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LETTER

Efficacy of temporal interference electrical stimulation for spinal cord injury rehabilitation

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Dear Editor,

Spinal cord injury (SCI) is a devastating neurological condition that often leads to severe motor, sensory, and autonomic impairments, profoundly affecting quality of life. Despite advances in acute care and rehabilitation, recovery remains limited, particularly in incomplete injuries.[1] While epidural spinal cord stimulation (eSCS) has shown the potential to restore motor function by modulating spinal circuits, its invasive nature, surgical risks, and high cost limit its broader clinical application.[2,3] Transcutaneous electrical stimulation (TES) offers a non-invasive alternative but is constrained by shallow penetration, primarily activating superficial dorsal roots rather than deeper spinal structures.[4]

Temporal interference (TI) stimulation, a novel non-invasive neuromodulation technique, delivers two high-frequency currents with slightly different frequencies to create a low-frequency envelope that penetrates deep neural structures while minimizing superficial activation.[5] Preclinical and early human studies have shown promising effects in modulating brain networks and have been preliminarily applied in clinical contexts such as movement disorders, depression, and neural regeneration.[6-8] However, to our knowledge, we report here the first exploratory attempt to apply targeted TI stimulation directly to the spinal cord in patients with incomplete SCI.

To achieve precise targeting of the cervical spinal cord injury site with TI stimulation, the intervention approach was primarily guided by a previous methodological study.[9] As shown in Figure 1A, electrode placement was symmetrically optimized around the target region, with a finite element lead-field simulations to maximize the envelope electric field at the target while minimizing off-target effects. Compared with conventional TES, our configuration generated higher field activation in deeper spinal structures.

TI stimulation (two sinusoidal currents at 1000 Hz and 1040 Hz, up to 4 mA) was delivered via Ag/AgCl hydrogel electrodes (MindMatrixes.Ltd, Hangzhou, China) for 20 minutes per session, 14 sessions over two weeks, alongside conventional therapy (Figure 1B). Clinical assessments were conducted at baseline (pre-intervention) and after the two-week intervention, including motor and functional scales: Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP), Upper Extremity Fugl-Meyer (UEFM), Lower Extremity Fugl-Meyer (LEFM), American Spinal Injury Association (ASIA) impairment scale, Berg Balance Scale (BBS), and Barthel Index (BI). Pain was evaluated using the Short-Form McGill Pain Questionnaire (SF-MPQ) and urinary diaries.

Additionally, EEG and EMG data were co-assessment pre- and post-intervention using a specific seated task. EEG was acquired with 22 scalp channels (FZ, F1-F4, FCZ, FC1-FC4, CZ, C1-C4, CP1-CP4, PZ, P3, P4) using active Ag/AgCl electrodes (64 channels, NeuSen W), while EMG signals from six muscles—including bilateral vastus lateralis oblique (VLO) and vastus medialis oblique (VMO)—were recorded using a wireless Noraxon Desktop DTS system at 1.5 kHz. To explore the neurophysiological underpinnings of these behavioral gains, we analyzed brain functional networks and corticomuscular coherence (CMC) before and after the TI intervention.

As shown in Figure 1C, we enrolled three adult male patients (ages 34, 39, and 70) with non-progressive cervical SCI (C4–C8, AIS D) of 1–6 months' duration, all medically stable and undergoing routine rehabilitation. Based on assessments conducted one week before and at the start of the TI stimulation, no changes were observed in the severity of spinal cord injury among the three participants. Ethical approval for this study was granted by the Ethics Committee of Zhejiang Provincial People's Hospital (No. KY2024103). All participants provided informed consent, agreeing to the use of their data in future publications and presentations.

Remarkably, after two weeks of TI stimulation, all participants demonstrated an improvement in neurological level of injury, gaining one to two segments (P1: C5→C7; P2: C4→C5; P3: C4→C6). GRASSP total scores increased bilaterally in all patients, with enhancements in strength, prehension performance, and sensibility. Upper Extremity Motor Scores improved by up to 6 points and Lower Extremity Motor Scores by up to 7 points. Sensory recovery was substantial, with light touch scores increasing by up to 16 points and pin prick sensation by up to 12 points. Balance also improved, with Berg Balance Scale scores rising by 6–32 points, and functional independence increased by 10–20 points on the Barthel Index. Two participants reported reduced pain intensity on the SF-MPQ. No serious adverse events occurred; only mild transient skin sensations were observed.

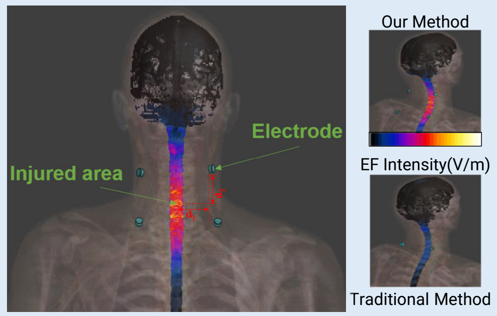
Figure 1D illustrates functional connectivity changes across multiple frequency bands. After TI stimulation, connectivity in both the theta and high beta bands increased, with a statistically significant enhancement in the high beta band. This suggests strengthened interactions among motor-related cortical regions during the seated task, potentially reflecting more efficient coordination of motor planning and execution. Figures 1E-F depict CMC between motor cortical areas and lower-limb muscles. Post-intervention, high beta and gamma band CMC at electrodes C1 and Cz showed a trend of enhancement. Previous studies have associated beta-band CMC with motor command signaling and gamma-band CMC with sensory feedback integration. The observed increase in CMC indicates enhanced sensorimotor coupling, consistent with the improvements in muscle strength, dexterity, and sensory perception observed behaviorally. Figure 1G presents spectral power differences pre- and post-stimulation across all three participants. The overall increase in power within sensorimotor-relevant bands further supports elevated cortical engagement induced by TI stimulation. Collectively, these neurophysiological findings provide evidence that targeted TI stimulation not only improves observable motor and sensory function but also promotes functional reorganization and enhanced communication within sensorimotor networks.

These consistent gains across motor, sensory, balance, and functional domains within such a short treatment window underscore the potential of TI stimulation as a transformative rehabilitation tool. Compared to eSCS, TI achieves depth-specific neuromodulation without surgery, and compared to TES, it effectively engages deeper spinal cord structures. The individualized targeting suggested that TI could be tailored for various lesion levels and patient profiles.

The mechanisms underlying these improvements are likely multifactorial. In incomplete cervical SCI, residual neural pathways often remain structurally intact but functionally suppressed, and TI stimulation may enhance excitability and synaptic reorganization within these spared pathways, facilitating descending motor command propagation and ascending sensory integration. The envelope interference pattern of TI could preferentially recruit interneuronal networks in the cervical spinal cord, strengthening sensorimotor loops and fostering activity-dependent plasticity. Supporting this interpretation, our

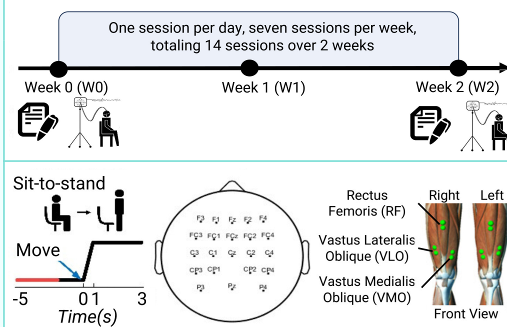
A

Schematic of temporal interference (TI) stimulation for spinal cord injury rehabilitation



B

Clinical trial paradigm and EEG/EMG co-recording experimental paradigm



C

Demographic and clinical characteristics of participants before and after the TI stimulation

Participant	P1		P2		P3	
Sex/Age (y)	Male/34		Male/39		Male/70	
Injury phase (m)	3.5		5		3	
Cause of injury	Vehicular		Intraspinal hematoma		Vehicular	
Assessments Pre/Post TI stimulation	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
American Spinal Injury Association Impairment Scale	D	D	D	D	D	D
Neurological level of injury	C5	C7	C4	C5	C4	C6
Upper Extremity Motor Scores (right/left/**total**)	19/20/**39**	19/21/**40**	18/22/**40**	21/25/**46**	15/16/**31**	17/17/**34**
Lower Extremity Motor Scores (right/left/**total**)	17/19/**36**	20/23/**43**	8/21/**29**	11/21/**32**	21/20/**41**	22/22/**44**
Light Touch Sensory Scores (right/left/**total**)	32/32/**64**	40/40/**80**	30/29/**59**	32/32/**64**	31/31/**62**	35/35/**70**
Pin Prick Sensory Scores (right/left/**total**)	26/32/**58**	37/39/**76**	51/32/**83**	53/34/**87**	32/31/**63**	34/33/**67**
Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP)						
Strength (right/left)	37/40	39/44	36/48	40/50	31/32	34/36
Sensibility (Dorsal + Palmar) (right/left)	22/19	19/22	10/16	16/19	13/9	15/12
Prehension ability (right/left)	11/11	11/12	11/12	12/12	12/12	12/12
Prehension performance	27/26	30/30	26/30	27/30	24/24	27/27
Total of GRASSP (right/left)	**97/96**	**99/108**	**83/106**	**95/111**	**80/77**	**88/87**
Fugl-Meyer upper extremity score (UEFM)	65/64	65/66	62/64	63/66	53/58	58/58
Fugl-Meyer assessment lower extremity score (LEFM)	28/28	33/34	26/30	28/30	13/13	30/29
Berg Balance Scale (BBS)	44	50	36	45	4	36
Barthel Index (BI)	60	70	50	70	25	45
SF-MPQ	10	7	5	4	4	4

D

Electrophysiological evaluations at the cortical level identify the rehabilitation effects of TI stimulation

avgWPLi	Pre			Post			*P* value
Frequency	P1	P2	P3	P1	P2	P3	
Delta	0.227	0.19	0.24	0.212	0.248	0.217	0.826
Theta	**0.256**	**0.237**	**0.191**	**0.259**	**0.244**	**0.211**	0.197
Alpha	0.179	0.162	0.235	0.193	0.207	0.181	0.962
Low Beta	0.204	0.188	0.214	0.189	0.211	0.231	0.562
High Beta	**0.207**	**0.194**	**0.256**	**0.231**	**0.246**	**0.303**	**0.04**
Gamma	0.222	0.209	0.283	0.215	0.271	0.3	0.363

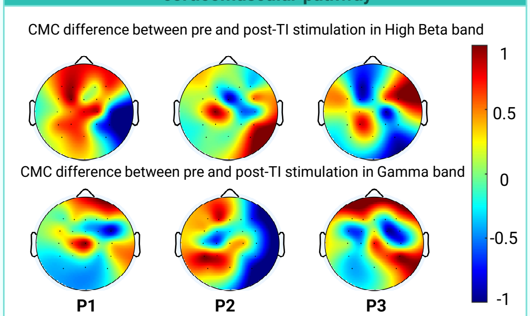
E

Corticomuscular coherence (CMC) between movement-related brain regions and lower extremity muscles

CMC	Ch	Pre			Post			
Frequency		P1	P2	P3	P1	P2	P3	*P* value
High beta	FCz	0.052	0.046	0.047	0.029	0.037	0.04	0.122
	Cz	0.032	0.041	0.037	0.032	0.047	0.037	0.455
	C1	**0.028**	**0.036**	**0.033**	**0.038**	**0.037**	**0.039**	0.156
	C2	0.046	0.039	0.057	0.03	0.046	0.038	0.37
	CP1	0.037	0.043	0.031	0.036	0.048	0.048	0.344
	CP2	0.037	0.054	0.044	0.028	0.034	0.035	0.074
Gamma	FCz	0.06	0.042	0.059	0.054	0.034	0.06	0.228
	Cz	**0.034**	**0.028**	**0.047**	**0.044**	**0.057**	**0.062**	0.083
	C1	0.046	0.021	0.06	0.03	0.042	0.046	0.806
	C2	0.038	0.036	0.042	0.053	0.038	0.036	0.627
	CP1	0.04	0.037	0.056	0.064	0.039	0.046	0.634
	CP2	0.048	0.04	0.046	0.044	0.034	0.059	0.893

F

Increased CMC in motor areas indicates accumulated effects of TI stimulation in modulating the corticomuscular pathway



G

TI stimulation reduced beta and gamma power in spinal trauma but increased it in spinal hemangioma hemorrhage

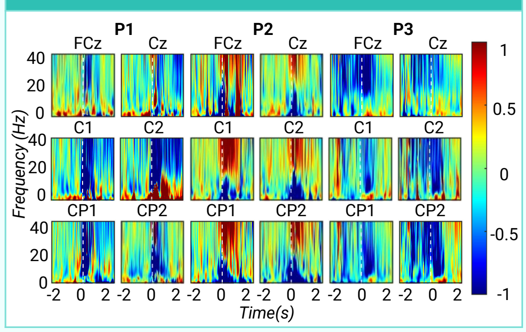


Figure 1. Efficacy of temporal interference electrical stimulation for spinal cord injury rehabilitation (A) Schematic of temporal interference stimulation. The left pair of electrodes forms one stimulation pair, while the right pair of electrodes forms another stimulation pair. (B) Clinical trial design and the experimental setup for EEG and EMG co-assessment. A visual cue-based paradigm was employed; each trial began with the participants seated in the chair for 5 seconds. They were instructed to initiate the sit-to-stand transition when the progress bar reached the designated position labeled 'move,' and then hold the standing position for 3 seconds. Following this, the progress bar updated, providing a similar visual cue to prompt the transition from stand-to-sit. In total, participants performed 40 alternating sit-to-stand transitions. (C) Demographic and clinical characteristics of the participants. (D) The brain functional network for different frequency bands: avgWPLi, functional connectivity between EEG channels was derived by weighted phase lag index (wPLI), which measures phase synchronization between EEG signals. As an extension of phase lag index (PLI), wPLI possessed two advantages over PLI in terms of reduced sensitivity to uncorrelated noise and increased ability to capture true changes in phase-synchronization. Briefly, the Hilbert transform was initially employed to obtain the instantaneous phase of signals. The graph metrics were generated through the integral of wPLI with a sparsity from 0.1 to 0.4 with an incremental step of 0.01. (E) The corticomuscular coherence (CMC) between movement-related brain regions and lower extremity muscles, EEG from one of the 6 EEG electrodes (Cz, C1, C2, CPz, CP1, CP2) and EMG from bilateral VLO VMO were combined into a single dataset, resulting in a total of 6 datasets. The peak CMC value of low beta, high beta and gamma bands in four muscles were averaged as the mean coherence. (F) CMC difference between pre and post-TI stimulation in high beta band and gamma band. (G) The time-frequency analysis of FCz, Cz, C1 C2, CP1, CP2 channels from -2s to 2s according to cue-onset. P1: Participant 1, P2: Participant 2, P3: Participant 3.

neurophysiological findings showed increased functional connectivity within the theta and high-beta bands on EEG after stimulation, indicating enhanced coordination among motor-related cortical regions. Concurrently, elevated CMC in both beta and gamma bands suggests more effective coupling between cortical motor commands and peripheral muscular responses. Because beta-band CMC reflects corticospinal drive and gamma-band CMC sensory feedback integration, these changes imply that TI stimulation reinforces bidirectional communication within the sensorimotor system, providing a neurophysiological substrate for the behavioral gains in motor control, dexterity, and sensory perception.

Although these preliminary results are encouraging, this study represents only an exploratory first step in applying TI stimulation to the injured spinal cord. The small sample size and lack of long-term follow-up limit the generalizability of the findings. Nevertheless, the rapid functional gains observed here provide a compelling rationale for larger, controlled clinical trials. Future studies should incorporate neurophysiological and neuroimaging measures to elucidate mechanisms and optimize stimulation parameters.[10]

In summary, this study offers initial clinical insights suggesting that targeted TI stimulation may represent a promising and feasible approach to promote motor and sensory recovery in individuals with incomplete cervical SCI.

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AUTHOR CONTRIBUTIONS

Ruidong Cheng and Yuling Shao conducted the clinical trial, collected and analyzed the data, and contributed to drafting parts of the manuscript. Yuchen Xu and Minmin Wang conceived and led the study, interpreted the data, and wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Ethical approval for this study was granted by the Ethics Committee of Zhejiang Provincial People's Hospital (No. KY2024103). All participants provided informed consent, agreeing to the use of their data in future publications and presentations.

DATA AND CODE AVAILABILITY

Data involved in this study are available upon reasonable request.