Letter to the editor

Difficulty of Comparing the Multiple Heterogeneous Approaches: Comment to Transcranial Direct Current Stimulation in Epilepsy

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We read with pleasure the paper of San-Juan and coworkers [1] published recently in Brain Stimulation. This review has provided a step forward in the direction of the use of this promising technique also in a therapeutic setting with patients suffering from epilepsy. At present, the technical approaches of transcranial direct current stimulation (tDCS) are still very heterogeneous. Nearly every study uses different patient categories, different stimulation protocols, different electrode sizes, stimulation sites and different stimulation current strength, so that comparison between the different studies is limited. It is therefore highly useful to compare all studies, and to provide standardizable measures in order to judge stimulation effects across them.

San-Juan and coworkers have calculated for every study the applied current density and the total electrical charge during stimulation. However, their calculation of the electrical charge is based on an incorrect formula. In the paragraph Data extraction (p.456), they define electrical charge as “Q = I / t”, and in both Table 1, Table 2, they report values of some hundred nanoCoulombs (nC). For example, for the study of Fregni et al. (2006), they report I = 1 mA and Q = 833 nC during a total of 20 min. stimulation. So they effectively calculated 0.001 A / (20 × 60 s) = 8.333e-7 = 833.333e-9 Coulomb. They did the like for every reported value of electrical charge Q.

Just above the formula “Q = I / t”, they also refer to Brunoni AR et al., 2011 [2]. But those authors defined correctly Q = I × t, which is consistent with the definition in physics of the electrical current as the flow rate of electrical charge per time (I = Q / t = Ampere = Coulomb per second). Calculating electrical charge using this correct formula in the same example of Fregni et al. (2006) in Table 1 results in Q = 1 mA × 20 min = 0.001 x (20 x 60 s) = 1.2 Coulomb.

In summary, all values of the electrical charge Q in Table 1, Table 2 are unfortunately calculated by an incorrect formula and therefore incorrect in values and an error of 9 orders of magnitude. We think that in the journal Brain Stimulation, which is the first address to look for valid reference values in the context of brain stimulation techniques, these wrong values should be corrected (see Table 1, Table 2 corrected).

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References

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[2] A.R. Brunoni, J. Amadera, B. Berbel, M.S. Volz, B.G. Rizzerio, F. Fregni A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol, 14 (2011), pp. 1133-1145.

Table 1. Summary the safety and efficacy of animal studies using tDCS in epilepsy models.

Author (year)	**Type and design of article**	**Animal**	**No. of total sample**	**Age (months)**	**Sex (% males)**	***I* = current dosage (A)** ***J* = current density (A/m^2)** ***Q* = electrical charge (C)**	**Montage**	**Model of epilepsy/type of epilepsy**
Liebetanz et al. (2006) [29]	Original Experimental	Rats	65	2	100	$\boldsymbol{I_{max}}$ **= 200 µA** $\boldsymbol{I_{min}}$ **= 100 µA** $J_{max} = 57.142\ A/m^2$ $J_{min} = 28.571\ A/m^2$ $\boldsymbol{Q_{max,\ 15\ min}}$ **= 0.18 C** $\boldsymbol{Q_{max,\ 30\ min}}$ **= 0.36 C** $\boldsymbol{Q_{max,\ 60\ min}}$ **= 0.72 C** $\boldsymbol{Q_{min,\ 15\ min}}$ **= 0.09 C** $\boldsymbol{Q_{min,\ 30\ min}}$ **= 0.18 C** $\boldsymbol{Q_{min,\ 60\ min}}$ **= 0.36 C**	2 mm left and 2 mm anterior to the bregma	*In vivo* ramp model
Kamida et al. (2011) [31]	Original Experimental	Rats	18	0.7	100	$I = 200\ \mu A$ $J = 57.142\ A/m^2$ ***Q* = 0.36 C**	1.5 mm to the right and 2 mm anterior to the bregma	*In vivo*pilocarpine-induced status epilepticus
Zobeiri et al. (2013) [32]	Original Experimental	Rats	26	6	100	$I_{I,II} = 100\ \mu A$ $I_{III} = 150\ \mu A$ $J_{I,II} = 28.571\ A/m^2$ $J_{III} = 42.857\ A/m^2$ $\boldsymbol{Q_{I,II}}$ **= 0.36 C** $\boldsymbol{Q_{III}}$ **= 0.54 C**	The active EEG electrode was placed on the motor cortex of the right hemisphere with two wires as ground and reference on top of the cerebellum	*In vivo*genetic model of absence epilepsy

Table 1. Summary the safety and efficacy of animal studies using tDCS in epilepsy models.

Author (year)	Type and size of electrodes	Frequency and duration of session	Adverse effects	Outcome
Liebetanz et al. (2006) [29]	3.5 mm^2 ($a = 3.5 \times 10^{-6} m^2$)	4 sessions (50 Hz, 2 ms pulse train) separated by one week 1. Cathodal tDCS for 30 and for 60 min, anodal tDCS for 60 min, and again 60 min of cathodal tDCS. 2. Cathodal tDCS for 15 and for 30 min, anodal tDCS for 30 min, and again cathodal tDCS for 30 min.	None	After tDCS, the threshold for localized seizure activity was determined repeatedly for 120 min at intervals of 15 min. The anticonvulsive effect induced by cathodal tDCS depends on stimulation duration and current strength and may be associated with the induction of alterations of cortical excitability that outlast the actual stimulation.
Kamida et al. (2011) [31]	2.1-mm inner diameter and 3.5 mm^3 ($a = 3.5 \times 10^{-6} m^2$)	2 weeks; 30 min	?	Neuroprotective effects on the immature rat hippocampus, including reduced sprouting and subsequent improvements in cognitive performance. The convulsions were reduced 21% in the postnatal day 55.
Zobeiri et al. (2013) [32]	Tripolar EEG recording electrode and inner diameter of 2.1 mm and a contact area of 3.5 mm^2 ($a = 3.5 \times 10^{-6} m^2$)	I. 10 rats received 4 series of 15 min cathodal and anodal stimulation of 100 µA with an interval of 1 h and 45 min in counter balanced order. II. 8 rats received 4 sessions of 15 min of cathodal stimulation of 100 µA III. 8 rats, similar protocol to II, except 150 µA	None	I. Neither anodal nor cathodal stimulation had significant long-lasting aftereffects on the number or on the mean duration of SWDs in the 1-h 45-min post-stimulation intervals. II and III. The number of SWDs was reduced on the stimulation day compared to baseline and increase (II) or decrease (III) in the mean duration of SWDs from baseline in 1-h 45 min post-stimulation. There were no significant differences for the number and mean duration of SWDs between the baseline day and post-stimulation day Bilateral cathodal tDCS has short lasting antiepileptic effects on the numbers of SWDs and longer lasting (1-h 45-min) intensity-dependent effects on the mean duration of the spike and slow-waves discharges.

Table 2. Summary the human studies of the safety and efficacy using tDCS in epileptic patients.

Author (year)	**Type and design of article**	**No. of total sample**	**Age (year [mean ± SD or range])**	**Sex (% females)**	**I = current; dosage (A)/*J* = current density (A/m^2)/*Q* = electrical charge (C)**	**Montage**	**Model of epilepsy/type of epilepsy**	**Type and size of electrodes**
Fregni et al. (2006) [9]	Experimental randomized sham controlled non blinded	19	24.16 ± 7.9	42	I = 1 mA $J = 0.285$ A/m^2 **$Q = 1.2$ C**	Cathodal stimulation over the epileptogenic focus according to EEG baseline	Focal refractory epilepsy due to cortical dysplasia	Sponge electrode 35 cm^2($a = 3.5 \times 10^{-3}$ m^2)
San Juan et al. (2011) [10]	Case report, experimental non controlled neither blinded	2	23	0	$I_{min} = 1$ mA $I_{max} = 2$ mA $J_{min} = 203.018$ A/m^2 $J_{max} = 406.091$ A/m^2 **$Q_{min} = 14.4$ C** **$Q_{max} = 28.8$ C**	C3, F2	Rasmussen's encephalitis	Subdermal needle 12 mm in length and 0.4 mm in diameter ($a = 4.925 \times 10^{-6}$ m^2) **calculating only surface area
Varga et al. (2011) [11]	Experimental double blinded sham-controlled crossover	5	6–11 8.5 ± 2.5	40	$I = 1$ mA $J = 0.4$ A/m^2 **$Q = 1.2$ C**	Determined by visualizing a 3D voltage-map of the focal epileptiform discharge	Continuous spikes and waves syndrome during slow sleep	Sponge electrode 25 cm^2 ($a = 2.5 \times 10^{-3}$ m^2)
Yook et al. (2011) [12]	Case report Experimental	1	11	100	$I = 2$ mA $J = 0.8$ A/m^2 **$Q_{20\ min} = 2.4$ C** **$Q_{5\ days} = 12$ C** **$Q_{2\ weeks} = 24$ C**	Midpoint between P4 and T4	Bilateral perisylvian syndrome	Sponge electrode 25 cm^2 ($a = 2.5 \times 10^{-3}$ m^2)
Faria Paula et al. (2012) [33]	Cross-over controlled trial	2	11 and 7	0	I = 1 mA/$J = 0.285$ A/m^2 **$Q = 1.8$ C**	Based in 10-10 International system positions in a cap (mostly C5-C6)	Drug-refractory continuous spike-wave discharges during slow sleep (CSWS)	Sponge electrode 35 cm^2 ($a = 3.5 \times 10^{-3}$ m^2)
Auvichayapat et al. (2013) [13]	Experimental randomized controlled with sham unblinded	36	6–15	28	$I = 1$ mA $J = 0.285$ A/m^2 **$Q = 1.2$ C**	Based in the international 10–20 EEG system (mostly C3-F3)	Focal refractory epilepsy with different etiologies	Sponge electrode 35 cm^2 ($a = 2.5 \times 10^{-3}$ m^2)

Table 2. Summary the human studies of the safety and efficacy using tDCS in epileptic patients.

Author (year)	Frequency and duration of session	Adverse effects	JADDAD	Outcome
Fregni et al. (2006) [9]	Single session; 20 min	Itching (3 active and 1 sham groups)	3	A significant reduction in the number of epileptiform discharges was found (mean 64.3%), however, not clinical reduction of seizure was seen in 30 days of follow-up.
San Juan et al. (2011) [10]	60 min in four sessions (on days 0, 7, 30, and 60)	None	1	One patient was seizure free and other patient with 50% of seizure frequency reduction within 6 month of follow-up.
Varga et al. (2011) [11]	20 min	None	2	Cathodal tDCS did not reduce the spike-index in any of the patients after 2 days of stimulation session in the evening; sham in the first night and tDCs in the second night.
Yook et al. (2011) [12]	5 days a week, during 2 weeks. Repeating procedure after 2 months; 20 min	None	0	During the first two months after treatment; the patient had only six seizures, with an evident clinical improvement, after the second intervention the patient had just one seizure attack over two months.
Faria Paula et al. (2012) [33]	Once weekly, to three afternoon sessions of 30 min each.	None	1	Cathodal tDCS is safe and well-tolerated in patients with refractory epilepsy. They found a large reduction in inter-ictal epileptiform EEG discharges in C5 (mean 32.1%) during and after the tDCS (10 min).
Auvichayapat et al. (2013) [13]	Single session; 20 min	One patient (2.7%) developed a transient (<2 h) erythematous rash with no pruritus or pain under the reference electrode	2	Cathodal tDCS can suppress epileptiform discharges in 57.6% for 48 h, but the effect of a single session on EEG abnormalities was not sustained for 4 weeks. A statistical reduction in the frequency of seizures was found (4.8%) in the post-hoc analysis.