The recent resurgence in the use of transcranial Direct Current Stimulation (tDCS) for electrotherapy and human cognition studies was motivated by studies demonstrating lasting changes 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 montage (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 electroportation), 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 con-
vienient to report stimulation intensity as average current density: cal-
culated by dividing the current delivered to the electrode by the total
spoon 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; Datta et al., 2008). 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). Conversely, over 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 dam-
nage observed by Liebetanz and colleagues. It would be premature to
arbitrarily apply this average 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 in-
clude studies on long-term morphological changes or behavioral
changes; and (2) details of human anatomy, including cortical fold-
ing, 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 proto-
col where average electrode current density exceeds this value is
necessarily hazardous: Firstly, Liebetanz and colleagues demon-
strate 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 diffu-
sion, 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 dam-
age for tDSC electrode montages does not preclude undesirable cog-
nitive side-effects; though to-date, reports of tDSC modulation of
cognitive function have generally indicated only transient improve-
ments 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 re-
lated limitation 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 forenoon
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 cor-
ducted, 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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