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Original Article

Robotic Rehabilitation in Spinal Cord Injury: A Pilot Study on End-Effectors and Neurophysiological Outcomes

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Abstract—Robot-aided gait training (RAGT) has been implemented to provide patients with spinal cord injury (SCI) with a physiological limb activation during gait, cognitive engagement, and an appropriate stimulation of peripheral receptors, which are essential to entrain neuroplasticity mechanisms supporting functional recovery. We aimed at assessing whether RAGT by means of an end-effector device equipped with body weight support could improve functional ambulation in patients with subacute, motor incomplete SCI. In this pilot study, 15 patients were provided with six RAGT sessions per week for eight consecutive weeks. The outcome measures were muscle strength, ambulation, going upstairs, and disease burden. Furthermore, we estimated the activation patterns of lower limb muscles during RAGT by means of surface electromyography and the resting state networks' functional connectivity (RSN-FC) before and after RAGT. Patients achieved a clinically significant improvement in the clinical outcome measures substantially up to six months post-treatment. These data were paralleled by an improvement in the stair-climbing cycle and a potentiating of frequency-specific and area-specific RSN-FC patterns. Therefore, RAGT, by means of an end-effector device equipped with body weight support, is promising in improving gait in patients with subacute, motor incomplete SCI, and it could produce additive benefit for the neuromuscular reeducation to gait in SCI when combined with conventional physiotherapy.

Keywords—End-effector devices, Functional connectivity (FC), Resting state networks (RSN), Robot-aided gait training (RAGT), Spinal cord injury (SCI).

INTRODUCTION

Spinal cord injury (SCI) is a major cause of disability often leading to significant gait impairment in terms of sensory-motor coordination, spasticity, impaired balance, and muscle weakness, up to wheelchair confinement.[2]

Intensive, repetitive, and task-oriented motor training is mandatory to maximize functional motor recovery and contain disability burden. In fact, providing patients with a physiological limb activation during the training of functional arm and hand movements, active physical and cognitive engagement, and an appropriate stimulation of peripheral receptors during the motor task practice, is essential to entrain the neuroplasticity mechanisms on which the recovery of sensorimotor function after brain/spinal damage is based.[8] In order to support this, robot-aided gait training (RAGT) employing treadmill training equipped with body weight support (BWSTT) has been implemented to provide patients with high-intensity therapy, adaptive support, and a globally entraining gait practice rather than single movement-focused gait practice, thus enhancing the effects of functional training.[25] Overall, RAGT with BWSTT seems to be as effective as physiotherapist-aided overground stepping concerning gait recovery after Central Nervous System damage. Particularly, BWSTT has been shown to allow similar stepping function with superior gait endurance as compared to a conventional rehabilitation approach in SCI.[45,48,65]

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The available grounded BWSTT devices can be grouped into exoskeletons and end-effector devices, which have distinct features.[23,63] Particularly, lower limb movements are driven by motorized gait orthoses directly acting on the joints in the former,[1,21] and by footplates acting on the feet (i.e. from the bottom) in the latter. In fact, the degrees of freedom (DOFS) are lower, the range of impedances is narrower, and the joints have higher inertia and friction at distal level in exoskeletons than in end-effector devices.[47] Both devices can be finely set for the output impedance (resulting from the orthoses as well as the actuators). In addition, end-effectors provide patients with a lower degree of movement constraint as compared to fixed overground exoskeletons. This is of noteworthy importance, as higher movement variability is critical for stimulating neural plasticity mechanisms for motor learning and thus for recovering motor functions.[13,40,52] In this regard, both fixed overground exoskeleton and end-effector rehabilitation can be qualified as ‘‘bottom-up’’ approaches (i.e., the action at the physical level is expected to affect the Central Neural System level). On the contrary, ‘‘top-down’’ approaches, such as drugs and brain stimulation protocols, directly entrain brain plasticity.[39] However, the higher movement variability during end-effector practice is thought to stimulate more significantly the neuroplasticity mechanism of recovery at the Central Nervous System level compared to exoskeleton training.[40,52] Last, end-effectors seem to respect more the spatial and temporal gait cycle features compared to other RAGT approaches, also reducing neuromuscular abnormalities,[31] promoting intra-limb and inter-limb coordination, and reducing the co-contraction between knee and ankle antagonistic muscles. In particular, end-effectors can change the onset (duration) of the activation of the quadriceps muscles during floor walking, the reaction forces during the initial contact, the variability of the individual patterns of shank muscle activation,[64] and can recover an extremely low muscle activity or the pathological co-activation during distinct parts of the gait cycle.

Overall, it seems that end-effectors allow achieving a greater gait recovery as compared to grounded exoskeletons in stroke populations.[12,16,27,52,61] Conversely, insufficient evidence is available to determine the superiority of one gait training strategy over another in patients with SCI.[63] Furthermore, there is very limited evidence on the use of end-effectors in the SCI populations.[16,52] Among the available end-effectors, the G-EO System device (Reha Technology AG; Olten, Switzerland) has been shown as useful in gait recovery in stroke populations[46] however, the effects of G-EO System have not been investigated yet in SCI patients. Interestingly, the G-EO System device provides patients also with going up- and downstairs. This is a very important property, given that stair climbing is an essential part of everyday mobility, and a non-negligible percentage of patients with Central Nervous System damage is unable to go up/downstairs at home discharge.[56]

The present pilot study was aimed at assessing whether RAGT with BWSTT by means of the G-EO System device may improve muscle strength, ambulation, going upstairs, and the disease burden of patients with subacute, motor incomplete SCI. In this regard, patients underwent 48 sessions of RAGT (including floor walking and going up/downstairs) by means of the end-effector G-EO System. Furthermore, we investigated the neurophysiological basis underpinning the abovementioned clinical changes by estimating the patterns of limb muscle activation during RAGT by means of surface electromyography and the resting state network’s functional connectivity (RSN-FC) changes.

MATERIALS AND METHODS

Patients

We screened all patients with SCI attending the Neurorehabilitation Unit of our Institute in the 2018–2019 period in inpatient regimen ($n = 78$) (Fig. 1). The inclusion criteria were: (1) traumatic or non-traumatic, non-progressive SCI at, or rostral to, the T10 (vertebral) level; (2) subacute phase (i.e. up to 18 months post-injury); (3) an American Spinal Injury Association (ASIA) of a grade of C or D (so that patients could voluntary move at least one leg, to rise to stand from a seated position with no more than moderate assistance, and to independently advance at least one leg); and (4) under age 65. Pressure ulcers, severe limitation of range of motion of the hips and knee joints, severe cognitive impairment, lower motor neuron lesion, previous RAGT before the inclusion in the present study, or severe pulmonary or heart disease were considered as exclusion criteria. We focused our pilot study on subacute SCI patients as these persons are more likely to harness a residual function of lower limb proximal muscles and have available different neurorecovery mechanisms (usually within 18 months post-injury, whereas chronic SCI generally refers to the following period when neurorecovery plateaus),[11] to benefit more likely from a successful training and to recover motor function. Specifically, the activation of load (reloading of the body as far as possible) and hip-joint related (hip extension) receptors leads to a physiological leg muscle activity pattern during stepping and, consequently, to dose-dependent training

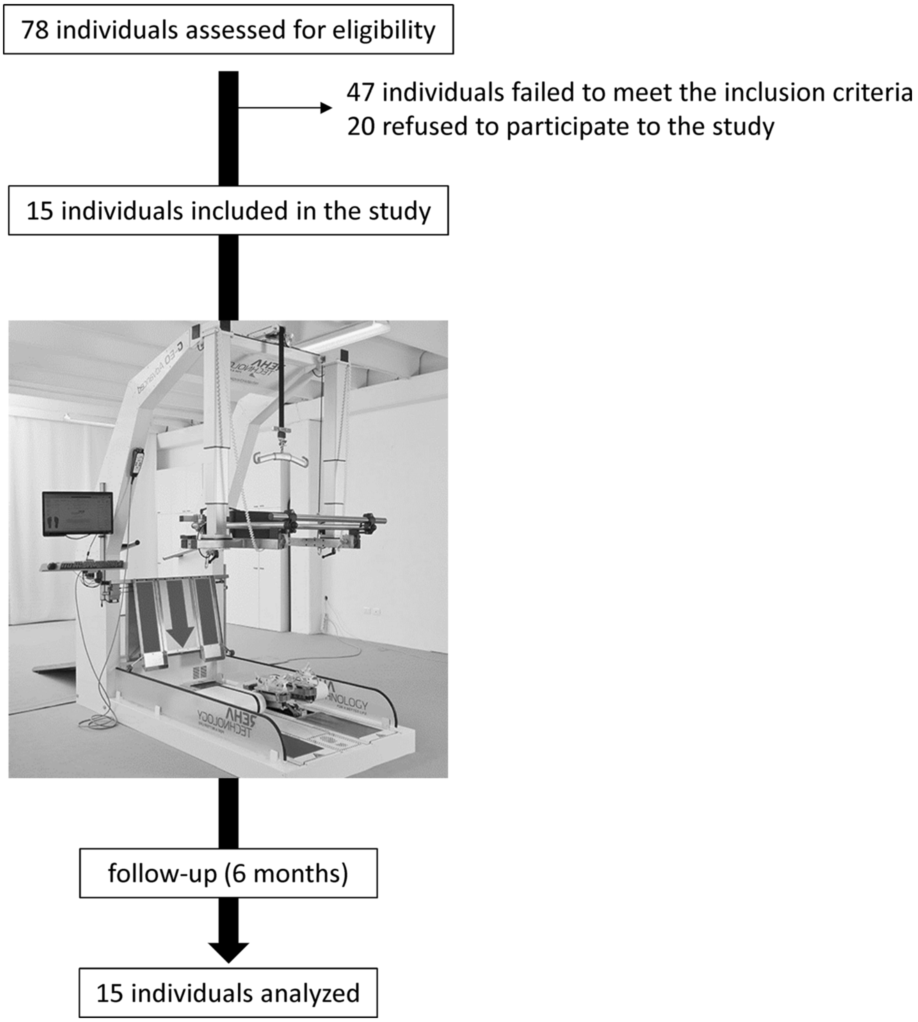

FIGURE 1. The G-EO system device and the experimental flow.

effects. Furthermore, these patients are more suitable for devices that can finely tune the support and impedance of individual joints according to patients' impairment.[25]

Fifteen patients were enrolled in the study according to the abovementioned inclusion/exclusion criteria; the remaining persons failed to meet the inclusion criteria ($n = 47$) or refused to take part in the study ($n = 20$) (Fig. 1). Clinical-demographic characteristics are summarized in Table 1. The local Institutional Review Board approved the study, and each patient provided his/her written informed consent to study participation and data publication.

Experimental Design

All of the enrolled patients were evaluated at baseline (T_{PRE}) using clinical scales, gait analysis during RAGT, and EEG recording in RS before starting RAGT. Thereafter, patients were provided with a daily session of the end-effector G-EO System, 6 days per week, for two months. All subjects continued all other rehab activities regularly (e.g., physiotherapy following the Bobath principles, occupational therapy, and functional electrical stimulation) during the study participation. In particular, physiotherapy lasted one hour per day and included muscle stretching and strengthening, balance training, postural stability control, sensory techniques, and functional daily activities.

All outcome measures were also collected right after (T_0), and three (T_3) and six (T_6) months after the end of the rehabilitation training. However, EEG and gait analyses were performed at T_0 only. During the 6-month follow-up, patients continued their ordinary, conventional treatment. Each patient was assessed over time by his/her own physiotherapist.

TABLE 1. Clinical-demographic characteristics (summarized as count or mean ± sd)

Sex	Age (y)	Time from SCI onset (m)	SCI level	Etiology	AIS score	Spasticity (yes/no), medication	Pain (yes/no), medication
M	22	5	C6	V	C	Yes (baclofen)	Yes (no medication)
F	29	13	T7	TM	D	Yes (baclofen)	No
M	37	7	C7	T	C	Yes (no medication)	Yes (carbamazepine)
F	45	14	T6	T	D	Yes (no medication)	Yes (amitriptyline)
M	38	11	T1	T	C	Yes (no medication)	No
M	55	6	T7	T	D	Yes (tizanidine)	Yes (no medication)
M	63	6	T7	V	D	Yes (no medication)	No
M	42	4	T10	TM	C	Yes (baclofen)	Yes (gabapentin)
F	39	4	C5	T	D	No	Yes (no medication)
F	67	3	T4	TM	C	Yes (baclofen)	Yes (paracetamol)
M	42	5	C5	T	C	Yes (baclofen)	No
F	42	13	T10	T	D	Yes (baclofen)	Yes (paracetamol)
M	61	3	C6	T	D	Yes (clonidine)	No
F	24	4	T10	T	C	Yes (no medication)	Yes (amitriptyline)
M	27	4	C6	T	C	Yes (baclofen)	Yes (no medication)
6F, 9M	42 ± 14	7 ± 4		2V, 3TM, 10T	8C, 7D		

AIS ASIA Impairment Scale, *F* female, *M* male, *m* months, *SCI* spinal cord injury, *T* trauma, *TM* transverse myelitis, *V* vascular, *y* years.

Robot-Aided Gait Training

The robotic treatment consisted of a block of floor walking in a passive and active assisted mode for 30 min, 5 min of rest, and 20 min of going up/downstairs in a passive and active assisted mode.

The G-EO System device is an (non-treadmill) end-effector made of two footplates with three degrees of freedom on which the harness secured patient stand. The footplates move the lower limbs from the bottom to the top with completely programmable trajectories, the length (up to 550 mm) and height (up to 400 mm) of the steps, footplate angles (up to ±90 degree), velocity of movements (up to 2.3 km/h) and acceleration peak (up to 10 m/s^2). The patient's feet are fixed to the footplates by means of Velcro straps. Each footplate is fixed on a pivoting arm that is, in turn, connected to a moving sledge. The latter is connected to the linear guide's transmission belt where, at the back end, there is a servomotor that drives the transmission belt. In this way, the footplates perform forward and backward movements, simulating the gait cycle in a physiological manner by implementing the scissor principle.[41,42] The device is also equipped with handrails at both sides and a BWS system that ensures the vertical motion of the patient's center of mass (CoM) by finely controlling the patient's lateral motion.[41,42]

The physiotherapist had to set the actual trajectories, the step length, step height, the toe-off, the initial contact inclination angles of the feet, the excursions of the CoM in the vertical and horizontal directions, and the relative position of the suspension point with respect to the footplates on the end-effector device. The 10-Meter Walk Test (10 MWT) was used to customize these mean basic parameters of the gait cycle. Specifically, the walking speed was set consistently with the time needed (m/s), the number of steps practiced, the cadence (steps/min), and the stride length (in meters, calculated as speed/(2 × cadence)) to cover a 10-m walkway at self-selected speed. All such settings were adapted throughout the rehabilitative training according to the patient's progress, except the vertical (lateral) movement of the hip, which was set to 2 ± 0.5 cm in all subjects. Specifically, the patient started with a comfortable walking speed (about 0.4 m/s) and was then increased by 0.5 m/s every three minutes of walking, up to the maximum tolerable velocity. When the patient achieved the maximum tolerable velocity, the session began. This procedure was repeated every day of treatment. The velocity value was kept if the patient was able to safely maintain the step length, cadence, step number, and stride length; otherwise, the training was conducted using the same velocity as in the previous session. Step cadence was kept constant in each session. The progression of the intensity of training was individually adapted in order to prevent fatigue, for which patients were monitored carefully; whenever fatigue was present, walking speed was reduced to a comfortable pace (about − 25%). Furthermore, heart rate and pulse oximetry were monitored during each session. Similarly, the time needed to go up/down a flight of stairs (stair by stair in an alternating fashion) was taken, and the speed (stairs/min) was calculated. Both parameters were adapted as conducted for floor walking, whereas the step rise was standard (18 cm), as well as the vertical (lateral) displacement of the hip (5 ± 2.5 cm). BWS was initially set at 80% discharge for both floor walking and going up/downstairs, and was progressively reduced by 10% every week, down to 10% or the maximum tolerable BWS (consistently with the patient's tolerance and fatigability).

Outcome Measures

The clinical outcome measures included the motor and sensory scores on the ASIA Impairment Scale (AIS), the Spinal Cord Independence Measure (SCIM III), the Walking Index for Spinal Cord Injury II (WISCI II), the 10 MWT, the Modified Ashworth Scale (MAS), the Beck Depression Inventory (BDI), and the Short Form (SF-36) health survey. Moreover, patients were submitted to gait analysis during an active-assisted gait training session once he/she became confident with the device (on average between the sixth and eighth session). This occurred to assess whether and how G-EO System influenced the patterns of limb muscle activation.

Surface myoelectric signals were recorded from vastus lateralis (VL), biceps femoris (BF), tibialis anterior (TA), and gastrocnemius medialis (GM) of both lower limbs by using adhesive surface electrodes wireless connected to the Smart Analyzer system (Version 1.10.469.0; BTS, Milan, Italy). We used a sampling rate of 1 kHz and a 5–400 Hz band-pass filter. Skin was carefully prepared for the positioning of bipolar adhesive surface electrodes. These were displaced in a belly-belly montage, at 2 cm from each other (to minimize cross talk between EMG signals), with the principal axis oriented parallel to muscle direction.[9,26] We quantified the root mean square (RMS) of the EMG signals to estimate the lower limb muscle activation during gait. We placed an accelerometer (G-Sensor; BTS, Milan, Italy) at the lumbar level using a Velcro strap to trigger the different phases of the gait cycle.

Lastly, patients underwent an EEG recording in RS (awake with eyes closed) before starting the first RAGT session. This was done to estimate the RS features related to gait disturbance. EEG analysis consisted of the computation of the power spectral density and the estimation of the RSN-FC using Exact Low-Resolution Brain Electromagnetic Tomography (eLORETA) and a subsequent Independent Component Analysis (ICA) decomposition. This allowed identifying (and removing) artifacts after eLORETA source reconstruction, namely eLORETA-ICA.[34]

EEG was recorded while the participant was seated on a comfortable reclining chair in RS (awake with eyes-closed) for about 15 min. Signals were acquired through a 19-channel pre-cabled cap, with internal Ag/AgCl flat disk electrodes coated with conductive gel, and placed according to the International 10–20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2). The cap was wired to a Brain-Quick System (Micromed, Mogliano Veneto, Italy). The ground was put on the forehead, and the reference on both mastoids. Signals were sampled at 512 Hz and band-pass filtered at 0.3–70 Hz (with a 50 Hz notch). The patient's skin at the electrode sites was abraded with gel and electrode impedance was always kept below 5 kΩ. Electrodes Raw data were pruned from artifacts by visual inspection and ICA. The obtained pruned EEG was then submitted to spectral analysis and eLORETA-ICA processing.

Spectrum analysis was carried out using a standard fast Fourier transform algorithm (Hanning-window, 0.7 Hz frequency resolution) within δ (2–4 Hz), K (4–7 Hz), μ (8–12 Hz), β (12–30 Hz), and γ (31–70 Hz) frequency bands on three groups of electrodes: frontal (Fp1/F7/F3, Fp2/F8/F4), central (T3/C3, T4/C4), and parietoccipital (T5/P3/O1, T6/P4/O2).[28] We opted to analyze these rhythms and electrode groups as a specific role of each oscillation, and electrode groups have been reported in the sensory-motor patterns.[18–20,43]

To estimate the RSN-FC, the pruned data were processed in eLORETA to reconstruct cortical electrical activities (obtaining 6239 voxels in the cortical gray matter at 5 mm spatial resolution using a realistic head model with the MNI152 template).[24,44,57] Then, an ICA was run to decompose the eLORETA-identified cortical activities into RSN (independent) and artefactual components. This was conducted using the eLORETA-ICA software.[57] The magnitude value ($\mu V^2/M^4$ Hz) of the RSN (independent) component activities (i.e., the electrical activities) identified using the eLORETA-ICA approach was estimated for the abovementioned frequency bands (delta, 2–4 Hz, theta, 4–8 Hz, alpha, 8–13 Hz, beta, 13–30 Hz, and gamma, 30–60 Hz) within the cortical regions of interest (ROIs) that were determined adopting a voxel-wise approach based on the Montreal Neurological Institute(MNI)-152 coordinates [44] of the cortical voxels underlying the electrode sites. Then, the RSN (independent) cortical components were clustered across subjects into a *subject×frequency-band×ROI* matrix. After that, the data matrix was subjected to a group-ICA, thus obtaining a set of ICs, of which we calculated the corresponding activity (magnitude value) by regression analysis.[14,17]

Data Analysis

Descriptive statistics were presented for all outcome measures. Treatment effects on clinical outcomes relative to baseline were carried out with Friedman analysis of variance (ANOVA). Significance was set at $p < 0.05$ for all tests, with Bonferroni correction for multiple comparisons. When available, the Minimal Clinically Important Difference (MCID) was considered to test the clinical relevance of absolute changes, described with a number (%) and compared by Chi^2 test. The EEG power and IC differences were estimated by using independent Student's *t*-tests. The treatment-induced changes in EEG power and ICs were assessed by paired Student's *t*-tests. The level of significance for *t*-test analyses was set at $p < 0.05$ with Bonferroni correction. Clinical-electrophysiological correlations after RAGT and the effects of the clinical-demographic characteristics on each clinical and neurophysiological outcome were assessed by Spearman's rank correlation analysis. The level of significance was set at $p < 0.05$ (uncorrected) for both correlation analyses. The statistical analyses were conducted using Stat-View® software (Hulinks Inc.; Tokyo, Japan).

RESULTS

Baseline (T_{PRE})

Eight patients were wheelchair-dependent with limited walking function, whereas the remaining subjects were wheelchair-independent and walked with an assistive device. All the patients required partial assistance (or were independent with adaptive devices in some functions) concerning their daily living activities (as per SCIM III) and complained of mild-to-moderate spasticity and pain (at T_{PRE}) (Table 1; Fig. 2). A gait cycle analysis disclosed a co-contraction of TA and MG in both lower limbs (Figs. 3 and 4). Furthermore, patients demonstrated reduced cadence, forward velocity, and stride length. Lastly, patients showed an RSN-FC decrease between FC and FPO ROIs (Figs. 5 and 6).

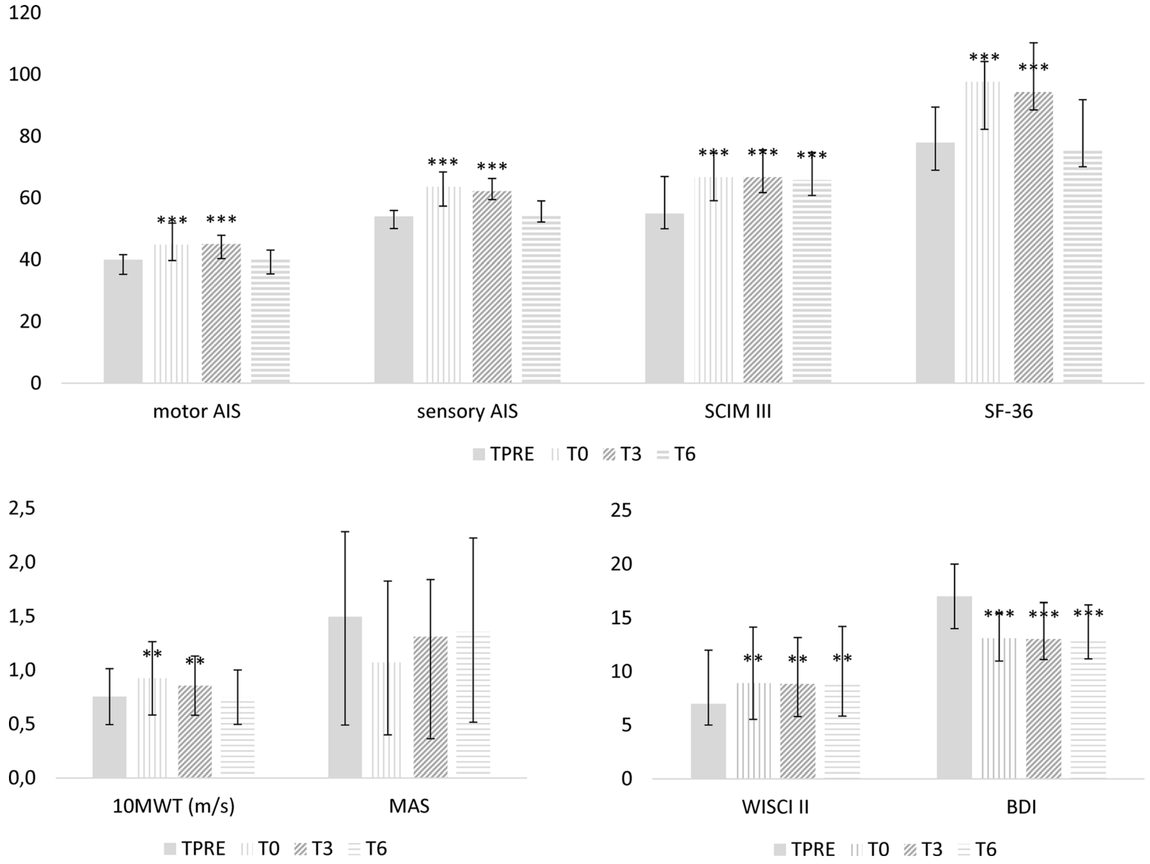

FIGURE 2. **RAGT-induced changes in outcome measures at baseline (T_{PRE}), after the training (T_0), and three and six months after the end of the training (T_3 and T_6, respectively). Data are reported as median ± iqr except for 10-Meter Walk Test (mean ± sd). The statistically significant results are highlighted using ***$p < 0.001$ and **$p < 0.01$. *AIS* the motor and sensory scores at the ASIA Impairment Scale, *SCIM III* the Spinal Cord Independence Measure, *10 MWT* 10-meter walk test, *WISCI II* the Walking Index for Spinal Cord Injury II, *MAS* the Modified Ashworth Scale, *BDI* the Beck Depression Inventory, *SF-36* the Short Form health survey.**

RAGT Aftereffects (T_0, T_3, and T_6)

None of the enrolled patients withdrew from the rehabilitation program or reported any side effects (such as pain or inflammation of the lower limb joints) during or after the rehabilitative sessions.

Even though none of the patients achieved a complete recovery of walking function at T_0, they showed a significant improvement in each outcome measure up to T_3, except MAS (Fig. 2). Specifically, patients achieved a significant improvement in the 10 MWT ($p = 0.004$; 80% of patients achieved the MCID, $p(\mathrm{Chi}^2) = 0.01$), BDI ($p < 0.001$; 93% of patients achieved the MCID, $p(\mathrm{Chi}^2) = 0.007$), motor AIS ($p < 0.001$; 93% of patients achieved the MCID, $p(\mathrm{Chi}^2) = 0.004$), SCIM III ($p < 0.001$; 65% of patients achieved the MCID, $p(\mathrm{Chi}^2) < 0.001$), sensory AIS ($p < 0.001$; 93% of patients achieved the MCID, $p(\mathrm{Chi}^2) = 0.001$), SF-36 ($p < 0.001$; all patients achieved the MCID, $p(\mathrm{Chi}^2) < 0.001$), and WISCI II ($p = 0.004$; all patients achieved the MCID, $p(\mathrm{Chi}^2) = 0.009$). All patients retained some improvements up to T_6 limitedly to SCIM III, WISCI II, and BDI (Fig. 2).

These findings were paralleled by non-significant changes in gait cycle features during floor walking in the end-effector BWSTT session (at T_0; Fig. 3). Instead, we detected large changes in muscle activation along the stance and swing phases while going upstairs after the completion of the entire training (at T_0; Fig. 4). In particular, left BF (time effect $F = 43$, $p < 0.001$), left GM ($F = 28$, $p < 0.001$), left TA ($F = 35$, $p < 0.001$), right GM ($F = 104$, $p < 0.001$), right TA ($F = 140$, $p < 0.001$), and right VL ($F = 22$, $p < 0.001$) showed the largest changes in stance and swing muscle activation over time (at T_0; Fig. 4).

EEG power in RS significantly changed in alpha ($p = 0.001$), beta ($p < 0.001$), and gamma frequencies ($p < 0.001$). Detailed pre-post EEG power changes are reported in Fig. 5 (at T_0). In particular, the most evident changes were appreciable within lF (decrease in the alpha-to-gamma range), rF (gamma decrease), lC (alpha increase), rC (delta decrease), lPO (gamma decrease), and rPO (delta increase and gamma decrease).

Last, eLORETA-ICA analysis disclosed three RSNs whose magnitude value of the Independent Component activities changed significantly after G-EO system

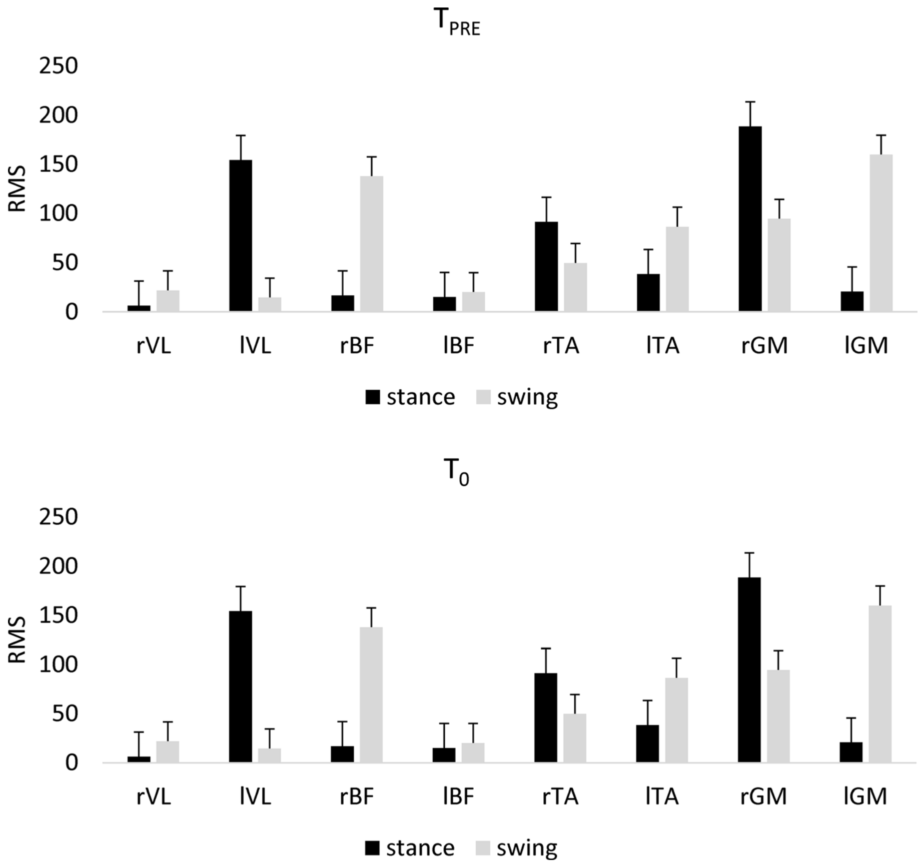

FIGURE 3. EMG activation pattern of lower limb muscle during floor walking measures at baseline (*T_{PRE}*) and after the training (*T_0*). The vertical error bars represent the standard deviation of the mean EMG envelopes. *VL* vastus lateralis, *BF* biceps femoris, *TA* tibialis anterior, *GM* gastrocnemius medialis, *RMS* root mean square.

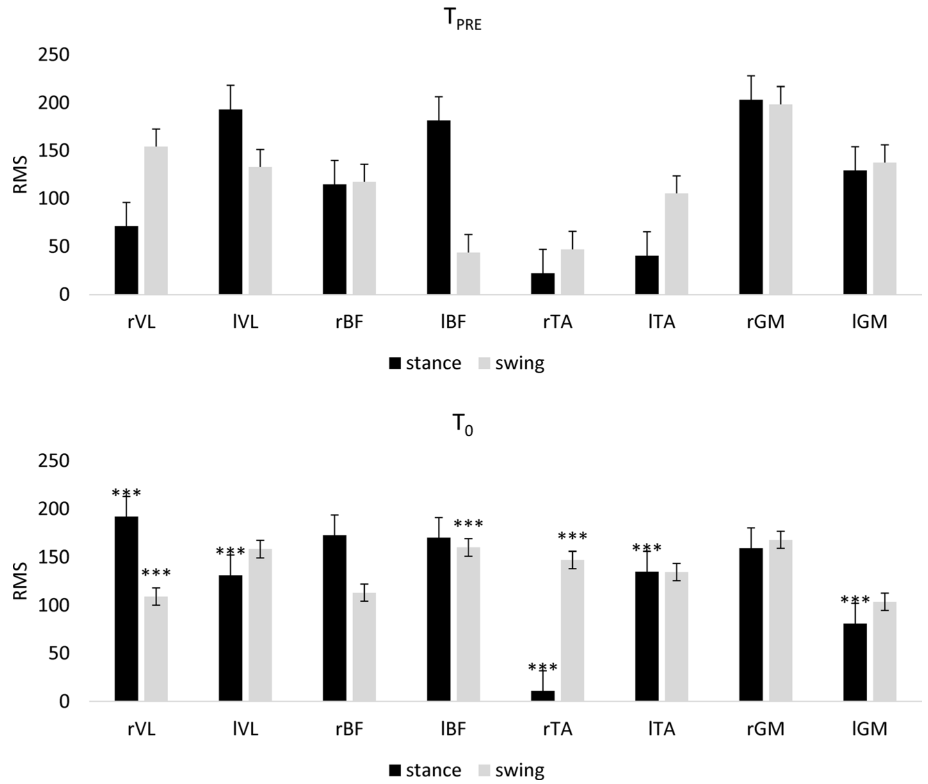

FIGURE 4. EMG activation pattern of lower limb muscle during going upstairs at baseline (T_{PRE}) and after the training (T_0). The vertical error bars represent the standard deviation of the mean EMG envelopes. The statistical significant results are highlighted with ***$p < 0.001$. *VL* vastus lateralis, BF biceps femoris, *TA* tibialis anterior, *GM* gastrocnemius medialis, *RMS* root mean square.

training in specific frequency bands, namely the intraparietal sulcus in the alpha frequency band (from – 4 ± 0.3 to − 6.4 ± 0.5, *post-hoc* $p < 0.001$), the prefrontal networks in the beta frequency band (from – 4.2 ± 0.2 to – 2.2 ± 0.2, *post-hoc* $p < 0.001$), and the superior parietal lobule in the gamma frequency band (from – 2.8 ± 0.5 to 2.2 ± 0.3, *post-hoc* $p < 0.001$) (at T_0; Fig. 6).

Concerning clinical-electrophysiological correlations, we found that the SCIM III improvement at T_6 significantly correlated with RSN-FC magnitude value increase in the superior parietal lobule in the gamma frequency band ($r = 0.724$, $p = 0.002$), the WISCI II improvement at T_6 with the intraparietal sulcus RSN-FC magnitude value decrease in the alpha frequency band ($r = 0.648$, $p = 0.004$), and the 10 MWT at T_0 with the prefrontal networks RSN-FC magnitude value increase in the beta frequency band ($r = 0.546$, $p = 0.03$) (Fig. 7).

DISCUSSION

To the best of our knowledge, this is the first time that patients with SCI have been provided with RAGT by means of the G-EO System device. Furthermore, patients were specifically trained in going up/downstairs thanks to the intrinsic properties of the device. Lastly and notably, we investigated RSN-FC in patients with subacute, motor incomplete SCI, whereas most studies were carried out in patients with chronic, complete SCI so far.[32,49,50]

We found that patients achieved a clinically significant improvement (consistently with the MCID values) in gait velocity (as per 10 MWT), mood (BDI), sensory and motor functions of ASIA scale, disability burden (SCIM III), functional ambulation (WISCI II), and quality of life (SF-36) up to six-month post-treatment. Similarly, also muscle strength and the ability to go up/downstairs improved up to T_6. Noteworthy, these clinical data were paralleled by the preservation of gait cycle physiology and the potentiation of frequency- specific and area-specific RSN-FC that supported the clinical improvements.

Given there are no consistent data in the literature concerning end-effector use in the SCI population and our data were not compared with those from a control group, we can only compare our findings with those available in the literature on the effectiveness of RAGT in improving gait in patients with SCI. It has been reported that patients with SCI undergoing RAGT with BWSTT improve significantly in muscle strength,

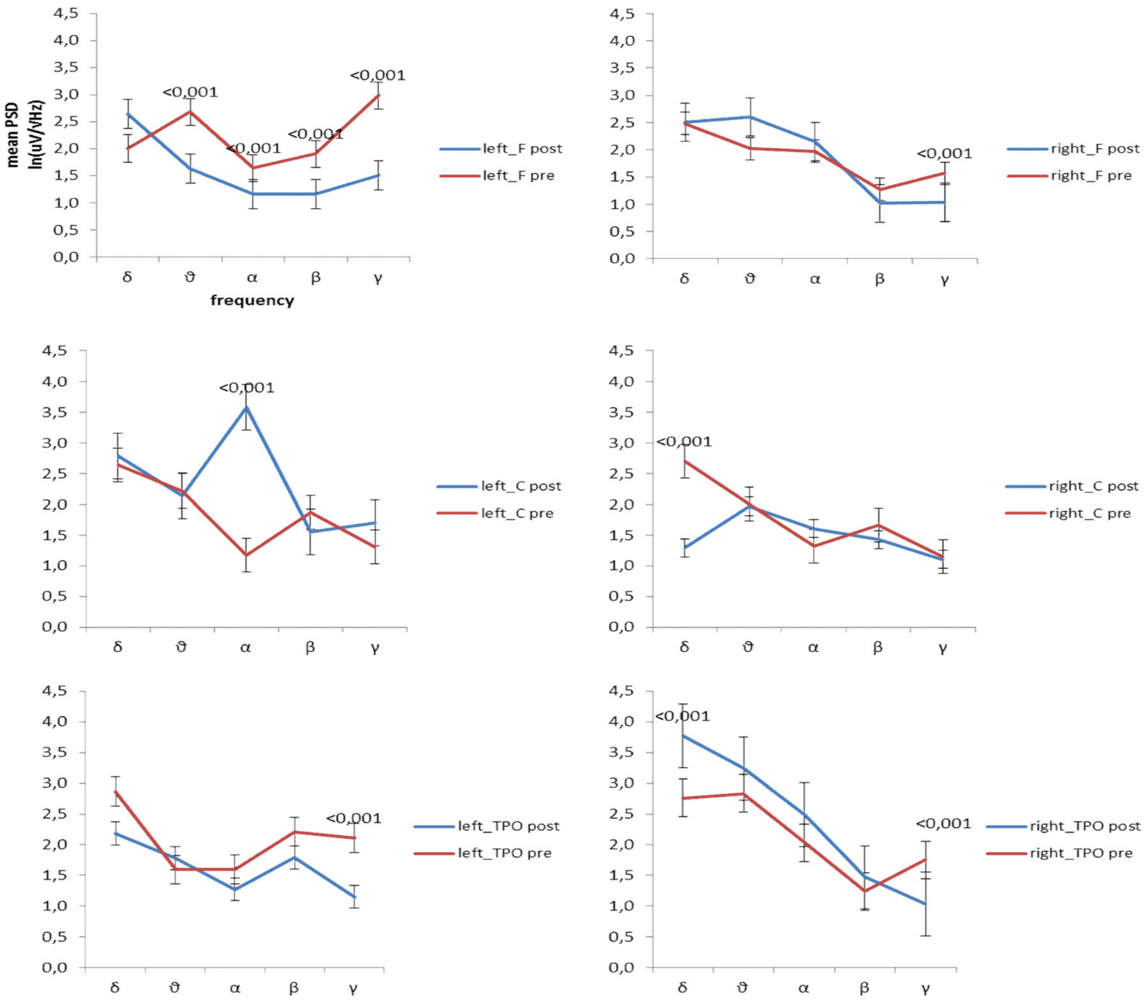

FIGURE 5. Power spectral density (PSD) averaged separately across patients for each electrode group. The p-values for the significant differences over time within each frequency band are reported. Data are expressed as mean ± se (vertical error bar). *VL* vastus lateralis, *BF* biceps femoris, *TA* tibialis anterior, *GM* gastrocnemius medialis, *RMS* root mean square.

ambulation, disease burden, confidence in walking performance, walking distance, self-image, and positive change of emotion,[1,38] as it occurred in our study. This is likely to depend on the fact that end-effector devices are intended mainly for patients who had recovered or spared locomotor function with a sufficient activation of proximal joints and muscles.[25] Therefore, a functional gait recovery could have been foreseeable in our population (subacute, low-cervical/thoracic, motor incomplete SCI). Furthermore, to rate to what extent recovery was influenced by spontaneous recovery, RAGT, or both may require further valuations, consistently with the SCI phase we studied and the lack of a control group. Nonetheless, end-effector devices, including G-EO System, have at least three peculiar characteristics that correspond to the three main findings in our study, thus suggesting end-effector implementation in SCI rehabilitation.[31]

Preservation of Spatial and Temporal Gait Cycle Features in Overground Walking but Not Going Up/Downstairs

G-EO System training did not affect any of the spatial and temporal features of the gait cycle during overground walking. This is an important issue, as it is known that leg muscle activation remains physiologic despite a SCI [29,64] and a better leg coordination and a spasticity reduction are critical for gait improvement in patients with SCI rather than changes muscle activity patterns.[30] The preservation of gait cycle integrity may depend on the fact that end-effectors drive movements in bottom-up directions, whereas fixed overground exoskeletons, which can perturb the gait cycle, drive lower limb movements according to a top-down direction. Therefore, our data suggest that a G-EO-System approach may be promisingly effective for gait improvement, as it does not perturb the physiology of

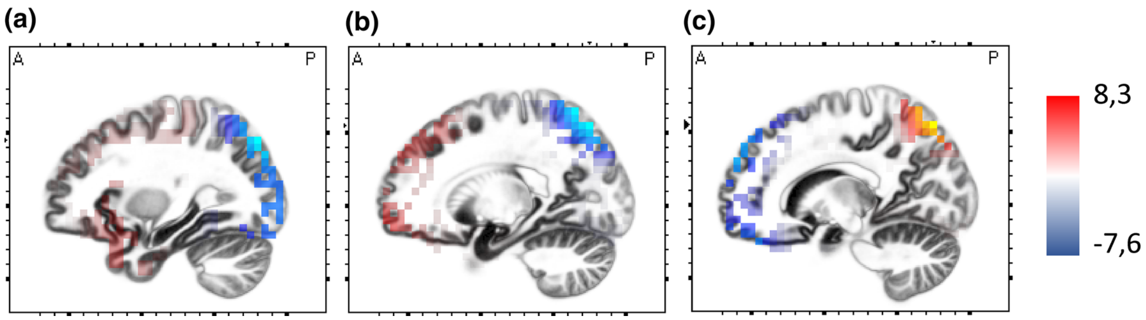

FIGURE 6. Axial images of the independent components (IC) in their frequency band (i.e. mean intrinsic frequencies of the cortical electrical activities) derived from eLORETA-ICA analysis of the EEG data in RS performed prior to and after G-EO System training competition. IC activity is color-coded, being red and blue power increase and decrease, respectively. (a) Intraparietal sulcus in the alpha frequency band. (b) Prefrontal networks in the beta frequency band. (c) Superior parietal lobule in the gamma frequency.

the gait cycle. However, patients' disease and characteristics may influence this finding, as specific abnormalities of gait cycle generation and patterning may depend on the level of spinal damage and the specific consequences on the spinal central pattern generators (CPG) of gait.[3,7,36]

Conversely, G-EO System training significantly modified the stair-climbing cycle. Specifically, gait cycle became as nearly physiological, with a reduction of the pathological co-activations in favor of an alternating and timely correct pattern, an improvement of the flexion of the hip and knee in the pre-swing phase and of hip extension at the end of the stance phase, and a more evident activity of the thigh muscles during the swing phase, which are all essential issues for initiating the stance-to-swing transition.[6] This different effect on proximal muscles, as observed following fixed exoskeleton practice, might depend on the required level of inertia counterbalancing or to the movement restrictions imposed by the device. Moreover, we have to take into account that the CPG for going up/downstairs may work differently from those overseeing floor walking.[37]

Cortical Excitability Increase by End-Effector Practice

G-EO System training induced significant modifications of EEG power within distinct electrode groups and frequency ranges (particularly α, β, and γ), which reflect cortical excitability increase.[62] This excitability increase can be interpreted as either an epiphenomenon of SCI or an adaptive change to foster SCI recovery. The specificity of changes within distinct electrode groups and frequency ranges concerning cortical excitability increase support the latter interpretation. Actually, these changes can be interpreted as the neurophysiologic signature of the strengthening of the neuroplasticity mechanisms of recovery induced by the rehabilitative paradigm inspired to motor learning principles.[10,22] About that, the intensive, repetitive, assisted-as-needed, and task-oriented exercises promote motor learning by simultaneously activating the efferent motor pathways and afferent sensory pathways during the training.[8] This dual activation is consistent with the significant cortical excitability increase.[8,10,22] Furthermore, this dual activation may yield specific effects on CPG, which receives and processes sensorimotor information coming from supraspinal centers (corticospinal drive and extra-pyramidal descending output) and peripheral inputs.[59] Indeed, the stronger sensory stimulation coming from end-effector practice in parallel to a high DOF of movements may mimic a more realistic gait, enhancing an effective recovery rather than simple behavioral compensation processes. Last, specific entrainment of CPG through both ascending and descending inputs may also explain the significant involvement of the lower limb distal muscle, contrary to what is usually observed following exoskeleton-based gait training. This may depend on the specific modality of activity of the end-effector, in which the movements are bottom-to-top driven by the footplates, compared to the top-to-bottom movement driven by the motorized orthoses.

Brain Connectivity Changes by End-Effector Practice

Brain connectivity is known to be affected in patients with complete SCI because of a functional reorganization phenomenon and macro/microstructural changes of white matter within and between the sensorimotor cortices, the midline sensorimotor network, the supplementary motor area, and the cingulate motor areas.[4,18–20,32,33,49,50,53,54,60,67] G-EO System training yielded a significant activation of the sensorimotor networks that are thought to be important for modeling motor functions and, at the same time, to be affected in relation to SCI,[32,33,35] including the intraparietal sulcus, the prefrontal cortex, and the superior

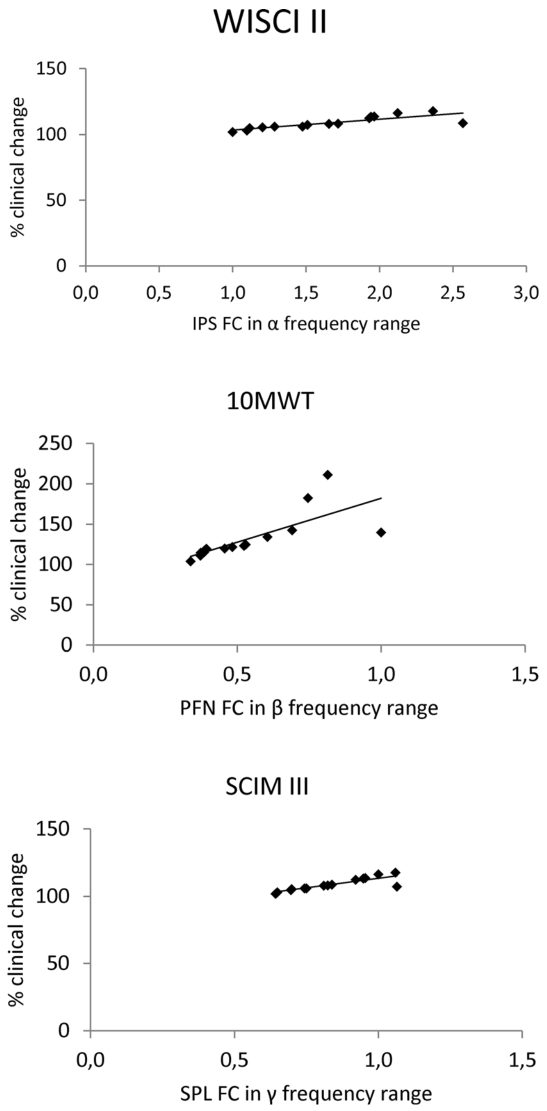

FIGURE 7. Scatter-plot of the overall changes in FC values within the superior parietal lobule in the gamma frequency band, the intraparietal sulcus in the alpha frequency band, and the prefrontal networks in the beta frequency band over WISCI II, SCIM III and 10 MWT and fitting line.

parietal lobule, suggesting an increase in the connectedness and, potentially, the number of paths between these areas.[18] This issue proposes that end-effector practice favored an improvement of the perceptual-motor coordination and visual attention, spatial attention, and attending, looking, and pointing functions,[55] which are all critical functions and brain areas involved in gait function. This functional significance of such cortical areas entrainment is confirmed by the subtending brain rhythms (alpha, beta, and gamma frequency ranges) that were mostly affected by the gait training.[51,58] Actually, these frequencies are involved in movement execution (alpha and gamma frequencies), and corticospinal output modulation (beta frequency).[66] Moreover, specific frequencies within distinct brain areas correlated significantly with the improvements in gait speed, ambulation, going upstairs, and disability.[5,15,49,60] Consistently with these issues and analogous with what was observed concerning cortical excitability changes, the variations in the RSN-FC following G-EO System practice should be interpreted as an effective, biological recovery related to gait training rather than as an epiphenomenon of SCI (i.e., adaptation/maladaptation).[43]

Limitations

The study has some limitations that do not allow generalizing the results. First, the sample enrolled was relatively small and involved only cervical and dorsal, incomplete SCI. Obviously, the results cannot be generalized to other types and levels of SCI. However, this was a pilot study to preliminarily assess the effects of the G-EO System in SCI people. Furthermore, the limited number of patients hinged mainly on the inclusion/exclusion criteria that depend, in a non-negligible part, on the technical details of the device.

Second, we did not have a control group, and only short-term outcomes were evaluated. Further studies with larger samples, longer follow-up, and control groups to discern between robotic device and physiotherapy aftereffects are therefore needed to confirm our promising results and to rate to what extent recovery is influenced by spontaneous recovery, standard interventions, and RAGT. However, the G-EO System did not perturb the physiology of the gait cycle. This is a noteworthy finding as it suggests *per se* that such an approach may be promisingly effective for gait improvement. Furthermore, the significant increase in cortical excitability and the specificity of changes within distinct electrode groups and frequency ranges support the hypothesis that clinical improvement depended on a strengthening of the neuroplasticity mechanisms of recovery induced by the rehabilitative paradigm inspired to motor learning principles, rather than lying on a spontaneous recovery.[10,22] Last, the specificity of brain connectivity changes also supports the reliability and specificity of RAGT on clinical aftereffects rather than a spontaneous recovery.

Finally, we studied RSNs using a realistic head model with the MNI152 template. The result might be thus biased by the predefined anatomical structures we used. A voxel-based network analysis may be needed to overcome such potential bias.

CONCLUSIONS

RAGT by means of the G-EO System is promising in the training gait of patients with subacute, motor incomplete SCI, with relevant aftereffects on muscle strength, ambulation, going up/downstairs, disability burden, and quality of life. Furthermore, the G-EO system practice does not perturb gait cycle physiology. Last, clinical aftereffects are achieved by means of specific (i.e., related to RAGT), motor-learning inspired, neuroplasticity mechanisms. Even though larger-sample studies are required to confirm our promising data, RAGT by means of the G-EO System in patients with subacute, motor incomplete SCI could produce an additive benefit to conventional physiotherapy with regard to the neuromuscular reeducation to gait. Furthermore, the issue that patients with SCI have preserved sensorimotor brain control may open the way to the design of connectivity-based brain-computer interfaces, assistive technologies for SCI patients, and invasive/non-invasive brain and spinal cord stimulation to favor the neuroplasticity-based recovery[3,21,46,50,51,58,66] mechanisms.

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CONFLICT OF INTEREST

None of the authors have potential conflicts of interest to be disclosed.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The local Institutional Review Board approved the study.

INFORMED CONSENT

Patients provided their written informed consent to study participation and data publication.

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