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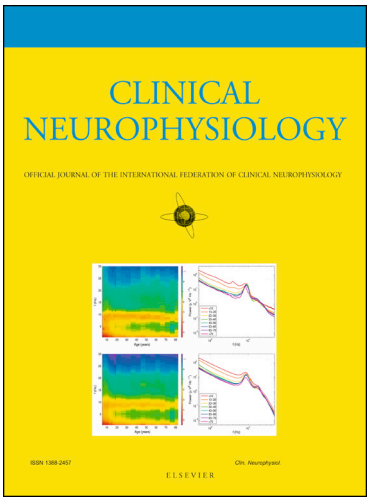

Letter to the Editor

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Progression of adverse effects over consecutive sessions of transcranial direct current stimulation

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Abbreviations

AE = Adverse effect

DLPFC = Dorsolateral prefrontal cortex

tDCS = Transcranial direct current stimulation

tES = Transcranial electrical stimulation

PSS = Perceived Stress Scale

ZIP = Zero-Inflated Poisson

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We read the paper by Antal et al. (2017) with great interest, and felt that it provided an excellent overview of the safety aspects of transcranial electrical stimulation (tES). However, we noticed that while multi-day stimulation studies were discussed, potential changes in adverse effects (AEs) over consecutive sessions were not, and the lack of knowledge on the matter was pointed out by the authors. We recently completed an experiment in which we investigated this issue.

This investigation formed part of the larger Optimizing Transcranial Electrical Stimulation for Clinical Applications (OptES) Study. The study protocol was approved by the Ethics Committee of the North Savo Hospital District, Finland. Written informed consent was obtained from all the participants.

We recruited 82 healthy, right-handed, transcranial direct current stimulation (tDCS) naïve males aged 18–40 years. The participants received either active (n=41) or sham (n=41) stimulation in a double-blind setting. Each participant took part in five consecutive experimental sessions. Prior to the onset of the study, the participants were instructed to abstain from alcohol use for 12 hours and consume no more than two doses during the preceding 24 hours, to abstain from caffeine for 3 hours, and to abstain from smoking and heavy physical exercise for one hour before each session. Before the first stimulation session, the participants completed the 10-item version of the Cohen's Perceived Stress Scale (PSS) questionnaire (Cohen et al. 1982). Each participant received 20 minutes of 2 mA stimulation using a neuroConn DC stimulator (neuroConn GmbH, Ilmenau, Germany).

The sham group received 15 seconds of ramping up and ramping down at the beginning, after which stimulation was discontinued. The duration of the session was constant, regardless of the stimulation type. The electrodes (5×5 cm) were conductive rubber placed inside sponge pads soaked with 12 ml of saline. The anode was placed at site F3 and the cathode at site F4 according to the international 10–20 electroencephalography electrode placement system. After the stimulation,

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both the participant and the experimenter filled in a form in which they were asked to estimate possible skin redness (using a mirror), tiredness, mood changes, headache and sensations under the electrodes on a scale of 0–100.

The data contained excess zeros and were non-normally distributed. We compared the variables of interest (i.e., skin redness, tiredness, mood changes, headache and sensations under the electrodes) between the groups using the Mann-Whitney U-test. For more detailed analysis, a fixed-effects zero-inflated Poisson (ZIP) model was used to investigate AE likelihood, and a mixed-effects ZIP to investigate AE intensity with age, PSS score and stimulation group used as predictors. The fixed- and mixed-effects ZIP consisted of a binary distribution generating structural zeros (which represent cases who were not susceptible to the effects) and a Poisson distribution generating the remaining cases. Separate models were constructed to investigate the main effects and interaction effects. Preliminary analyses were conducted with the SPSS 21 software package, and the Poisson model was constructed with the R scripting language (version 3.3.2) package glmmADMB (version 0.8.3.3).

In Mann-Whitney U-test analyses, the intensity of skin redness under the electrodes was significantly ($p<0.05$) higher in the active group on all days when reported by the participant, and on days 2, 3 and 5 when reported by the experimenter. The active group reported less headache than the sham group on days 4 and 5.

Belonging to the active group predicted a higher likelihood of skin redness in fixed-effects ZIP. Higher age predicted a stronger erythema reaction in participant-reported mixed-effects ZIP, while in the experimenter-reported model, age, belonging to the active group and higher baseline scores for perceived stress were significant predictors. There was a significant interaction, suggesting that higher age was a stronger predictor of skin redness in the active group than in the sham group in the model utilizing experimenter-reported scores, and borderline significant ($p=0.0547$) in the model

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utilizing participant-reported scores. There was a significant interaction between PSS scores and belonging to the active group in both models, but in opposite directions. The number of stimulation sessions was not a predictor (Table 1).

In power calculations based on effects sizes (ES; Cohen's D) drawn from this data, the group sizes needed to detect participant-reported AEs were as follows: tiredness: ES = 0.161, n = 604; sensations under the electrodes: ES = 0.150, n = 695; mood changes: ES = 0.298, n = 178; headache: ES = 0.358, n = 124; and skin redness: ES = 0.705, n = 33. For the experimenter-reported AEs, the respective figures were as follows: tiredness: ES = 0.131, n = 922; mood changes: ES = 0.204, n = 379; and skin redness: ES = 0.659, n = 38.

While confirming that receiving active tDCS predicted skin redness (Ezquerro et al. 2017; Antal et al. 2017), we observed that increased age predicted an increased intensity of redness, particularly in the active group. Sensations under the electrodes, tiredness and mood did not differ between the groups, perhaps reflecting the successful sham protocol, particularly in the case of the sensations induced. However, our power calculations suggest that higher-than-expected numbers of participants may be needed to detect most of the above side effects.

We saw no changes in AEs over the stimulation period of five days, which suggests that repetitive sessions do not modify tDCS AEs. However, these observations need to be confirmed with different stimulation protocols and populations. In general, both the participants and the experimenter reported the same AEs.

As Antal and co-workers pointed out, while the tDCS AEs are mild and thus manageable, there are still several aspects to them that the community of researchers and clinicians are not familiar with, including the effect of repeated sessions and factors predicting different AEs. However, there is an abundance of existing data that could be used to gain more detailed insights into the predictors of

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tES AEs. Therefore, investigating such predictors could help in identifying protocols suitable for different groups of individuals, and in achieving an ideal risk–benefit ratio for tES treatments.

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Conflicts of interest

None.

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Table

Table 1. Fixed- and mixed-effects zero-inflated Poisson models (ZIP) for skin redness under the electrodes following transcranial direct current stimulation. The participant-reported fixed-effects model for day 1 could not be statistically fitted, and is thus not presented here. PSS = Perceived Stress Scale.

				Participants		Experimenter	
				Coefficient	P-value	Coefficient	P-value
Fixed-effects model - Zero Inflation	Day 1	Main-effect model	Group			-0.392	0.421
			Age			-0.029	0.502
			PSS score			0.138	**0.004**
		Interaction model	Group×Age			0.072	0.409
			Group×PSS score			-0.144	0.185
	Day 2	Main-effect model	Group	-1.914	**0.001**	-0.897	0.059
			Age	0.028	0.541	-0.017	0.677
			PSS score	0.020	0.668	0.035	0.409
		Interaction model	Group×Age	-0.021	0.835	-0.065	0.452
			Group×PSS score	-0.029	0.769	0.013	0.877
	Day 3	Main-effect model	Group	-1.589	**0.004**	-1.408	**0.004**
			Age	0.042	0.358	-0.015	0.718
			PSS score	0.024	0.613	0.034	0.422
		Interaction model	Group×Age	0.007	0.952	0.024	0.773
			Group×PSS score	0.068	0.473	0.010	0.900
	Day 4	Main-effect model	Group	-1.000	**0.037**	-0.388	0.405
			Age	0.008	0.845	-0.046	0.263
			PSS score	0.013	0.751	0.058	0.165
		Interaction model	Group×Age	0.059	0.482	0.050	0.555
			Group×PSS score	-0.022	0.796	-0.041	0.630
	Day 5	Main-effect model	Group	-1.829	**<0.001**	-2.316	**<0.001**
			Age	0.040	0.364	-0.018	0.692
			PSS score	-0.009	0.842	0.061	0.213
		Interaction model	Group×Age	0.045	0.676	-0.067	0.500
			Group×PSS score	0.267	0.149	0.022	0.822
Mixed-effects model - Poisson		Main-effect model	Group	0.205	0.107	0.455	**<0.001**
			Day	0.035	0.346	-0.016	0.587
			Age	0.038	**<0.001**	0.019	**0.008**
			PSS score	-0.022	0.065	-0.024	**0.008**
		Interaction model	Group×Day	0.063	0.464	-0.042	0.503
			Group×Age	0.041	0.055	0.047	**0.005**
			Group×PSS score	0.073	**0.029**	-0.052	**0.004**

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