

# Exploring the infinite parameter space: rethinking assumptions underpinning the use of transcranial direct current stimulation to induce long-term effects

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Conflicts of Interest

I declare that I have no conflicts of interest

## Perspective

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation approach that has been gathering increasing interest in recent years as a potential adjunct therapy for rehabilitation after brain injury. Essentially a very simple technique, tDCS relies on the application of a low-level constant current (in the order of a few milliamps) passed between two or more electrodes placed on the scalp. Early animal work demonstrated that electric currents applied over the cortex had polarity-specific effects on ongoing neural signalling, with anodal stimulation (where the anode is positioned over the region of interest) increasing firing rates and cathodal stimulation decreasing them (Creutzfeldt & Fromm, 1962). It took some time for this finding to be followed-up in humans, with the first paper reporting similar, polarity-specific effects appearing in the *Journal of Physiology* in 2000 (Nitsche & Paulus, 2000). Subsequent studies demonstrated that longer durations of tDCS induce cortical excitability changes that outlast the stimulation period by some minutes to hours.

In line with these neurophysiological findings, it has been repeatedly demonstrated that tDCS is able to modulate behaviour. In healthy controls, a single session of tDCS improves behaviour for a few hours, but 5 daily sessions paired with a learning task induced greater learning than sham stimulation, evidence of which was present many months later (Reis *et al.*, 2009). This gave rise to a large number of studies combining tDCS with rehabilitative training post-stroke, with the hope of inducing long-lasting, clinically-meaningful effects, something that has shown significant promise (Kang *et al.*, 2016).

However, the initial enthusiasm for tDCS has been somewhat dampened by the substantial variability in stimulation-induced effects both between subjects and across studies that has become evident. The sources of this variability are yet to be fully understood, but dosing is probably a major factor. Classically, all subjects within a study have been stimulated using the same parameters with no allowance made for the inter-individual differences which will substantially alter the amount of current reaching the cortex. In addition, the decision to use a once-daily stimulation pattern being made pragmatically in most studies; the optimum spacing of tDCS sessions has not been systematically explored.

Here, the authors set out to test two major components of the “infinite parameter space” of tDCS: that of intensity and inter-stimulation interval (Samani *et al.*, 2019). Samani and colleagues explored cortical-excitability after-effects of a commonly used cathodal tDCS protocol (1mA for 15 minutes) against a more intense protocol (3mA for 20 minutes), both as single interventions and as repeated interventions with a short (20 minute) or long (24 hours) interval. They investigated the effects of tDCS using Transcranial Magnetic Stimulation (TMS), which indexes cortical excitability, at time points from 5 minutes after the end of stimulation to the next evening.

Both the normal and high-intensity tDCS protocols led to the expected decrease in cortical excitability after a single session. The magnitude of the decrease in cortical excitability was similar across protocols but the duration of the after-effects of the high intensity protocol was increased, lasting up to 120 minutes. Repeating the stimulation after a short interval did not change the pattern of after-effects. However, repeating the tDCS 24 hours after the initial session substantially decreased the after-effects: only the 3mA stimulation led to any significant decrease in cortical excitability, and that was only for 30 minutes after stimulation.

There is substantial evidence for tDCS inducing changes in NMDA-dependent glutamatergic signalling, however this study suggests that cathodal tDCS may not modulate the metabotropic glutamatergic receptor expression, thought to be a key mechanism of late-phase LTD and not significantly involved in early induction.

These results have important implications. An underlying assumption of much tDCS research, as outlined above, is that repeated interventions will lead to longer after-effects than a single session, an idea that is at odds with the data presented here. However, no one study can completely address every aspect of an important question and this manuscript raises a number of questions for the field to address.

This was a purely neurophysiological study: tDCS was delivered in the absence of a task, and only neurophysiological metrics were acquired. While these are necessary and important studies, using these findings to predict behavioural effects, particularly in regions outside the primary motor cortex, is not trivial. In addition, by studying two tDCS protocols that differ in

both current intensity and length, it is impossible to separate out the effects of these two metrics, both of which have been shown previously to have significant effects on cortical excitability after-effects. Finally, while this is a detailed study of cathodal tDCS in healthy controls, it does not necessarily inform us as to the effects of anodal tDCS and nor does it translate clearly into effects post-stroke.

In conclusion, this study provides important evidence as to the physiological mechanisms underlying tDCS. It challenges commonly-held assumptions in the field that daily interventions will by definition be more efficacious than either single sessions or repeated interventions spaced at less than a day apart. The questions raised by the paper as to the mechanisms underpinning the effects of cathodal tDCS, and optimal protocol to optimise its effects are important ones to answer.

## References

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