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Increased thalamic activity and less neuropathic pain after tDCS observed with PET in a patient with multiple sclerosis: A case report

To the Editor:

Neuropathic pain has been described as the "most terrible of all tortures which a nerve wound may inflict" and arises as a consequence of nerve injury either of the peripheral or central nervous system [1]. Central neuropathic pain is defined as present if the distribution of pain is consistent with a central nervous system lesion, and if a thorough evaluation for nociceptive and peripheral neuropathic, psychiatric disease, pure back pain, headache, or optic neuritis is negative. Despite a prevalence of 29 up to 86% [2,3] in people with multiple sclerosis (PwMS), pharmacological treatment for MS-related neuropathic pain mostly remains unsatisfactory [4]. Recent studies have shown that the use of noninvasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) can produce analgesic effects on several painful conditions [5]. Specifically, tDCS applied over the dorsolateral prefrontal and motor cortex has been reported to reduce central neuropathic pain in PwMS [6]. However, detailed mechanisms accounting for the analgesic effect of tDCS have not yet been elucidated. [^{18}F] fluorodeoxyglucose positron emission tomography ([^{18}F] FDG-PET) may potentially be used to investigate the neural mechanisms underlying the effects of tDCS. Being a glucose analogue, [^{18}F] FDG allows the assessment of integrated synaptic activity in components of the pain network that may contribute to pain relief by tDCS [7].

A 52-year old man with a 13-year history of relapsing-remitting MS and moderate disability (current patient determined disease steps score of 3 was treated with tDCS and evaluated with FDG-PET. The local institutional review board approved the protocol and the participant gave written informed consent to participate. The patient reported no relapse, steroid treatment, or change in disease-modifying medications in the last 60 days prior to the intervention.

The patient underwent anodal tDCS (Neuroelectrics Inc., Simi Valley, CA, USA) over the left primary motor cortex (M1) contralateral to the worst somatic pain area (C3, EEG 10/20 system) and the cathode was positioned over the supraorbital area on the less-affected side. A constant current of 2 mA intensity was applied via two sponge electrodes (5×5 cm^2) for 20 minutes once a day for 5 consecutive days. Evaluations using the visual analog scale (VAS) for pain and the Neuropathic Pain Symptom Inventory (NPSI) took place before the first session, after each treatment session, and after the final treatment. The tDCS sessions were well tolerated and no serious side-effects were reported at any time. Both clinical pain scores improved after the five tDCS sessions (Fig. 1 A).

The effect of tDCS on regional cerebral glucose uptake was evaluated via [^{18}F] FDG-PET imaging before and 24 hours post the final tDCS treatment. Tracer uptake occurred under standard conditions (i.e., quiet, darkened room, ears unplugged, eyes open) with imaging at approximately 50 minutes post-injection during the same time of the day. Prior to injection of [^{18}F] FDG, the participant rested in a dimly lit room for 30–45 min with their eyes open. Images were analyzed by image subtraction (post-pre), globally-normalized regional SUV subtraction, and comparison to two different commercially-available software packages designed for analysis of FDG images (MIM Neuro FDG – Analysis (MIM Software Version 6.6.10) and NeuroQ (Syntermed, Inc.,v 3.75.20171019). These software packages each have their own proprietary FDG databases for comparison to a normal metabolic distribution.

Subtraction of pre-therapy from post-therapy globally-normalized SUV images indicated that the bilateral thalami, especially the right thalamus, exhibited increased glucose metabolism after tDCS treatment (Fig. 1B). Regional semi-quantitative analyses indicated that FDG uptake increased 9.1 and 12.2% in the left and right thalami, respectively. Comparisons to normal databases found that pre-therapy, the bilateral thalami were hypometabolic (MIM Z scores −2.0 and −2.5, respectively) but that after tDCS treatment, the metabolism normalized in these regions (MIM Z scores −1.0 and −0.7, respectively). Similar findings were observed with NeuroQ where the Z score improved by 1.1 and 1.5 units, respectively.

Discussion

This study presents, for the first time, the effects of tDCS on regional glucose uptake in a PwMS with neuropathic pain in order to identify potential mechanisms underlying the analgesic effects of tDCS. Pain scores improved after 5 sessions of tDCS in line with previous works on the same topic [6]. This result provides further evidence that anodal tDCS may be able to reduce neuropathic pain in PwMS. Since pharmacological treatment in MS-related neuropathic pain is usually unsatisfactory and in the face of the opioid epidemic, the current approach might be of interest for these specific symptoms in MS patients. The effects of tDCS on the specific brain networks involved in pain processing are poorly understood. The present study shows, at a very preliminary stage, that tDCS may induce functional changes in interconnected brain structures, critical in the pathogenesis of neuropathic pain syndromes, such as the thalamus. The important role of the thalamus in modulating pain is well described [8,9]. The thalami are also involved in the descending inhibition to modulate nociceptive inputs at the dorsal horn of the spinal cord. Changes in the biochemistry, thalamic blood flow

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A

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5
VAS (Pain)	64	73	72	91	56	56
NPSI	68	60	51	63	52	55

B

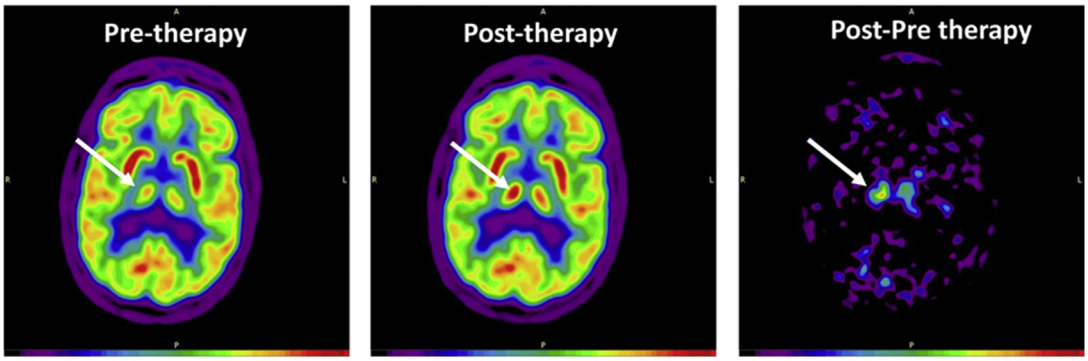

Figure 1. A clinical data before, during and after the tDcs protocol. VAS: Visual Analog Scale; NPSI: Netropathic pain sysptom inventory. **B**. FDG-PET transaxial images acquired pre and post-tDCS theerapy. Image are Scaled in standardized uptake values normalized to the global mean value (Max = 1.88 for pre-and post-therapy and 0.5 for post-pre therapy). The white arrow indicates the right thalamus, the area with the greatest difference between the image.

and the response properties of thalamic neurons have been demonstrated in neuropathic pain models. tDCS is known to cause polarity-specific shifts of the resting membrane potential and might consequently change neuronal excitability at the site of stimulation and in the connected areas. The increase in [^{18}F] FDG-PET uptake after motor cortex tDCS in the thalamus may thus suggest that tDCS can modulate sensory discriminative (lateral pain pathway) and affective-motivational (medial pain pathway) components of the pain system. Furthermore, Iadarola et al. [10] showed lower thalamic activity in patients with neuropathic pain contralateral to the symptomatic side using [^{15}O] water bolus PET, which suggests that functional adjustments in thalamic pain processing circuits may be an important factor of chronic neuropathic pain.

The preliminary findings of this study underline the need for future imaging studies combining tDCS with sensory stimulation in a large sample. Doing so could then provide valuable information on the mechanisms of the analgesic effect induced by tDCS and ultimately assist PwMS and clinicians in the decision-making regarding the use of tDCS as a rehabilitative tool.

Conflicts of interest

None.

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