



Extending the parameter range for tDCS: Safety and tolerability of 4 mA stimulation



Non-invasive brain stimulation with direct currents (tDCS) is increasingly applied to modulate brain physiology, psychological and motor processes, and behavior in humans. The efficacy of tDCS, similar to other non-invasive brain stimulation (NIBS) protocols, is currently limited, including significant variability in individual response. The potential of tDCS to modify respective physiological and psychological processes safely and to a maximum extent, which is of critical importance for clinical application, has so far not been explored systematically for many potentially important parameters. These include electrode positioning, stimulation duration, intensity, timing in relation to task performance, individualization of stimulation protocols, amongst others. Taking into account non-linear features of neuroplasticity, such as the switch from long term depression to potentiation, depending on intra-neuronal calcium concentration [1], and brain state-dependency of tDCS, optimization of stimulation effects is not trivial. Previous studies have shown that prolongation of stimulation duration can lead to a switch of directionality of effects [2], and a similar switch from long-term depression to potentiation-like plasticity has been demonstrated for higher stimulation intensity [3]. Moreover, dependent on baseline excitability, different stimulation intensities seem to have maximum efficacy [4]. Thus systematic exploration of safety and effects of extended tDCS protocols is critical for identification of maximally efficient stimulation approaches.

One approach to potentially boost efficacy is increasing stimulation intensity from the conventional limit of 2 mA, but the assumption that higher current boost clinical outcome has not been systematically explored. While animal models suggest a relatively large intensity range of tDCS to enhance neuromodulation at high current densities [5] with no evidence of tissue damage [6], human neurophysiology shows potential non-monotonic effects [3]. Thus, systematic studies to probe extension of tDCS protocol intensity are important. A report in this issue [7] provides initial evidence for the safety of tDCS intensities up to 4 mA.

The authors adapted a 3+3 study design derived mainly from animal studies to probe safety and tolerability of stimulation intensities between 1 and 4 mA for a stimulation duration of 30 min in patients after ischemic stroke, and combined the intervention with occupational therapy. Safety and tolerability of respective protocols were determined via stopping rules in case of serious side effects, tolerability questionnaires, body resistance and skin temperature. The results of this study are in accordance with safety

and good tolerability of these extended protocols. No major adverse events did occur, body resistance and skin temperature did not change. The most frequent side effect was a transient skin redness in 50% of all patients, which was however not associated with skin damage.

The results of this study are important, because they deliver first evidence about the safety profile and tolerability of tDCS intensity relevantly higher than that used thus far in most clinical trials. Studies of this type are required to extend the parameter space to optimize efficacy of tDCS, which is of evidently important for optimized clinical studies. However, some relevant caveats have to be taken into consideration. This pilot clinical trial allows no statement about non-deterministic/infrequent side effects, because an inherent design aspect of the study is that only a very limited number of subjects were tested for each stimulation intensity. While this design is sufficient to identify deterministic side effects, it is not well suited to identify infrequent or rare adverse events. Moreover, the obtained tolerability and safety parameters are not suited to rule out subtle tissue alterations, which may not be associated to clinical side effects or the imaging sequences selected for this study, but might be detectable by other imaging techniques or laboratory tests (e.g. MRI, NSE etc.). Though conversely, there is no scientific basis to expect injury based on totality of evidence from animal and human trials [6]. In animal studies, much higher current density was required to induce tissue damage [6,8].

It is important to emphasize that the safety and tolerability of tDCS, as with any NIBS protocol, can be specific to the equipment and accessories used, including electrode size and distance, which are relevant for resulting current density at skin and brain levels, all details of the respective trial protocol including inclusion/exclusion criteria, operator training, and monitoring plan [9]. Thus, the report in this issue is an important step in expanding the range of dose available to researchers. As noted by the authors, prospective physiological and clinical test are required to test usefulness – including potentially individualized dose - within the new range. This is relevant because of the above-mentioned non-linearity of stimulation effects, because stronger stimulation might also involve deeper structures not modulated by “conventional” protocols, which might result in qualitatively different effects, and presumably non-linear effects on task performance, which are well known for other neuromodulatory agents, such as pharmacological interventions. Thus this study represents an important first step to broaden the applicable parameter space for tDCS. Especially for therapeutic applications, more of these studies are required to evaluate the therapeutic usefulness of this intervention. Follow up studies to explore

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physiological and clinical effects are required to determine its suitability for practical application. Finally, in no way does this study represent a “carte blanche” for tDCS with high currents outside of rigorous human trials.

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