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Quantitative Reassessment of Safety Limits of tDCS for Two Animal Studies

Pratik Y. Chhatbar, MD PhD[1], **Mark S. George, MD**[2,4], **Steven A. Kautz, PhD**[3,4], and **Wuwei Feng, MD MS**[1,3]

[1]Department of Neurology, Medical University of South Carolina

[2]Brain Stimulation Laboratory, Department of Behavioral Science & Psychiatry, Medical University of South Carolina

[3]Department of Health Science & Research, Medical University of South Carolina

[4]Ralph H. Johnson VA Medical Center, Charleston, SC

Dear Editor

We read the article by Jackson *et al*.[1] with great interest. The authors concluded that the threshold for causing a brain lesion in a rat model using transcranial direct current stimulation (tDCS) is well below the level previously reported by Liebetanz *et al*.[2] Using a computational modeling approach, they also indicated that current density at the level of the brain is a better predictor of brain damage than current density at the level of electrode or electrode-skin interface. While we admire their scientific rigor and the use of computational modeling, we are concerned that the units of tDCS dose they chose has affected the relevance of the conclusions in the paper. Our analysis of their data suggests that Liebetanz *et al*.[2] still offers an estimate of tDCS dose that may result in brain injury that is conservative by an order of magnitude.[1]

First, there is a need to clarify the tDCS stimulation parameters for a single session[3]:

The primary parameters of tDCS dose are:

- Current (mA)
- Duration (minutes)
- Electrode/pad size (cm^2)

The derived parameters of tDCS dose are:

- Charge (C) = (Current (mA) ÷ 1000) × (Duration (minutes) × 60)

For correspondence: Wuwei Feng MD MS, 19 Hagood Avenue, HOT-501, Charleston, SC 29425, Department of Neurology, Medical University of South Carolina, feng@musc.edu.

- Current density (A/m^2) = (Current (mA) ÷ 1000) ÷ (Pad size (cm^2) ÷ 10,000)
- Charge density (kC/m^2) = (Charge (C) ÷ 1000) ÷ (Pad size (cm^2) ÷ 10,000)

Second, Jackson *et al.*[1] claim that anodal stimulation with a current density of 20.0 A/m^2 can cause brain lesion, which is "well below" the current density of 142.9 A/m^2 reported by Liebetanz *et al.*[2] However, Liebetanz *et al.*[2] also showed that "for current densities between 142.9 and 285.7 A/m^2, lesion size increased linearly with charge density," we believe that the charge density would be the most relevant variable for determining a lesion threshold. As shown above, current density is an instantaneous measure that does not consider or involve the duration of stimulation. In other words, current density does not change whether the tDCS is applied for 1 minute or 60 minutes, only offering a "snapshot" in time without the duration factored in. Computational models of tDCS-generated electric fields (EF) also offer a similar snapshot that does not account for duration. When the duration of stimulation is constant between various stimulation scenarios, then current density and charge density (which involves duration of stimulation) are interchangeable and the computational models prove very useful. We argue that any tDCS dose parameter that does not take into account the duration of stimulation is not a good candidate to measure lesion threshold, as it can be compared to the intravenous drip of a medicine of a given concentration at a given rate without defining the duration of the drip (and therefore without determination of total amount of medicine delivered inside the body). Elegant work by McCreery *et al.*[4] almost 3 decades ago also emphasize the involvement of stimulation duration by comparing how various stimulation parameters like charge density and charge per phase factor in the neural injury. When making a comparison to Liebetanz *et al.*[2], Jackson *et al.* do not account for the duration of stimulation. We believe this limits the generalizability of their conclusion, as shown in Table 1.

Although Jackson *et al.*[1] use 0.5 mA current with a 25 mm^2 electrode to achieve a current density of 20.0 A/m^2, they use a longer duration of stimulation lasting 60 minutes which is 6-times the 10-minute stimulation duration in Liebetanz *et al.*[2] with a current density of 142.9 A/m^2 (0.5 mA current with 3.5 mm^2 electrode). Therefore, while current density was very different, the charge density was comparable between the two studies (72.0 kC/m^2 for Jackson *et al.*[1] and 85.7 kC/m^2 for Liebetanz *et al.*[2], respectively). Note that a charge density of 72.0 kC/m^2 (see Table 2 of Jackson *et al.*[1] and Table 1 here) exceeds the lesion threshold of 52.4 kC/m^2 derived by Liebetanz *et al.*[2] using the extrapolation method (see Fig. 4 of Liebetanz *et al.*[2] and Fig. 1A here).

Third, the lesion threshold determined by Jackson et al may have also been influenced by the methodology as well. The cranium diffuses current as it reaches the brain because of its low electrical conductivity. Because a removal of periosteum will decrease the thickness of cranium, the experimental set-up of Jackson *et al.*[1] may incur a more focused stimulation with a higher current density at the level of the cortex, making it more likely to induce brain injury when compared with Liebetanz *et al.*[2] where the cranial thickness is not compromised.

Fourth, by generalizing a statement by Jackson *et al.*[1], we concur that tDCS dose at the level of the cortex is more relevant than dose at the level of the scalp since the skull diffuses

direct current due to its low conductivity. If we assume a complete diffusion of current in the brain over time (i.e., total charge), the dose levels determined by Jackson *et al.*[1] to cause brain lesion (1.80 kC) are an order of magnitude higher than the dose levels established by Liebetanz *et al.*[2] (0.18 kC) as presented in Table 1 and Fig. 1B.

Finally, Jackson *et al.*[1] state that "clinical" tDCS typically uses a current density of 2 A/m^2. This is about an order of magnitude higher current density than the ones used in human clinical trials, which commonly use 1 mA of current over 35 cm^2 pads for 20 minutes (current density: 0.29 A/m^2; charge: 1.2 C; and charge density: 0.34 kC/m^2, see Fig. 1). Even the recent safety and tolerability study of single session 30-minutes of 4 mA tDCS in stroke patients[5] offered 1.14 A/m^2 current density (charge: 7.2 C; charge density: 2.06 kC/m^2, see Fig. 1). Note that although higher absolute charges delivered in human studies, the relative charge is much less as the volume of the human brain is ~2000 times greater than the rat brain (~1200 cm^3 vs. ~600 mm^3)[6, 7].

We have mathematically demonstrated that when charge density is used to represent tCDS dose, the safety limits established by Liebetanz *et al.*[2], were substantially exceeded in the study of Jackson *et al.*[1].,By expressing tDCS dose levels as current density instead of charge density, we believe that Jackson *et al.*[1] reached an incorrect conclusion regarding safety limits for the animal brain.

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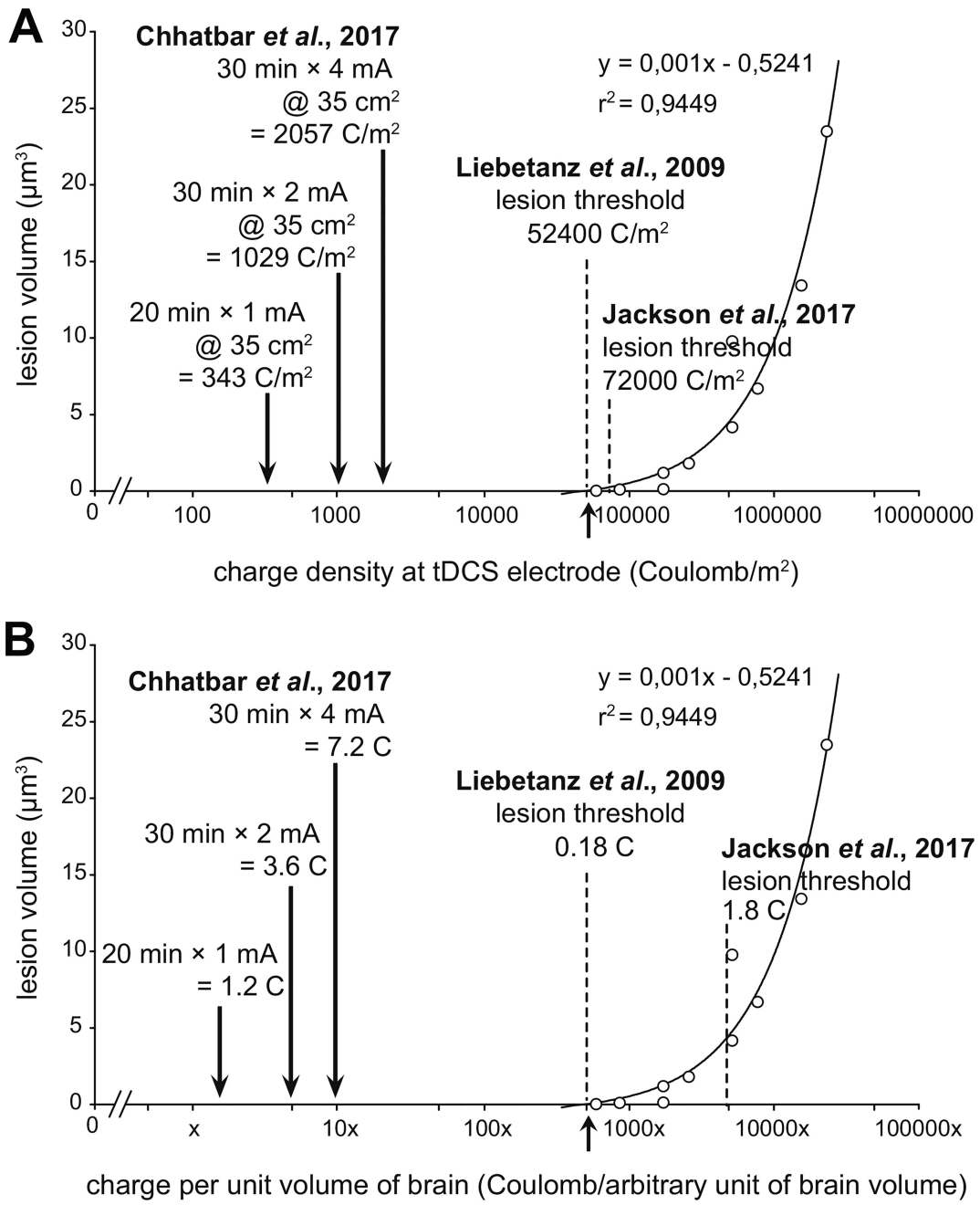

Figure 1. Comparison of brain lesion threshold between Liebetanz *et al*. 2009 and Jackson *et al*. 2017 along with conventional human tDCS dose with the highest dose with evidence of safety on humans

(A) Charge density plot shows that lesion threshold of Jackson *et al.* 2017 (72.0 kC/m^2) is higher than Liebetanz *et al.* 2009 (52.4 kC/m^2), with much smaller charge densities for typical human studies. (B) Charge delivery per unit volume of the brain (arbitrary, assuming 2000× human to rat brain volume ratio) show almost an order of magnitude higher lesion threshold by Jackson *et al.* 2017 (1.80 C) when compared with Liebetanz *et al.* 2009 (0.18 C). Given the much bigger size of the human brain, the total charge delivered to the human

brain is much smaller when compared with the rat brain. Note the logarithmic scale on the azimuth in both the plots.

Table 1

Comparison of tDCS dose parameters

Publication	Current (mA)	Pad Size (mm^2)	Duration (min)	Current Density (A/m^2)	Charge (C)	Charge Density (kC/m^2)
Jackson *et al.* 2017	0.50	25.00	60.00	20.00	1.80	72.00
Liebetanz *et al.* 2009	0.50	3.50	10.00	142.90	0.30	85.74
Liebetanz *et al.* 2009 lesion threshold	0.31	3.50	10.00	87.33	0.18	52.40
Typical human tDCS study	1.00	3500.00	20.00	0.29	1.20	0.34
Chhatbar *et al.* 2017	4.00	3500.00	30.00	1.14	7.20	2.06