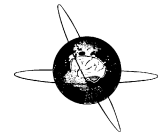




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Editorial

Establishing safety limits for transcranial direct current stimulation

See Article, pages 1161–1167

The recent resurgence in the use of transcranial Direct Current Stimulation (tDCS) for electrotherapy and human cognition studies was motivated by studies demonstrating lasting change in corticospinal excitability following tDCS (Priori et al., 1998; Nitsche and Paulus, 2000, 2001) including at the University of Gottingen. Subsequent tDCS studies have largely adapted the Gottingen protocols including the use of relatively-large wet sponges with size nominally 25–35 cm² and currents of 1–2 mA applied for durations up to 20 min (resulting in charge densities of 343–960 C/m²). Reproduction of these protocols across a wide range of applications and subjects (Nitsche et al., 2003a; Fregni et al., 2006; Webster et al., 2006; Boggio et al., 2007), has resulted in only isolated published reports on injury, limited to (acute) skin irritation under the sponges (Poreisz et al., 2007; Dundas et al., 2007; Bikson et al., 2008; Lagopoulos et al., 2008; Palm et al., 2008) such that current tDCS procedures are considered “safe” (Nitsche and Paulus, 2001; Nitsche et al., 2003b,c, 2004a; Iyer et al., 2005). None-the-less, the need for continued vigilance in examining potential hazards, combined with the desire by clinicians to explore increasing intensity protocols and duration of after effects (Nitsche et al., 2004b; Fregni et al., 2006) warrants investigation of the thresholds and mechanisms of potential tDCS hazards.

In developing safety guidelines for tDCS, several biophysical qualifications should be made. Firstly, if and what type of injury results from electrical stimulation is wholly dependent on the precise stimulation hardware and waveform applied; thus while one can draw general insights from a broad range of electrical safety studies (Agnew and McCreery, 1987; Merrill et al., 2005), it is neither accurate nor prudent to determine quantitative safety standards for tDCS from these reports. Moreover, tDCS itself represents a constellation of technologies and approaches (e.g. sponge salinity, electrode configurations, ramp waveform, intensity; Bikson et al., 2008) such that the safety standards may be tDCS protocol specific. Second, the injurious effects of tDCS on skin and brain are not necessarily linked, and should be considered independently from both the risk and mitigation stand-point. Acute pain and tissue damage of skin can further be distinguished, as should brain cognitive impairment versus brain tissue damage factors.

The report in this edition by Liebetanz and colleagues in Gottingen is a valuable contribution towards this last factor. Brain tissue damage was accessed in a rat model following epicranial electrode stimulation (Liebetanz et al., 2009). By fixing the electrode directly on the cranium, and using a large counter electrode on the ventral thorax, the study design maximized the electrode current that crosses directly into the skull; thus in this model the peak current density in the rat brain may approach the current density at the electrode. Liebetanz and colleagues report that brain lesions were

observed at a minimum cathodal electrode current density 142.9 A/m² for durations greater than 10 min. For current densities between 142.9 and 285.7 A/m², lesion size increased linearly with charge density (current density × time); with an extrapolated zero lesion size intercept of 52400 C/m². Thus Liebetanz and colleagues conclude that *both* the stated cathodal current density and charge density thresholds must be exceeded to induce histopathologically visible brain tissue damage. These findings must be interpreted in the context of limited understanding of damage mechanisms, and translational issues relating to clinical electrode montages and human anatomy.

The authors propose tissue heating (burning) as a probable mechanism for damage. Though temperature measurements were not conducted in the present study, the requirement for a current density threshold, as well as the increased lesion size with time/charge density once current density threshold is exceeded, are consistent with burning. Electrical current generates heat in tissue through joule heat, which is linearly dependent on current density. For analogy: Touching a moderately warm plate, even for a long time, will not induce skin burns when passive (heat conduction) and active (blood flow) mechanisms control peak temperature rise. Similarly, the temperature changes generated by low levels of current density in the brain may be regulated to non-harmful levels. Returning to the hot plate analogy: Even if the plate is heated to a potentially harmful temperature, just touching the plate *briefly* will not cause a burn, because: (1) it takes time for tissue to heat; and (2) exposure at that temperature only for an extended time will lead to tissue damage (Lee et al., 2000; Kiyatkin, 2004; Elwassif et al., 2006).

Hence, damage by heating is critically dependent on exposure time (in contrast, for example, to immediate damage by electroporation), which is consistent with the dependence of tissue lesion size on time/charge density observed by Liebetanz and colleagues. We calculate that a uniform current density of 142.9 A/m² will increase the temperature of brain tissue to 47.75 °C in 10 min (assuming no blood flow and metabolic heat source; initial temperature = 37 °C; electrical conductivity = 0.3 S/m; specific heat = 3650 J/(Kg °C); density = 1040 kg/m³). If temperature changes result only from joule heating, without a contribution from electrical alteration in neuronal metabolic activity, then tissue damage thresholds would be polarity independent. However, in the absence of a verified tissue damage mechanism and explicit testing of anodal stimulation, safety results from cathodal stimulation do not necessarily apply for anodal stimulation.

In relating the findings of this report to human safety standards, Liebetanz and colleagues acknowledge the (unavoidable) limitations of the animal model but correctly indicate that the epicranial electrode montage may provide a worst case scenario for the fraction

of electrode current entering the brain. In clinical studies, it is convenient to report stimulation intensity as *average* current density: calculated by dividing the current delivered to the electrode by the total sponge contact area. Using sponge electrodes, the current density at the scalp is concentrated near the sponge edges and thus exceeds the average current density (Miranda et al., 2006; Wagner et al., 2007). The scalp-skull interface, however, acts to diffuse current flow such that these concentrations are not reflected on the brain surface (Miranda et al., 2006; Datta et al., 2008; Datta et al., in press). Moreover, depending on the clinical electrode montage used, a significant portion of the applied current may be 'shunted' by the scalp and not enter the brain. Simplistically, if one speculates that average current density at the tDCS electrodes reflects an *upper-limit* on current density in the brain, then the average electrode current density may be rationally limited to 142.9 A/m² in order to prevent the tissue damage observed by Liebetanz and colleagues. It would be premature to arbitrarily apply this average electrode current density standard in clinical testing because: (1) as emphasized by the authors, these results "are solely based on morphological [animal data] and do not include studies on long-term morphological changes or behavioral changes"; and (2) details of human anatomy, including cortical folding, will affect current flow and can result in regional cerebral blood flow/current density "clustering" (Lang et al., 2005; Datta et al., in press). Conversely, this standard does *not* imply that any tDCS protocol where average electrode current density exceeds this value is necessarily hazardous: Firstly, Liebetanz and colleagues demonstrate a second concurrent charge-density threshold which indicates a pivotal role for exposure time. Second, the reduction in current density from the electrode to brain surface (due to scalp-skull diffusion, scalp/CSF shunting) adds an additional safety factor that can be determined for each montage (Wagner et al., 2007; Datta et al., 2008; Datta et al., in press).

Finally, regarding other safety factors: Prevention of brain damage for tDCS electrode montages does not preclude undesirable cognitive side-effects; though to-date, reports of tDCS modulation of cognitive function have generally indicated only *transient* improvements or impairment in performance, if any change at all (Nitsche et al., 2003a; Antal et al., 2004a,b; Iyer et al., 2005; Kuo et al., 2008). Skin irritation and damage can be readily accessed in human subjects. Especially given the limitation of animal models and the related importance of exactly reproducing electrode montages (e.g. size); a rational approach to skin safety is controlled and incremental evaluation in human subjects. For example, results by our group indicate that with appropriate hardware (electrodes, adapters, and gels), current densities of 25.46 A/m² can be applied for 20 min with minimal sensation and no skin damage (unpublished observations). In these studies, subjects scored pain perception during forearm stimulation under anode and cathode electrodes; in addition pH and temperature changes in the customized stimulation gel were not detected.

In summary, the contribution by Liebetanz and colleagues is correctly, a "first estimate of a safety threshold for deleterious DC" transcranial stimulation; the potential of tDCS as a clinical and experimental tool supports further safety studies in both humans and animals as well as the continued development of tDCS technologies.

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