseases. Multiple sclerosis, spinal cord injury, and sarcopenia are substantially underrepresented, and the evidence is insufficient to guide clinical practice [15,17,18]. Seventh, there is no consensus on outcome measures and safety reporting, which limits translation to clinical practice [22,23].

To address these limitations, future research should pursue multiple complementary directions. Standardized stimulation and training parameters should be established through large-scale dose-response trials, with broader adoption of HD-tDCS and individualized electric field modeling to enhance targeting precision and efficacy stability [9,19,21]. Multicenter cross-disease comparative studies with unified designs and outcome measures should be conducted to identify optimal indications [7,15]. Extended follow-up combined with multimodal imaging (fNIRS, EEG, fMRI, MEP) should be employed to elucidate the mechanisms of network reorganization and plasticity regulation [3,6,16]. Predictive models integrating imaging, electrophysiology, clinical baselines, and genotyping should be developed to enable patient- and disease-tailored rehabilitation [4,19,21]. Large-sample, double-blind, multicenter RCTs with standardized outcome repositories and adverse event reporting should be prioritized to improve evidence quality [10,13,23]. Home-based wearable devices combined with community rehabilitation should be examined, and the intervention's applicability to cerebral palsy, aphasia, and cognitive impairment should be further investigated [1,17,20]. Health economic evaluations assessing cost-effectiveness should be conducted to support clinical translation and policy development, to advance tDCS combined with neuromuscular training as a routine standardized intervention in rehabilitation practice.

6. Conclusion

The central-peripheral combined rehabilitation model, centered on tDCS and complemented by neuromuscular training, represents a promising approach with substantial clinical potential across diverse motor dysfunction conditions. Based on the current evidence, stroke research provides the most comprehensive foundation. Knee osteoarthritis and chronic low back pain consistently demonstrate clear synergistic benefits from central-peripheral combined intervention. Parkinson's disease trials have been increasing in number, but meta-analytic findings remain divergent. Research on multiple sclerosis and spinal cord injury is at an earlier stage but shows considerable promise. The differentiation in treatment responses across diseases stems from differences in pathological characteristics, neuroplasticity reserves, and protocol heterogeneity. Future research should focus on developing standardized protocols, establishing individualized prediction models, conducting cross-disease comparative trials, integrating multimodal assessments to elucidate the deeper mechanisms, thereby continuously strengthening the evidence chain and establishing this intervention model as a core approach in precision rehabilitation, and ultimately improving long-term functional outcomes and quality of life for patients with motor dysfunction.

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References

[1] Miniussi C, Pellicciari MC. Learning from missteps: Potential of transcranial electrical

stimulation in neuropsychological rehabilitation. J Neuropsychol. 2025; 19(3): 655-681. doi: 10.1111/jnp.12425.

[2] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000; 527(3): 633-639. doi: 10.1111/ j.1469-7793.2000.t01-1-00633.x.

[3] Fritsch B, Reis J, Martinowich K, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron. 2010; 66(2):198-204. doi:10.1016/j.neuron. 2010.03.035.

[4] Yang LX, Chen ZH, Liu F. Effects of transcranial electrical stimulation combined with rehabilitation training on motor function and GAP-43 expression in rats with cerebral infarction. Chin J Rehabil Theory Pract. 2010; 16(12):1136-1139. doi: 10.3969 /j.issn.1006-9771.2010.12.013.

[5] Yang LX, Liu F. Effects of transcranial direct current stimulation combined with rehabilitation training on MAP-2 expression in rats with cerebral ischemia-reperfusion. Chin J Rehabil Med. 2011; 26(8): 750-753. doi: 10.3969/j.issn.1001-1242.2011.08.013.

[6] Hou B, Zhao HF, Che PC, et al. Effects of short-term transcranial direct current stimulation on upper limb motor function and cortical activation patterns in stroke patients. Chin J Tissue Eng Res. 2026; 30(12):3066-3074.

[7] Zheng K, Guo L, Liang W, Liu P. Comparison of the effects of transcranial direct current stimulation combined with different rehabilitation interventions on motor function in people suffering from stroke-related symptoms: a systematic review and network meta-analysis. Front Neurol. 2025; 16: 1586685. doi: 10.3389/ fneur.2025.1586685.

[8] Tang X, Zhang N, Shen Z, et al. Transcranial direct current stimulation for upper extremity motor dysfunction in poststroke patients: A systematic review and meta-analysis. Clin Rehabil. 2024; 38(6):749-769. doi: 10.1177/ 02692155241235336.

[9] Zeng Y, Cheng R, Zhang L, et al. Clinical Comparison between HD-tDCS and tDCS for Improving Upper Limb Motor Function: A Randomized, Double-Blinded, Sham-Controlled Trial. Neural Plast. 2024; 2024: 2512796. doi:10.1155/2024/2512796.

[10] NETS Trial Collaboration Group. Efficacy and safety of transcranial direct current stimulation to the ipsilesional motor cortex in subacute stroke (NETS): a multicenter, randomized, double-blind, placebo-controlled trial. Lancet Reg Health Eur. 2024; 38: 100825. doi:10.1016/j.lanepe. 2023.100825.

[11] Lee JH, Jun JS, Kang N, et al. Transcranial direct current stimulation combined with motor training for motor symptoms in Parkinson‘s disease: A systematic review and meta-analysis. Ageing Res Rev. 2025; 109:102781. doi:10.1016/j.arr.2025.102781.

[12] Qiu S, Wei Y, Gao C, et al. Effects of combined transcranial direct current stimulation and gait training in Parkinson’s disease: a systematic review and meta-analysis of randomized controlled trials. Syst Rev. 2025; 14(1):187. doi: 10.1186/s13643-025-02924-x.

[13] Domínguez-Pera I, Lucena-Anton D, Estebanez-Perez MJ, et al. Efficacy of transcranial direct current stimulation combined with gait training in patients with Parkinson‘s disease: Systematic review and meta-analysis. CNS Spectr. 2025; 30(1):e79. doi: 10.1017/S1092852925100618.

[14] Cinbaz G, Sarı Z, Oğuz S, et al. Effects of Transcranial and Trans-Spinal Direct Current Stimulation Combined with Robot-Assisted Gait Training on Gait and Fatigue in Patients with Multiple Sclerosis: A Double-Blind, Randomized, Sham-Controlled Study. J Clin Med. 2024; 13(24):7632. doi: 10.3390/jcm13247632.

[15] Nombela-Cabrera R, Pérez-Nombela S, Avendaño-Coy J, et al. Effectiveness of transcranial direct current stimulation on balance and gait in patients with multiple sclerosis: systematic review and meta-analysis of randomized clinical trials. J Neuroeng Rehabil. 2023; 20(1):142. doi: 10.1186/s12984-023-01266-w.

[16] McKay WB, Stokic DS, Dimitrijevic MR. Assessment of corticospinal function in spinal cord injury using transcranial motor cortex stimulation: a review. J Neurotrauma. 1997; 14(8):539-548. doi:10.1089/neu.1997. 14.539.

[17] Sarraj AR, Allaw J, Rached E, et al.

Additive effect of tDCS and neuromotor recruitment on functional recovery in chronic paraplegia: A randomized controlled trial. PLoS One. 2026; 21(6):e0352320. doi:10.1371/journal.pone.0352320.

[18] Chen H, Xia C, Yao W, et al. Impact of High-Definition Cathodal tDCS Preconditioning on Enhancing the Therapeutic Efficacy of iTBS Combined With FES for Improving Walking Function in Patients With Spinal Cord Injury: A Randomized Controlled Trial. CNS Neurosci Ther. 2026; 32(5):e70932. doi:10.1002/cns.70932.

[19] Luo X, Song Q, Ge Y, et al. Efficacy and Sustainability of tDCS Combined with TENS in Alleviating Pain and Improving Functional Mobility in Older Adults with Knee Osteoarthritis. Med Sci Sports Exerc. 2026; 58(3):454-463. doi:10.1249/ MSS.0000000000003689.

[20] Zhang X, Wang D, Song Q, et al. Effects of tDCS combined with TENS in relieving pain and improving gait patterns during stepping over obstacles among older adults with knee osteoarthritis. Front Sports Act Living. 2025; 7: 1631357. doi: 10.3389/ fspor.2025.1631357.

[21] Kaboodi AT, Gandomi F, Soufivand P, Assar S. The impacts of transcranial direct current stimulation combined with aquatic neuromuscular training on pain, function, kinesiophobia, knee instability, and quality of life in knee osteoarthritis: a double-blind randomized trial. J Neuroeng Rehabil. 2025; 22(1):151. doi: 10.1186/s12984-025-01670-4.

[22] Sornkaew K, Thu KW, Silfies SP, et al. Effects of combined anodal transcranial direct current stimulation and motor control exercise on cortical topography and muscle activation in individuals with chronic low back pain: A randomized controlled study. Physiother Res Int. 2024; 29(3):e2111. doi:10.1002/pri.2111.

[23] Xia R, Lu S, Zhao L. Transcranial direct current stimulation combined with exercise therapy for chronic low back pain: a systematic review and meta-analysis. Front Hum Neurosci. 2026; 19: 1721182. doi:10.3389/fnhum.2025.1721182.

