Mediterranean Journal of Clinical Psychology

ISSN 2282-1619

Volume 8, n 1, 2020

Letter to the Editor

Letter to the Editor: the application of transcranial direct current stimulation on phantom phenomena

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Keywords:
Transcranial direct current stimulation; tDCS- Amputation; Phantom limb phenomena; Phantom limb; Phantom limb pain.

Received: 4 February 2020
Accepted: 19 March 2020
Published: 20 April 2020

Citation: Orrù, G., Cesari, V., Baroni, M., Conversano, C., Ciacchini, R., Menicucci, D., Gemignani, A. Letter to the Editor: the application of transcranial direct current stimulation on phantom phenomena. *Mediterranean Journal of Clinical Psychology, 8*(1). Doi: https://doi.org/10.6092/2282-1619/mjcp-2382

To the Editor,

Phantom limb phenomena are often reported by patients after the amputation or deafferentation of limbs. The most debilitating condition is named phantom limb pain and, to present, an efficacious treatment is not been identify, yet. However, alternative non-invasive treatments such as transcranial direct current stimulation could be a valid approach in order to modulate pain. Based on the studies considered, tDCS might represent a potential novel tool able to reduce phantom limb symptoms. Due to the limited number of investigations, the positive outcomes summarized in this letter to editor need to be interpreted with caution.

Following amputation or deafferentation of specific body districts, such as limbs, it is often reported by amputees a subjective feeling of the presence of the missing limb, as well as specific sensory and kinesthetic. The aforementioned phenomena, named "*phantom limb awareness*", "*phantom sensation*" and "*phantom pain*" are commonly experienced by patients after amputation.

These phenomena might be also modulated by some psychological factors such as depression, anxiety, tension and stress (Fuchs et al., 2018), even if to a lesser extent if compared to other chronic conditions in which they play a critical role (Conversano, 2019; Martino, Langher, Cazzato, & Vicario, 2019; Merlo, 2019; Piccinni et al., 2012). Phantom limb (PL) phenomena can be partially explained by a maladaptive plastic reorganization of the cortex, occurring after the amputation (Flor & Andoh, 2017). Although, the growing knowledge about the pathophysiological mechanisms of PL phenomena no universally efficacious treatments are available. Recently, a novel approach to treat phantom limb phenomena has been proposed, which is the application of transcranial direct current stimulation (tDCS), a non-invasive brain technique able to modulate cortical excitability eliciting membrane changes *via* subthreshold mechanisms. TDCS is widely used in neurological diseases such as stroke (Hesse et al., 2011; Sattler et al., 2015; Orrù, Conversano, Hitchcott, & Gemignani, 2020), Parkinson's disease (Ferrucci et al., 2016; Ferrucci, Mameli, Ruggiero, & Priori, 2016; Orrù et al., 2019) and Alzheimer's disease (Ferrucci et al., 2008) amongst others and a variety of psychiatric conditions such as specific phobias, social anxiety disorder, panic disorder, agoraphobia, and generalized anxiety disorder (Vicario, Salehinejad, Felmingham, Martino, & Nitsche, 2019). Moreover, tDCS can support cognitive recovery in chronic diseases (Gangemi et al., 2018)

A strong motivation to identify alternative tools is that the phantom pain relief become the most important goal for the improvement of patients' quality of life.

In order to investigate the state of art of tDCS on PL phenomena, an online search in the Pubmed, Scopus and Cochrane databases was performed using specific search terms related to the topic. Our search identified a total of eleven records, after duplicates removal and title and abstract reading. According to our inclusion criteria, we retained five studies for the qualitative synthesis. Of these, one study involved single tDCS sessions (total patients = 14) and four involved repeated tDCS sessions studies (total patients = 29). The results of five studies included will be shown (Table 1).

Table 1. Detailed intervention parameters of tDCS sessions.

Author	Sample	Amputation site	Trial type	Polarity	Electrode position and reference	Current intensity and duration	FU	Outcomes
Bolognini et al., 2013a	Trial 1 N=8; Trial 2 N=7	Unilateral lower or upper limb	Double-blind, sham-controlled	Trial 1 atDCS/sham Trial 2 atDCS/ctDCS /sham	Trial 1 Anode: M1 contralateral to the amputation Cathode: contralateral supraorbital area Trial 2 Anode: PPC Cathode: PPC Reference: PPC contralateral to the amputation	Trial 1 2 mA; 15 min; 1 session Trial 2 2 mA: 14 min; 3 sessions	90 minutes	Shorting lasting decrease effects on PLP (p<0.01) after M1 atDCS and on non-painful phantom sensations (p< 0.05) after PPC atDCS. No significant effects on stump pain (p=0.8) and non-painful phantom sensations (p= 0.6) and telescoping (p<0.05) after M1 atDCS. No significant effects for PLP (p=0.7), stump pain (p=0.1) and telescoping (p=0.4) after PPC tDCS
Bolognini et al., 2013b	N=1	Below-the-knee amputation	Single-blind	atDCS/sham	Anode: motor cortex contralateral to the amputation site Cathode: contralateral supraorbital area	2 mA; 15 min; 5 sessions (2 weeks)	2 months	Significant reduction of stump pain (p<0.0001). No significant reduction of non-painful phantom sensation (p=0.2) and telescoping (p=0.3)
Bolognini et al., 2015	N=7	Unilateral lower limb or the upper limb	Crossover, double-blind, sham-controlled	atDCS/sham	Anode: M1 contralateral to the amputation Cathode: contralateral supraorbital area	1.5 mA; 5 min; 5 sessions	1 week	Immediate tDCS: significant effect on PLP intensity (p=0.04) and PL movement (p=0.05) compared to sham; significant negative correlation between PL movement and PL relief (p=0.003). No significant effect on non-painful phantom limb sensations. Sustained tDCS: significant effect on PL relief (p=0.04) and significant reduction of PLP paroxysms (p=0.05)
Pan et al., 2015	N=6	Unilateral transradial (below-elbow)	Randomized, sham-controlled	atDCS/sham	Anode: motor cortex contralateral to the affected side Cathode: contralateral supraorbital area	1 mA; 20 min; 1 session	No	Significant reduction of the average CER of the eleven phantom motions of the affected side from 27.3% to 17.2% (p<0.001).
Bocci et al., 2019	N=14	Unilateral upper limb amputation	Crossover, double-blind, sham-controlled	Bilateral a-ctDCS/ sham	Anode: 2 cm below the inion Cathode: right shoulder	2 mA; 20 min; 5 sessions; (1 week)	4 weeks	Significant amplitude reduction of LEP after a-ctDCS compared to sham (N1, p=0.021 and N2/P2, p=0.0034), significant reduction of paroxysmal pain (p<0.0001), non-painful phantom limb sensations (p<0.0001) and phantom limb movements (p=0.0003) evaluated by VAS scale and negative significant correlation between the reduction of LEP amplitude and VAS (p=0.0004)

Notes: atDCS, anodal tDCS; *a-ctDCS*, anodal cerebellar tDCS; *CER*, classification error rate; *ctDCS*, cathodal tDCS; *LEP*, laser-evoke potential; *M1*, primary motor cortex; *PLP,* phantom limb pain; *PPC*; posterior parietal cortex; *VAS*, visual analogue scores; *FU*, follow-up.

Bolognini, Olgiati, Maravita, Ferraro, & Fregni, (2013) conducted two trials. In the first experiment, participants with unilateral lower or upper limb amputation underwent to anodal tDCS (atDCS) and sham stimulation. The anode was positioned over the primary motor cortex (M1) contralateral to the limb amputation. In a second trial, participants underwent to atDCS, cathodal tDCS (ctDCS) and sham stimulation targeting the posterior parietal cortex (PPC). The results of the trials showed, a shorting lasting decrease effects on PL pain after M1 atDCS, whereas no significant effect on stump pain and non-painful phantom sensations was detected. Conversely, atDCS over PPC showed a shorting lasting decrease of non-painful phantom sensations. Both stump pain and telescoping didn't show any significant changes after parietal and motor tDCS. In the same year, Bolognini et al., (2013) conducted an experiment including a patient with a below-the-knee amputation. The patient underwent to five atDCS sessions and sham stimulation targeting the motor cortex contralateral to the amputation site, while the cathode was placed over the contralateral supraorbital area. Results showed a significant effect in reducing stump pain and relief from PL pain. However, no significant effects were shown for non-painful phantom sensations and telescoping.

In an additional study, Bolognini et al., (2015) performed a trial in order to investigate the effect of tDCS on PL pain where patients underwent to five sessions of atDCS and sham stimulation. The anode was positioned on M1, contralateral to the amputation limb, while the cathode was placed contralateral supraorbital area. The results showed a significant effect of tDCS on PL pain intensity and PL movement compared to sham stimulation, and a significant negative correlation between PL movement and PL relief. Conversely, no significant effect was detected on non-painful PL sensations. Moreover, a significant long-lasting tDCS effect was observed on PL relief, as well as of PL pain paroxysms for one week after the treatment. While Bolognini and colleagues (2015) tested the effect of atDCS delivered over M1 contralateral to the amputation site, Pan, Zhang, Sheng, & Zhu (2015), targeted M1 ipsilateral to the amputation site, in a sample of 6 transradial (below-elbow) unilateral amputees. The aim of the study was to evaluate the effect of tDCS on myoelectric control performance of hand and wrist motions. After a single session of atDCS, a significant improvement in the average classification error rate of eleven phantom motions of the affected side was detected, whereas an increase of the same parameter was shown for the non-affected one.

Bocci and colleagues (2019), conducted a study to investigate the effect of cerebellar tDCS on PL phenomena. For this purpose, fourteen upper limb amputees underwent five sessions of anodal cerebellar tDCS and sham stimulation targeting cerebellum, bilaterally. The clinical evaluation showed a significant decrease of paroxysmal pain and non-painful sensation.

In conclusion, it is possible to suggest that the use of tDCS could represent a valid approach to improve PL phenomena caused by amputation by exerting effects both on cortical and subcortical level and, thus, modulating pain processing phenomena. At the same time, important consideration needs to be given to limiting factors, mostly addressed to the lack of studies on phantom limb phenomena and the use of tDCS for therapeutic purpose. Another limitation is the heterogeneity of the amputation sites (upper or lower limb; bilateral or unilateral amputation) that precludes a direct comparison among the selected studies, as well as the small sample size of the studies considered. Furthermore, additional positive reporting bias that may affect the literature searches were the exclusion of grey literature and non-English language studies.

Further investigations with larger sample sizes, high levels of quality, homogeneous protocol and amputation sites are needed to support scientific robust conclusions about the effectiveness of tDCS on PL phenomena. These aspects are essential in order to communicate effectively scientific products from specific scientific areas (Settineri & Femminò, 2019; Settineri & Merlo, 2019).

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