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Developing Transcranial Direct Current Stimulation as a Treatment for Phantom Limb Pain: From Pilot Mechanistic Studies to Large Clinical Studies

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Introduction

Phantom limb pain (PLP)–which occurs in 60-85% of amputees–causes tingling, stabbing, and/or throbbing sensations in a patient's amputated limb (Hanyu-Deutmeyer et al., 2024). While the exact cause of PLP remains unknown, it is thought to stem from maladaptive neuroplasticity in the sensorimotor cortex. Cortical circuitry may undergo rewiring to transmit conflicting sensory signals related to a limb that is no longer present, potentially inducing erroneous sensations of pain (Hanyu-Deutmeyer et al., 2024). Thus, current approaches in PLP treatment–such as behavioral therapies and neuromodulation techniques–aim to potentially restore plasticity and cortical organization.

Neuromodulatory treatment approaches, which attempt to correct these miswired networks, have been widely explored in clinical research with demonstrated effectiveness in multiple studies. In this article, we discuss our 12-year experience developing tDCS as a potential clinical tool for phantom limb pain. Our research center initially explored two techniques of noninvasive brain stimulation: transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) (Figure 1). TMS stimulates specific regions of the brain with small pulses from an electromagnetic coil. tDCS applies small electrical currents to the scalp that either inhibit (cathodal) or facilitate (anodal) neuronal firing. These interventions are noninvasive, painless, and lack significant side effects–making it an appealing treatment option for PLP.

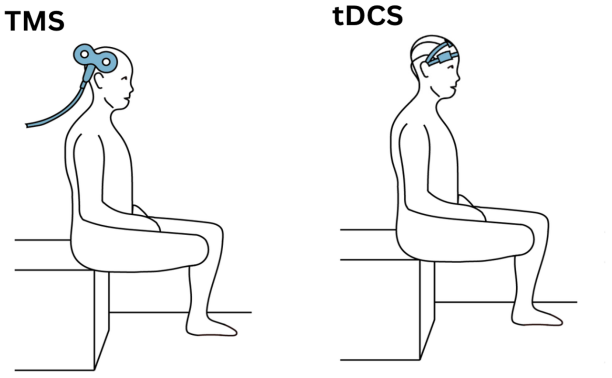

Figure 1: *Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).*

TMS has been an FDA-approved treatment for depression since 2008, with approvals for chronic migraine pain and OCD following soon after. However, despite positive results, TMS has not yet been approved for PLP treatment. Furthermore, tDCS is currently not an FDA-approved treatment for any disorder. Many obstacles have hindered the translation of these techniques into clinical practice, including concerns over accessibility and the lack of a definite, large-scale conclusion on the efficacy of these interventions (Pacheco-Barrios et al., 2020). Multiple studies report a variety of outcomes and response durations, and it is evident that there is no one-size-fits-all approach to neuromodulatory PLP rehabilitation. Thus, more concrete proof of effectiveness and applicability to a broad range of patients must be found for these treatments.

The development of medical devices into clinical practice does not have a path so well established com-

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pared to the development of pharmacological agents. The development of medical devices usually has two steps: preliminary trials and pivotal trials. However, their characteristics are usually less stringent compared to drug trials. In this paper, we discuss a narrative of our experience in this field, starting with initial pilot trials and then moving to explanatory trials to increase our understanding of the mechanisms of this intervention that aim to induce motor cortex plasticity to reduce PLP.

1st Step: Clinical Trials to Define Best Cortical Stimulation Target

Our initial trials using TMS and tDCS have yielded promising yet variable results for treating PLP (Figure 2). Using repetitive TMS (rTMS) on M1, Malavera et al. (2016, N = 54) found a 30.44% mean difference in pain reduction between treatment and sham groups, with 70.3% of subjects attaining clinically significant pain reduction 15 days post-treatment (compared to 40.7% in the sham group) (Malavera et al., 2016). However, this effect was non-significant 30 days post-treatment. Bolognini et al. (2013, case study; 2015, N = 8) confirmed that anodal tDCS applied to the M1 region for several sessions resulted in immediate relief as well as a sustained decrease in PLP intensity and frequency for 1 week following treatment–these responses are considered long-lasting (Bolognini et al., 2015, Castillo et al., 2014). Selective short-lasting pain reduction was observed in PLP patients (N = 13) who were administered one session of anodal M1 tDCS (Bolognini et al., 2013) On the other hand, cathodal tDCS of the posterior parietal cortex led to selective short-lasting decreases of nonpainful phantom sensations (Bolognini et al., 2013).

These findings indicate that the primary cortex stimulation seemed the best target of stimulation for PLP, similar to our studies in other chronic pain conditions (Castillo et al., 2014) Thus, the initial pilot studies helped define the motor cortex as the optimal target for PLP treatment. Furthermore, they underscore the potential for TMS and tDCS to be used as clinical treatments for PLP. As shown by Bolognini et al., treatments selectively relieve pain for variable durations, raising questions regarding how these techniques can be better understood to induce long-lasting benefits for individual patient cases. We then defined M1 as the stimulation target but chose to proceed with tDCS given the potential of this technique to combine with behavioral interventions (Pinto et al., 2016).

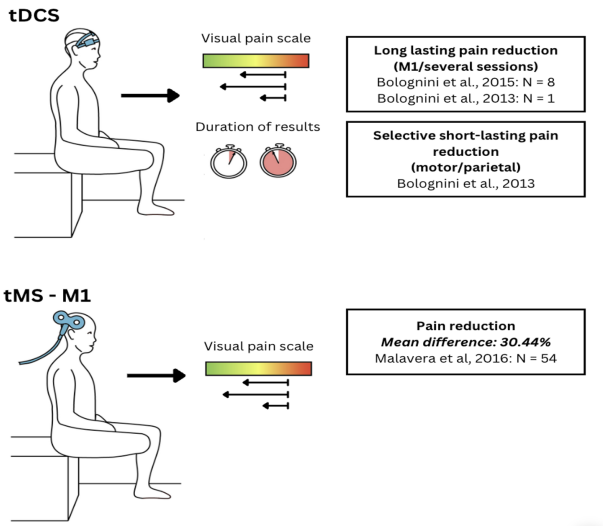

Figure 2: *Clinical trials indicate that tMS/tDCS yield promising yet variable results for treating PLP.*

2nd step: Designing and conducting a mechanistic clinical trial

We then moved on to evaluating the neural mechanisms and efficacy of combined tDCS and mirror therapy (MT) (Figure 3). Mirror therapy involves placing a mirror between the two limbs, creating an illusion of functioning movement in the amputated limb when the normal limb is moved. This visual feedback activates motor and sensory regions in the brain, which is thought to allow neural circuitry to correctly "rewire" and alleviate painful sensations. Mirror therapy has been a widely-used rehabilitation technique for treating PLP, with conflicting reports of effectiveness.

In our clinical trial, patients with PLP were randomly allocated to the following groups: active tDCS and active MT, sham tDCS and active MT, active tDCS and sham MT, and sham tDCS and sham MT (Castillo et al., 2014) TMS and fMRI was conducted in order to assess connections between cortical reorganization and clinical outcomes. From this study we were able to gain several mechanistic insights as explained below.

Clinical Predictors of PLP Intensity

Variable results of neuromodulatory PLP interventions–in both the success of rehabilitation and duration of outcomes–indicate that certain outcome determinants may be overlooked or understudied. An important factor that may influence the course of treatment is a patient's baseline PLP severity. Upon exploring potential clinical determinants of PLP severity in a cross-sectional analysis, Münger et al. (2020) identified two significant protective fac-

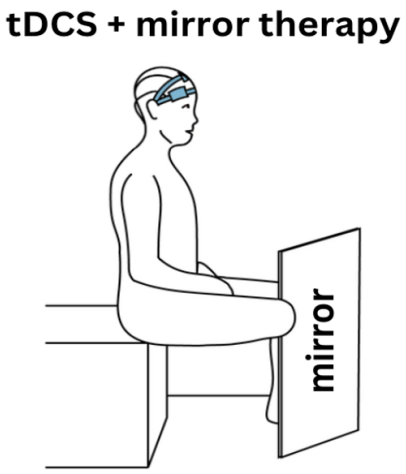

Figure 3: *tDCS and MT schematic.*

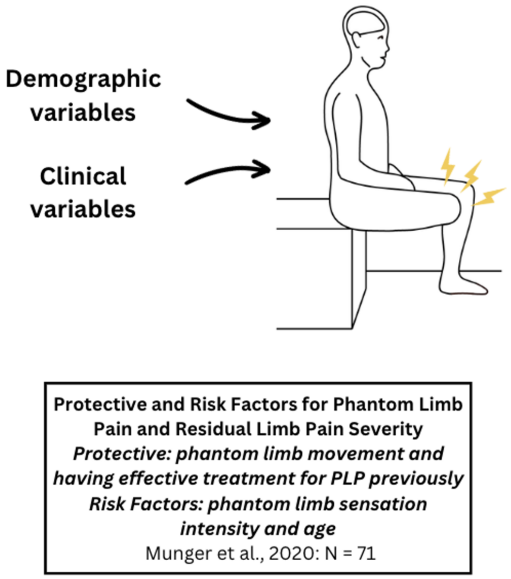

Figure 4: *Predictors of PLP intensity.*

tors–phantom limb movement and having previously effective treatment for PLP–as well as two significant risk factors–phantom limb sensation intensity and age (Münger et al., 2020). Teixeira et al. (2021) (N = 98) found that ICF was negatively associated with patient age and PLP intensity at baseline but positively associated with time since amputation was positively associated (Teixeira et al., 2021).

Understanding the Adaptive and Maladaptive Neural Circuits in PLP from Neuroimaging Data

Neuroimaging techniques have also been employed to probe the neural mechanisms underlying individual PLP manifestations and mixed responses to treatment (Figure 5). Using a combination of functional near-infrared spectroscopy (fNIRS) and functional magnetic resonance imaging (fMRI), Duarte et al. (2020) found that increased activity in the primary motor (M1) and somatosensory (S1) cortex was positively associated with time since amputation, but not associated with PLP intensity (N = 18) (Duarte et al., 2020). Additionally, they found that the Euclidean distance between the affected motor region and the surrounding region in the brain was not associated with pain intensity, further confirming the PLP may not be primary due to structural cortical alterations (Duarte et al., 2020).

Simis et al. (2024) furthered understanding of

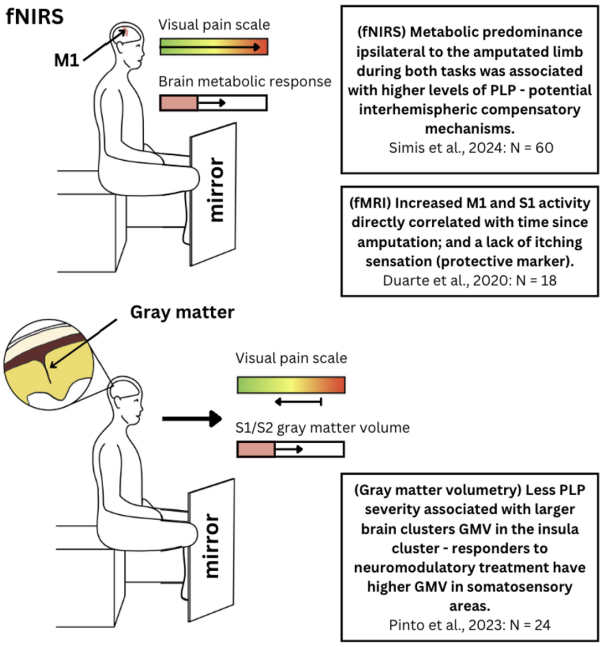

Figure 5: *Neuroimaging studies show how multiple factors lead to variable results to PLP interventions.*

the motor circuits associated with pain by utilizing fNIRS to investigate associations between PLP and brain metabolic responses in the motor cortex. Importantly, they demonstrated that patients' (N = 60) brain metabolic activation was highest in the hemisphere ipsilateral to the amputated limb, with the level of activation being positively associated with the level of PLP during both motor execution and motor mirror tasks (Simis et al., 2024). These results highlight potential clinical and neurophysiological markers for PLP. While these factors mostly had no relationship with the outcome of treatment, greater consideration of these predictors may be important to inform more personalized PLP treatment. In healthy patients, brain compensatory reserve mechanisms make up for losses of sensory input and other stresses on sensorimotor function. In PLP patients, cortical structure changes may serve as more of an indication of disruptions in these compensatory mechanisms that generally lead to PLP rather than a factor that defines pain intensity. Clinical sensory markers, such as itching, may index these compensatory mechanisms, which may explain why heightened M1 activity in PLP patients was associated with a lack of itching sensation (Duarte et al., 2020).

A neurophysiological marker of these compensatory disruptions is gray matter volume (GMV). In PLP patients (N = 24), Pinto et al. (2023) revealed that PLP severity is inversely correlated with insula GMV volume, and patients who responded to combined tDCS-mirror therapy have higher GMV in somatosensory areas (Pinto et al., 2023). Other compensatory mechanisms include measures of intracortical facilitation (ICF) or inhibition (ICI), with ICF being a marker of cortical excitability (Pacheco-Barrios et al., 2020). Lower PLP intensity was correlated with higher ICF in M1 in the contralateral hemisphere–raising the possibility that PLP may be mainly caused by functional modulations rather than structural changes. Higher activation of interneurons associated with ICF may be regulating endogenous pain mechanisms. As the dynamic engagement of the sensorimotor cortex is associated with pain intensity, the primary aim should be increasing the activity of facilitatory interneurons rather than purely restoring cortical circuitry.

Sensorimotor Plasticity in PLP with TMS data

The hallmark of PLP–real perception of pain from an amputated limb–has been attributed to mismatched signals resulting from the reorganization of sensorimotor circuits. Thus, in developing treatments, it is of interest to assess the structural and physiological features of these potentially altered circuits as well as their relationship to PLP intensity.

PLP was initially thought to be caused by a structural cortical rearrangement. Flor et al. (1995) showed through imaging studies that lip and face representation in the motor cortex and sensory cortex may invade the region associated with the amputated limb (Flor et al., 1995). They found that this reorganization was highly correlated with the level of pain.

Pacheco-Barrios et al. (2020) confirmed the presence of asymmetrical motor cortex disorganization in patients with PLP (N = 62) that decreases with time since amputation, alongside shifted hand cortical representation and loss of gray matter volume in the hemisphere contralateral to the amputated limb (Pacheco-Barrios et al., 2020). However, the level of organization did not appear to be associated with PLP intensity.

Studying the associations of these compensatory mechanisms with PLP intensity provided a better understanding of how anodal tDCS treats PLP and ultimately how maladaptive neuroplasticity may be targeted. These studies changed our approach to developing neuromodulatory PLP treatments. Previous trials often tested neuromodulation alone with hopes of restoring the altered cortical map; however, at rest, interneurons associated with ICF or ICI are not activated.

During a task that actively engages a region of the brain, TMS or tDCS can be used to enhance the brain's response to the task. Therefore, neuromodulatory treatment alone may not be sufficient–it needs to be paired with a task to activate sensorimotor interneurons to control the intensity of their activation.

Our Clinical Data: Impact of Paired Mirror Therapy and tDCS on M1 Plasticity

With the understanding that neuromodulatory techniques mainly serve to enhance responses to rehabilitation tasks, Teixeira et al. (2021) evaluated the effects of a mirror therapy-tDCS combination intervention on M1 plasticity (Teixeira et al., 2021).

After mirror therapy was used in conjunction with anodal M1 tDCS to treat PLP, Teixeira et al. (2021) found that changes in ICF did not correlate with PLP intensity (Teixeira et al., 2021). These results are supported by Gunduz et al. (2021), who conducted a 2x2 factorial trial studying the effects of active/sham tDCS and active/covered mirror therapy in PLP patients (N = 112) (Gunduz et al., 2021). Critically, while tDCS was associated with reduced PLP pain as well as increased M1 plasticity, mirror therapy was not associated with M1 plasticity changes (Figure 7) (Gunduz et al., 2021). Covered mirror therapy (a sham control group), however, was associated with a reduction in pain and changes in M1 plasticity even though it removed the visual illusory effects of mir-

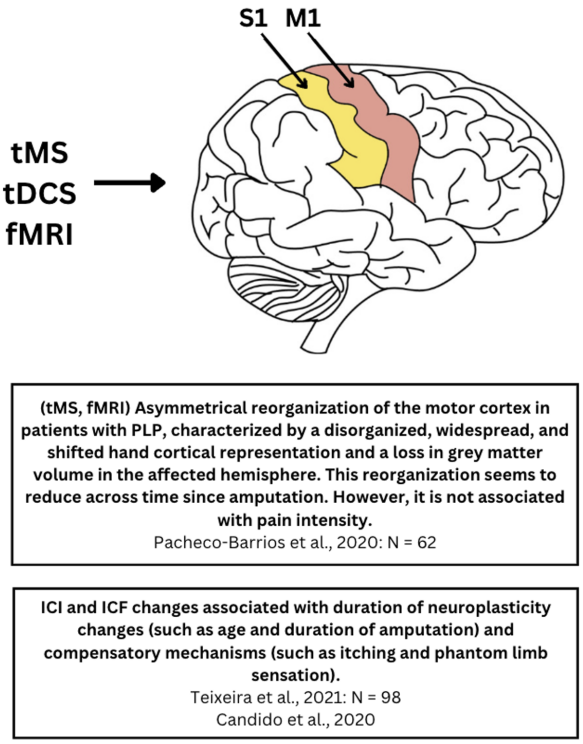

Figure 6: *PLP is associated with sensorimotor neuroplasticity.*

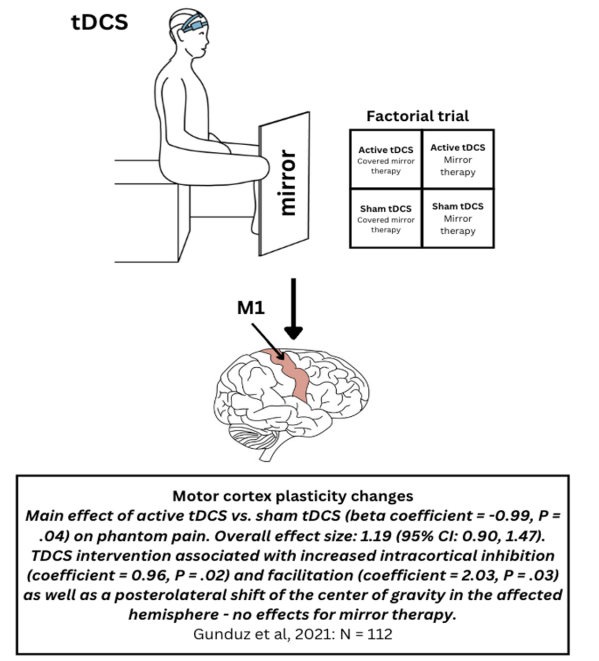

Figure 7: *tDCS paired with mirror therapy does not induce M1 plasticity changes.*

ror therapy. Though combined mirror therapy and tDCS may alleviate PLP in some patients, these results suggest that this intervention may not directly target maladaptive sensorimotor plasticity impacted by PLP. Mirror therapy may not have been effective in altering M1 plasticity because it mainly involves visual-cognitive engagement rather than somatosensory engagement. On the other hand, under covered mirrored therapy, patients were found to be imagining moving the phantom limb, which may activate somatosensory regions. These findings serve as behavioral confirmation of the PLP protective factor of phantom limb movement found in Münger et al. (2020), and open the door to developing therapies that directly pair tDCS with somatosensory activation to strengthen its impact on affected sensorimotor pathways. Specifically, phantom limb movement may be a more effective approach to PLP treatment.

Moving to a Clinical Application: A Pragmatic Trial to Advance Clinical Applicability

Given our mechanistic findings and our clinical findings, we then moved on to designing a pragmatic trial. Traditional clinical trials are often conducted in highly controlled settings. Pragmatic trials, on the other hand, incorporate the intervention in the patient's existing regimen and setting. This approach may yield outcomes that are more applicable to the real-world implementation of the therapeutic.

The PLP-EVEREST (PLP-EffectiVEness pRagmatic Stimulation Trial) was developed to advance the progression of tDCS technology to a real-world clinical setting. PLP-EVEREST aims to assess PLP patients' responses to a home-based version of a previously validated PLP combination therapy involving both transcranial direct current stimulation (tDCS) and somatosensory training (Figure 8). Phantom limb exercises–which involve imagined repetitive movements of the phantom limb–replace mirror therapy as they lead to greater stimulation of affected somatosensory pathways. Anodal tDCS in M1 contralateral to the amputated leg links M1 excitation with somatosensory activation, amplifying responses from phantom limb exercises.

Critically, the home-based format of the study provides a more accessible avenue for PLP patients to receive tDCS treatment. Not only does remote tDCS remove many time and travel-related barriers, but it also reduces the need for bulky equipment typically required for neuromodulatory therapeutics. Furthermore, PLP-EVEREST will incorporate machine-learning approaches to identify clinical and neurophysiological predictors of patient outcomes, adding to current research in this area. Thus, the PLP-EVEREST study seeks to promote clinical translation by making treatment more inclusive for diverse populations and obtaining more metrics on the factors that should go into personalized PLP treatment.

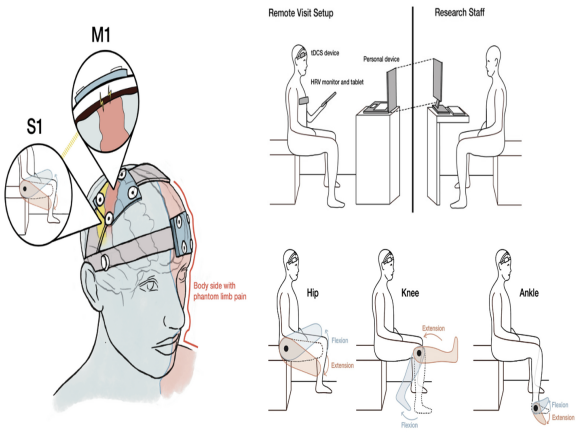

Figure 8: *Pragmatic trial of tDCS and somatosensory training.*

Conclusion

Collectively, these studies underscore the importance of investigating clinical factors, neuroplasticity, and other neural features in relation to PLP severity before and after treatment to improve the generalizability of rehabilitation outcomes. More research is warranted to understand the role of motor cortex reorganization in patients with PLP as well as the neural mechanisms underlying neuromodulatory treatment methods, particularly the approach tested in the PLP-EVEREST trial. For instance, a deeper look into compensatory changes in specific brain regions may explain their potential role in motor circuitry imbalance highlighted by Simis et al.. Furthermore, itching and other PLP-associated sensory phenomena, such as tingling, may be further explored as protective or harmful markers. Continuous research in this area using a variety of neuroimaging approaches would allow for more nuanced developments of treatment plans tailored to the individual physiology and conditions of each individual. With the existing findings as our groundwork, we believe that the ongoing PLP-EVEREST trial could become the standard of care for PLP treatment in the future.

Funding

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Conflicts of Interest

The authors declare no conflict of interest.

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