



Mindful SensoriMotor Therapy combined with brain modulation for the treatment of pain in individuals with disarticulation or nerve injuries: a

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BMJ Open Mindful SensoriMotor Therapy combined with brain modulation for the treatment of pain in individuals with disarticulation or nerve injuries: a single-arm clinical trial

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ABSTRACT

Introduction Neuropathic pain is a complex and demanding medical condition that is often difficult to treat. Regardless of the cause, the impairment, lesion or damage to the nervous system can lead to neuropathic pain, such as phantom limb pain (PLP). No treatment has been found widely effective for PLP, but plasticity-guided therapies have shown the least severe side effects in comparison to pharmacological or surgical interventions. Phantom motor execution (PME) is a plasticity-guided intervention that has shown promising results in alleviating PLP. The potential mechanism underlying the effectiveness of PME can be explained by the Stochastic Entanglement hypothesis for neurogenesis of neuropathic pain resulting from sensorimotor impairment. We have built on this hypothesis to investigate the efficacy of enhancing PME interventions by using phantom motor imagery to facilitate execution and with the addition of sensory training. We refer to this new treatment concept as Mindful SensoriMotor Therapy (MiSMT). In this study, we further complement MiSMT with non-invasive brain modulation, specifically transcranial direct current stimulation (tDCS), for the treatment of neuropathic pain in patients with disarticulation or peripheral nerve injury.

Methods and analysis This single-arm clinical trial investigates the efficacy of MiSMT and tDCS as a treatment of neuropathic pain resulting from highly impaired extremity or peripheral nerve injury in eight participants. The study consists of 12 sessions of MiSMT with anodal tDCS in the motor cortex, pretreatment and post-treatment assessments, and follow-up sessions (up to 6 months). The primary outcome is the change in pain intensity as measured by the Pain Rating Index between the first and last treatment sessions.

Ethics and dissemination The study is performed under the approval of the governing ethical committee in Sweden (approval number 2020-07157) and in accordance with the Declaration of Helsinki.

Trial registration number NCT04897425.

INTRODUCTION

Background and rationale

Neuropathic pain, pain caused by a lesion or disease of the somatosensory nervous

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The experimental treatment allows the inclusion of individuals with highly impaired extremities.
- ⇒ The study includes long-term follow-ups (6 months) to evaluate the clinical impact and to disassociate pain reduction from the effect of distraction.
- ⇒ This study is limited to eight participants to examine the feasibility of the experimental treatment.
- ⇒ The treatment is limited to 12 sessions of a maximum of 2 hours each, which might be insufficient to show long-term pain relief (over 6 months).

system,¹ is a challenging and often intractable complex medical condition.² Injury at any level of the nervous system can lead to neuropathic pain that presents similar characteristics even though its aetiology can differ.³ For instance, individuals with highly impaired extremities may all suffer from neuropathic pain regardless of the cause of impairment.⁴ Treatment of neuropathic pain often entails pharmaceutical, surgical or plasticity-guided interventions.⁵ Pharmaceutical approaches are mostly limited to pain management and they have been found successful at reducing acute pain but are less effective for neuropathic pain that is often chronic.⁶ Plasticity-guided interventions tend to generate the least side effects and have shown promising results in several neurological disorders.^{7–11} However, plasticity-guided approaches are diverse and are not suitable for all the conditions that cause neuropathic pain.

Phantom limb pain (PLP), pain perceived in the phantom limb, is a type of neuropathic pain experienced by the majority of people with limb amputation.^{12 13} A recent systematic review and meta-analysis by Limakatso *et al* estimated the prevalence of PLP at 64%.¹⁴ The pathophysiology of the PLP

phenomenon is not completely understood and it is associated with alterations of the peripheral and central nervous system.^{3 4} Besides that, psychogenic factors such as depression, anxiety and increased stress are counted as PLP triggers.^{15 16}

The evidence for the efficacy of pharmacological therapy for PLP is limited,^{17 18} and surgical approaches have been shown to be effective at treating neuroma pain¹⁹ but do not always alleviate PLP.²⁰ Whereas plasticity-guided approaches are unlikely to reduce PLP due to neuroma (nociceptive input), they have been found effective against PLP,^{17 21} arguably when the neurogenesis is due to maladaptive plasticity.⁴ It has been hypothesised that maladaptive plasticity can arise from the pathological entanglement between pain and sensorimotor neural circuitries after amputation (stochastic entanglement), and that independent activation of the sensorimotor network can weaken the said entanglement resulting in pain relief.⁴ Phantom motor execution (PME), a plasticity-guided intervention with theoretical basis on the stochastic entanglement hypothesis,⁴ has shown promising results in the treatment of PLP in a case study,⁷ and statistically and clinically significant improvement (~50% pain reduction) in a single-arm clinical trial in patients with chronic and intractable PLP.⁸ In the said clinical trial, it was also observed a significant reduction (~50%) in the intrusion of pain in sleep and activities of daily living. Furthermore, an international randomised controlled clinical trial is currently underway to further validate its efficacy.²²

PME requires patients to execute movements with their phantom limbs (phantom limb movement), as opposed to simply imagining the movement (phantom motor imagery). This treatment can be facilitated by myoelectric pattern recognition (MPR) to decode phantom motor volition, while real-time visual feedback is provided in virtual environments.⁷ Worthy of notice is that functional muscles in the residual limb are necessary for MPR to decode phantom movements, and therefore, it is difficult to use this technology in patients with shoulder or hip disarticulation, or patients with peripheral nerve injuries depriving of motor function. This is because having voluntary control of muscles in the residual limb is a requirement for MPR. Nevertheless, the PME concept can still be used in such patient population by clearly instructing the patient to execute phantom limb movements. Worthy of notice is that although distal phantom movements cannot be verified using PMR in patients with disarticulations and nerve injuries because of the lack of relevant myoelectric sources (eg, hand close in a shoulder disarticulation), the most proximal phantom movements can still be inferred from available and viable muscles (eg, arm abduction in a shoulder disarticulation using the MPR on the supraspinatus, deltoid and/or serratus anterior muscles), and thus there is often phantom movements that can be verified, whereas others cannot.

In cases where movement execution is not feasible (eg, frozen phantom), patients can start by performing

imaginary movements until control over the phantom is regained. Motor execution and imagery activate similar neural resources,^{23 24} and we can use motor imagery as a way to ease a 'frozen' phantom limb into a moving one (responding to motor execution).

We hypothesise that the effectiveness of PME can be increased by integrating motor imagery and sensory training (ie, increasing sensory acuity), both enabling the engagement of a larger portion of the neural networks affected by the amputation or nerve injury.^{4 25 26} Hereafter, we refer to this approach as Mindful SensoriMotor Therapy (MiSMT). Furthermore, the recruitment of sensorimotor neural circuitry during MiSMT can be facilitated by non-invasive brain modulation.^{27 28} It has been shown that the outcomes of MPR can be improved by transcranial direct current stimulation (tDCS),^{29 30} and therefore, it has been hypothesised that this should enhance the effectiveness of PME,⁴ and by extension MiSMT.

The purpose of this single-arm clinical trial is to investigate the efficacy of MiSMT enhanced by brain modulation (tDCS) as a treatment for chronic neuropathic pain in a population of patients who do not meet the inclusion criteria for conventional MPR (eg, nerve injuries or disarticulations). MiSMT will be applied using non-invasive devices and with minimal side effects.^{8 31} We will evaluate the efficacy of the intervention based on the difference in pain using the Pain Rating Index (PRI)³² pretreatment and post-treatment in eight participants with disarticulations or peripheral nerve injuries. We are studying this patient population as they share the lack of control and sensory perception of an absent or severely impaired limb, and thus the underlying cause of their pain can be attributed to this common factor. In addition, we will explore other consequences of the treatment such as sensory acuity.

OBJECTIVES

We present the protocol for a single-arm clinical investigation for a new treatment for neuropathic pain due to highly impaired or absent extremities. The primary and secondary objectives are to evaluate the difference in the participant's PRI and whether the treatment improves the participation quality of life pretreatment and post-treatment, respectively. The latter will be done by comparing each participant's EuroQoL-5D-5L (EQ-5D-5L).³³

Trial design

This study is a single-arm clinical trial in which all participants will receive the same treatment. The study will be conducted by the Center for Bionics and Pain Research, which is a collaboration between Chalmers University of Technology, Sahlgrenska University Hospital and the Sahlgrenska Academy at the University of Gothenburg, all in Sweden. The study is expected to be performed from January 2023 to January 2024. A flow chart of the study is introduced below and summarised in [table 1](#).

Table 1 Flowchart

Visit	Screening visit 0	Baseline assessments	Intervention visit 1	Intervention visits 2–11	Intervention visit 12	Post-treatment assessments	Follow-ups, 3 visits
Time span (weeks)	0	0–10	2–12	2–21	4–24	5–25	8–50
Study milestones							
Informed consent form	X						
Inclusion/exclusion criteria*	X						
Medical history	X						
Treatment start			X				
Treatment end					X		
Study end†							X
Assessments							
Questionnaires		X	X	X	X	X	X
Functional assessments		X		X‡		X	
Semistructured interview						X	

*Not all tasks at each visit and includes minor functional evaluation required for determining whether inclusion criteria are fulfilled.

†Study ends after the last long-term follow-up visit (up to 6 months/24 weeks after last treatment visit).

‡Functional assessments at the end of visit 6.

Screening visit

Participants will attend the screening visit to determine their suitability for participation as per inclusion/exclusion criteria. In this visit, participants will be requested to choose the frequency of treatment (once per week, twice per week or daily on working days), which once selected, must be kept for the entire treatment.

Baseline assessments

Baseline assessments will be performed as described in the Outcomes section in up to five sessions about 2 weeks prior to treatment.

Treatment period

The treatment will be provided in 12 sessions, each for 2 hours, over a maximum period of 6 months. Depending on the participant's availability, the treatment regimen will be between one and five sessions per week.

Post-treatment assessments

Participants will take part in a post-treatment assessment, up to five sessions, within 2 weeks of the last session.

Follow-ups

Participants will be followed up for up to 6 months after the last treatment and will be invited to participate in a maximum of three follow-up visits.

METHODS: PARTICIPANTS, TREATMENTS AND OUTCOMES

Patient and public involvement statement

Potential participants are identified by healthcare professionals or had contact with the principal investigator of

the study. Interested participants are notified of the study and invited to participate in a screening visit.

Eligibility criteria

Potential participants take part in a screening visit to assess their eligibility. The study is described to the person and any questions are answered. In addition, the potential participant is informed that he/she may withdraw their participation in the study at any time without any consequence. If they decide to participate, they are asked to sign the informed consent form and provided with a copy. The following are the eligibility criteria:

- ▶ Participants must be older than 18 years.
- ▶ The participant has provided written informed consent to participate.
- ▶ The participant must have chronic neuropathic pain ≥ 5 NRS (Numeric Rating Scale) (mentioned in their medical history and longer than 6 months) due to sensorimotor impairment (eg, PLP).
- ▶ At least 6 months should have passed since the date of injury (to avoid including acute pain).
- ▶ If the participant is under pharmacological treatments, there must be no variations in the medication dosages (steady consumption) for at least 1 month prior to inclusion.
- ▶ If the participant has previously been treated for neuropathic pain, the last session of that/those treatment(s) must be at least 3 months before inclusion.
- ▶ No pain reduction potentially related to previous pain treatments must have been observed for at least 3 months prior to the screening visit, as reported by the participant.

- ▶ In the case of having a prosthesis, the participant must be in a stable prosthetic situation (ie, satisfied with the fitting of the prosthesis).
- ▶ Participants must be able to perceive haptic stimulation near the injury or amputation at the time of the screening visit.
- ▶ Participants must not experience painful sensations from haptic stimulation (ie, allodynia).
- ▶ The participant has sufficient understanding of Swedish or English to be able to participate in all study assessments.
- ▶ Participants should not have any other condition or symptoms that can prevent them from participating in the study, that is, limited movement capability or cognitive impairment in the researcher's opinion.
- ▶ The participant should not have mental inability, reluctance or language difficulties that result in difficulty understanding the meaning of study participation.

The researcher can at any time terminate the study for a participant due to safety concerns or because the participant does not pursue procedures as planned.

Intervention

The intervention aims to re-engage the motor and sensory circuitry previously used to control the affected limb.⁴ We aim to accomplish this by exposing the patients to exercises to train predominantly motor control or sensory acuity, as well as exercises in which both are combined. The intervention uses two wearable devices: a sensorimotor training device, an in-house developed device (figure 1) which enables myoelectric acquisition system and mechanosensory stimulation³⁴ (ie, including actuators to provide touch and vibration feedback), and a tDCS device for neuromodulation. The latter (neuromodulation) is used to facilitate the former (sensorimotor training). Excluding the first intervention session, each session is up to 3 hours, comprising of system setup, breaks and a blinded outcome assessment. A schematic



Figure 1 Sensorimotor training device: a myoelectric acquisition system with two grids (vibrotactile display) to produce mechanosensory stimulation.

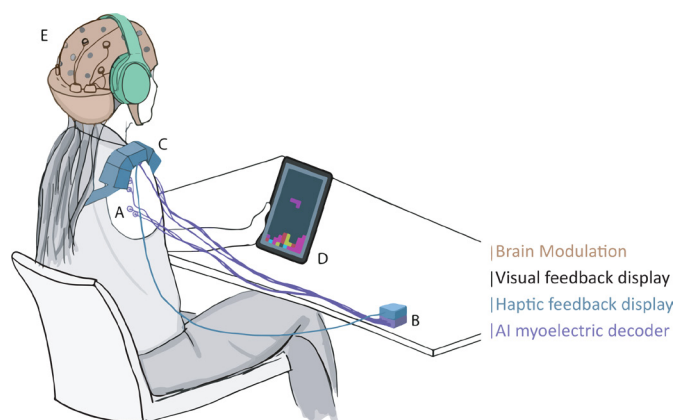


Figure 2 Schematic illustration of the setup used in a participant with amputation and nerve injury (eg, brachial plexus injury). Myoelectric signals are recorded through surface electrodes (A) and decoded by a myoelectric pattern recognition decoder (B). The acquired signals are processed by a custom software. A user-interface is displayed on a screen providing the participant with instructions and virtual environment related to the therapy. Tactile (C) and/or visual (D) feedback is perceived as a response to the movement. Concurrent to performing the training, the brain modulation is used by a transcranial direct current stimulation system (E).

illustration of the setup employed in this clinical investigation used by an elbow disarticulation participant is shown in figure 2.

Intervention session

Each intervention session consists of the following steps (figure 3):

1. Assessment

- a. Pain questionnaire (Numeric Rating Scale).

2. Preparation

- a. Positioning of the participant in a comfortable sitting position for training.
- b. Placement of the surface myoelectric electrodes over the neighbouring musculature to decode the volition of proximal movements (eg, figure 2A and figure 2B).
- c. Positioning of the sensorimotor training wearable device over the neighbouring musculature (eg, figure 2C) and the screen at an appropriate height (figure 2D).
- d. Placement of the brain modulation cap (eg, figure 2E).

3. Treatment modalities

Three training modalities are performed during each session (figure 4). The time dedicated to each modality is divided according to the individual's progress. During the first few sessions, the proportion of motor training and sensory training modules is larger, and later, while it will be shifted towards more complex and challenging tasks, the proportion of sensorimotor module increases.

- a. *Phantom motor training*, consisting of a few repetitions of the following cycle for each movement:
 - i. Movement recording session.
 - ii. Motor training in virtual reality (VR).
 - iii. Movement practice, practising the selected in movements in VR.

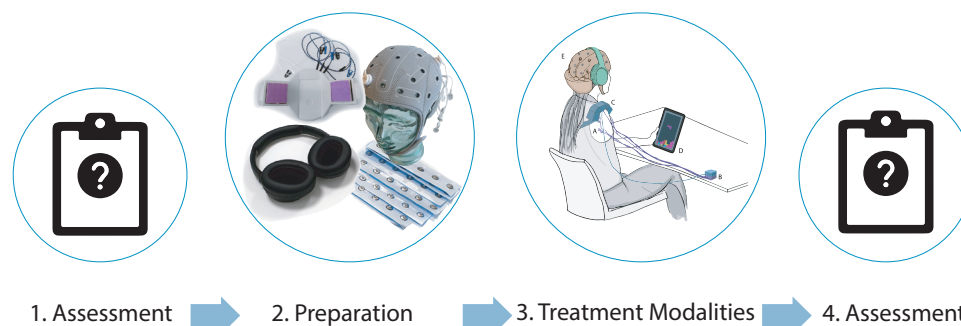


Figure 3 Steps of each intervention session.

- iv. Motor task, matching random target postures of a virtual arm.
- v. Serious games, using phantom movements to control games, for example, SpaceShip (figure 5).

A phantom motor training cycle for a specific set is shown in figure 5.

- b. *Sensory training*, which consists of the following:
 - i. Demonstration of the applied stimulation.
 - ii. Serious games using tactile stimulation: multiple choice, find matches, similar or different and vibration scale.

A sensory training session is shown in figure 6.

- c. *Sensorimotor training*, consisting of the following:
 - i. Movements recording session.
 - ii. Serious gaming (based on motor training and sensory training games) using phantom movements, visual and tactile feedback.

Concurrent to performing motor, sensory and sensorimotor training, the participant receives anodal tDCS over the sensorimotor cortex (S1/M1) with an intensity of 2 mA^{27 28 35} for 15 min at the beginning of each modality.

4. Assessments

- a. Questionnaire for PLP (Q-PLP); described in the Outcomes section.

Progression of the training modalities (levels of difficulty)

The level of difficulty is gradually increased by the therapist (ie, an instructed researcher) during the treatment period to challenge the participants according to their capability. The consistent challenge to fully focus on motor control and/or sensory perception is why the therapy is deemed as 'mindful'. The level of difficulty is gradually increased as follows:

Motor training

The level of difficulty is increased by increasing the number of degree of freedom (df) and moving from

movement imagination to execution. The participant starts the training with 1 df, for example, knee flex/extend, then multiple degrees, for example, knee flex/extend and ankle inversion/eversion but not simultaneously, and later advances to simultaneous movements involving at least 2 df, for example, knee flex/extend and ankle inversion/eversion simultaneously. Concurrently, the transition from movement imagination to execution is based on the reported difficulty of execution.

Sensory training

The level of difficulty is increased by reducing the difference between the stimuli delivered using the tactile displays (eg, activation of actuators at different locations such as the further they are away from each other, the easier they are to discriminate; by the number of activated actuators such as one vs all; or by the shapes created using the different actuators such as an 'x' vs '+'), and mixing different stimulation modalities (eg, vibration or sustained touch) or illusions of direction (eg, serial activation of actuators column by column to create the perception of direction left-to-right or right-to-left, or row by row for top-to-bottom or bottom-to-top).

Sensorimotor training

The level of difficulty is increased through a combination of motor and sensory difficulty levels. The therapist increases the level of difficulty gradually and returns to the previous level if the participant cannot achieve the new tasks.

Outcomes

Following the schedule presented in table 2, the therapist (T) conducts the interventions, and the evaluator (E) registers the outcomes.

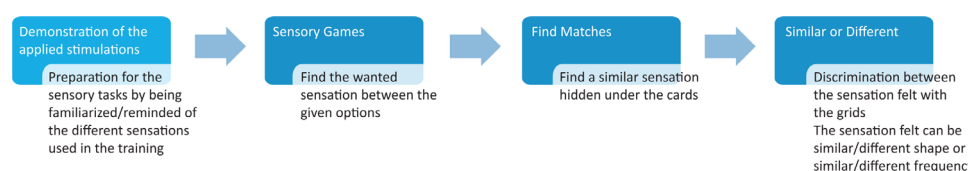


Figure 4 Before starting the treatment modalities, the preliminary plan is finalised with the patient. Based on that, the phantom motor training, sensory training and sensorimotor training modalities will be performed.

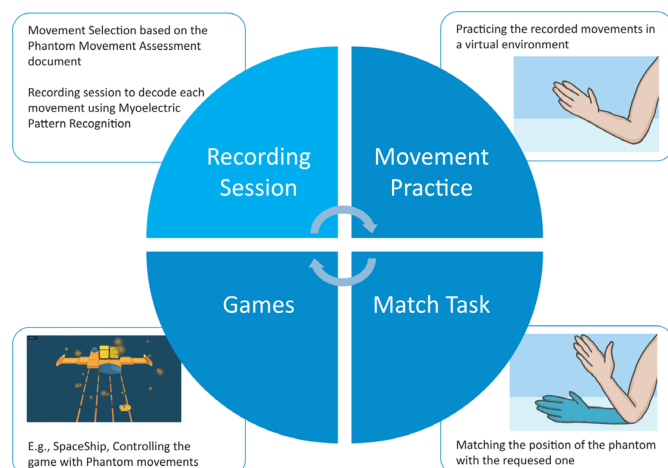


Figure 5 Phantom motor training is intended to regain the control over the phantom movement by practising different movements in virtual reality environments, such as an environment for movement practice, match task and serious games.

Primary outcome: Pain Rating Index (PRI)

The primary outcome, PRI, measures the changes in PLP before and after treatment and is calculated as the sum of the values for all the descriptors of the Short Form of the McGill Pain Questionnaire. In this study, the PRI is included in the Questionnaire for PLP (Q-PLP), described later in this section.

Secondary outcome: EuroQoL-5D-5L (EQ-5D-5L)

EQ-5D-5L is a questionnaire to measure health-related quality of life by evaluating the health conditions.³³ Health conditions regards to five items of mobility, self-care, usual activities, pain/discomfort and anxiety/depression, where each item is scored from 0 to 5. Health

Demonstration of the applied stimulations

- Preparation for the sensory tasks by being familiarized/reminded of the different sensations used in the training

Multiple Choice

- Find the wanted sensation between the given choices

Find Matches

- Find a similar sensation hidden under the cards

Similar Different

- Discrimination between the sensation felt with the grids
- The sensation felt can be similar/different shape or similar/different frequency

Vibration Scale

- Find the given vibration between the available options

Figure 6 Sensory training starts with a demonstration of the applied sensations and continues with serious games such as multiple choice, find matches similar or different, and vibration scale.

Table 2 Summary of the different actions occurring in different visits

Session	Actions occurring in different visits
Screening visit	<ul style="list-style-type: none"> ► Medical history (T) ► Study consent (T) ► Assessment of inclusion criteria (T)
Baseline assessments	<ul style="list-style-type: none"> ► Questionnaires: Q-PLP, EQ-5D-5L, PDI, PMA, PSEQ-2, PCS-6, PHQ-2, Expect-SF (E) ► Functional assessments (E)
Intervention visit 1	<ul style="list-style-type: none"> ► Intervention (T) ► Questionnaires: NRS, Q-PLP (E)
Intervention visits 2 to visit 11	<ul style="list-style-type: none"> ► Intervention (T) ► Functional assessments (E) ► Questionnaires: NRS, Q-PLP, PMA (E)
Intervention visit 12	<ul style="list-style-type: none"> ► Intervention (T) ► Questionnaires: NRS, Q-PLP, PDI, EQ-5D-5L, PSEQ-2, PCS-SF, PHQ-2 (E) ► Functional assessments (E)
Post-treatment assessments	<ul style="list-style-type: none"> ► Questionnaires: NRS, Q-PLP, PDI, PMA, EQ-5D-5L, PSEQ-2, PCS-SF, PHQ-2 (E) ► Functional assessments (E)
Follow-ups, at 1, 3 and 6 months after the last intervention	<ul style="list-style-type: none"> ► Questionnaires: NRS, Q-PLP, PDI, EQ-5D-5L, PSEQ-2, PCS-SF, PHQ-2 (E)

The remaining abbreviations are described in the text after the table. The informed consent form and all the questionnaires are available in both English and Swedish.
 E, Evaluator; EQ-5D-5L, EuroQoL-5D-5L; NRS, Numeric Rating Scale; PCS-6, Pain Catastrophizing Scale-6; PCS-SF, Pain Catastrophizing Scale Short Form; PDI, Pain Disability Index; PHQ-2, Patient Health Questionnaire-2; PMA, Phantom Movement Assessment; PSEQ-2, Pain Self-Efficacy Questionnaire-2; Q-PLP, Questionnaire for PLP; T, Therapist.

evaluation section of the questionnaire measures the best health condition that the participant can imagine on a scale of 0 to 100, with 0 as the worst and 100 as the best.

Participant's medical history

The medical history is collected to determine factors related to PLP and its aetiology. This information includes type and time of amputation, previous treatments for pain, medications, and comorbidities.

Pain Disability Index (PDI)

PDI consists of seven items measuring the aspects of life affected by pain.³⁶ PDI value is computed by the sum of the values of all items.

In addition to the primary and secondary outcomes, the study also includes the following outcomes:

Numeric Rating Scale (NRS)

This is a one-item questionnaire scaled from 0 to 10 to measure the pain every intervention.

Questionnaire for PLP tracking (Q-PLP)

This is a questionnaire based on the short version of the McGill Pain Questionnaire (SF-MPQ)³⁷ to investigate components of PLP. Q-PLP also includes specific questions that have been modified to fit the study population, as well as additional relevant questions. Taken together, the Q-PLP includes questions addressing the intensity, quality, duration and frequency of pain, as well as intrusion of pain in sleep, work and activities of daily living.^{7 8 22}

Phantom Movement Assessment (PMA)

Assessment based on Movement Imagery Questionnaire-Revised Second version³⁸ to evaluate the ability to imagine or execute a specific movement on a scale from 0 to 10; frozen to fluid movement.

Pain Self-Efficacy Questionnaire (PSEQ-2)

PSEQ-2 is a survey with two questions to measure self-efficacy regarding the ability to perform activities in individuals with chronic pain, on a scale from 0 to 6.³⁹

Pain Catastrophizing Scale-6 (PCS-6)

This is a six-item questionnaire to measure catastrophising thinking on a scale from 0 to 4.^{40 41}

Patient Health Questionnaire-2 (PHQ-2)

This is a two-item questionnaire to assess the existence of a depressed mood and loss of interest in daily activities.⁴² Each item is scored from 0 to 3.

Patients' Global Impression of Change (PGIC) scale

This is a one-item questionnaire assessed after receiving the treatment to measure the participant's belief about the efficacy of the treatment, on a scale from 0 to 7.⁴³

Short Form of the EXPECT Questionnaire (EXPECT-SF)

This is a questionnaire to evaluate the effects that the treatment may have on the participant's pain and how the pain might impact their life. Each question relates to the expected results at the end of the treatment period.

Opinion About Treatment (OAT)

This is a three-item questionnaire with regard to the participant's opinion about the treatment.

Functional assessments

Functional assessments are performed to investigate changes in sensory and motor function before and after our intervention.

- ▶ *Sensory acuity.* The Semmes-Weinstein monofilament test and the two-point discrimination test^{44 45} are used to assess tactile sensitivity by measuring the ability to discriminate pressure at a single point of contact and the minimal distance between two points of contact, respectively. The tests are performed on the stimulated areas (underneath the two vibrotactile grids) and the area in between as a control.
- ▶ *Affected and intact limb movement.* Affected limb movement is assessed by executing movements at different joints and/or parts of the affected limb depending on

the level of amputation or the injured nerves. In case of amputation, participants are asked to imitate movements by their intact limb. The changes in the range of motion pretreatment and post-treatment are measured by using an adapted motion capture system for upper limb and a goniometer for lower limb.

Semistructured qualitative interviews

Participants are asked to participate in brief, semistructured interviews that aim to more deeply understand how they have experienced the treatment and how it has affected their quality of life in general. Interviews are recorded and transcribed, then coded and categorised into themes for analysis, as described by Malterud.⁴⁶ Interviews will be performed in Swedish or English and, if necessary, translated into English for analysis.

Sample size

The sample size was calculated using the primary outcome (PRI) of a previous study on PME for treatment of PLP.⁸ Eight participants were deemed necessary for a power of 80% and an alpha value of 5%. No dropouts are expected. In case that participants miss a visit or an assessment, missing values will not be included in statistical analyses.

METHODS: DATA COLLECTION, MANAGEMENT, MONITORING AND ANALYSIS

Data collection and management

The data collected in this study include images, video recordings, assessments results and numerical values. Data obtained within this project are confidential and stored digitally in accordance with the European General Data Protection Regulation requirements, on a password-protected computer with restricted access. The data are pseudonymised with a code consisting of two letters and three digits. All collected data are assigned a code, and the document which relates the identity of the participant to their unique code is password-protected and saved separately. Once the data collection is accomplished, the deidentified and password-protected database is prepared to be processed and analysed.

Images and video recordings are only shared with the written consent of the participant. Participants can choose whether images for scientific presentations have their faces blurred or cropped out, and whether they can be shared in scientific publications, for teaching and research purposes, and/or on social media for research promotion.

The principal investigator, MO-C, is responsible for granting data accessibility to the researchers directly involved in the study. Deidentified data may be made available on reasonable request and as part of publications in peer-reviewed journals. Data will be stored for at least 10 years after study completion, or as required by law.

Data monitoring

Compliance with this clinical protocol will be assured by a monitor independent to this study before, during and after the execution of this clinical trial. The monitor ensures that the study is carried out according to this research plan and that data are collected, documented and reported according to International Conference on Harmonisation-Good Clinical Practice and applicable ethical and regulatory requirements.

Analysis

Statistical analyses of the primary and secondary outcomes will be performed regarding changes in measurement pretreatment and post-treatment. Analyses will be conducted within participant and between participants for descriptive purposes of mean, median, absolute value, SD, range and 95% CIs for means and proportions.

Statistical significance will be calculated with Wilcoxon signed-rank test, at $p < 0.05$. Furthermore, in case of changes in the occurrence of each quality of pain, the sign test for those qualities pretreatment and post-treatment with exact binomial probabilities will be used. For the sign test, the statistical significance will be considered at $p < 0.05$.

The results of the analyses will be presented in the form of graphical and numerical summaries where applicable. Moreover, a comprehensive statistical analysis plan will be written before completion of the analyses. The principal investigator, MO-C, takes responsibility for assuring the accuracy and quality of the data analysis process.

Adverse events

Tiredness and muscle soreness can be experienced after motor training. The disposable electrodes used to record myoelectric signals might cause temporary skin irritations, and when necessary, these can be replaced by electrodes for sensitive skin. We do not anticipate adverse events due to sensory training as the device employed is placed over the skin with limited pressure and it is low power (the levels of stimulation are too low to cause discomfort or pain). Brain modulation will be applied using a commercially available tDCS system (Neuroelectrics Startstim tES-EEG system). tDCS has been reported to cause discomfort and skin redness in the site of stimulation. No serious adverse effects have been associated with tDCS use.³¹

ETHICS AND DISSEMINATION

Research ethics approval

This clinical trial is conducted in agreement with the Declaration of Helsinki and is approved with the approval number 2020-07157 by Etikprövningsmyndigheten (Lund adelning 2 medicin).

Protocol amendments

Prior to applying any modification to the study protocol, the ethical committee will be informed to obtain ethical approval in form of an amendment to the study.

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Competing interests MO-C and MB have filed a patent (PCT/SE2022/050148) for technology to deliver haptic feedback and decode motor volition.

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