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How to consider animal data in tDCS safety standards

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Dear Editor,

We thank Chhatbar and colleagues for the editorial commentary [1] on the original paper "Safety parameter considerations of anodal transcranial Direct Current Stimulation in rats" [2]. We would like to respond to their itemized concerns:

1) We agree that both electrode current density and stimulation duration are commonly used factors for measuring tDCS, but they are among many others that influence the safety of tDCS. We also understand the simplistic appeal of electrode charge density as a "catch-all" measurement because it integrates current density and time (in seconds rather than minutes) and is easy to quantify even across animal and human studies [3]. But reliance solely on charge density as a safety measurement assumes a trivial relationship between any possible combination of stimulation time and current intensity while ignoring all other factors – for example, simply doubling the current intensity does not necessarily decrease the maximum duration before an identical injury occurs by half. Rather, Jackson et al. directly demonstrate that electrode current density threshold (and so charge density threshold) varies with montage [2] and animal model [4] proving a more nuanced approach to safety is required.
2) Work by McCreery et al. using short pulsed, charge-balanced stimulation with implanted micro-electrodes is indeed "elegant", but we would refer to a comprehensive analyses of electrochemical safety [5] to avoid extrapolating these results to non-invasive, sustained direct current [6].

In any case, the canonical Liebetanz et al. study [7] should not be saddled with extrapolation beyond (or even contrary to) the data. Indeed, Liebetanz et al. show that applying high charge densities (>52.4 kC/m^2) by increasing stimulation duration rather than current density does not result in brain injury below 142.9 A/m^2. Liebetanz et al. are careful to qualify the implications of their study (e.g. "For current densities between 142.9 and 285.7 A/m^2, lesion size increased linearly with charge density; …") as are Jackson et al. (e.g. by emphasizing the use of "anodal" tDCS and avoiding direct comparisons to Liebetanz's "cathodal" tDCS study). These are critical nuances to distinguish before collapsing and comparing results from animal studies, including Jackson et al. with that of Liebetanz et al.

tDCS protocols in humans circa 1970 used relatively low current intensities but with smaller electrodes and longer durations than are common today, resulting in cases of electrode charge density >100 kC/m^2, with no reports of lasting side-effects [8]. It would be unreasonable to apply *only* electrode charge density-safety threshold values from rodent studies (using small epicranial electrodes) as evidence these tDCS protocols were in fact injurious.

3) By cleaning the cranium, Liebetanz et al. likely also removed periosteum. However, the presence of the periosteum is less pivotal than a myriad of other factors such as an animal weight, sex, montage, and stimulation polarity – all of these factors would influence (the reliance on a simple) electrode charge density threshold for injury. We agree with Chhatbar et al. that any animal model of tDCS safety is subject to its methodology, and Jackson et al. included a computational model of current flow to support interpretation. In most cases, methodological caveats makes safety predictions from animal models conservative [6].
4) We agree with Chattbar et al. that by relying only on charge density as a metric, the thresholds we report are greater than Liebetanz observed [7]. But consider the experimental design of Jackson et al.: using a 60-min duration is conservative to detect possible injury at shorter stimulation durations, assuming the current density threshold for injury monotonically decreases with stimulation duration.
5) Chattbar et al. correctly note that 2 A/m^2 is above electrode current densities that are used in conventional sponge-pad tDCS, but 2 A/m^2 is in line with High-Definition tDCS [9–13] and so represents a conservative comparison for brain injury. We do not understand the implication by Chattbar et al. that the ratio of human to rat brain volume supports a ~2000-fold safety factor; a large brain does not tolerate higher intensities per se, and the lesions from rodent studies [2,7] were observed beneath the electrodes. We refer to published current flow studies in rat and human models.

Even disregarding all points above, we do agree with the assertion by Chattbar et al. that "by expressing tDCS dose levels as current density … reached an incorrect conclusion regarding safety limits for the animal brain". This conclusion relies on accepting electrode charge density as singularly relevant for tDCS safety, which apparently makes our reporting of electrode current density "incorrect". We respectfully note that by "mathematically demonstrated", Chattbar et al. mean "multiplication" rather than inference

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or proof. This multiplication is applied without regard for explicitly stated variations across animal models, including factors where evidence undermines the reliance of only electrode charge density. In the context of developing safety standards, confusing arithmetic with a demonstration of safety is a dangerous numbers game. The methods, and so results, of Jackson et al. should not be conflated with work by Liebetanz and colleagues – but rather carefully contrasted.

Jackson et al. report both the methodology and resulting data in the animal brain, specifically where current density was varied, going so far as to contrast varied electrode montages and simulate current flow. Jackson et al. qualified their conclusions, which may err on the conservative side (reasonably given the subject matter) and emphasized: "translationally meaningful animal tDCS safety models must be carefully rationalized." Given general limitations of animal models [4] and unknowns about injurious mechanisms and dynamics, we would not agree with the implicit assertion that the evidence presented by Jackson et al. on reduced electrode current density thresholds is not a valuable consideration for tDCS safety. Dogmatic reliance on any single dose metric (including electrode charge density) can set unscientific standards for safety, both restricting worthwhile dose-response studies while endorsing unjustified interventions.

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