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Mindful SensoriMotor Therapy with Brain Modulation for the Treatment of Pain in Individuals with Disarticulation or Nerve Injuries: A Single-arm clinical trial

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Method Article

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Abstract

Neuropathic pain is a complex and demanding medical condition that is often difficult to treat. Regardless the cause of impairment, lesion or damage of the nervous system can lead to neuropathic pain, such as Phantom Limb Pain (PLP). No treatment has been found widely effective for PLP but guided plasticity therapies have shown the least severe side effects in comparison to pharmacological or surgical interventions. Phantom Motor Execution (PME) is a guided-plasticity intervention that has shown promising results alleviating PLP. The Stochastic Entanglement hypothesis suggests an origin for neuropathic pain resulting from sensorimotor impairment. In this study we build on this hypothesis to investigate the efficacy of enhancing PME interventions with the addition of sensory training. We refer to this concept as Mindful SensoriMotor Therapy (MiSMT), that in this study we further complement with non-invasive brain modulation, specifically transcranial Direct Current Stimulation (tDCS), for the treatment of neuropathic pain because of disarticulation or peripheral nerve injury.

Methods and analysis

This single-arm clinical trial investigates the efficacy 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 15 sessions of MiSMT with anodal tDCS in the motor cortex, pre- and post-treatment assessments, and follow-up sessions. The primary outcome is the change in pain intensity using the Pain Rating Index between the first and last session.

Ethics and dissemination

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

Trial Registration Number NCT04897425

Strengths And Limitations Of This Study

- Study in participants for whom conventional treatments are usually not applicable.
- Long-term follow-up (six months) will help to evaluate the effect of distraction in pain reduction.
- The results of this study will be the basis for a larger randomized controlled clinical trial.
- Proof-of-concept limited to eight participants.
- The treatment is limited to 15 sessions of a maximum of three hours each, which might be insufficient to show long-term (> six months) pain relief.

Introduction

Background and rationale

Neuropathic pain is a challenging and often intractable complex medical condition [1]. Injury at any level of the nervous system can lead to neuropathic pain that presents similar characteristics even though its etiology can differ [2]. For instance, individuals with highly impaired extremities may all suffer from neuropathic pain despite the cause of impairment [3]. Treatment of neuropathic pain often entails pharmaceutical, surgical, or plasticity-guided interventions [4]. Guided plasticity interventions tend to generate the least side effects and have shown promising results in several neurological disorders [5]–[7]. However, guided plasticity approaches are diverse and are not suitable to all conditions that cause neuropathic pain.

Phantom Limb Pain (PLP) is one type of neuropathic pain experienced by the majority of people with limb amputation [8], [9]. Phantom Motor Execution (PME), a guided plasticity intervention, has shown promising results in the treatment of PLP [5], [6], and an international randomized controlled clinical trial is currently underway to further validate its efficacy [7]. PME has been facilitated by Myoelectric Pattern Recognition (MPR) to decode phantom limb motor volition while real-time visual feedback is provided in virtual environments. Worthy of notice is that stump musculature is necessary to decode distal movements and therefore the technology used to facilitate PME cannot be used in patients with shoulder or hip disarticulation, nor in nerve injuries depriving from motor function. Nevertheless, the PME concept can still be used in such patient population by clearly instructing the patient to execute distal movements rather than just imagining them [3]. In addition, the effectiveness of PME can be increased by including sensory training, as this would engage a larger portion of the affected neural networks [3]. 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 [10], [11]. It has been shown that the outcomes of MPR can be improved by transcranial direct current stimulation (tDCS) [12], and therefore it has been hypothesized that this should enhance the effectiveness of PME [3], 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. MiSMT will be applied using non-invasive devices and with minimal side effects [6], [13]. We will evaluate the efficacy of the intervention based on the difference in pain using the Pain Rating Index, PRI [14], pre- and post-treatment in eight participants with disarticulations or peripheral nerve injuries. In addition, we will explore other consequences of the treatment such as brain plasticity and sensory acuity.

Objectives

We present the protocol for a single-arm clinical investigation for a new treatment for pain due to highly impaired extremities. The primary objective is to evaluate the difference in the participant's PRI pre- and post- treatment. The secondary objective is to evaluate whether the treatment improves the participation in activities of daily living. This will be done by comparing each participant's Pain Disability Index (PDI) [15] pre- and post- treatment.

Trial design

This study is a single-arm, clinical trial in which all participants receive the same treatment. The study is conducted at 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, Sweden. The study is expected to be finalized within a year. A flow chart of the study is introduced below and summarized in Table 1.

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

Baseline assessments. Baseline assessments are performed as described in the outcome section on up to five sessions about two weeks prior to treatment.

Treatment period. The treatment is provided in 15 sessions over a maximum period of six months. The treatment regimen is between one to five sessions per week.

Post treatment assessments. Participants take part in a post treatment assessment, up to five sessions, within two weeks of the last session.

Follow-ups. Participants are followed-up for up to six months after the last treatment and invited to participate in a maximum of three follow-up visits.

Table 1
Flow Chart

Visit	Screening visit 0	Baseline assessments *	Intervention visit 1	Intervention visits 2–14	Intervention visit 15	Post treatment assessments*	Follow-ups, 3 visits
Timespan (weeks)	0	0–10	2–12	2–23	4–24	5–26	8–50
	STUDY MILESTONES						
Informed consent form	X						
Incl/excl criteria**	X						
Medical history	X						
Treatment start			X				
Treatment end					X		
Study end***							X
	ASSESSMENTS						
Questionnaires		X	X	X	X	X	X
Imaging assessments		X (EEG, fMRI)	X (EEG)	X (EEG)	X (EEG)	X (EEG, fMRI)	X (EEG, fMRI)
Functional assessments		X		X		X	X
Semi-structured interview							X

EEG: Electroencephalography; fMRI: functional Magnetic Resonance Imaging.

*Not all tasks at each visit

**Including minor functional evaluation required for determining whether inclusion criteria are fulfilled.

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

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 is 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 due to sensorimotor impairment (for instance PLP).
- At least six 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 one-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 three months before inclusion.
- No pain reduction potentially related to previous pain treatments must have been observed for at least three months prior the screening visit, as reported by the participant.
- In the case of having a prosthesis, the participant must be in a stable prosthetic situation (*i.e.*, 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 (i.e., 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 to the study, 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 participant should not have any condition associated with risk of poor protocol compliance.

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 uses two wearable devices: a myoelectric acquisition system with mechanosensory stimulation capabilities [16] (*i.e.*, including actuators for haptic feedback), and a tDCS device for neuromodulation. Excluding the first intervention session, each session is up to three hours comprising of system setup, breaks, and a blinded outcome assessment. A schematic illustration of the setup employed in this clinical investigation used by an elbow disarticulation participant is shown in Figure 1.

Intervention session

Each intervention session, excluding first and last sessions, consist of:

1. Assessment

1a. Pain questionnaire (numeric rating scale)

2. Preparation

2a. Positioning of the participant in a comfortable sitting position for training

2b. Placement of the surface myoelectric electrodes

2c. Positioning of the haptic feedback wearable device

2d. Placement of the brain modulation cap

3. Treatment modalities

Three training modalities are performed during each session. The time dedicated to each modality is equally divided.

3a. Motor training, consisting of:

a. Movement recording session

b. Motor training in Virtual Reality (VR)

c. Motor training by matching random target postures of a virtual arm

d. Serious gaming using visual feedback

3b. Sensory training, consisting of:

a. Haptic feedback discrimination tasks

b. Serious gaming using haptic feedback

3c. Sensorimotor training, consisting of:

a. Movements recording session
b. Motor training in VR
c. Serious gaming using phantom movements, visual, and haptic feedback

Concurrent to performing motor, sensory, and sensorimotor training, the participant receives anodal tDCS over sensorimotor cortex (S1 / M1) with an intensity of 2 mA [10], [11] for 15 minutes at the beginning of each modality.

4. Assessments

4a. Questionnaire for PLP Tracking (Q-PLPT); described in the Outcomes section

Level of difficulty of the training modalities

The level of difficulty is gradually increased by the therapist (*i.e.*, an instructed researcher) during the treatment period to challenge the participant 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:

a) Motor training

The level of difficulty is increased by increasing the number of degrees of freedom. The participant starts the training with one degree of freedom, then multiple degrees, and later advances to simultaneous movements involving at least two degrees of freedom.

b) Sensory training

Level of difficulty is increased using different actuators for haptic feedback and mixing different perceptions, directions, and moving from gross to fine perception tasks.

c) Sensorimotor training

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.

Table 2 Summary of the different actions occurring in different visits. T = Therapist, E = Evaluator.

Session	Actions occurring in different visits
Screening visit	• Medical history (T) • Study Consent (T)
Baseline assessments	• Questionnaires: Q-PLPT, EQ-5D-5L, PDI, PSEQ-2, PCS-06, PHQ-2, Expect-SF (E) • Brain imaging assessments: fMRI and EEG (T)
Intervention visit 1	• Intervention (T) • Functional Assessments (E) • Questionnaires: NRS, Q-PLPT, OAT (E) • Brain imaging assessment: EEG (T)
Intervention visits 2 to visit 14	• Intervention (T) • Functional Assessments (E) • · Questionnaires: NRS, Q-PLPT (E) • Imaging assessment: EEG (T)
Intervention visit 15	• Intervention (T) • Functional Assessments (E) • Questionnaires: NRS, Q-PLPT, PDI, EQ5D-5L, PSEQ-2, PCS-SF, PHQ-2 (E) • Imaging assessment: EEG (T)
Post treatment assessments	• Functional Assessments (E) • Questionnaires: NRS, Q-PLPT, PDI, EQ5D-5L, PSEQ-2, PCS-SF, PHQ-2 (E) • Imaging assessments: fMRI and EEG (T/E)
Follow-ups, at 1, 3, and 6 months after the last intervention	• Functional Assessments (E) • Questionnaires: NRS, Q-PLPT, PDI, EQ5D-5L, PSEQ-2, PCS-SF, PHQ-2 (E)

Primary outcome: Pain Rating Index (PRI)

The primary outcome, PRI measures the changes in PLP before and after treatment and is calculated as 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 Tracking (Q-PLPT), described later in this section.

Secondary outcome: Pain Disability Index (PDI)

PDI consists of seven items measuring the aspects of life affected by pain [15]. PDI value is computed by sum of the values of all items.

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

Participant's medical history

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

Numeric Rating Scale (NRS)

This is a one item questionnaire scaled from zero to ten to measure the pain every intervention.

Questionnaire for PLP Tracking (Q-PLPT)

Questionnaire based on the short version of the McGill Pain Questionnaire (SF-MPQ) [17] to investigate components of PLP. Q-PLPT also includes specific questions that have been modified to fit the study population, as well as additional relevant questions. Taken together, the Q-PLPT includes questions addressing the intensity, quality, duration, and frequency of pain, as well as intrusion of pain in sleep, and how the participant perceives pain [14], [18]–[20].

EuroQoL-5D-5L (EQ-5D-5L)

Questionnaire to measure health-related quality of life by evaluating the health conditions[21]. Health conditions regards to five-items of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression where each item is scored from zero to five. Health evaluation section of the questionnaire measures the best health condition that the participant can imagine on scale of hundred with zero as the worst and hundred as the best.

Pain Self-Efficacy Questionnaire (PSEQ-2)

PSEQ-2 is a survey with two questions to measure self-efficacy regarding ability to perform activities in individuals with chronic pain, on a scale from zero to six [22].

Pain Catastrophizing scale-6 (PCS-6)

Six-item questionnaire to measure catastrophizing thinking on a scale from zero to four [23], [24].

Patient Health Questionnaire-2 (PHQ-2)

Two-item questionnaire to assess the existence of a depressed mood and loss of interest in daily activities [25]. Each item is scored from zero to three.

Patients' Global Impression of Change (PGIC) scale

One-item questionnaire assessed after receiving the treatment to measure the participant's belief about the efficacy of the treatment, on a scale from zero to seven [26].

Short Form of the EXPECT Questionnaire (EXPECT-SF)

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)

Three-item questionnaire regards to the participant's opinion about the treatment.

Imaging assessments

Non-invasive brain imaging assessments such as functional Magnetic Resonance Imaging (fMRI) and Electroencephalography (EEG) are performed to conduct further exploratory studies on neural correlates of pain.

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 [27], [28] 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.
- *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 pre- and post-treatment are measured by using an adapted motion capture system for upper limb and a goniometer for lower limb.

Semi-structured qualitative interviews

Participants are asked to participate in brief, semi-structured 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 categorized into themes for analysis, as described by Malterud [29]. Interviews will be performed in Swedish or English and, if necessary, translated into English for analysis.

Sample size

The sample size was calculated based on the result of the primary outcome, comparing PRI, of the study on PME for treatment of PLP in a previous study [6]. Eight participants were deemed necessary for a power of 80% and an alpha value of 5%. No dropouts are expected. In the 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 includes images, video recordings, assessments result, and numerical values. Data obtained within this project is confidential and stored digitally in accordance with the European General Data Protection

Regulation (GDPR) requirements, on a password-protected computer with restricted access. The data is pseudonymized with a code consisting of two letters and three digits. All collected data is assigned a coded, 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 de-identified and password protected database is prepared to be processed and analyzed.

Images and video recordings are only shared with the written consent of the participant. Participants can choose whether images for scientific presentations have their face 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. De-identified data may be made available upon reasonable request and as part of publications in peer-reviewed journals. Data will be stored for at least ten 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 is collected, documented, and reported according to International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) and applicable ethical and regulatory requirements.

Analysis

Statistical analysis on the primary and secondary outcomes are performed regarding changes in measurement pre- and post-treatment. Analyses are conducted within-participant and between participants for descriptive purposes of mean, median, absolute value, standard deviation, range, and 95% confidence intervals for means and proportions.

Statistical significance is calculated with Wilcoxon signed-rank test, at p smaller than 0.05. Furthermore, in case of changes in the occurrence of each quality of pain, the sign test for those qualities pre- and post- treatment with exact binomial probabilities are used. For the sign test, the statistical significance is considered at p smaller than 0.05.

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

Declarations

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 Etikprovningsmyndigheten (Lund avdelning 2 medicin).

Protocol amendments

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

Trial Registration

The study is registered at ClinicalTrials.gov with NCT04897425 trial identifier number.

Protocol version

Version 1, July 2021

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Authors Contributions

SD and MO-C drafted the study protocol and its ethical approval. SD registered the trial and oversaw the ethical application. SD and MO-C drafted the manuscript. MO-C ideated PME and MiSMT, and obtained funding for the project. MB developed the technology for the wearable device for haptic feedback. All authors reviewed and approved this manuscript before submission.

Disclaimer

Funders were not involved in the design of the study.

Competing Interests

MOC and MB hold a patent for technology to deliver haptic feedback and decode motor volition

Access to data

The principal investigator of the study, MO-C, has access to all the collected data. However, documents including the connection between participant's identity and their assigned code, will be disclosed after the completion of the study.

Data Sharing

De-identified data may be made available upon reasonable request

Dissemination policy

Regardless of the direction or significance of findings, the research team will publish the outcome of the study in scientific and peer-reviewed journals and conferences following the Consolidated Standards of Reporting Trials guidelines. All the researchers involved in the study will author the publications resulting the finding of the study. Moreover, the result of the study will be distributed to all participants as a report.

Access to the comprehensive clinical investigation plan, participant dataset, and statistical code will be available upon acceptable requests after publishing the finding of the study.

Trial Status

This clinical trial is in the early phase of participant enrollment and no participant has been recruited yet. The study is anticipated to be completed by December 2022.

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Figures

Figure 1

Schematic illustration of the setup used in a participant with amputation and nerve injury (e.g., 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 (C) is displayed on a screen providing the participant with instructions and virtual environment related to the therapy. Visual (C) and/or tactile (D) feedback is

perceived as a response to the movement. Concurrent to performing the training, the brain modulation is utilized by a tDCS system (E).