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Cerebellar Transcranial Direct Current Stimulation (ctDCS) Effect in Perception and Modulation of Pain

Tommaso Bocci, Roberta Ferrucci, Alberto Priori, Massimiliano Valeriani and Ferdinando Sartucci

Abstract

Transcranial direct stimulation (tDCS) in the treatment of intractable or marginally tractable pain is experiencing an increasing diffusion in many fields worldwide. Recently, new modality of tDCS application has been proposed and applied, as cerebellar transcranial direct current stimulation (ctDCS). Indeed, the cerebellum has been proved to play a role in pain processing and to be involved in a wide number of integrative functions. In this chapter, we encompass the history of the technique, analysis of principles, a general description, including the methodological procedures of ctDCS; then, main clinical applications and their main effects in perceptive threshold of pain and other sensation, pain intensity, and laser evoked potentials (LEPs) changes.

Keywords: cerebellum, tDCS, cerebellar stimulation, pain, phantom limb pain

1. Introduction

Pain still remains a challenge for clinicians and neuroscientists, and current pharmacological therapies are often ineffective for the prevention and treatment of chronic pain. In particular, chronization of pain represents a multi-step phenomenon, comprising spinal phenotypic switch in the expression of neuropeptides, as well as elusive brain mechanisms, ranging from the so-called "thalamo-cortical dysrhythmia" to a functional reorganization of sensorimotor maps (**Figure 1**) [1–4]. In this scenario, the putative relationship between pain and the cerebellum is particularly intriguing, as the cerebellum is anatomically located between the spinal cord and the brain, possibly interfering both with top-down and bottom-up mechanisms underlying pain control and ultimately responsible for central pain sensitization.

The cerebellum is involved in a wide range of integrative functions, ranging from motor adaptation to working memory and associative learning, but its role in nociceptive experience and pain processing remains debated [5–10].

Overall, the cerebellum likely belongs to a widespread network that mediates reactions stronger to negative external stimuli than to positive ones [11, 12]; recent
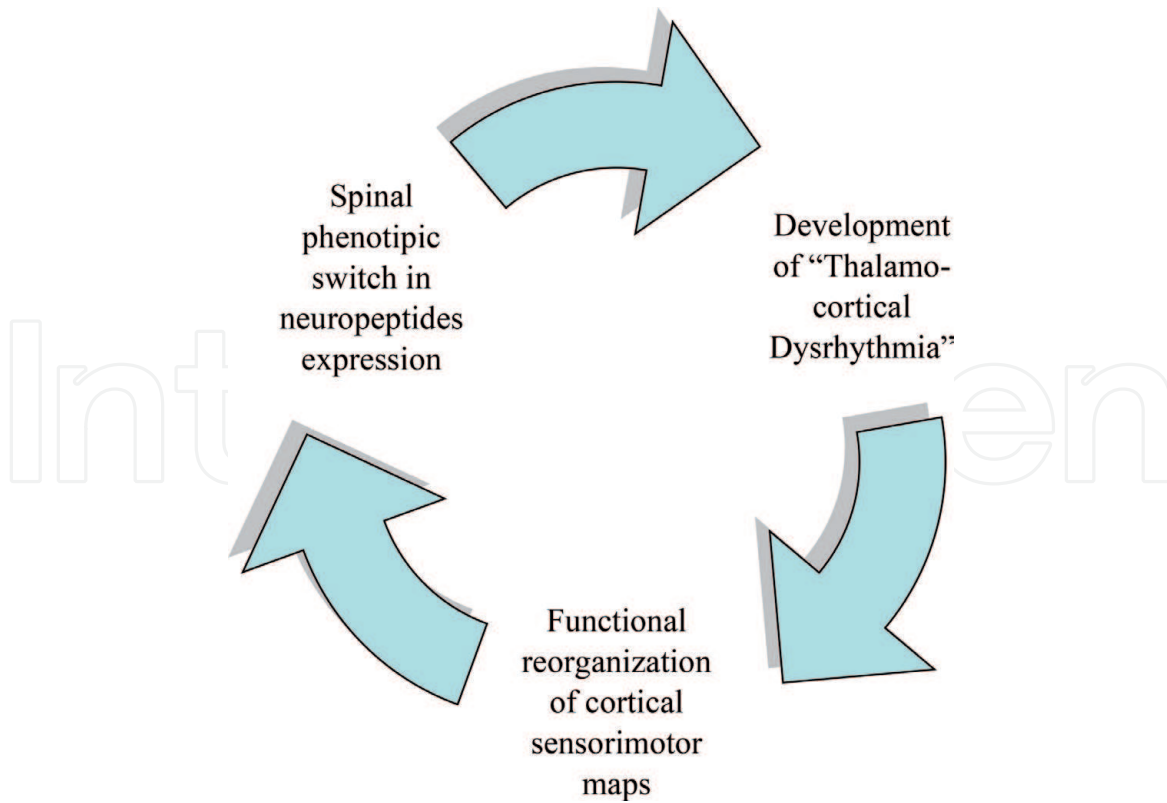
Figure 1.
"Red Flags" responsible for chronization of pain. Chronic pain is a multi-level and multi-step phenomenon, comprising changes at brain as well as spinal levels, and involves different neurotransmitters and neuronal pathways.
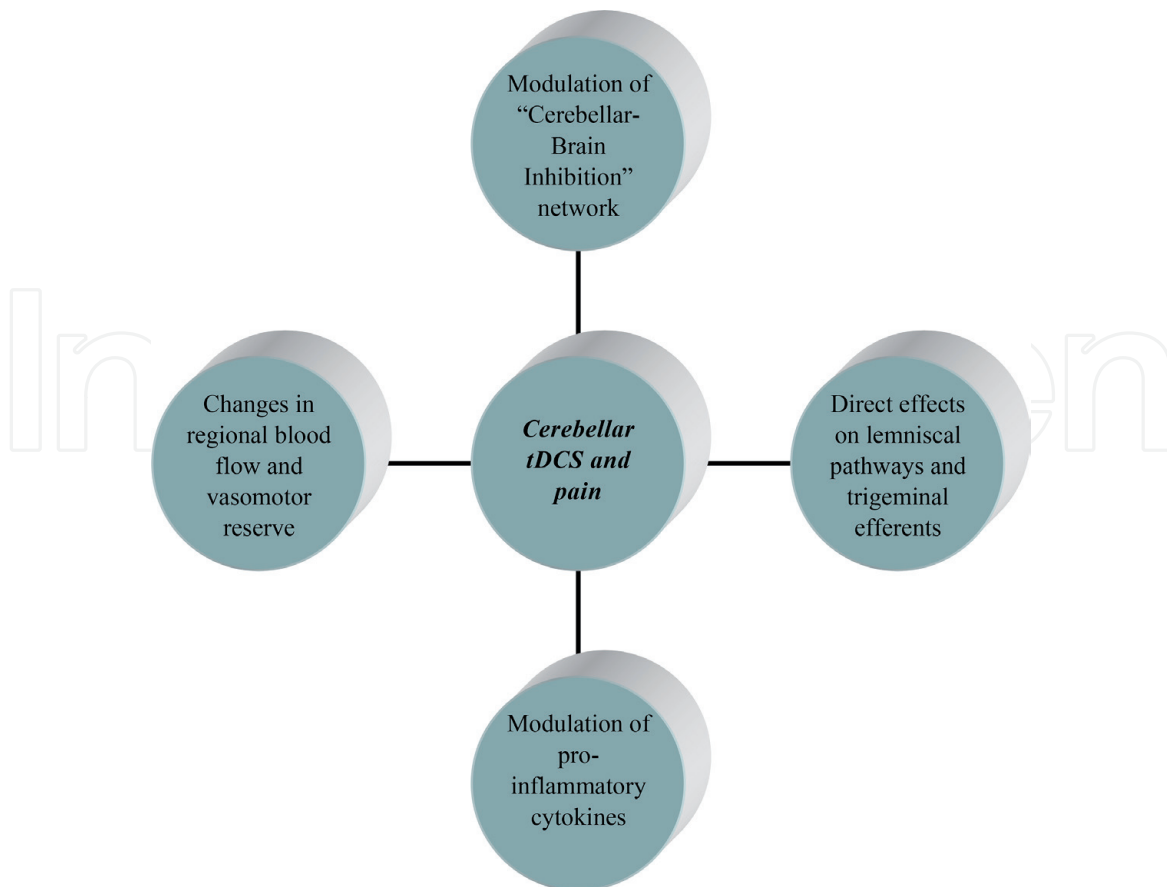

Figure 2.
Rationale for the use of cerebellar tDCS (tcDCS) for pain treatment: possible mechanisms of action and molecular pathways.

evidence has strengthened the hypothesis that plasticity subserving the storage and retention of unconditioned responses selectively occurs in the cerebellum [13–16]; recently we have proved a cerebellar role in learning of aversive reactions inside the peripersonal space [17], and studies in humans have highlighted a cerebellar engagement both in pain empathy and nocifensive withdrawal [18–20].

Nonetheless, some important questions remain open: (1) whether the cerebellum is engaged in the primary sensory-discriminative dimension of pain; (2) how it interacts with the cerebral cortex for pain processing; (3) whether it may be used as a putative target for non-pharmacological therapies, as non-invasive brain stimulation techniques (NIBS).

In this chapter, we encompass the current knowledge about the cerebellar role in pain processing, suggesting novel strategies for pain control and therapy in the emerging field of non-invasive neuromodulation (**Figure 2**).

2. Current pitfalls for the use of NIBS in pain treatment

Cerebellar direct current stimulation has been widely used for the treatment of several neuropsychiatric diseases, ranging from movement disorders [21–25] to autism and schizophrenia [26, 27], but only few evidence has been reached so far regarding pain therapy.

In general, transcranial direct current stimulation (tDCS) has been proposed for pain therapy, especially when applied over the primary motor area (M1) or the dorsolateral prefrontal cortex [28, 29]; nonetheless, the too small sample sizes and the extreme variability of stimulation parameters have limited its efficacy: as a result, pain improvement is often weak and brief, in line with the so-called "placebo-effect." There are also other possible explanations.

First, pain is a complex experience, involving phenomena at a sensory, affective-emotional and cognitive level: thus, clinical scales are often inappropriate to describe the whole phenomenon and follow putative effects of therapies over time.

Second, chronic pain involves different neurotransmitters and neuronal circuitries at a spinal and supra-spinal level: therefore, non-invasive stimulation applied over a limited brain target usually induces a transient pain improvement.

Third, only few groups have enough experience about the use of neurophysiological tools for pain assessment [30]; among these techniques, laser evoked potentials (LEPs) offer an unique opportunity to study the sensory-discriminative, as well as the affective-emotional dimension of pain, which are differently carried by medial and lateral spinal nociceptive systems and rely on the activation of distinct cortical areas [31–33].

3. Transcranial direct current stimulation (tDCS) and the cerebellum: an overview

3.1 Putative mechanisms of action of cerebellar tDCS and implications for pain treatment

Transcranial direct current stimulation (tDCS) has emerged in the past few years as a novel, noninvasive, inexpensive, and safe technique to modulate cortical excitability, both in health and disease. tDCS uses subthreshold currents (1.0–2.5 mA), too weak to induce neuronal activity independent from afferent input, but sufficient *per se* to alter both the excitability and spontaneous neuronal firing rate.

tDCS shows short- and long-term effects; the first ones outlast the end of stimulation for only a few minutes and involve non-synaptic mechanisms, comprising changes in membrane polarity, migration, and steric conformation of transmembrane proteins. Conversely, the long-term after-effects are mainly driven by synaptic modifications. In particular, anodal tDCS seems to have an overall excitatory effect, probably reducing intra-cortical GABA, whereas cathodal polarization dampens cortical excitability by reducing glutamate [34, 35]. Many studies reported the same polarity-specific effects for cerebellar tDCS, although they also depend on the position of the return electrode (namely, the "reference"), as well as on the size of electrodes and duration of the stimulation [36, 37].

Direct current polarization has both on-line and off-line effects on cerebellar excitability. This is in agreement with the effects elicited by tDCS in the cerebral cortex that are observable after both short-term and long-term delays and most likely interfering with long-term potentiation (LTP-like) phenomena [38]. From a cellular point of view, animal studies suggest that the electrical stimulation of Purkinje cells mediates on-line effects [39], whereas depolarization of Golgi inhibitory neurons is responsible for long-lasting changes [40]. Nonetheless, electrical fields induced by cerebellar tDCS in humans are much smaller than those used in animals, thus making it difficult to compare their mechanisms of action [41].

Purkinje cells represent the output from the cerebellar cortex, and their activation leads to the inhibition of cerebellar nuclei, ultimately dampening motor cortex excitability. Cerebellar tDCS (ctDCS) may interfere with this connectivity, influencing the so-called "Cerebellar-Brain Inhibition" (CBI); consequently, anodal ctDCS may reduce pain perception by increasing the inhibitory tone exerted by the cerebellum on different brain targets, whereas cathodal ctDCS could elicit opposite effects by inducing hyperalgesia. This tentative model has been recently confirmed by a clinical study of Ruscheweyh and co-workers [42], showing that patients with cerebellar infarctions have reduced pain thresholds, as concerns both placebo and offset analgesia.

Apart from non-synaptic and synaptic (neuroplastic) changes, tDCS may modulate pain experience and processing through different mechanisms. In recent years, a growing body of evidence has strengthen the importance of tDCS after-effects on regional blood flow and immune responses. In particular, animal studies have proved that tDCS elicits neural stem cells (NSCs) activation in vivo, thus influencing the development and the distribution of microglia in the adult brain [43]. In addition, tDCS likely modulates inflammatory response by regulating pro-inflammatory cytokines and increasing glutathione levels [44].

3.2 Cerebellar tDCS: setting parameters

Commonly, tDCS uses two electrodes, a cathode and an anode, but montages with multiple electrodes are possible. Their sizes vary among different studies and critically depend on the target; small electrodes (3 × 5 cm, 3 × 3 cm) are used for cerebellar polarization [36], whereas larger ones are commonly applied for direct spinal stimulation [45].

The return electrode (namely, the "reference") may be applied either over another cortical region or extra-cranially (e.g., the shoulder); the second choice should be preferred because cutaneous impedance is reduced and opposite effects of anodal and cathodal stimulation emerge more clearly.

Both electrodes are connected to a standard tDCS stimulator, delivering currents for 15–25 min, at an intensity ranging from 1 to 2 mA. This stimulation intensity
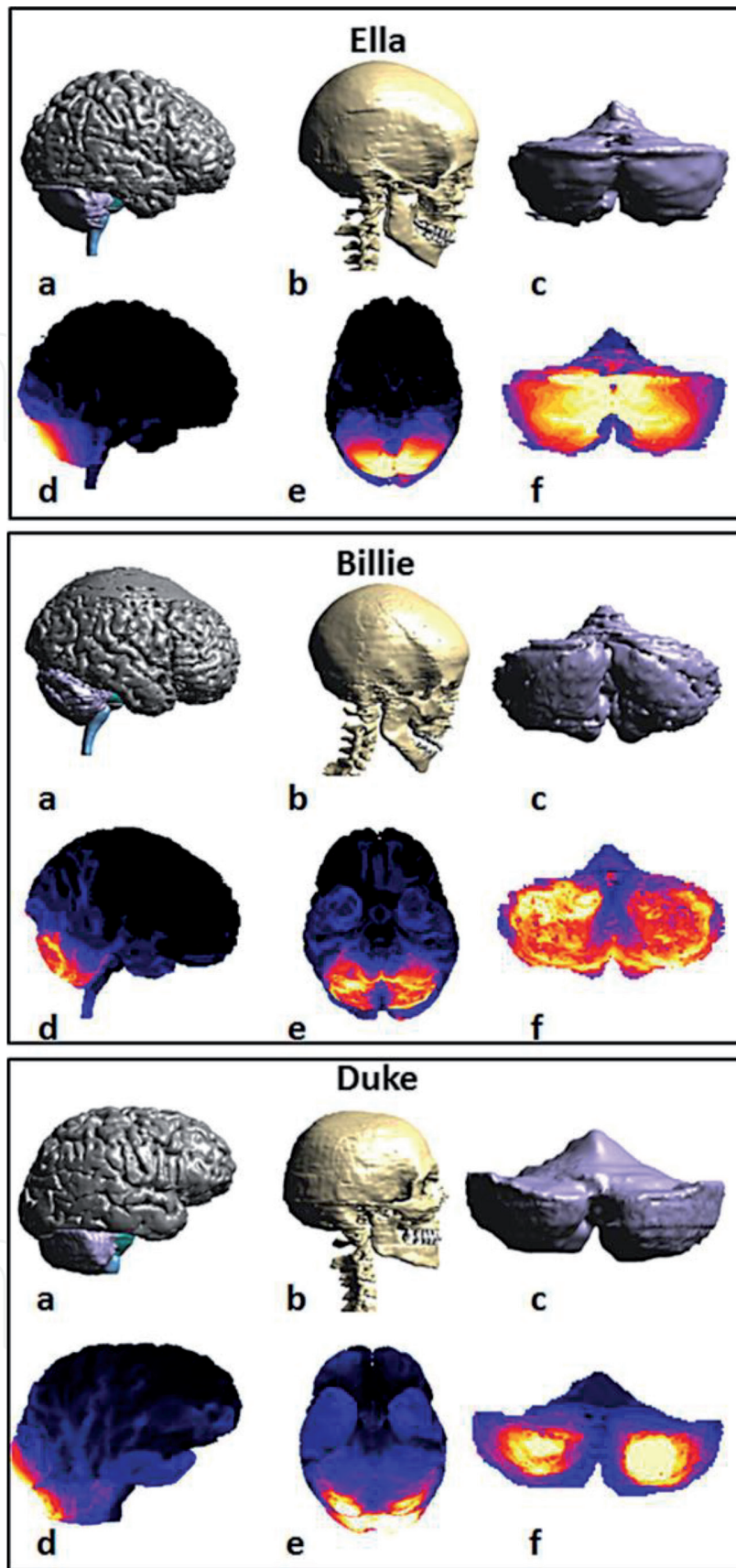
Figure 3.
Current density generated by cerebellar transcranial direct current stimulation (cerebellar tDCS) in humans. Examples of segmented tissues in two human realistic virtual family models (Ella and Duke) undergoing cerebellar tDCS. The spread of the current density (J) over the occipital cortex—quantified as the percentage of occipital volume where the amplitude of J-field is greater than 70% of the peak of J in the cerebellum—was only 4% for "Duke" and much less than 1% for "Ella" [modified from Parazzini et al. [49], with permission].

induces an electric field of the same order of magnitude as that influencing the cerebellar neuron activity in animal experiments [37].

3.3 Cerebellar tDCS: safety

When the procedure is correctly delivered, according to the safety guidelines, no adverse effects occur, except for a transient itching of tingling sensation.

In most subjects, cerebellar tDCS evokes no sensation likely because cutaneous nerves in the occipital region show a higher threshold than those located in the frontal trigeminal dermatomes [46].

Researchers and therapists should keep in mind only few exclusion criteria, such as the presence of metallic implants in the skull or in the brain [47], and subjects' skin should be lightly cleaned with a swab. Second, electrode sponges should be soaked with saline solution to reduce skin impedance. Finally, a current density limit of 0.029–0.142 mA/cm^2, corresponding to a maximum of charge density of about 40 μC/cm^2 at the stimulating electrode, has considered to be safe [48].

Notably, despite some inter-individual differences, recent modeling researches have revealed that the current spread to other structures outside the cerebellum is negligible and unlikely to produce functional effects (**Figure 3**) [49].

4. Cerebellar tDCS: emerging evidence for pain treatment

In previous papers from our laboratory, we have demonstrated for the first time that cerebellar tDCS modulates pain processing in healthy humans, probably by interfering with the CBI network [50–52]. In particular, ctDCS exerts polarity-specific effects on the amplitude of laser evoked potentials (LEPs), thus modifying the perception of experimentally induced pain in young volunteers: anodal stimulation leads to analgesia, whereas cathodal polarization increases pain perception.

This is in line with the theory that cerebellum exerts an overall inhibitory effect on pain processing at a cortical level, similar to that induced within motor pathways.

Because tDCS is effective on the modulation of both N1 and N2/P2 components of LEPs and these responses are generated by parallel and partially segregated spinal pathways reaching different cortical targets [32], we argue that the cerebellum is involved in pain processing by modulating the activity of both somatosensory and cingulate cortices. Indeed, from a functional point of view, the cerebellum is engaged in the sensory-discriminative, as well as in the emotional and cognitive dimension of pain [53, 54]: therefore, non-invasive cerebellar current stimulation may modulate pain experience and the associated cortical activities through different, not mutually exclusive mechanisms. Moreover, our results indicate, for the first time in humans, that the cerebellum is also engaged in the primary sensory-discriminative dimension of pain.

A recent paper by Pereira and co-workers [55] has confirmed our results, showing that anodal cerebellar tDCS reduces lower extremity pain perception in healthy humans.

However, in a previous study, Zunhammer and colleagues [56] failed to demonstrate analgesic effects of rTMS applied over the cerebellum; the discrepancy with our results, may be due to different factors: the authors evaluated changes in subjective pain thresholds, without any neurophysiological support, and used a different neuromodulation technique (rTMS vs. tDCS).

The efficacy of cerebellar tDCS on pain treatment has been recently confirmed also in patients suffered from "phantom limb pain" (PLP) [51].
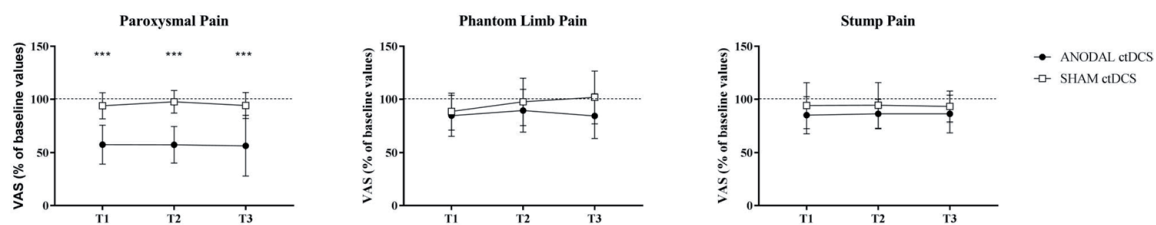
Figure 4.
Painful (top row) phantom limb phenomena: changes in VAS scores overtime. Note that anodal ctDCS (black circles) significantly improved paroxysmal pain compared to the sham condition (white squares). Data are given as percentage of baseline value ±1 S.D. At each time interval, the statistical significance refers to the comparison between anodal (active) and sham (placebo) stimulation (***p < 0.001, Bonferroni post-hoc comparison; modified from [51], with permission).

PLP remains a challenge for clinicians and neuroscientists. The short and long-term effectiveness of pharmacological interventions is unclear; most of the studies were limited by their small sample sizes and by different pharmacological effects on either painful and non-painful phenomena; also invasive spinal cord stimulation (SCS), probably due to its poor somatotopic specificity, failed to demonstrate significant and long-lasting effects specificity [57, 58].

Recent studies have shown that tDCS applied over the motor cortex represents a promising therapeutic tool in PLP, with effects likely arising from a transient restoration of the cortical representation of the phantom limb [59–62]. Based on this, we have recently shown that anodal ctDCS improves both paroxysmal pain and non-painful phantom limb sensations in subjects with upper limb amputations (**Figure 4**), as confirmed by changes observed in LEP amplitudes, with anodal tDCS significantly reducing the amplitude of both N1 and N2/P2 components [51]. We argue that, different from other brain targets and depending on the extent of anatomical connections between the cerebellum and the brain, ctDCS may reduce both painful and non-painful phantom limb sensations, which are induced by maladaptive changes in the sensorimotor network and posterior parietal cortex, respectively [59].

5. Laser evoked potentials (LEPs) as a valuable outcome measure: setting and method

Laser evoked potentials (LEPs) allow to evaluate both the lateral and the medial pain pathways, two different, parallel and partially segregated spinal "highways," targeting cortical areas differently involved in nociceptive experience and pain processing. In particular, the two main LEP components, formally named N1 and N2/P2 potentials, correspond, respectively, to the activation of the secondary somatosensory cortex (SII) and of the insular region; from a functional perspective, N1 reflects the sensory-discriminative, whereas N2/P2 complex the affective-emotional dimension of pain [32, 33].

A solid-state laser is commonly used in clinical trials (neodymium: yttrium-aluminum-perovskite, Nd: YAP; wavelength 1.04 mm, pulse duration 2–20 ms, maximum energy 7J: Stimul 1340VR, Electronical Engineering®, Florence, Italy). The laser beam was transmitted from the generator to the stimulating probe via a 10 m length optical fiber; signals were amplified, band pass filtered (0.1–200 Hz, time analysis 1000 ms) and fed to a computer for analysis [30, 63, 64]. Compared to CO_2 laser, Nd: YAP uses pulses with a shorter duration and lower wavelengths, thus resulting in a better synchronization of afferent inputs, reducing at the same time the possibility of tissue damage (**Figure 5**).

In our paper [51], the stump was stimulated by laser pulses (individual variability: 15.75–24.91 J/cm^2) with short duration (5 ms) and small diameter spots (5 mm), inducing pinprick sensations. Twenty stimuli, whose intensity was established on the basis of the perceptive threshold of each patient, were delivered: we used a fixed intensity set at two times the individual sensory threshold, defined as the lower stimulus intensity that elicited a distinct painful pinprick sensation. In order to reduce both skin lesions and fatigue of peripheral nociceptors, the laser beam was shifted slightly by ~10 mm in a random direction between consecutive pulses [64]. Patients were reclined on a couch, wore protective goggles, and were instructed to keep their eyes open and gaze slightly downwards; they were requested to mentally count the number of stimuli, to keep their attention level constant. The interstimulus interval varied randomly between 15 and 30 s.

The main Aδ-LEP complex, N2/P2, and the earlier lateralized N1 component were recorded through standard disc, nonpolarizable Ag/AgCl surface electrodes (diameter 10 mm; BiomedVR, Florence, Italy). N2 and P2 components were recorded from the vertex (Cz), referenced to the earlobes; the N1 component was recorded from the contralateral temporal leads (T3 or T4), referenced to Fz [63]. The baseline-to-peak and the peak-to-peak amplitudes of N1 and N2/P2 components, respectively, were evaluated. Blinks and saccades were recorded with an EOG electrode placed on the supero-lateral right canthus connected to the system reference. Ground was placed on the mid-forehead.

Skin impedance was kept below 5 kΩ. An automatic artifact rejection system excluded all trials contaminated by transient signals exceeding the average value by ±65 μV on each recording channel, including the EOG.

6. Theoretical limitations to tDCS for cerebellar stimulation

Cerebellar tDCS has still some limitations. First, the variability in outcome measures as well as the applied stimulation parameters across studies prompts further research about montage, duration, intensity of stimulation, electrodes number, and placement.

Second, direct current stimulation may exert different, sometimes opposite, effects on motor and non-motor cerebellar functions; in this view, while studies exploring cognitive and emotional domains have used a classical monopolar configuration, others focusing on motor functions have adopted a different montage, in which the return electrode is positioned over the ipsilateral face. Only in the second case, tDCS has demonstrated long-lasting polarity-specific effects. That
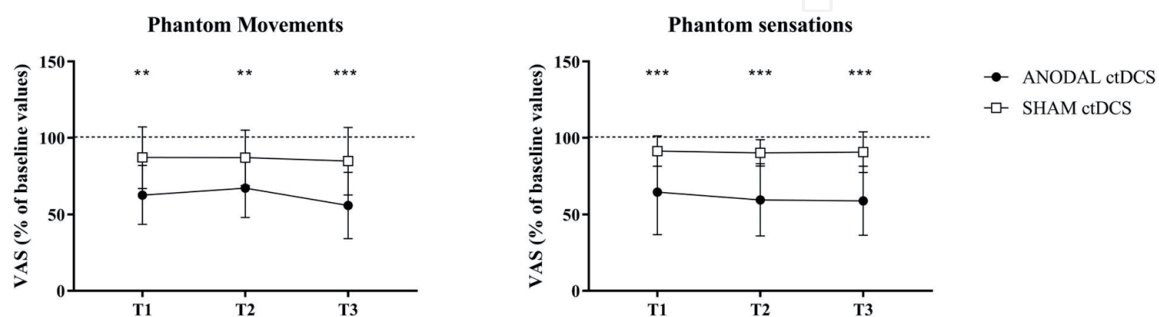

Figure 5.
Non-painful (top row) phantom limb phenomena: changes in VAS scores overtime. Note that anodal ctDCS (black circles) significantly improved phantom movements and sensations compared to the sham condition (white squares). Data are given as percentage of baseline value ±1 S.D. At each time interval, the statistical significance refers to the comparison between anodal (active) and sham (placebo) stimulation (***p < 0.001, Bonferroni post-hoc comparison; modified from [51], with permission).

could be critically depend also on the cerebellar somatotopy: the motor cerebellum is mainly represented within the anterior areas, whereas non-motor functions are likely located in the posterior regions. In this connection, only few studies have demonstrated to date the "reverse effect" between anodal and cathodal polarization [45, 52, 65].

Third, tDCS effects critically depend on the structure orientation relative to the electric field direction: neurons of the cerebellum are not identically orientated and follow complex anatomical distributions over folia. That might cause a hyperpolarization in some cells, while others are depolarized at the same time [66, 67].

7. Conclusions

Cerebellar current stimulation represents an emerging, safe, and effective neuromodulation strategy for pain treatment. The possibility to interfere with cerebellar activity is particularly fascinating in the field of chronic pain syndromes, given that the cerebellum itself regulates both ascending and descending pathways involved in pain processing and nociception. However, the exact mechanisms of action are not fully understood, and some stimulation parameters have to be clearly defined, comprising duration, intensity, and charge density. Moreover, more attention will be deserved to combine and integrate different NIBS techniques, as well as different targets at the same time; for instance, by using the same device, cerebellar tDCS may be associate to spinal direct current polarization, in order to improve the clinical outcome and possibly extend putative effects over time.

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