CEREBELLAR DIRECT CURRENT STIMULATION MODULATES PAIN PERCEPTION IN HUMANS

Tommaso Bocci [1], Enrica Santarcangelo [2], Davide Barloscio [1,3], Beatrice Vannini [1], Laura Parenti [1,3], Giancarlo Carli 4, Roberta Ferrucci [5], Alberto Priori [5], Massimiliano Valeriani [6,7], Ferdinando Sartucci [1,3]

1 Department of Clinical and Experimental Medicine, Unit of Neurology, Pisa University Medical School, Pisa, Italy; 2 Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa Pisa, Italy; 3 Department of Clinical and Experimental Medicine, Cisanello Neurology Unit, Pisa University Medical School, Pisa, Italy; 4 Department of Medical and Surgical Sciences and Neuroscience, University of Siena, Siena, Italy; 5 Department of Neurological Sciences, University of Milan, Fondazione IRCCS Ospedale Maggiore Policlinico, Milan, Italy; 6 Division of Neurology, Ospedale Bambino Gesù, IRCCS, Rome, Italy; 7 Center for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark.

Background

The cerebellum is involved in a wide number of integrative functions, but its role in pain experience and in the nociceptive information processing is poorly understood. In healthy volunteers we evaluated the effects of transcranial cerebellar direct current stimulation (tcDCS) by studying the changes in the perceptive threshold, pain intensity at given stimulation intensities (VAS:0-10) and laser evoked potentials (LEPs) variables (N1 and N2/P2 amplitudes and latencies).

Materials and Methods

Fifteen healthy subjects were enrolled. LEPs were obtained using a neodymium:yttrium–aluminium–perovskite (Nd:YAP) laser and recorded from the dorsum of the left hand. The main Aδ-LEP vertex complex, N2–P2, and the lateralised N1 component were recorded through standard disc, non-polarizable Ag/AgCl surface electrodes. N2 and P2 components were recorded from the vertex (Cz) referenced to the earlobes; the N1 component was recorded from the temporal leads (T4) referenced to Fz. VAS was evaluated by delivering laser pulses at two different intensities, respectively two and three times the perceptive threshold. After the PT assessment, participants were instructed to pay attention to incoming laser nociceptive stimuli in order to verbally rate the perceived intensity about 2-3 seconds after each laser stimulation, which was performed before tcDCS (T0), immediately after its termination (T1) and 60 min later (T2).

Anodal, cathodal and sham tcDCS stimulations were administered in three different sessions and separated by at least 1 week to avoid possible carry-over effects.

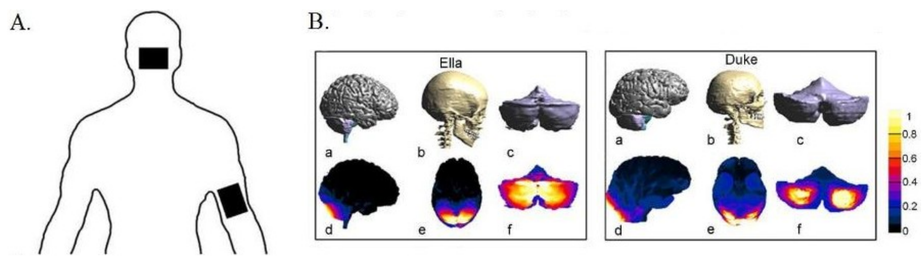


Figure 1 *– Current density generated by cerebellar transcranial direct current stimulation (cerebellar tDCS) in humans. **A**. Top panel shows (viewed from the back) the electrode positions for cerebellar tDCS. **B**. Examples of segmented tissues in two human realistic Virtual Family models (Ella and Duke) undergoing cerebellar tDCS. Simulations were conducted using the simulation platform SEMCAD X (modified from Priori et al., J Physiol 2014, with permission)*

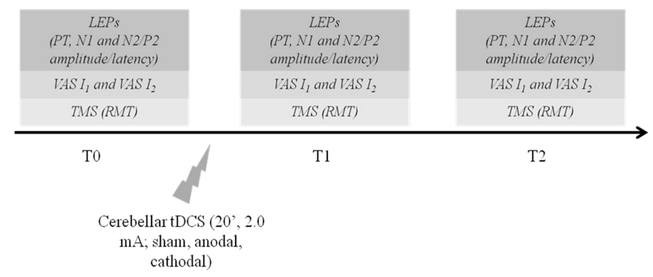


Figure 1 – Experimental protocol. Psychophysical and electrophysiological variables evaluated at baseline (T0) and at two different time points (T1, T2) following anodal, cathodal and sham tcDCS.

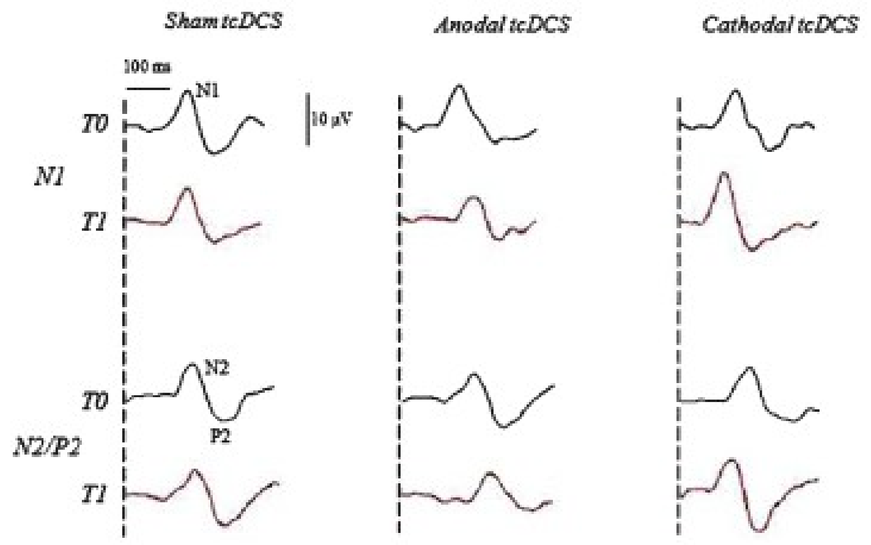
Results

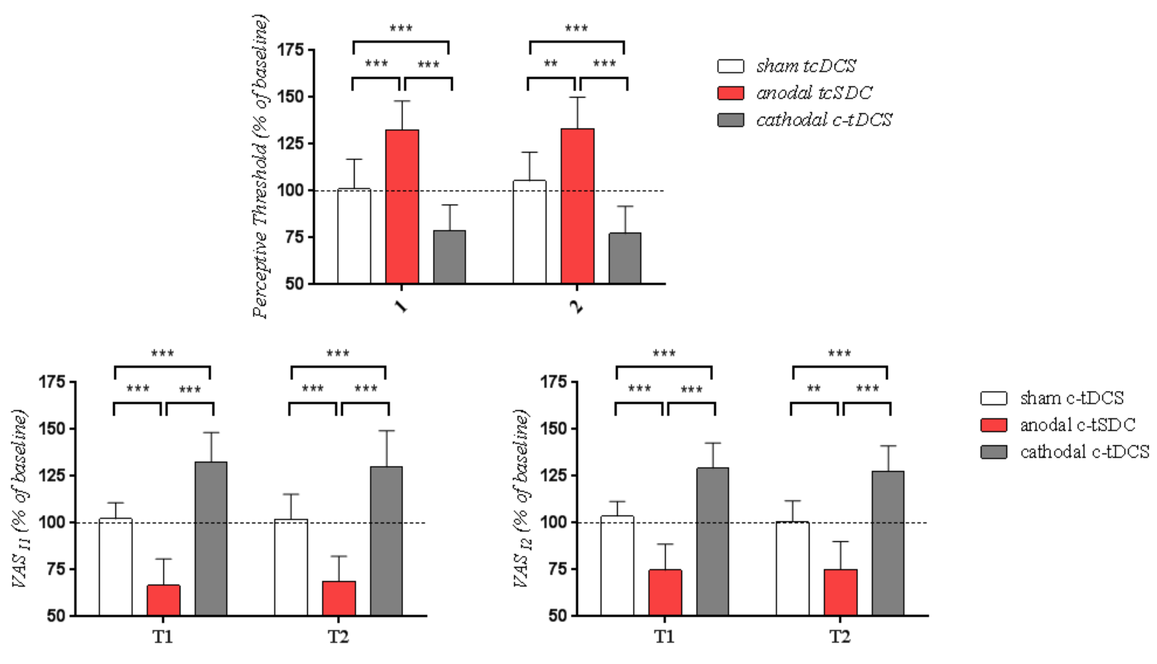
		aT0	aT1	aT2	cT0	cT1	cT2	shT0	shT1	shT2
PT	Mean	4.62	6.07	6.09	4.85	3.76	3.68	4.72	4.66	4.89
	S.D.	0.80	0.95	0.92	0.86	0.62	0.67	0.98	0.62	0.81
VAS I_1	Mean	3.89	2.55	2.65	3.67	4.93	4.67	3.87	3.93	3.87
	S.D.	0.84	0.57	0.62	0.82	0.96	0.82	0.74	0.70	0.92
VAS I_2	Mean	5.40	4.02	4.03	5.24	6.73	6.65	5.33	5.49	5.30
	S.D.	0.63	0.82	0.71	0.48	0.47	0.49	0.78	0.69	0.64
N1 amplitude (μV)	Mean	12.92	8.48	8.01	11.04	14.96	14.94	11.01	11.11	11.21
	S.D.	3.18	2.98	2.58	2.65	2.58	3.33	2.50	2.67	2.83
N1 latency (ms)	Mean	124.19	161.46	157.10	127.04	107.15	104.05	128.17	128.67	130.66
	S.D.	10.90	13.38	13.68	10.75	6.75	9.12	13.20	12.71	12.09
N2/P2 amplitude (μV)	Mean	11.14	7.38	7.57	10.52	14.53	13.75	11.14	11.25	11.47
	S.D.	2.62	2.37	2.33	2.65	2.96	3.29	2.72	2.69	2.16
N2/P2 latency (ms)	Mean	151.57	189.32	187.26	148.78	126.73	132.30	153.90	151.08	155.51
	S.D.	13.12	17.49	21.39	22.01	18.49	18.70	14.33	15.07	16.75

Table 1. Row data (expressed as mean value ± 1 standard deviation, S.D.). VAS were studied in each subject in response to nociceptive laser stimuli applied at two different stimulation intensities , corresponding to two and three times the subjective perceptive threshold, formally named VAS I_1 and VAS I_2, respectively (a = anodal stimulation; c = cathodal stimulation; sh = sham condition; PT: perceptive threshold).

		anodal	*cathodal*	*sham*
PT	time	F(2,28)=44.30	F(2,28)=18.67	ns
	T0 vs T1	F(1,14)=77.669)	F=27.523	
	T0 vs T2	F(1,14)=78.745	F=27.827	
	T1 vs T2	ns	ns	
		anodal vs sham	*cathodal vs sham*	
	T0	ns	ns	
	T1: t(1,14)=5.069		t= 6.991	
	T2: t(1,14)=3.709, p<.002		t=5.849	
VAS		*anodal*	*cathodal*	*sham*
	time	F=41.954	F=31.448	ns
	T0 vs T1	F=56.968	F=48.596	
	T0 vs T2	F=52.289	F=52.5	
	T1 vs T2	ns	ns	
		anodal vs sham	*cathodal vs sham*	
	T0	ns	ns	
	T1	t=6.44	t=5.916	
	T2	t=5.294	t=5.82	

Table 2. Contrast analyses: all comparisons were highly significant ($p < 0.0001$).





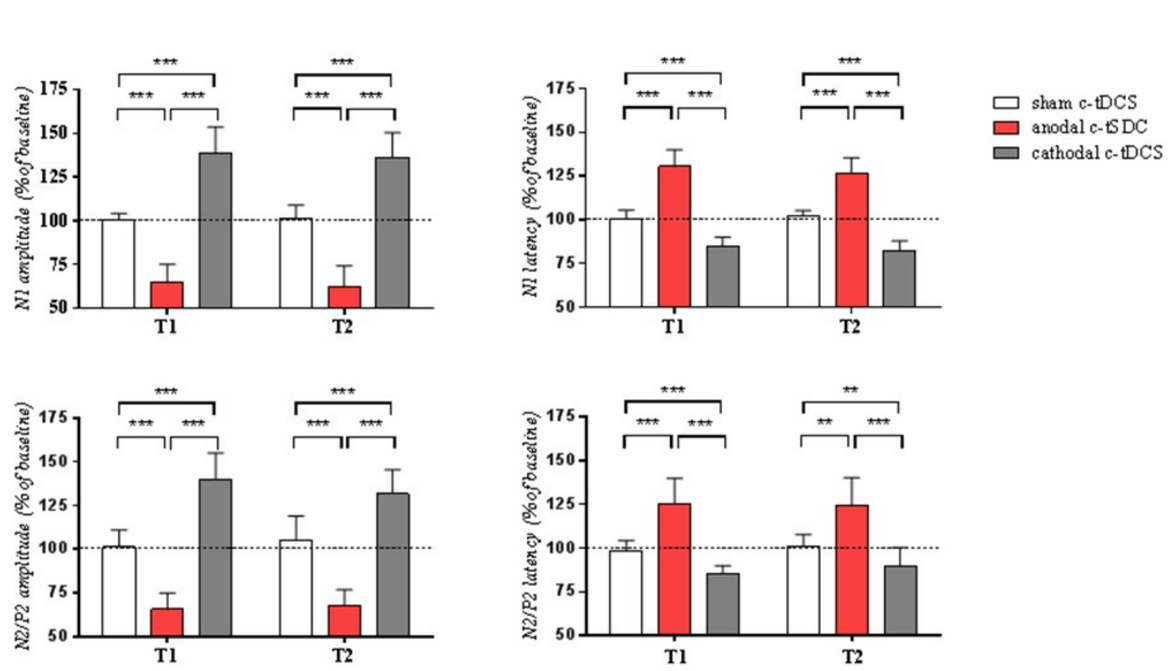


Figure 2 *– Correlations between electrophysiological data (iSPOL, iSPD, TCT), motor scores and mutational load. Note that iSPOL and TCT are directly correlated with CAG-length and motor score, as well as with the Disease Burden Index, while iSPD shows an inverse correlation. Correlation lines (black) and error bars (dotted lines) are shown.*

Figure 1 *– **A.** Averaged LEPs across subject. Traces recorded at baseline (T0) and immediately after cerebellar polarization (T1) 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 (** $p < 0.001$; *** $p < 0.0001$).*

Discussion and Conclusions

- Our study shows that cerebellar direct current polarization modulates nociceptive perception and its cortical correlates in healthy humans.
- Cathodal suprathreshold tcDCS increases pain perception, increases amplitudes and decreases LEPs latencies, likely though reduction of the inhibitory tone exerted by the cerebellum on brain targets. Anodal polarization elicits opposite effects producing analgesia.
- As tDCS is effective on both N1 and N2/P2 components, we speculate that the cerebellum engagement in pain processing modulates the activity of both somatosensory and cingulate cortices.
- Non-invasive cerebellar current stimulation may modulate pain experience and the associated cortical activity through many, not alternative mechanisms. In particular, changes in N1 reflects the modulation of the sensory component of pain, while the vertex N2/P2 represents the neural correlate of affective aspects of pain experience (Garcia-Larrea et al. 1997; Valeriani et al. 2007).

For further informations: bocci.tommaso@gmail.com