XXIX Congresso Nazionale SIPF

"Beyond the lockdown of the brain"

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Aula Magna di Economia "Vincenzo Li Donni" - Università degli Studi di Palermo

The "painful" cerebellum: new evidence for an old debate

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Background

- The cerebellum is involved in a wide number of integrative functions, ranging from working memory and associative learning to motor control (Schmahmann, 1991; Ito, 2006; Stoodley & Schmahmann, 2009; Strick et al., 2009; Balsters et al., 2013).
- During the past 15-20 years, there has been growing interest to define the cerebellar role in pain processing and perception (Welman et al., 2018; Baarbe et al., 2018; Mehnert et al., 2019). However, its role in pain processing is only poorly understood
- Cerebellum is involved in the sensory, cognitive and affective dimensions of pain (Borsook et al., 2008).

Animal studies suggest that..

- In cats, stimulation of cutaneous Aδ and C fibers nociceptors activates climbing fibers and mossy fibers that terminate on Purkinje cells (Ekerot et al., 1987; Wu and Chen, 1992).
- In rats, visceral pain activates visceral nociceptive-specific neurons in the lateral medullary reticular formation, including several with direct projections to the cerebellar vermis (Ness et al., 1998), and can modulate Purkinje cell activity in the posterior cerebellar vermis (Saab and Willis, 2001).

- However, evidence of how nociceptive information is encoded once it reaches the cerebellum is lacking.

Review > Brain Res Rev. 2010 Oct 5;65(1):14-27. doi: 10.1016/j.brainresrev.2010.05.005. Epub 2010 May 27.

The cerebellum and pain: passive integrator or active participator?

Eric A Moulton [1], Jeremy D Schmahmann, Lino Becerra, David Borsook

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Cerebellar Cortical Stimulation Increases Spinal Visceral Nociceptive Responses

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Exp Brain Res (2002) 146:117–121
DOI 10.1007/s00221-002-1107-8

RESEARCH NOTE

C. Y. Saab · W. D. Willis

Cerebellar stimulation modulates the intensity of a visceral nociceptive reflex in the rat

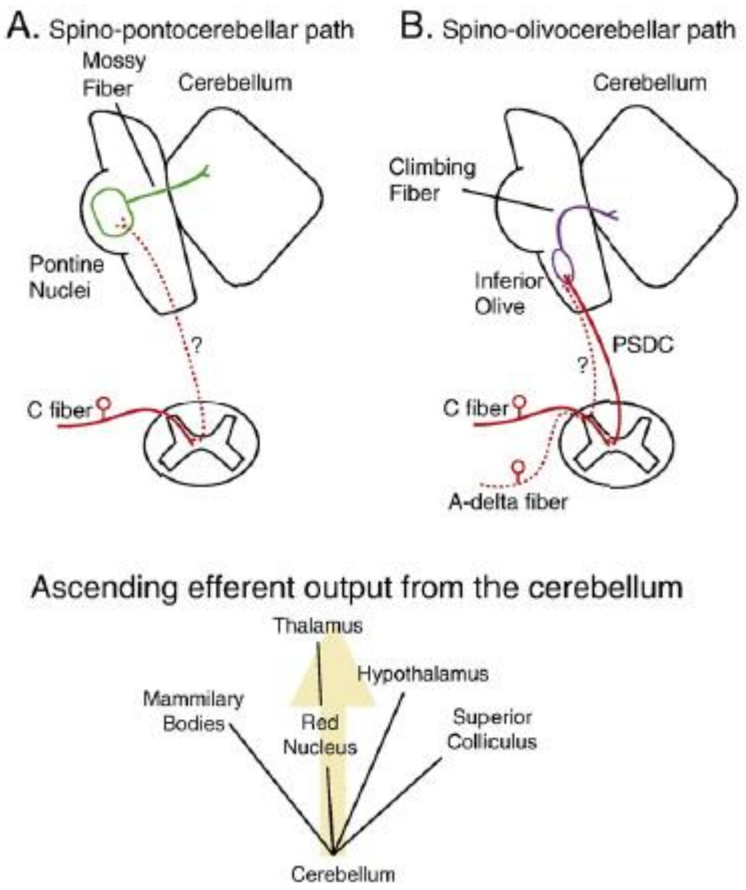
- In squirrel monkeys, electrical stimulation of the anterior cerebellar lobe can raise nociceptive thresholds to tail shock (Siegel and Wepsic, 1974).
- Microinjection of morphine into the anterior portion of the cerebellum of rats results in acute analgesia that is reversible by electrical stimulation at the site of the microinjection (Dey and Ray, 1982).
- Stimulation of rat cerebellar cortex using electrical stimulation increases neural responses to a noxious visceral stimulus in and around the termination sites of nociceptive afferents in the spinal cord (Saab and Willis, 2001).

- However, the relation between electrical stimulation and the experience of pain is still not well defined.

… and what about humans?

- Studies in humans have demonstrated that the cerebellum is critically involved in the visceral pain (Claassen et al., 2020).
- Studies have suggested that the cerebellum may exert a key role in the sensory-motor integration aimed at antinociceptive behavior (Borsook et al., 2008) and in behavioral responses to nociceptive stimulation (Duerden et al., 2013).
- A clinical study showed that patients with cerebellar infarctions have reduced pain thresholds (Ruscheweyh et al., 2014).

- *Putative pathways*

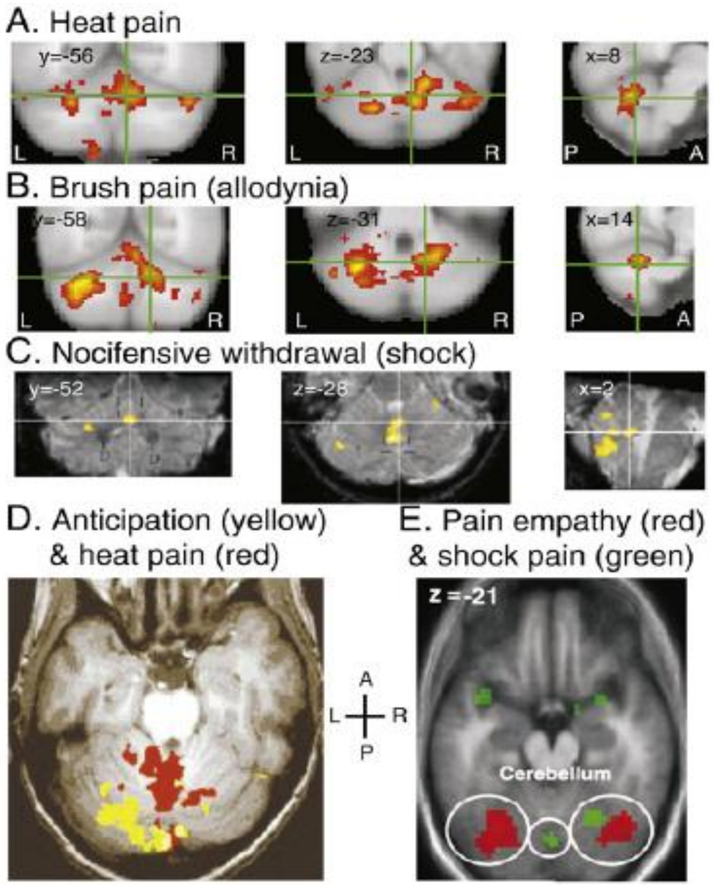


Moulton et al., *Brain Res Rev* 2010

… and what about humans?

- *fMRI studies*

- Changes in structural volume and functional connectivity of the cerebellum seem to predict chronicization and long-term disability in migraine (Qin et al., 2019; Liu et al., 2020).
- Functional neuroimaging has demonstrated that the posterior cerebellum plays a key role in pain-related adaptations for motor control (Coombes et al., 2016; Fernandez et al., 2017).



Borsook et al., *Cerebellum* 2008; Dimitrova et al., *J Neurophysiol* 2003; Plogahus, *Science* 1999

tDCS and pain

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Neurosci Lett. 2016 Jul 28;626:149-57. doi: 10.1016/j.neulet.2016.05.034. Epub 2016 May 18.

Effects of left primary motor and dorsolateral prefrontal cortex transcranial direct current stimulation on laser-evoked potentials in migraine patients and normal subjects

Eleonora Vecchio [1], Katia Ricci [2], Anna Montemurno [2], Marianna Delussi [2], Sara Invitto [3], Marina de Tommaso [2]

Randomized Controlled Trial Eur J Pain. 2018 Aug;22(7):1312-1320. doi: 10.1002/ejp.1220. Epub 2018 Apr 17.

Transcranial direct current stimulation for upper limb neuropathic pain: A double-blind randomized controlled trial

G N Lewis [1], D A Rice [1 2], M Kluger [2 3], P J McNair [1]

Review J ECT. 2018 Sep;34(3):e36-e50. doi: 10.1097/YCT.0000000000000518.

Transcranial Direct Current Stimulation as a Therapeutic Tool for Chronic Pain

Camila Bonin Pinto [1], Beatriz Teixeira Costa, Dante Duarte, Felipe Fregni

Review J Pain. Nov-Dec 2020;21(11-12):1085-1100. doi: 10.1016/j.jpain.2020.01.003. Epub 2020 Jan 23.

Is Transcranial Direct Current Stimulation (tDCS) Effective for the Treatment of Pain in Fibromyalgia? A Systematic Review and Meta-Analysis

Donna M Lloyd [1], Priscilla G Wittkopf [2], Laura J Arendsen [3], Anthony K P Jones [4]

Randomized Controlled Trial Pain. 2021 Jun 1;162(6):1659-1668. doi: 10.1097/j.pain.0000000000002187.

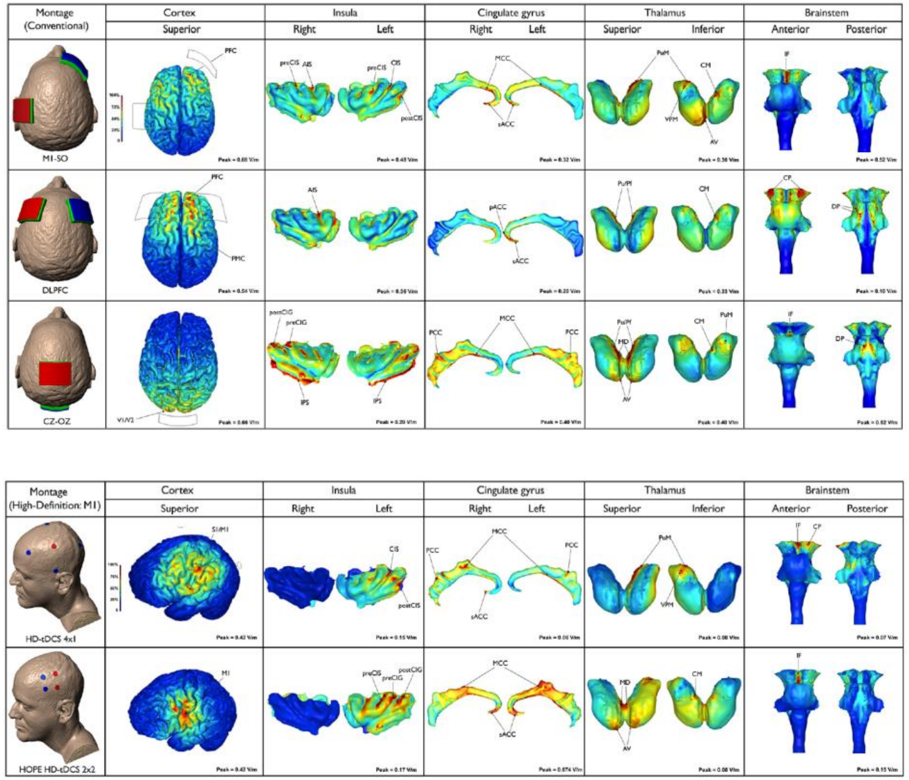
Effect of anodal high-definition transcranial direct current stimulation on the pain sensitivity in a healthy population: a double-blind, sham-controlled study

Sebastian Kold [1], Thomas Graven-Nielsen

Princ Pract Clin Res. Jan-Apr 2020;6(1):23-26. doi: 10.21801/ppcrj.2020.61.5. Epub 2020 May 21.

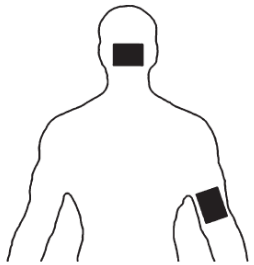
The Analgesic Effect of Transcranial Direct Current Stimulation (tDCS) combined with Physical Therapy on Common Musculoskeletal Conditions: A Systematic Review and Meta-Analysis

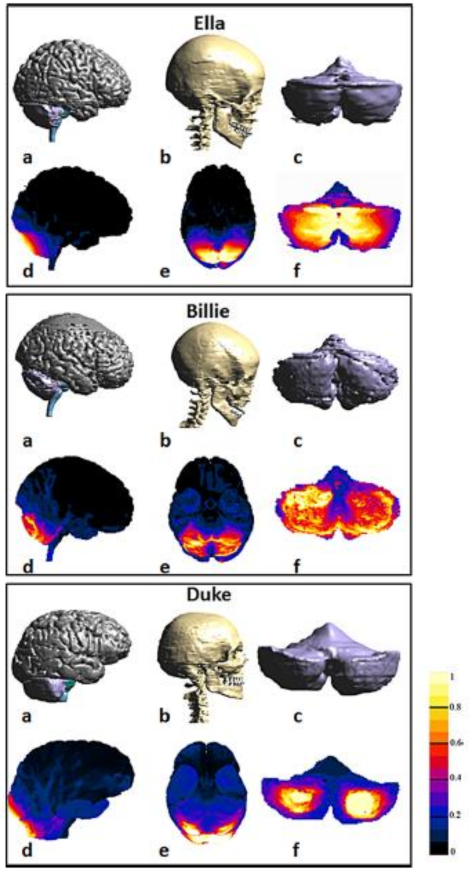
Paulo E P Teixeira [1 2], Laila Alawdah [3], Hassan Adam A Alhassan [4], Matteo Guidetti [5], Alberto Priori [5], Stefania Papatheodorou [4], Felipe Fregni [2]



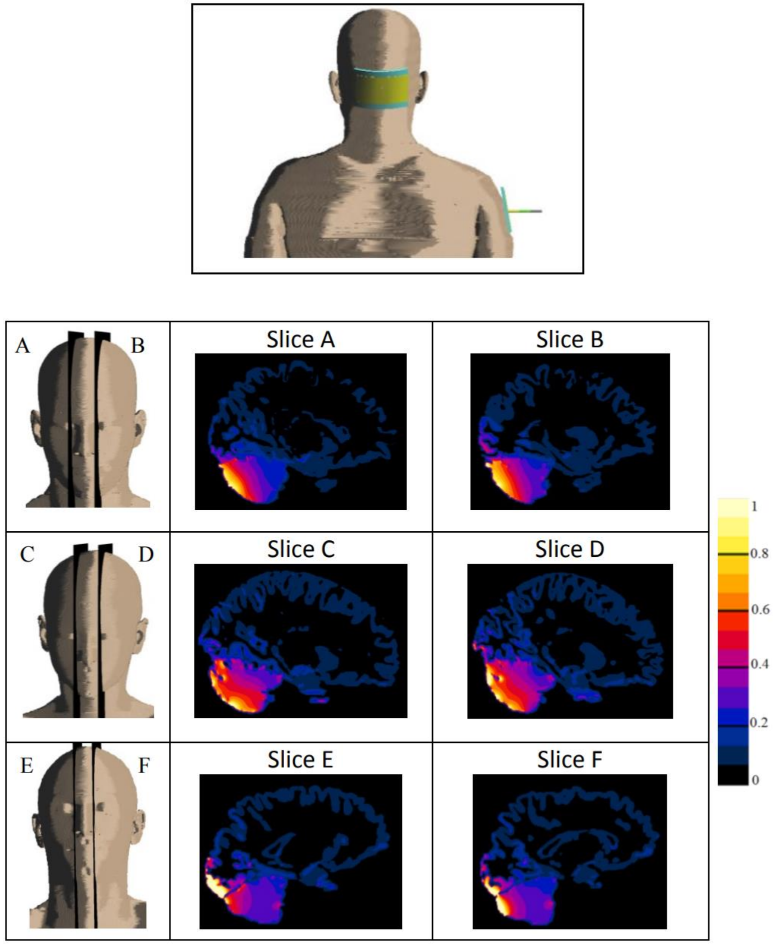
DaSilva et al., *Front. Neuroanat*,, 2015

Cerebellar tDCS and pain

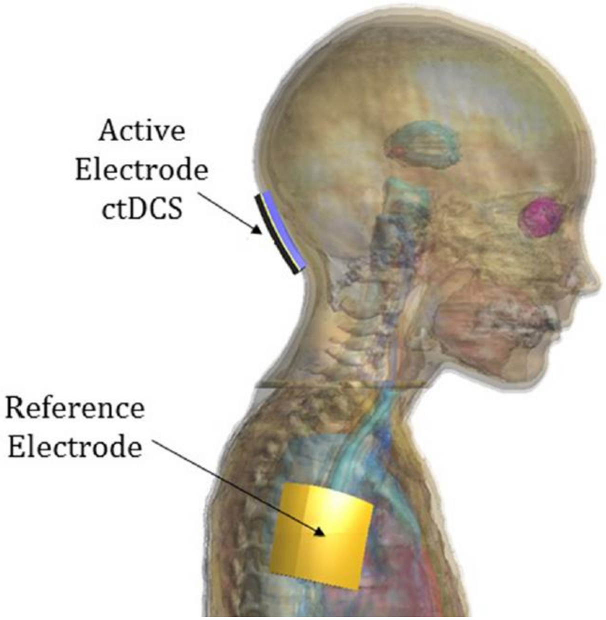




Parazzini et al., *Clin Neurophysiol* 2013



Parazzini et al., *35th Annual International Conference of the IEEE EMBS* 2013



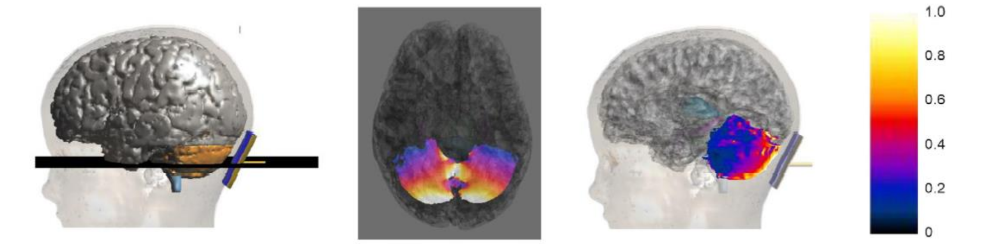


FIGURE 4 | Axial section across the cerebellum (2nd column) of the E amplitude distribution for Roberta. The first column on the left shows the plane where the section was calculated. The third column shows the sagittal view of the **E** amplitude distribution over the cerebellar surface. The colored scale on the right is normalized with respect to the maximum of the **E** amplitude in the cerebellum.

Parazzini et al., *Front. Hum. Neurosci., 2016*

Cerebellar tDCS and pain – healthy subject

- Recent papers have suggested that ctDCS modulates pain processing in healthy humans.
- ctDCS seems to exert polarity-specific effects on the amplitude of Laser Evoked Potentials (LEPs), thus modifying the perception of experimentally induced pain in young volunteers (Bocci et al., 2015).
- In a following study, highly hypnotizable participants have showed an effect of cerebellar tDCS opposite to that observed in the general population: highs did not change their subjective pain perception and, modulated only the N2/P2 amplitude, which paradoxically increased after cerebellar anodal tDCS (Bocci et al., 2016).

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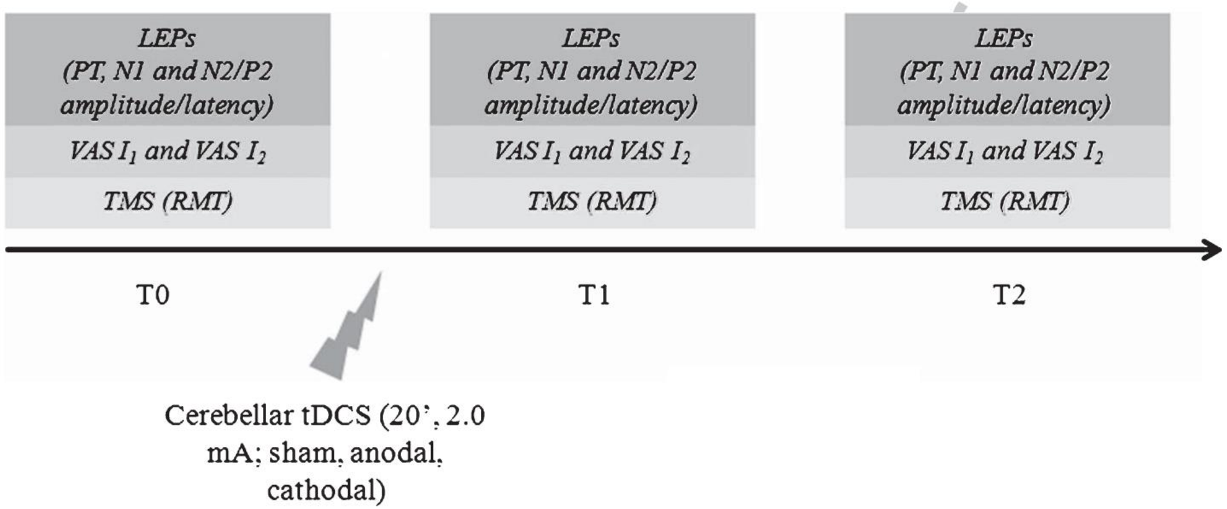


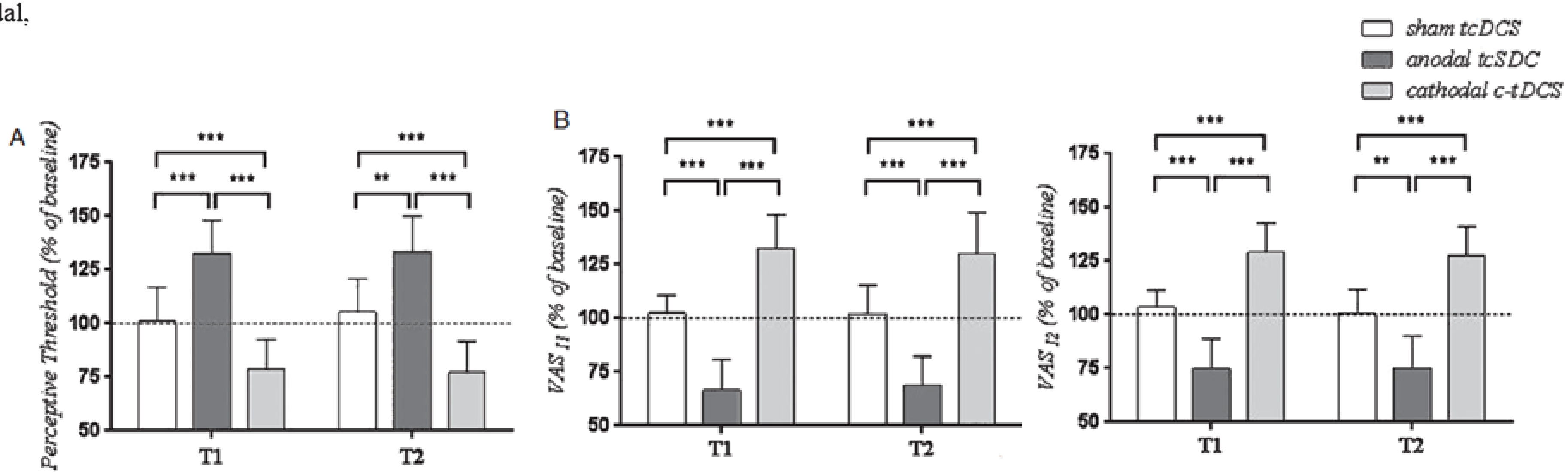


Figure 1 – A. Fig. 3. - A. Perceptive Threshold. Changes (mean±S.D) at T1 and T2 with respect to baseline values (T1/T0, T2/T0), following sham (black), anodal (white) and cathodal (grey) tcDCS. (∗∗p < 0.001; ∗∗∗p < 0.0001). B. Changes in visual analogue scale (VAS) scores over time. VAS scores at two different stimulus intensity, respectively two (A, left) and three (B, right) times higher than the PT. (∗∗p < 0.001; ∗∗∗p < 0.0001).

Bocci et al., *Restor Neurol Neurosci* 2015

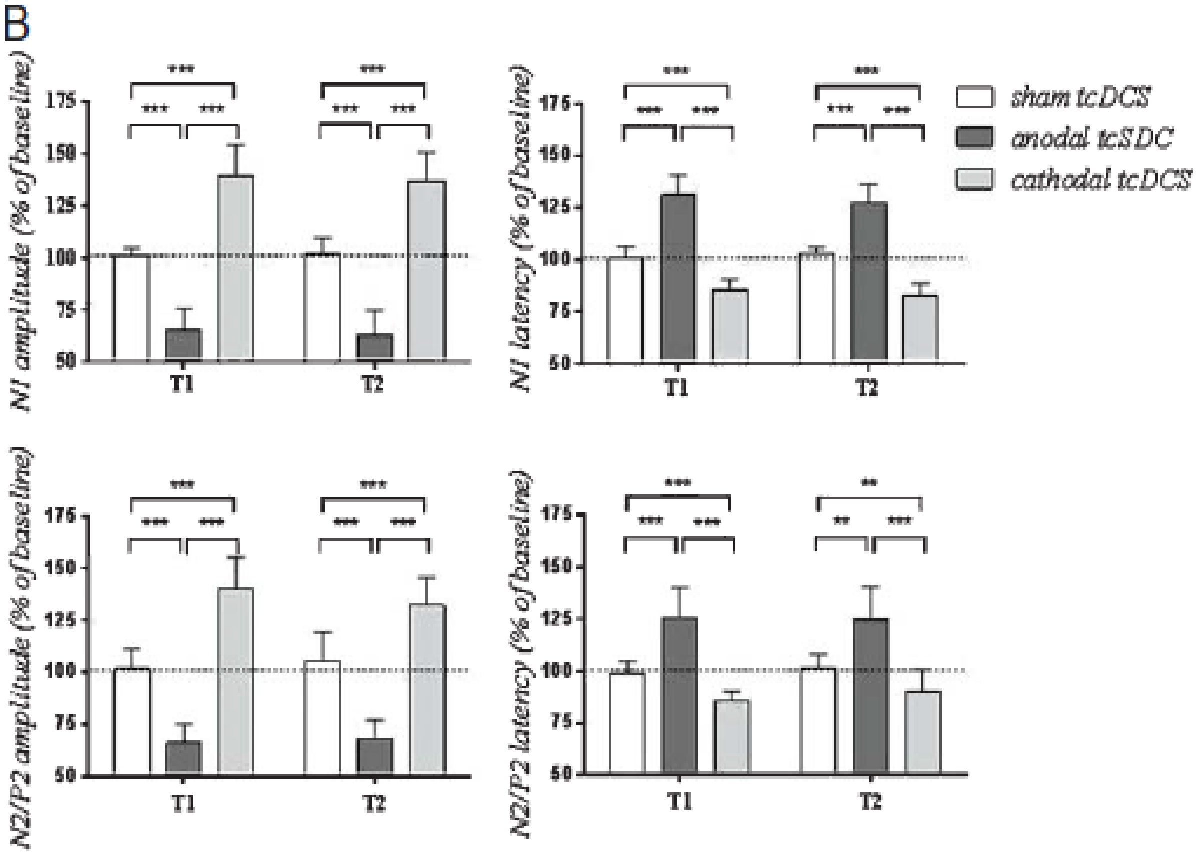


Figure 2 – LEPs grand averaging: traces were recorded at baseline (T0, black) and immediately after cerebellar polarization (T1, red) due to sham (left column), anodal (middle) and cathodal (right) tcDCS. B. Histograms showing LEPs variables and VAS scores changes (mean±S.D) after sham (black), anodal (white) or cathodal (grey) tcDCS with respect to baseline. Top panels: changes in N1 variables (amplitude and latency) over time; bottom panels: changes in N2/P2 complex (∗∗$p < 0.001$; ∗∗∗$p < 0.0001$).

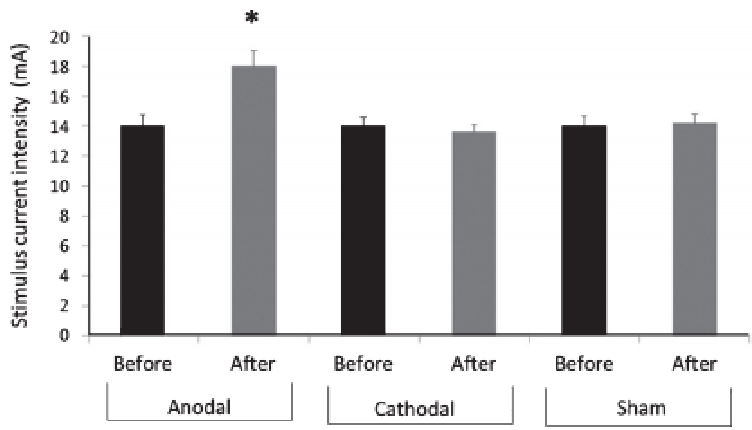
Bocci et al., *Restor Neurol Neurosci* 2015

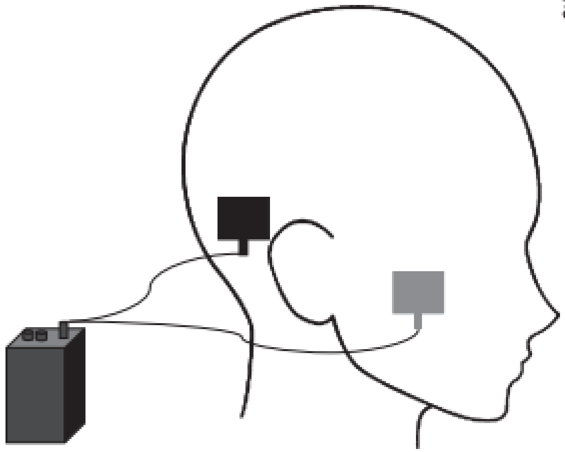
- The study by Bocci et al. (2015) suggests that:
  - *cerebellum interferes with nociceptive processing following a CBI-like mechanism*. Consequently, anodal ctDCS may reduce pain perception by increasing the inhibitory tone exerted by the cerebellum on different brain targets, whereas cathodal ctDCS could elicit opposite effects by inducing hyperalgesia.
- A recent paper has confirmed these results (but partially), showing that anodal ctDCS reduces lower extremity pain perception in healthy humans (Pereir et al., 2017)

NeuroRehabilitation 40 (2017) 195–200
DOI:10.3233/NRE-161404
IOS Press

Anodal cerebellar tDCS modulates lower extremity pain perception

Manuel Pereira[a], Basil Rafiq[a], Einul Chowdhury[a], Jacqueline Babayev[a], HyunJi Boo[a], Rowan Metwaly[a], Priam Sandilya[a], Eileen Chusid[a] and Fortunato Battaglia[b,*]
[a]*Department of Pre-Clinical Sciences, New York College of Podiatric Medicine, New York, NY, USA*
[b]*Department of Interprofessional Health Sciences & Health Administration, School of Health and Medical Sciences, Seton Hall University, South Orange, NJ, USA*





From bench to bedside

Cerebellar tDCS and pain – phantom limb pain

- A recent study have recently shown that anodal ctDCS improves both paroxysmal pain and non-painful phantom limb sensations in subjects with upper limb amputations (Bocci et al., 2019).

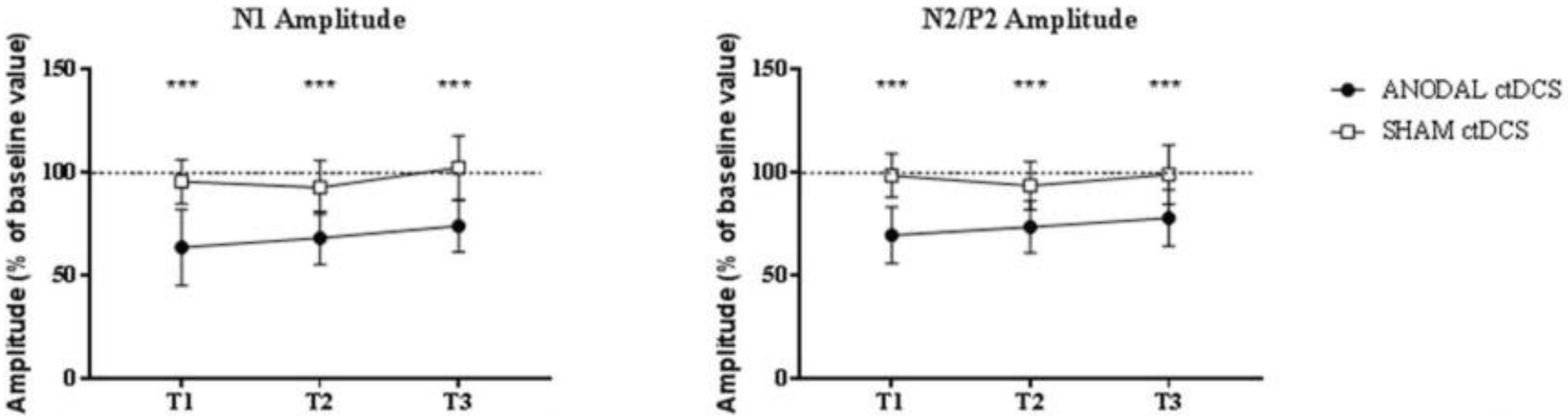


Fig. 1 LEP changes. **a** Exemplificative LEPs recorded at baseline (T_0), immediately after (T_1), at 1 week (T_2), and 3 weeks (T_3) following the completion of anodal ctDCS. Note the reduction of LEP amplitudes over time both for N1 and N2/P2 components. **b** Changes in LEP amplitudes between the anodal (black circles) and sham condition (white squares). Data are given as percentage of baseline value ± 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)

Cerebellar tDCS and pain – phantom limb pain

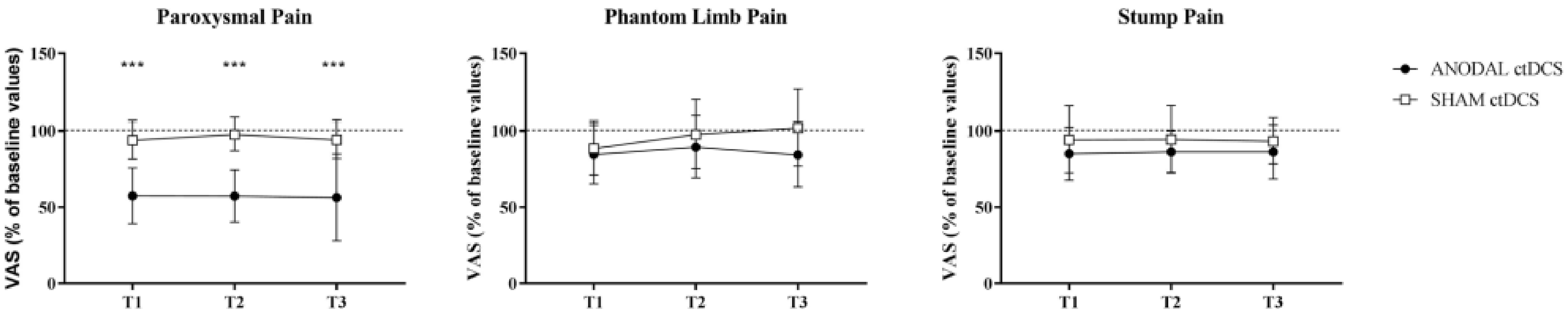


Fig. 2 Painful phantom limb phenomena. Changes in VAS scores over time (paroxysmal pain, phantom limb pain, and stump pain); note that anodal ctDCS (black circles) significantly improved paroxysmal pain compared to the sham condition (white squares). Data are reported as percentage of baseline value ± 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)

Next steps?

- Further studies are needed to improve the technique (montage, stimulation protocol)
- Further studies are needed to assess the ctDCS in association with other strategies (behavioral, pharmacological..)
- Further studies are needed to assess the role of individual factors (baseline neuronal state and features, anatomy, age).

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Grazie per l'attenzione