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# Letters to the editor

## Safety criteria for transcranial direct current stimulation (tDCS) in humans

In recent years, the possibility of inducing cortical excitability modulations in humans non-invasively by the transcranial application of weak direct currents (tDCS) was systematically evaluated by using transcranial magnetic stimulation (TMS) for evaluation. Present data demonstrate that tDCS of the primary motor cortex increases or decreases cortical excitability for up to an hour after the end of stimulation. The direction and duration of these shifts in excitability depend on the polarity, intensity and duration of the applied stimulation (Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003). Similar effects can be achieved in the visual cortex (Antal et al., 2001, 2003). This technique is thus evolving as a promising tool to induce cortical neuroplasticity.

In his recently published article "Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability" (*Clinical Neurophysiology*, Volume 14, Issue 4) Priori stated that "Interpreting the criteria of Agnew and McCreery (1987) who proposed a maximum charge density at the stimulating electrode of $<40$ $\mu C/cm^2$ for the safety of transcranial electric and magnetic brain stimulation, DC stimulation for several minutes, at 1 mA intensity with an electrode area of 35 $cm^2$, was considered safe by Nitsche and Paulus (2000, 2001). How Nitsche and Paulus (2000)—according to the safety limits proposed by Agnew and McCreery (1987)—considered their protocol safe is unclear: 5 min of stimulation at 1 mA through one electrode with an area of 35 $cm^2$ implies a charge density of about 8500 $\mu C/cm^2$, well above the limit of 40 $\mu C/cm^2$." (Priori, 2003)

From this a reader might be led to think that the studies conducted by our group were not safe. We assume that Priori's statement is due to a simple misunderstanding which we aim to clear up here. Because the safety issue is of central importance for the future application of tDCS in humans, it seems necessary to go into a detailed discussion and a reanalysis of the existing literature. Additionally we will propose a standard for safe DC stimulation according to currently available criteria.

Generally, it has to be clarified which mechanisms of electrical stimulation could cause neuronal or brain tissue damage. These are described in detail in the article of Agnew and McCreery (1987) and represent the crucial information which demonstrates that the tDCS protocols used by our group should be regarded as safe.

First, general mechanisms of current-induced tissue damage, which are not restricted to suprathreshold pulsed stimulation protocols, but are also applicable to weak continuous DC stimulation, need to be considered. According to Agnew and McCreery (1987), important possible features of electrical brain stimulation, which could lead to brain damage, include electrochemically produced toxic brain products and (metallic) electrode dissolution products caused by the electrode–tissue interface. Clearly, as Agnew and McCreery (1987) point out, these factors are not important in the case of transcranial stimulation, because stimulation electrodes and brain tissue do not come into direct contact. In order to minimize chemical processes at the electrode–skin interface, special electrodes (see below) should be used. According to Agnew and McCreery (1987), another possible way in which the skin could be damaged at the interface would be heat development under the electrodes. This has been shown not to occur under the tDCS protocols we use (Nitsche and Paulus, 2000).

Second, the electrical stimulation could cause tissue damage by inducing neuronal hyperactivity and brain tissue heating (Agnew and McCreery, 1987). Damaging effects due to cortical hyperactivity refer to the effect of high-frequency suprathreshold stimulation over hours (Agnew et al., 1983). However, tDCS using our protocols induces only moderate changes in cortical excitability (TMS-elicited, muscle-evoked, potential amplitude changes are about 40%, with baseline-values of 1 mV, and a maximum elicitable amplitude of about 5 mV) (Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003). Moreover, the effects of tDCS are subthreshold with regard to eliciting action potentials in neurons at resting membrane potential. Thus a damaging effect by neuronal hyperactivity seems improbable. Damage from the heating of neuronal tissue can be ruled out, in view of the fact that this was not even the case directly under the electrodes (Nitsche and Paulus, 2000) and that the critical current density or total charge entering the brain will only be about 50% of that directly under the electrode on the skin (Rush and Driscoll, 1968).

However, the question arises whether safety parameters for stimulation can be derived from currently available data. For repetitive suprathreshold electrical stimulation, factors

that have been tested experimentally to determine the safety limits of stimulation are:

1. current density (stimulation strength (A)/electrode size ($cm^2$)),
2. total charge (stimulation strength (A)/electrode size ($cm^2$) × total stimulation duration (pulse duration × number of pulses) (s) [$C/cm^2$]) (in contrast to the original physical formula, here charge refers to the stimulated area),
3. charge per phase (stimulation strength (A) × duration of a single pulse (μs) = μC), and
4. charge density (stimulation strength (A)/electrode size ($cm^2$) × duration of a single pulse (μs) [$\mu C/cm^2$])

(Agnew and McCreery, 1987; McCreery et al., 1990; Yuen et al., 1981).

It is important to note that current density is independent of stimulation duration and total charge reflects the product of current density and stimulation duration for a whole stimulation session, whereas charge per phase and charge density refer to only one pulse of a train of high-frequency suprathreshold stimuli applied over hours. Also, it is essential to realize that the safety limits stated for charge per phase and charge density apply only if repetitive high-frequency stimulation is given for several hours. This is the very reason why charge density and charge per phase are *not* applicable to tDCS, because in tDCS only one (continuous) stimulus is given in a whole session. Unfortunately, the only safety limit Priori refers to is charge density. In the opinion of McCreery (personal communication) the appropriate parameter for deriving safety limits for tDCS should be current density. As shown by McCreery et al. (1990), current densities below 25 $mA/cm^2$ do not induce brain tissue damage even by applying high-frequency stimulation over several hours. In our protocols, we stimulate with a maximum current density of 0.02857 $mA/cm^2$ which is a thousand fold lower than this limit. Because duration of stimulation is an important additional factor in causing tissue damage, total charge is the other important parameter for tDCS safety criteria. Tissue damage has been detected at a minimum total charge of 216 $C/cm^2$ (Yuen et al., 1981). Our protocols so far encompass maximum total charges of 0.022 $C/cm^2$ and, again, are far below these thresholds. This demonstrates that our study protocols are *not* beyond the safety limits described by Agnew and McCreery's group, if the possible mechanisms of electrically induced tissue damage and the *applicability* of safety limits are considered.

Although these safety criteria derived from the studies of Agnew and McCreery's group should generally be applicable to tDCS, due to technical differences between the stimulation protocols tested in their studies and tDCS, comparability may be restricted with regard to the exact values of the safety limits. We propose that unless more data are available than at present, current density and total charge should not be extended much beyond the limits of protocols used by our group. Additional studies have now been performed for these protocols, which produced no evidence that these may be harmful: they show that tDCS under our protocols does not cause heating effects under the electrodes (Nitsche and Paulus, 2000), does not elevate serum neurone-specific enolase level (Nitsche and Paulus, 2001; Nitsche et al., 2003) (a sensitive marker of neuronal damage (Steinhoff et al., 1999) and does not result in changes of diffusion-weighted or contrast-enhanced MRI, or pathological EEG changes (unpublished observations). Additionally, the accomplished excitability changes of about 40% compared to baseline should not result in neuronal damages due to hyperactivity, and the restricted duration of the effects do not induce stable (in terms of days or weeks) functional or structural cortical modifications, which could be undesirable in healthy subjects. This protocol has been tested in about 500 subjects in our laboratory so far without any side-effects, apart from a slight tingling sensation under the electrode during the first seconds of stimulation or the sensation of a short light flash if the stimulation was switched on or off abruptly. With regard to the latter point, we now prefer a wedge-shaped on and off-current switch. As it seems that current densities above 0.02857 $mA/cm^2$ (which refers to 1 mA/35 $cm^2$) could be painful (unpublished observations), we recommend that this value should not be exceeded. Also, electrode montages that could result in brainstem or heart nerve stimulation can be dangerous and should be avoided. After stimulating the brainstem, Lippold and Redfearn (1964) described one case of disturbed breathing, speech arrest and psychosis, and it cannot be ruled out completely that a current flow could modulate rhythmogenesis of the heart. Thus, according to currently available knowledge, not only the cortical stimulation electrode, but also the remote one should be positioned so as to avoid current flow through the brainstem. The stimulation device should guarantee a constant current density, since current density and not voltage is the relevant parameter for inducing neuronal damage (Agnew and McCreery, 1987) and a constant voltage device could result in unwanted changes of current density if resistance is unstable. To minimize chemical reactions at the electrode–skin interface, tDCS should be performed with non-metallic, conductive rubber electrodes, covered completely by saline-soaked sponges (Nitsche and Paulus 2000). These sponges are then the only material in direct contact with the skin and chemical reactions should be minimized. If the stimulation is applied above foramina, currents could be focused and the effective electrode size diminished (Agnew and McCreery, 1987; Rush and Driscoll, 1968). Consequently, this should be avoided. Stimulation durations which are likely to result in excitability changes of more than an hour should be applied cautiously in healthy subjects, since excitability changes lasting for such a long time consolidate and stabilize (Abraham et al., 1993), and could

be dysfunctional. For the same reason, long-term excitability changes should not be induced more than once a week, since repetitive daily stimulation in animals results in excitability changes that are stable for weeks or even months (Weiss et al., 1998).

We are aware that an extension of the after-effects, most probably inducible by a further prolongation of stimulation duration, is the prerequisite for possible clinical applications of this technique. However, in our opinion additional systematic safety studies must be performed before stimulation duration can be extended. These studies are currently being performed in our laboratory.

If all of these preconditions are met, which in total constitute a regimen for effective, but safe tDCS, there is no reason to suspect that tDCS could be harmful.

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