Trials

STUDY PROTOCOL

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# Investigating the role of therapist-patient interaction during robot-assisted gait training after incomplete spinal cord injury: the INTER-RO-GAIT randomized controlled trial

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## Abstract

**Background** In the neurorehabilitation framework of treadmill-based robot-assisted gait training (t-RAGT), a three-fold relationship among physiotherapist (Pht), patient (Pt), and the selected robotic device should be considered. Furthermore, the type of visual FeedBack (FB) selected for the training and how the Pht guides and supports the Pt have an important impact on Pt's engagement. Pht-Pt interaction is mostly effective when FB with high technical content is employed, and it affects Pt's visual attention and emotional experience during training. The INTER-RO-GAIT project proposes an experimental modulation of Pht-Pt interaction during the training with the Lokomat device, to primarily investigate its role in the effectiveness of t-RAGT for individuals with subacute and chronic incomplete spinal cord injury (i-SCI) through a longitudinal randomized controlled trial (RCT), by means of clinical scales and biomechanical data. Timed walking tests for gait speed evaluation (10-Meter Walking Test and 6-Minute Walking Test) are considered as primary outcome measures, while clinical scales for the assessment of lower limbs' force, spasticity, pain, clonus, spasms, and independence in activities of daily living are selected as secondary outcome measures. The biomechanical assessment includes overground gait analysis to assess recovery of motor functions, and human-Lokomat interaction analysis to measure the active Pt participation in the exercise and evaluate its evolution along training. Secondary aims are as follows: (i) to identify neurophysiological indices derived from electroencephalography (EEG) hyperscanning data monitoring the Pht-Pt relationship along t-RAGT; (ii) to evaluate the Pt's engagement in terms of Visual Attention during the RAGT; (iii) to investigate the correlation between the rehabilitation outcome and the neurophysiological indices or the psychological metrics referring to Pht-Pt relationship.

**Methods** Fifty participants from I.R.C.C.S. Fondazione Santa Lucia (Rome, Italy) will be enrolled and randomized into a single-blind RCT to investigate the effects of 12 Lokomat t-RAGT sessions administered with two different levels of Pht-Pt interaction (high level of interaction for the experimental (EXP) group and low level of interaction for the control (CTRL) group), as an add-on training to conventional rehabilitation. Before and after the whole t-RAGT, as well as at the first, the mid, and the last training session, a battery of clinical, biomechanical, psychological, and neurophysiological assessments will be conducted.

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**Discussion** Given that incomplete subacute or chronic SCI may lead to long-term disability for which cost-effective rehabilitation options are critically needed, INTER-RO-GAIT aims at providing evidence for an optimal Pht-Pt interaction to potentially boost the t-RAGT effects on Pts' performance, improving robotic rehabilitation protocols and devices development even beyond the specific gait application.

**Trial registration** Patient-therapist INTERaction During RObotic GAIT Rehabilitation After Spinal Cord Injury (INTER-RO-GAIT); ClinicalTrial.gov platform registration number: GR-2019–12369207 on 31st July 2024.

**Keywords** Body weight support, EEG hyperscanning, Incomplete SCI, Lokomat, Physiotherapist–patient interaction, T-RAGT, Treadmill

## Introduction

### Background and rationale

The main goal of rehabilitation interventions for individuals with spinal cord injury (SCI) is regaining independence and thus a good quality of life [1]. From the patient's point of view, regaining ambulation is of high priority for individuals with incomplete SCI (i-SCI), regardless of the severity, the time elapsed from the injury, and the age at the time of injury [2]. Modern approaches for gait recovery favor task-specific repetitive rehabilitation, with high intensity and early multisensorial stimulation such as those entailing treadmill-based robot-assisted gait training (t-RAGT) [3]. Lower limb robotic systems also reduce the physical burden on therapists while still preserving patient engagement and therapeutic effectiveness during goal-oriented rehabilitation training [4]. The Lokomat (Hocoma AG, Switzerland) is a widely used device for t-RAGT. It includes a treadmill, a body weight support (BWS) system to adjust weight-bearing effects, and a bilateral active robotic orthosis that assists hip and knee joint flexion/extension [5].

In recent decades, several studies have been conducted to investigate the effects of t-RAGT devices on functional abilities or clinical outcomes in individuals with neurological disorders, including SCI [6, 7]. In this regard, a consensus is being reached on the importance of top-down approaches, particularly when dealing with robotic devices [8]. The critical aspects of top-down approaches are multifarious and include motivation, active participation, error-driven skills learning, evidencing the key aspects of FeedBack (FB) information to guide and improve robotic therapy [3]. FB, such as visual, auditory, or haptic cues, is widely recognized as a critical component of robotic neurorehabilitation. It enhances plasticity-dependent mechanisms that improve motor learning and performance, particularly in the context of t-RAGT [9]. Furthermore, FB fosters active patient (Pt) participation, which is essential for achieving successful rehabilitation outcomes, and must be adapted to meet individual patient needs and tailored to patient-specific requirements [10, 11]. In the case of the Lokomat device, the FB is simultaneously provided to both Pt and Physical Therapist (Pht), and the Pht can utilize its information to provide the Pt with enhanced instructions, suggestions, and corrections, thereby reinforcing the input already delivered through the FB system itself. It has been previously demonstrated that Pht-Pt interaction is a key aspect for success in rehabilitation: physical, verbal (motivational and technical) exchanges between the Pht and Pt highly influence the outcome [12]. In the literature, four main themes are recognized as influencing patient-therapist interactions: (i) interpersonal and communication skills of the physical therapist (e.g., listening, encouragement, confidence, empathy, friendliness, and nonverbal communication); (ii) practical skills of the physical therapist (e.g., expertise and level of training); (iii) individualized patient-centered care taking patient's opinions into account; and (iv) organizational and environmental factors, such as time and flexibility with appointments [13]. Although further research is required to clarify which factors most strongly influence Pht-Pt interaction, and despite the recognized importance of FB in t-RAGT, the specific role of the therapist within the complex patient–robot interaction remains unclear. In some cases, the Pt may be left to interpret the FB independently without verbal support from the therapist; in others, the therapist may provide continuous real-time encouragement, facilitating the correct interpretation of the FB through a positive social relationship characterized by mutual respect, therapist empathy, and patient trust [14].

The hypothesis that Pht-Pt interaction, i.e., cooperative rehabilitation, could promote learning motor strategies was recently tested in subacute stroke Pts [12]. Pht-guided therapy involving active collaboration with a Pt through shared visual FB showed that sharing exercise-related biomechanical information significantly improved the efficacy of the conventional approach for treating ankle spasticity. These findings suggest that the introduction of a device or a shared FB as a third entity in the traditional one-to-one Pht-Pt relationship modifies the classic dyadic dynamics, shifting to a triadic interaction paradigm.

A recent study [15] investigated whether different types of visual FB combined with different modalities of Pht's

verbal interaction towards the Pt affect the Pts' visual attention and emotional engagement during t-RAGT. Pts' participation in the rehabilitative exercise, when game-like FB is used, is less influenced by the presence of the Pht, whereas synthetic or less intuitive FB necessitates greater involvement from the Pht to guide the Pt during rehabilitation. Pts show decreased visual attention to the FB when verbal support from the Pht is minimal, compared to conditions with higher levels of verbal and technical interaction between the Pht and the Pt. Importantly, a reduced Pht-Pt interaction is associated with insula activation, regardless of the type of visual FB, which was interpreted as indicative of a negative emotional response. Based on these results, it was concluded that the contributions of the FB and the Pht-Pt interaction are not mutually exclusive but can synergistically enhance Pt's focus on the exercises during t-RAGT [15].

Besides these data, the literature is vast on the effects of t-RAGT on i-SCI gait performance: t-RAGT, particularly for individuals with subacute i-SCI, allows significant improvements in walking speed, covered distance, functional mobility and independence in activities of daily living [16, 17]. However, trials assessing the effects of the Pht and Pt interaction on Pt's performances and clinical outcomes during t-RAGT are still missing. We will approach this issue within a Randomized Controlled Trial (RCT) in which we will compare Lokomat training conditions that differ only in terms of the degree of Pht-Pt interaction. This design grounds on a preliminary study demonstrating the important contribution of therapist in focusing patients' visual attention toward FB promoting a higher cognitive engagement in the t-RAGT exercise [15]. Specifically, in the high-level interaction group the Pht will provide continuous verbal support for the correct interpretation of the FB from the Lokomat; conversely, in the low-level interaction group, the verbal communication between the PhT and the Pt will be reduced to a minimum, with the Pt guided only by the visual FB without technical exchanges with the Pht. Indeed, we hypothesize that in the context of the same rehabilitative training executed with the same robotic device, a low level of interaction still generates effects, but to a lesser extent than a high level of interaction. The effects on gait rehabilitation outcome will be evaluated through clinical and biomechanical data analyses, while an extensive assessment of psychological, neurophysiological and visual attention processes will be also carried out to assess the establishment of Pht-Pt interaction.

Recently, a new conceptual and methodological framework has been proposed to investigate the neural basis of human social interaction: the two-person neuroscience. It focuses on studying the dual exchange rather than only on the individual behaviour, by using simultaneous neurophysiological recordings from two or more subjects, commonly referred to as hyperscanning or dual scanning [18, 19]. This approach can provide a viable way to untangle the social interaction from two-persons data as in multiple-brain connectivity (also referred to, in some studies, as hyperconnectivity). Thereby temporal correlations (or causality in the statistical sense) between signals derived from the brain regions of different subjects during their interaction are studied to understand how the brain activity of each subject is correlated to the activity in the brain of the other one. Inter-subject connectivity was described by functional magnetic resonance imaging [18, 20], magnetoelectroencephalography [21] and electroencephalography (EEG) studies, the latter allowing for an ecological setting [22, 23]. In addition, such technique demonstrated to be promising also in the assessment of therapeutic alliance establishment between clinicians and Pht-Pt [24, 25]. Furthermore, the use of indices derived from graph theory allows to characterize the multiple-brain system by means of its properties [26]. Thus, EEG hyperscanning will be employed in this RCT to objectively measure the Pht-Pt interaction, and possibly relate it to the rehabilitation outcome.

### Objectives

In t-RAGT a triadic relationship among Pht, Pt and a robotic device emerges. Furthermore, the type of FB selected for the training and how the PhT guides and supports the Pt, have an important impact on Pt's engagement and are key elements to be considered in planning the rehabilitation sessions [9]. Indeed, it has been recently demonstrated that Pht-Pt interaction is mostly effective when a FB with high technical content is employed [15], and that the experimental manipulation of PhT-Pt interaction affects Pts' visual attention and emotional experience during the training. Our main hypothesis is that different levels of Pht-Pt interaction also influence functional rehabilitation efficacy and consequently the Pts' clinical and functional outcome. INTER-RO-GAIT proposes an experimental modulation of Pht-Pt interaction during the Lokomat training, which is based on previous findings [15] and is organized as follows. In the high-level interaction group (EXP group), the Pht will provide continuous verbal support for the correct interpretation of the FB from the Lokomat. The PhT will give specific instructions when the FB indicates incorrect movement, assigning tasks focused on individual joints during specific gait phases, directing visual attention to the screen displaying the FB, and consistently motivating Pts to actively engage in the rehabilitation exercise. Conversely, in the low-level interaction group (CTRL group), the verbal communication between the PhT and the Pt will be reduced to a minimum (e.g., Pht only monitors Pt's safety

and general conditions), and the Pt will be guided only by the visual FB without exchanges with the Pht. According to Patarini et al. [15], the FB used for the trial will be the c*hart* FB, which displays trend graphs for swing/stance phases and for each assisted joint (hip/knee) indicating cycle-by-cycle human-Lokomat interaction information. In particular, each displayed data, calculated on interaction torques and joint-specific weighting functions, indicates active participation (positive values) or passive behavior or even resistance (negative values).

The main aim of INTER-RO-GAIT is to investigate the relevance of the Pht-Pt interaction in t-RAGT effectiveness for subacute and chronic i-SCI subjects through a longitudinal RCT, by means of clinical scales and biomechanical data. As primary outcomes, we identified the scores of the 10-Meter Walking Test and the 6-Minute Walking Test. Secondary outcomes will be assessed using clinical scales evaluating lower limbs' force, spasticity, pain, clonus, spasms, as well as independence in activities of daily living. Biomechanical assessment will include overground gait analysis to examine motor function recovery, and human-Lokomat interaction analysis to evaluate the progression of the active patient participation along training. Secondary aims are as follows: (i) to identify neurophysiological indices derived from High Density EEG (HD-EEG) hyperscanning data monitoring the Pht-Pt relationship along the entire t-RAGT rehabilitation pathway; (ii) to evaluate the Pt's engagement in terms of Visual Attention during a single t-RAGT session; (iii) to investigate the correlation between the rehabilitation outcome and the establishment of an effective Pht-Pt relationship as assessed via the neurophysiological indices or the psychological metrics. In terms of neurophysiological indices, Pht-Pt interaction will be explored through the analysis of the following: (i) neural responses related to a specific HD-EEG task selected to provide a measure to characterize the (potentially) empathic Pht-Pt interaction established along the rehabilitation pathway, (ii) spectral activation maps to highlight brain areas related to social cognition processes; (iii) multiple-brain connectivity indices quantifying the levels of social interaction between Pht-Pt. As psychological metrics, several questionnaires will be administered to the Pt to assess anxiety, presence and severity of depressive symptoms, emotional regulation, overall perception of QOL and health, motivation, mood and satisfaction, perceived workload in using Lokomat and related usability and satisfaction, as well as the empathy in the context of the Pht-Pt relationship. As regards the Pht, questionnaires will be administered to address the dispositional empathy, the assertiveness, the will and ability to modify how one is perceived by others, the alexithymia, the attitudes and beliefs related to the sense of responsibility. In association with the neurophysiological assessment, both Pt and Pht will undergo questionnaires to measure their impression of one another and their emotional reaction in a specific context.

### Trial design

The INTER-RO-GAIT trial is designed as a randomized, controlled, assessor-blinded single-center trial with 2 parallel groups with a 1:1 allocation ratio. The study flow chart is reported in Fig. 1.

The enrollment of individuals with i-SCI, the intervention delivery and the data collection will take place at the Spinal Unit (SU). Upon admission, Pts with i-SCI will be screened for eligibility criteria by the neurologists' clinical staff according to the inclusion criteria of the study defined below. Eligible participants will be introduced to the study protocol by an authorized Medical Doctor (neurologist), and they will be presented with informed consent. Individuals with i-SCI will be randomized (within 1 week of first contact with the participants) to one of 2 groups: the high Pht-Pt interaction (experimental condition–EXP group) or the low Pht-Pt interaction (control condition–CTRL group). The primary outcome is the gait speed on short and long distances, while secondary outcomes are lower limb muscle strength, spasticity, pain, and functional ability as well as EEG and visual attention data, and psychological metrics. The overall outcome assessments are detailed in the "Outcome" section. The study is presented according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [27]. Table 1 shows the SPIRIT schedule of enrolment, interventions, and assessments.

## Methods: participants, interventions, and outcomes

### Study setting

A total cohort of 50 participants from a single center (I.R.C.C.S. Fondazione Santa Lucia, Rome, Italy) will be enrolled and randomized into a single-blind RCT to investigate the effects of Lokomat t-RAGT administered with two different levels of Pht-Pt interaction (high for the EXP group and low for the CTRL group) on clinical, biomechanical, psychological, and neurophysiological variables as well as on Pt's visual attention. The training with the Lokomat will be administered during hospitalization, as an add-on training to the treatment as usual (TAU) [22] planned at SU of Fondazione Santa Lucia. The outcome measures will be collected from individuals assigned to the EXP group and compared with those of individuals who receive an equivalent dose of Lokomat t-RAGT with a low level of Pt-Pht interaction (CTRL group).

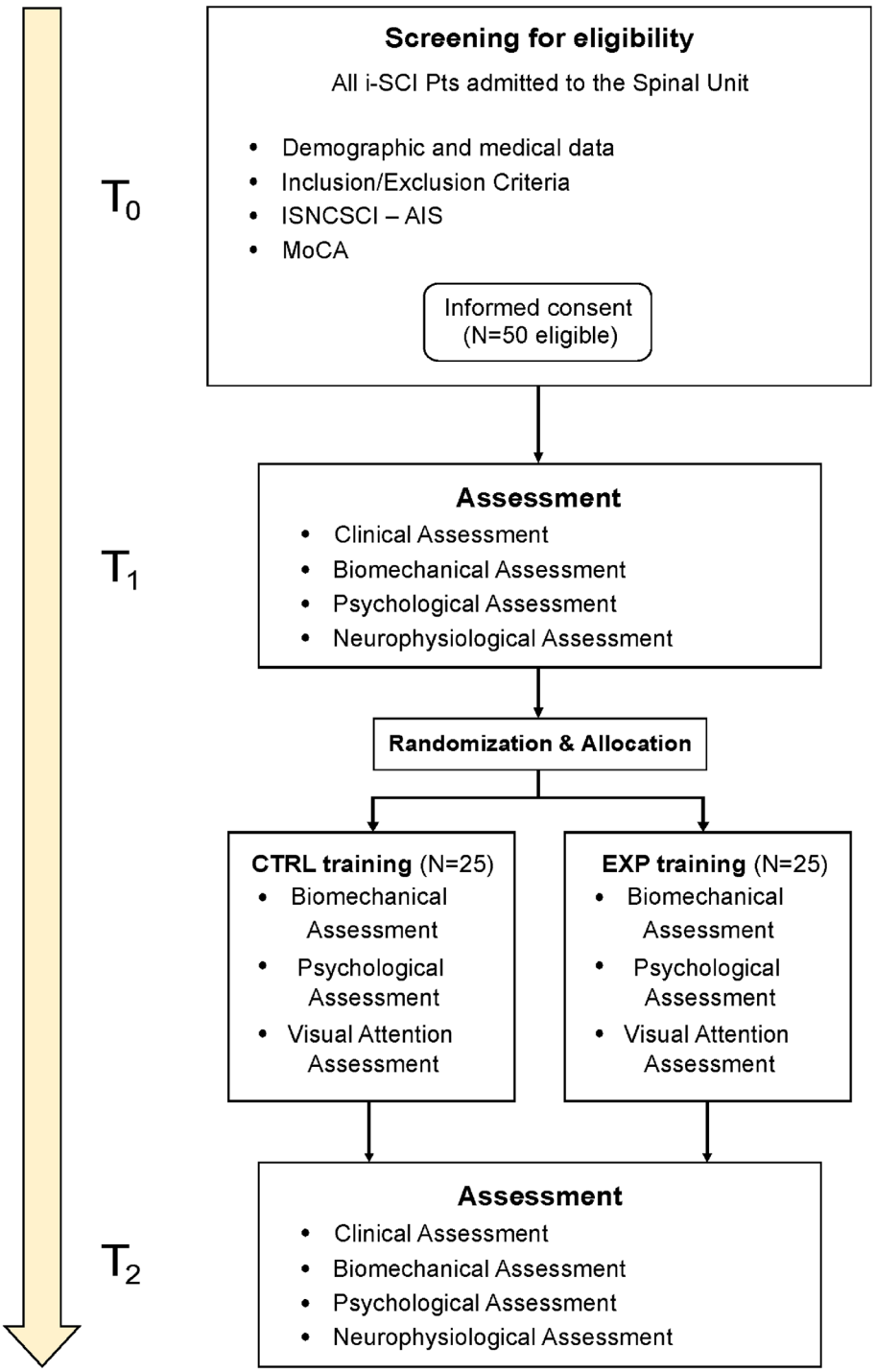


**Fig. 1** INTER-RO-GAIT randomized controlled trial flow chart

All procedures conducted in this trial follow national institutional ethical standards and the Helsinki Declaration. The study protocol and related procedures are approved by the institutional review board: the Independent Ethical Committee of the I.R.C.C.S. Fondazione Santa Lucia (PROT.CE/PROG. 883). The trial is registered on clinicaltrials.gov (NCT06531304).

**Table 1** Standard protocol items as recommended for Interventional Trials (SPIRIT)

| | | | Study Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Enrollment | Assessment | Intervention | | | | | | | | | Assessment |
| | | | | | S1 | | | S6 | | | S12 | | | |
| | | | T0 | T1 | Pre training | During training | Post training | Pre training | During training | Post training | Pre training | During training | Post training | T2 |
| Patient | Enrollment | Eligility Screen: Demographic and medical data; Inclusion/Exclusion Criteria; ISNCSCI – AIS; MoCA, BDI-II, STAI | X | | | | | | | | | | | |
| | | Informed Consent | | | | | | | | | | | | |
| | Interventions | Intervention (CTRL/EXP) | | | ← | | | | | | | | → | |
| | Outcome Variables | Clinical Assessment: 10MWT, 6MWT, BORG, LEMS, MAS, NRS, PSFS, SCATS, SCIM-III | | X | | | | | | | | | | X |
| | | Biomechanical Assessment: Overground Gait Analysis | | X | | | | | | | | | | X |
| | | Biomechanical Assessment: Human-Lokomat interaction analysis | | | | X | | | X | | | X | | |
| | | Psychological assessement: STAI-Y, BDI-II, DERS, GRIT, WHOQOL, Impression Scale, Emotional Response Scale | | X | | | | | | | | | | X (WHOQOL, Impression Scale, Emotional Response Scale) |
| | | Psychological assessement: QCM, VAS Mood, VAS Motivation | | | X | | | X | | | X | | | |
| | | Psychological assessement: VAS Satisfaction, NASA-TLX | | | | | X | | | X | | | X | |
| | | Psychological assessement: CARE | | | | | X | | | | | | X | |
| | | Psychological assessement: SUS, QUEST 2.0 | | | | | | | | | | | X | |
| | | Neurophysiological Assessment | | X | | | | | | | | | | X |
| | | Visual Attention Assessment | | | | X | | | X | | | X | | |
| Therapist | Outcome Variables | Psychological assessement: STAI-Y, BDI, DERS, IRI, EQ, Assertion Inventory, SMS, TAS-20, RAS, Impression Scale, Emotional Response Scale | | X | | | | | | | | | | X (Impression Scale, Emotional Response Scale) |
| | | Neurophysiological Assessment | | X | | | | | | | | | | X |

*T0*, enrollment; *T1*, assessment before training; *T2*, assessment after intervention; *S1*, first training session; *S6*, sixth training session; *S12*, last training session; *ISNCSCI*, International Standards for Neurological and Functional Classification; *AIS*, Asia Impairment Scale; *MoCA*, Montreal Cognitive Assessment; *BDI-II*, Beck Depression Inventory-II; *STAI-Y*, State-Trait Anxiety Inventory-Y form; *CTRL*, control group; *EXP*, experimental group; *10MWT*, 10-Meter Walk Test; *6MWT*, 6-Minute Walking Test; *LEMS*, Lower Extremity Motor Score; *MAS*, Modified Ashworth Scale; *NRS*, Numeric Rating Scale; *PSFS*, Penn Spasm Frequency Scale; *SCATS*, Spinal Cord Assessment Tool for Spastic Reflexes; *SCIM-III*, Spinal Cord Independence Measure III; *STAI-Y*, State-Trait Anxiety Inventory-Y form; *BDI-II*, Beck Depression Inventory-II; *DERS*, Difficulties in Emotion Regulation Scale; *GRIT*, Short Grit Scale; *WHOQOL*, World Health Organization Quality of Life Questionnaire; *QCM*, Questionnaire on Current Motivation; *VAS*, Visual Analogue Scale; *NASA-TLX*, NASA Task Load Index; *SUS*, System Usability Scale; *QUEST 2.0*, Quebec User Evaluation of Satisfaction with Assistive Technology; *IRI*, Interpersonal Reactivity Index; *EQ*, empathy quotient; *SMS*, Self Monitoring Scale; *TAS-20*, Toronto Alexithymia Scale; *RAS*, Responsibility Attitude Scale

### Eligibility criteria

The specific criteria are listed below. Inclusion criteria are as follows:

- i-SCI lesion (ISNCSCI AIS level C or D);
- Subacute (2–6 months) or chronic (more than 6 months) SCI;
- Traumatic and non-traumatic aetiology;
- SCI at or above T12 level;
- Age 18–85;
- Absence of severe cognitive impairment such as to interfere with the protocol, assessed by Montreal Cognitive Assessment (MoCA, cutoff > 26) [ 28].

Exclusion criteria are as follows:

- Lack of the clinical requirement for using Lokomat;
- Anything preventing EEG recording, such as skin conditions on the scalp as determined by open or recent wounds, dermatitis, or deformations of the cranial lid as determined by trauma or neurosurgery, preventing the EEG cap positioning.

## Intervention

### Dosage of intervention training

Before starting the training, all Pts will undergo a familiarization session (SS0) with the Lokomat, allowing the Pht to properly adjust and customize the device parameters according to Pt clinical and functional performance: the joint trajectories, the BWS, the Gait Speed (GS), and the level of assistance, indicated as guidance force (GF). These parameters will be properly adjusted over the course of the 12 sessions to allow the Pt to progressively ambulate on the Lokomat with lower BWS, lower GF, and greater speed. However, at T1 and T2 for a biomechanical quantification of Pt participation during human–Lokomat interaction, these device parameters will be kept constant to prevent any impact on Pt's performance

during assessments. BWS, GS, and GF data are collected by means of the Case Report Form as detailed in the dedicated session (Data collection and management section).

Both EXP and CTRL groups will perform 12 sessions (SS1, SS2,..., SS12) of Lokomat t-RAGT with a weekly delivery of 3 times/week, 45 min duration including the time for donning and doffing the harness. The surroundings will be carefully monitored during the RAGT sessions in the rehabilitation environment, in order to avoid distractions. To monitor any possible deviation from the training intervention protocols (e.g., missing sessions for intervening illness), a report form for each participant will be compiled at each planned training session by the training personnel as part of the CRF (CRF-Training section; details in "Data collection and management" section). The Lokomat training sessions are conceived as an add-on to the TAU, and both groups will receive the same dosage of TAU and add-on training. To ensure comparability between and within groups, TAU will be delivered according to the same intensive regimen for both groups, including neurorehabilitation sessions of 40 min each, twice a day, Monday through Friday. In addition, a single 40-min therapy will be also delivered on Saturday or Sunday. During the administration of TAU, no modulation of PhT-Pt interaction will be imposed (for each patient, the therapist involved in the t-RAGT sessions will be different from those involved in the TAU administration). Furthermore, as the neurorehabilitation hospital in which the study will take place is a multi-storey building and PhTs are usually working on one specific floor/ward, the couples Pht-Pt for our t-RAGT training will be recruited from different wards to further control for possible contamination of the collections.

#### t-RAGT description

Based on a recent work, where it was demonstrated that the effects of Pht-Pt interaction are the highest when FB with high technical content is employed [15], *chart* FB will be selected for both EXP and CTRL groups and used for the entire training intervention.

Each training session will be composed of four 5-min blocks, where the Pt will be asked to selectively focus on a joint (right or left hip, right or left knee). Each block will be additionally split into two periods of 2.5 min, one focusing on the stance phase and the other one on the swing phase, for a total of eight tasks (right hip stance, right hip swing, left hip stance, left hip swing, right knee stance, right knee swing, left knee stance, left knee swing). The order of the tasks will be randomly selected across Pts. In the EXP group, the Pht will provide continuous verbal support for the correct interpretation of the FB with specific instructions when the FB indicates incorrect movement, assigning tasks focused on individual joints during specific gait phases, directing visual attention to the screen displaying the FB, and consistently motivating Pts to actively engage in the rehabilitation exercise. On the contrary, for the CTRL group, the Pt will be guided only by the visual FB without verbal exchanges with the PhT who will only monitor the Pt's safety and general conditions.

## Outcomes

Upon enrollment, demographic data of individuals with SCI will be collected as well as SCI neurological features. The International Standards for Neurological and Functional Classification (ISNCSCI) of SCI will be used to determine the lesion level and the severity of the SCI (the Asia Impairment Scale (AIS) level) [29]. Data about aetiology and time since SCI will also be collected.

Outcome measures refer to the assessments that are conducted before (T1) and after t-RAGT intervention (T2) and also during the execution of the first (SS1), the mid (SS6), and the last (SS12) rehabilitation session with the Lokomat. Trained clinical/research neurologists, neuropsychologists, physiologists, and Pht-Pt will perform the assessments and will be blinded to the participant intervention allocation except for recruiting neurologists who will not participate in the assessment. Data will be recorded in an ad-hoc Case Report Form (CRF; details in "Data collection and management" section). The outcome variables collected at the assessments will be classified as clinical, biomechanical, psychological, neurophysiological, and visual attention data.

#### Clinical outcome assessment

The primary clinical outcome measures will be the changes from T1 to T2 in gait time tests on short and long distances, addressed per the the following:

- 10MWT (10-Meters Walking Test) [30] performed at the self-selected WISCI-II level [31];
- 6MWT (6-Minute Walking Test) [30] associated with BORG scale [32] for fatigue perception.

We will adopt both measures in order to allow a comprehensive assessment of walking function, which includes speed, endurance, the use of walking aids, braces, or physical assistance.

For the clinical secondary outcome measures, the following scales will be administered:

- Lower Extremity Motor Score (LEMS) of International Standards for Neurological and Functional Classification (INSCI) of Spinal Cord Injury [29] for the force assessment;

- Modified Ashworth Scale (MAS) [33] for the bilateral assessment of hip, knee and ankle flexor and extensor muscle spasticity;
- Numeric Rating Scale (NRS) [34] for lower limbs pain assessment;
- Penn Spasm Frequency Scale (PSFS) [35] for measurement of frequency and severity of muscle spasms in the lower limbs;
- Spinal Cord Assessment Tool for Spastic Reflexes (SCATS) [36] for the specific assessment of clonus, flexor spasms, extensor spasms of lower limbs;
- Spinal Cord Independence Measure III (SCIM-III) [37] for measuring the level of independence and self-sufficiency in performing activities of daily living.

#### Biomechanical outcome assessment

The biomechanical assessment will include two different investigations. From one side, overground gait analysis will be performed to assess quantitatively the recovery of motor functions at T1 and T2. From the other side, human-Lokomat interaction analysis will be carried out to evaluate the evolution of the active Pt participation during robot-assisted walking along the training at SS1, SS6, and SS12.

For the biomechanical analysis of overground gait, the aim is to quantify free walking with standard biomechanical metrics commonly used in gait analysis. For this assessment, Pts will be asked to walk overground at least 5 times on a 5-m path with self-selected WISCI level and at a comfortable walking speed. The assessment set-up will include the following: (i) an optoelectronic motion capture system (Optitrack, Natural Point, US) composed of 12 cameras (Flex13) with 1.3 MP and 120 Hz; (ii) a surface EMG recording system composed of 16 wireless sensors (Trigno, Delsys, US) to measure muscular activity; (iii) four P6000 force plates (BTS Bioengineering, Italy) to record ground reaction forces at 500 Hz.

Reflective spherical markers will be placed on Pt anatomical landmarks according to the Rizzoli lower body protocol, and markers will be added on big toes, acromions, sternum, and C4 (total: 36 markers). EMG surface electrodes will be placed according to the SENIAM protocol [38] on the main lower limb muscles responsible for walking: rectus femoris, vastus lateralis, biceps femoris, gastrocnemius medialis, gastrocnemius lateralis, tibialis anterior, semitendinosus, and soleus. Marker data will be imported into the OpenSim software [39] to calculate inverse kinematics and dynamics data. Lower limb joint data will be time-normalized based on heel strike events to be represented as a function of the gait cycle duration and to be further analyzed. Typical spatio-temporal parameters will also be extracted (e.g., gait speed, stance/swing percentage, step and stride length, width, and duration).

Raw EMG data will be filtered by using a third-order, zero-lag Butterworth band-pass filter in the frequency range 20–400 Hz, rectified and then filtered by a third-order, zero-lag Butterworth low-pass filter with a cutoff frequency of 5 Hz for envelope calculation.

As regards the biomechanical quantification of active Pt participation during human-Lokomat interaction, the assessment will be based on the fundamental rehabilitation concept according to which the useful joint torques exerted by the Pts are expected to have most of the time the same sign as the joint angular velocity (i.e., they should point in the same direction of the desired movement). For this assessment the Lokomat device will be configured in research mode to export, through a research output module, real-time analog data, specifically bilateral hip/knee joint angles (coming from robot encoders) and human–robot interaction torques (coming from force sensors in the robot linear actuators). Data will be collected with a NI USB-6218 acquisition board (National Instruments, Austin, TX, USA) and recorded on a PC running the Analog Input Recorder tool of MATLAB (Mathworks, Natick, MA, USA) at a sampling frequency of 500 Hz.

Joint angle data will be differentiated to obtain angular velocity. To account for inter-participant variability, human–robot interaction torques will be normalized to the Pts' body mass. Both angular velocity and normalized torque data will be smoothed by using a third-order, zero-lag Butterworth low-pass filter with a cutoff frequency of 5 Hz. Data will be segmented based on heel strike events and time-normalized to express all variables as a function of the percentage of the gait cycle. For each gait cycle, the joint interaction torques will be multiplied by the corresponding angular velocities to compute the interaction power. For the knee joint, angular velocity will be used with no changes. For the hip, angular velocity will be quenched during mid-swing by using a cosine function. This approach is motivated by the need to mitigate the potential contribution from passive effects, such as gravity, that could otherwise lead to an overestimation of the interaction power, as suggested in [40, 41]. The interaction power will then be integrated over specific time windows of the gait cycle to calculate the interaction work for the stance and swing phases. In accordance with [40], the window for the stance phase will be defined as 0–50% of the gait cycle for both joints; the window for the swing phase will be defined as 55–82% of the gait cycle for the hip and 51–90% of the gait cycle for the knee. By definition, positive interaction work values indicate active contribution, whereas negative values represent passive or even resistive behaviour.

This process yields eight work values for each stride: hip stance/swing and knee stance/swing, which will be calculated for the left and right sides. For each experimental condition, these values will be separately averaged across all gait cycles within the trial.

#### Psychological outcome assessment

The psychological assessment includes several questionnaires, which will be administered to both PhT and Pt at different time points (see Table 1). Data will be acquired before (T1) and after t-RAGT intervention (T2), and within the intervention.

Before t-RAGT intervention (T1), the following questionnaires will be administered to the Pt:(i) State-Trait Anxiety Inventory-Y form (STAI-Y, trait) [42] to detect and measure anxiety as a personal characteristic (scores often classified as follows: "no or low anxiety" (20–37), "moderate anxiety" (38–44), and "high anxiety" (45–80)); (ii) Beck Depression Inventory-II (BDI-II) [43] to identify the presence and severity of depressive symptoms (0–13 no depression, 14–19 mild depression, 20–29 medium depression, and 30–63 severe depression); (iii) Difficulties in Emotion Regulation Scale (DERS) [44] to assess emotional regulation with higher scores then suggesting greater problems with emotion regulation; (iv) Short Grit Scale [45] (GRIT) to measure trait-level perseverance and passion for goals with maximum score for extremely gritty individuals; (v) World Health Organization Quality of Life Questionnaire (WHOQOL-bref) [46] to assess Pt overall perception of QOL and health (higher scores indicate a higher QOL). WHOQOL-bref questionnaire will also be repeated at T2.

As regard the Pht, the following questionnaires will be administered at T1: (i) STAI-Y; (ii) BDI-II; (iii) DERS; (iv) Interpersonal Reactivity Index (IRI) [47] as a measure of dispositional empathy considering Perspective Taking, Fantasy, Empathic Concern, Personal Distress subscales; (v) Empathy Quotient (EQ) [48] as a measure of empathy, the ability to understand and share the emotions of other people (scores > 30 indicate a good level of empathy); (vi) Assertion inventory [49] to evaluate assertiveness, using the perceived degree of discomfort in specific situations and the judged probability of engaging in a behaviour; (vii) Self Monitoring Scale (SMS) [50] to measure the will and ability to modify how one is perceived by others distinguishing between low (score range 0–8) and high (score range 15–22) self-monitor subjects); (viii) Toronto Alexithymia Scale (TAS-20) [51] to assess alexithymia and the ability to differentiate, recognize or express emotions (a score equal to or less than 51 corresponds to non-alexithymia, scores from 52 to 60 means possible alexithymia, while a score that is equal to or greater than 61 indicates alexithymia); (ix) Responsibility Attitude Scale (RAS) [52] to measure attitudes and beliefs related to the sense of responsibility, ranging from 26 (low responsibility) to 182 (high responsibility).

At T1, in association with the neurophysiological assessment detailed below, both Pt and Pht will be administered the Impression Scale [53] to measure their impression of one another (lower scores indicate a more positive impression of the other person) and the Emotional Response Scale [47] to assess emotional reaction in a specific context on a Likert scale from 1 to 7. These measures will be repeated at T2.

In addition to T1 and T2 assessments, psychological evaluations will also be conducted during the sessions administered to Pt with the Lokomat specifically before and after the first, sixth, and twelfth Lokomat t-RAGT training sessions (respectively SS1, SS6, and SS12). Before starting SS1, SS6, and SS12, the following questionnaires will be administered: (i) Questionnaire on Current Motivation (QCM) [54] for the motivation in using Lokomat, concerning 4 components (Mastery Confidence, Incompetence Fear, Challenge, Interest). The evaluation is on a 7-point Likert scale (from 1 "I completely disagree" to 7 "I completely agree"); (ii) Visual Analogue Scale (VAS) Mood [44] from 0, "very bad mood" to 10, "very good mood" to monitor the Pt's daily mood; (iii) VAS Motivation [44] to assess motivation in performing the session, from 0 "not motivated at all" to 10 "very motivated".

After ending SS1, SS6, and SS12, Pts will answer the following: (i) VAS satisfaction [55] for the satisfaction with the session (from 0 "not satisfied at all" to 10 "very satisfied"); (ii) NASA Task Load Index (NASA-TLX) [56] to measure the perceived workload in using Lokomat, according to different requests (mental demand, physical demand, temporal demand, performance, effort, frustration), on a 0–100 scale. Furthermore, after the conclusion of SS1 and SS12, Consultation and Relational Empathy (CARE) [57] will be administered to the Pt to assess empathy in the context of the Pht-Pt relationship and the Pt's perception of the Phts' interpersonal qualities. The overall score is the sum of the ten items, with 10 being the lowest possible score and 50 the highest, indicating a positive perception of the relation.

Only after SS12, the following questionnaires will be administered to Pts: (i) System Usability Scale (SUS) [42] for the assessment of the usability of the technology with score ranges from 0 to 100, with higher scores indicating greater usability; (ii) Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST 2.0) [58] to assess satisfaction with the Lokomat with a total score that varies between 1 and 5 for each of the analyzed dimensions (satisfaction with the product, service, and overall satisfaction). The user is also asked to specify the three most important aspects of the technology.

### Neurophysiological outcome assessment

For the neurophysiological assessment we designed a specific HD-EEG task to provide a measure to characterize the (potentially) empathic Pht-Pt interaction established along the rehabilitation pathway at the neuro-cognitive level. In this HD-EEG task, Pts in the EXP group will participate in a card game implemented through a PC with their referring Pht, while EEG data will be recorded simultaneously. The Pt and Pht will be introduced to each other for the first time during this task (at T1) which consists of a PC-based card game in which participants are asked to independently choose one of the two cards shown to them. Once both participants have made their choice, the PC randomly draws one of the cards that was shown. The card game involves alternating phases of winning and losing, during which Pts either gain or lose points by choosing or not choosing the card drawn by the PC. The loss of points can be attributed to the responsibility of either the Pt, the Pht, or both, highlighting different levels of personal responsibility. This dynamic allows the exploration of how empathy and personal responsibility developed between both participants during positive events, such as winning, or negative ones such as losing providing a measure to characterize empathic Pht-Pt interaction modulated by responsibility at the neurocognitive level. The EEG task will be repeated at T2 in order to assess the following: (i) any brain-to-brain changes associated to the potential establishment of a therapeutic alliance between Pt and Pht and (ii) eventual between-groups differences in these changes.

At T1 and T2, HD-EEG data will be simultaneously acquired from Pht-Pt by using two EEG systems with 61-channel active electrodes (BrainAmp DC amplifiers, Brain Products GmbH, Germany) positioned according to an extension of the 10–20 International System, with the ground and reference placed on the right and left mastoid respectively. The EEG signals will be recorded at a sampling rate of 250 Hz. An *ad hoc* EEG pre-processing pipeline will be developed to perform three main analyses to investigate the Pht-Pt interaction: (i) event-related potential (ERP) components associated with empathic and personal responsibility processes [59, 60] to explore neural responses related to different phases of winning and losing during the card game; (ii) EEG source localization to extrapolate spectral activation maps to highlight brain areas related to social cognition processes [15]: (iii) multiple-brain connectivity combined with multiple-brain indices quantifying the levels of social interaction between Pht-Pt [19, 23, 26].

### Visual attention outcome assessment

To understand the effect of Pht-Pt interaction on Pt's engagement in terms of visual attention, Eye-Tracking (ET) data will be recorded during the SS1, SS6, and SS12. In fact, ET has proven to be a valuable tool for detecting human emotional and cognitive processes by monitoring eye behaviour [61]. Selected ET metrics for the study of Pts' visual attention during training sessions are fixations and saccades. The fixations are periods of time between 100 and 600 ms during which the eyes are focused on a specific area of interest [62], whereas saccades are fast and accurate ballistic eye movements used to reposition the fovea to a new location in the visual environment [63].

Eye movements will be recorded by using a properly calibrated wearable eye tracker system (Tobii Pro Glasses3, Tobii, Sweden), with a sampling frequency of 50 Hz. ET data will be analyzed by means of the Tobii Pro Lab software (Tobii, Sweden), which allows visualization of the recorded scenes and the extraction of eye-gaze metrics [64] within defined Areas of Interest (AoIs) to assess the Pts' visual attention during the t-RAGT sessions. The ET pipeline analysis will include the following: (i) the segmentation of the data according to the experimental conditions (see *Training sessions* paragraph) and (ii) the definition of three AoIs by importing a snapshot of the Pt's visual field (the Lokomat monitor that provides the visual FB to both Pt and Pht, the Pht's silhouette, and the remaining elements in the field of view, which may act as potential sources of distraction). An automatic assisted mapping approach will then be applied to map the gaze data onto the snapshot, assigning each gaze point to the corresponding AoI for every frame within the designated time window. This approach enables tracking the rehabilitation process across the training sessions, offering an insight into how visual attention can serve as a tool for monitoring Pt adherence to treatment, highlighting potential differences in engagement and attentional focus between the experimental and control groups, which may influence the intervention's effectiveness.

## Sample size

The sample size was calculated using the statistical software STATISTICA 8.0 (StatSoft) and based on the primary hypothesis, claiming that experimental intervention (Lokomat t-RAGT with Chart FB + high Pht-Pt interaction) is superior in improving the primary outcome measures (10MWT and 6MWT) with respect to the control one (Lokomat t-RAGT with Chart FB + low Pht-Pt interaction). Based on preliminary findings [15] in 10MWT as assessed before and after a 1-month Lokomat t-RAGT training (mean ± SD, 0.06 ± 0.08 vs 0.16 ± 0.15), alpha level at 5%, statistical power at 80%, and one-tailed

*t*-test, 18 participants per group are needed. To account for possible loss during the t-RAGT intervention (assuming a drop-out rate = 30%), 25 participants per group will be enrolled in the study.

## Assignment of interventions: allocation

### Sequence generation

The random allocation sequence of individuals with i-SCI to EXP or CTRL groups will be generated by using STATISTICA 8.0 (StatSoft). The allocation sequence will be securely stored at FSL SU.

## Data collection and management

### Data management

A CRF will be designed to accommodate all types and timings of assessments. The CRF will be divided into three sections: (i) The "Baseline and Randomization Section," which encompasses each participant's demographic, neurological and clinical data, along with all information gathered during the screening phase, including the Informed Consent and the allocated randomized treatment. This section will be completed by unblinded personnel; (ii) The "Outcome Section," which excludes any data on the assigned experimental treatment. This section documents all outcome measures collected at T1 and T2, SS1, SS6, and SS12, and it will be completed by the outcome assessors blinded to group allocation; (iii) The "Training Section," which is used to collect data about t-RAGT device parameters selected for each session, or to monitor any protocol deviation (e.g., missed sessions due to intervening illness). This section will be completed by Pht performing t-RAGT and will include the recording and description of any adverse event.

### Confidentiality

Confidentiality and privacy will be managed in strict accordance with Italian National Law. Personal data will be treated with the highest level of confidentiality. Original paper CRFs containing study data will be securely stored at FSL and adhere to all GDPR (EU 2016/679) security regulations and backup protocols as mandated for clinical/medical records. Data entry will be performed using unique participant study codes (pseudoanonymization). Access to all study files will be restricted exclusively to authorized FSL personnel involved in the study.

## Statistical methods

### Primary analysis

Baseline characteristics will be described by summary statistics for each study group. The primary analysis will be performed in per protocol (PP) population on 10MWT and 6MWT changes between T1 and T2. The PP will include all randomized participants who will perform (minimum) 6 training sessions in 1 month up to 12 training sessions in 6 weeks (both EXP and CTRL interventions). A two-way mixed Analysis of Variance (ANOVA) will be used considering as dependent variables the two primary outcomes separately, as within-group factor the time points (two levels: T1, T2) and as between-group factor the groups (two levels: EXP, CTRL). Non-parametric tests will be used as an alternative in the absence of a Gaussian distribution.

### Secondary analyses

In the secondary analyses, the variation from T1 to T2 in secondary outcomes (scores of clinical scales different from 10 and 6MWT, biomechanical, psychological, HD-EEG and visual attention data) will be compared between groups in the PP population. We will adopt the same design implemented for the primary analysis. To investigate a relationship between patients' outcomes and the establishment of a therapeutic alliance as described by inter-brain neurophysiological indices, a correlation between these two categories of variables will be implemented.

## Oversight and monitoring

### Trial monitoring

Database collection within and between EXP and CTRL intervention groups will be monitored and the trial responsible will be alerted if any deviation occurs. Any modifications to the protocol that may impact on the conduction of the study, including changes in study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects, will require a formal amendment to the protocol. Such an amendment will be agreed upon by the principal investigator and approved by the Ethics Committee prior to implementation and notified to the sponsor National Ministry of Health (MoH).

## Dissemination plans

Main results will be subjected to publication in scientific peer-reviewed journals. The results will also be presented at clinical neuroscience and/or bioengineering, neuroengineering and robotics and/or neurorehabilitation conferences. Media and public outreach are planned.

## Discussion

Incomplete subacute or chronic SCI may lead to long-term disability for which effective rehabilitation options are critically needed. INTER-RO-GAIT aims at providing evidence for the optimal Pht-Pt interaction to potentially boost the t-RAGT effects on Pt's performance. This study will generate crucial knowledge for effectively including

gait rehabilitation devices in the SCI neurorehabilitation field, also influencing robotic rehabilitation protocols and devices development even beyond the investigated application (i.e., Lokomat for gait rehabilitation in i-SCI patients). There are several foreseeable limitations and risks endowed in our protocol, some of which are intrinsic to the issue in study. Human social interactions are indeed influenced by a potentially infinite number of variables, that are related, e.g., to personal inclination towards empathy and cooperation. In our specific case, the Pts are also experiencing a major change in their life, and their reaction to the traumatic event may constitute a further unpredictable element in our attempt to experimentally modulate Pht-Pt interaction. Our efforts and strategies to minimize these risks are based on extensive clinical, biomechanical, neuropsychological and neurophysiological evaluations performed by blinded assessors, which will eventually allow us to identify even small differences. Furthermore, we will explore correlations among the different outcome measurements, in order to strengthen their reliability and support the interpretation of our results. At this stage, we do not foresee a follow-up evaluation. The main reason is the small difference imposed in the overall rehabilitation treatment in the two groups (interaction modulation during the t-RAGT, delivered in addition to TAU). Indeed, we expect that the effects of our experimental modulation of patient-therapist interaction during t-RAGT will be strongly related to the t-RAGT sessions. To highlight them, we included many neurophysiological and biomechanical outcome variables along with the clinical scales. Our results will eventually suggest the most relevant ones for a subsequent, larger RCT including a follow-up evaluation.

## Trial status

The protocol described is version CE/PROG.883, dated March 1, 2023. The recruitment started on September 19, 2022. The estimated study completion date is May 2025; indeed, the study is currently ongoing and we are actively recruiting participants among I.R.C.C.S. Fondazione Santa Lucia.

### Abbreviation

| | |
|---|---|
| 10MWT | 10-Meter Walking Test |
| 6MWT | 6-Minute Walking Test |
| AIS | Asia Impairment Scale |
| ANOVA | Analysis of variance |
| AOI | Area of interest |
| BDI-II | Beck Depression Inventory-II |
| BWS | Body weight support |
| CARE | Consultation and relational empathy |
| CRF | Case Report Form |
| CTRL | Control group |
| DERS | Difficulties in Emotion Regulation Scale |
| EEG | Electroencephalography |
| EMG | Electromyography |
| EQ | Empathy quotient |
| ERP | Event-related potential |
| ET | Eye-tracking |
| EXP | Experimental group |
| FB | Feedback |
| FSL | Fondazione Santa Lucia |
| GF | Guidance force |
| GRIT | Short Grit Scale |
| GS | Gait speed |
| HD-EEG | High density EEG |
| INSCI | International Standards for Neurological and Functional Classification |
| IRI | Interpersonal Reactivity Index |
| i-SCI | Incomplete spinal cord injury |
| ISNCSCI | International Standards for Neurological and Functional Classification |
| LEMS | Lower Extremity Motor Score |
| MAS | Modified Ashworth Scale |
| MoCA | Montreal Cognitive Assessment |
| MoH | National Ministry of Health |
| NASA-TLX | NASA Task Load Index |
| NRS | Numeric Rating Scale |
| Pht | Physiotherapist |
| PP | Per protocol |
| PSFS | Penn Spasm Frequency Scale |
| Pt | Patient |
| QCM | Questionnaire on Current Motivation |
| QUEST 2.0 | Quebec User Evaluation of Satisfaction with Assistive Technology |
| RAS | Responsibility Attitude Scale |
| RCT | Randomized controlled trial |
| SCATS | Spinal Cord Assessment Tool for Spastic Reflexes |
| SCI | Spinal cord injury |
| SCIM-III | Spinal Cord Independence Measure III |
| SD | Standard deviation |
| SMS | Self Monitoring Scale |
| SPIRIT | Standard Protocol Items: Recommendations for Interventional Trials |
| SS | Session with Lokomat device |
| STAI-Y | State-Trait Anxiety Inventory-Y form |
| SU | Spinal unit |
| SUS | System Usability Scale |
| TAS-20 | Toronto Alexithymia Scale |
| TAU | Treatment as usual |
| t-RAGT | Treadmill based Robotic Assisted Gait |
| VAS | Visual Analogue Scale |
| WHOQOL | World Health Organization Quality of Life Questionnaire |
| WISCI | Walking Index for Spinal Cord Injury |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-026-09644-0.

Additional file 1: SPIRIT checklist Interrogait.

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### Authors' contributions

FT, JT, and FP lead the study conceptualization, design, and application for funding; F.T. is the grant holder and responsible for the clinical trial; F.T. and G. Scivoletto are responsible for patients' enrollment; F.T., J.P., F.P., D.M., G. Scivoletto, A.C., and M.S. are responsible for data interpretation; JT supervises HD-EEG and ET analyses; NLG supervises the analysis of biomechanical data; F.T., G. Scivoletto, G. Serratore, and G.G. are responsible for t-RAGT sessions and clinical evaluation of patients; S.M. and F.P. are responsible for EEG and ET acquisition and analysis; A.B., A.C., and M.S. are responsible for the acquisition, analysis, and interpretation of psychological data; M.F. and F.D.T. are responsible for the acquisition and analysis of biomechanical data; JT is responsible for

the statistical plan. All authors have provided critical review of the manuscript and have given final approval to this version.

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**Data availability**
Not applicable.

## Declarations

**Competing interests**
The authors declare that they have no competing interests.

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