AARON KORTTEENNIEMI, ALFREDO ORTEGA-ALONSO, AMIR-HOMAYOUN JAVADI, OWEN THOMAS, TOMMI TOLMUNEN, TUUKKA KOTILAINEN, JAN WIKGREN , SOILI M. LEHTO

THE IMPACT OF LIFESTYLE FACTORS ON THE INTENSITY OF ADVERSE EFFECTS IN SINGLE AND REPEATED SESSION PROTOCOLS OF TRANSCRANIAL ELECTRICAL STIMULATION: AN EXPLORATORY PILOT STUDY

ABSTRACT

Transcranial electrical stimulation (tES) has shown promise in the treatment of conditions such as depression and chronic pain with mild-to-moderate adverse effects (AEs). Few previous studies have attempted to identify factors predicting tES-induced AEs. In particular, AEs resulting from repeated sessions of tES remain understudied. We conducted an exploratory retrospective analysis of two independent randomized controlled studies to investigate whether lifestyle factors (i.e. chronic alcohol use, smoking, exercise, and quality and length of sleep) modify the severity and frequency of tES-induced AEs, and evaluated the progression of AEs over repeated sessions.

We utilized two double-blinded samples: 1) a male sample (n=82) randomized to receive transcranial direct current stimulation (tDCS) or sham for 5 days, and 2) a mixed-sex sample (n=60) who received both transcranial random noise stimulation (tRNS) and sham in a crossover setting. The severity of AEs was recorded on a scale of 0-100. The data was analysed using negative binomial models. In addition, we performed power calculations and, to guide future research, evaluated the numbers of individuals needed to detect non-significant observations as significant.

By day 5, the tDCS group experienced more sensations under the electrodes than the sham group. Alcohol use, smoking, exercise, or quality or duration of sleep did not appear to be associated with the intensity of the AEs. The subsequent power analyses indicated that substantially larger samples would be needed to detect the observed associations as significant.

Repetitive sessions do not appear to introduce additional AE burden to individuals receiving either tDCS or tRNS, at least with protocols lasting up to 5 days. Alcohol use, smoking, exercise, or quality or duration of sleep appear to only have an effect of negligible size, if any, on AEs induced by tDCS or tRNS, and studies with sample sizes ranging from roughly 100 individuals to hundreds of thousands of individuals would be required to detect such effects as significant.

KEY WORDS: TDCS, TRNS, BRAIN STIMULATION, ADVERSE EFFECTS

INTRODUCTION

Transcranial electrical stimulation (tES), a non-invasive method for modulating neuronal activity, has attracted increasing interest among both clinicians and researchers during the past decade. In tES, a small electrical current is introduced into the brain via electrodes placed on the scalp, with the aim being to modulate the sensitivity and activity of neurons (1–6). The term tES encompasses several methods, including transcranial direct current stimulation (tDCS) and transcranial random noise stimulation (tRNS). The electrical fields generated by tES are not considered sufficient to evoke action potentials by themselves, although they can modulate neuronal excitability (7).

tDCS is the oldest tES method in present-day use; its relatively low costs, its favourable safety profile, and the potential for home application have made it an attractive option for the clinical treatment of a variety of psychiatric and neurological conditions. tDCS has shown promise in the treatment of non-drug resistant major depressive disorder, fibromyalgia pain and addiction disorders (8–10). tRNS, as a newer variation of tES, has received far less attention in the literature. The cortical effects of tRNS appear to be similar to those of anodal tDCS, i.e. the excitability of the underlying cortex has been suggested to be enhanced after stimulation (11). Perhaps as a consequence, tRNS has been investigated for indications similar to tDCS. Since knowledge on the potential clinical indications of tRNS remains limited, it would be advantageous to have a detailed awareness of its adverse effects in order to assess its true clinical potential.

The typical adverse effects (AEs) of tES include both local, skin-related effects such as itching or tingling sensations under the electrodes and skin redness under the electrodes after the treatment (12–14), and more generalized effects, such as tiredness and headache (15). Adverse effects, however, are quite rare. In a systematic review by Aparício et al., (16) looking at acceptability and tolerability of tES across 64 studies and 2262 participants, the authors indicated that due to the inadequate or non-existent reporting of AEs they were unable to conduct a statistical analysis of the tolerability (i.e. frequency of adverse effects). Furthermore, Moffa et al. (17) pooled all adverse effects together in their analysis, and found that the presence of anxiety disorders and a higher current density both predicted a higher number of AEs. Another study conducted by McFadden (18) stated that prior application of a topical anaesthetic was linked with less intense skin sensations. A larger electrode size, when keeping current density constant (19), and the use of tap water as the contact media (20) have been reported to be associated with more AEs. Nevertheless, while some research has been conducted on factors predicting tES-induced adverse effects, the significance of these factors remains unresolved.

Lifestyle factors such as smoking (21) and exercise habits (22) have been reported to modulate the motor evoked potential changes induced by tDCS. Thus, as some lifestyle factors modulate the neural effects of tES, they may also have an impact on tES-induced AEs. Smoking and insufficient sleep have also been associated with an increased likelihood for headaches (23), potentially creating an adverse add-on effect together with tES. Physical exercise has been shown to prevent both tension-type headache and migraines (24), whereas insufficient sleep has been claimed to be associated with headache (25). Chronic smoking is known to reduce cutaneous blood flow and impair the vasodilatory response (26). Chronic alcohol use can also cause oxidative stress and chronic inflammation of the skin (27), which could in turn sensitize the skin. Poor sleep quality and quantity increase skin aging, decrease its barrier function and worsen recovery from erythema, perhaps making skin more susceptible to adverse effects (28). However, even though one can speculate that these factors provide a potential linkage between lifestyle factors and tES-induced AEs, we are not aware of any studies investigating their impact.

In addition to lifestyle factors, repeated stimulation sessions could also exacerbate adverse effects – skin irritation and damage could be cumulative, leading to more intense effects as stimulation sessions are repeated. In recent years, longer stimulation protocols have become more and more common, several of these protocols have been described recently (29–31). We have previously observed (32) that repeated stimulation sessions do not appear to affect skin erythema, but as far as we are aware, there are no reports on the impact of repeated sessions on other AEs.

In conclusion, there are only a limited number of studies which have examined predictors for tES-induced adverse effects, and to the best of our knowledge, none of them have focused on lifestyle factors. In addition, the effects of cumulative stimulations are also largely unknown. Therefore, we performed a retrospective exploratory analysis to take the first steps to understand whether chronic alcohol use, smoking, exercise, and quality and duration of sleep would have any effect on the intensity of the adverse effects of tDCS or tRNS. We hypothesized that tobacco and alcohol use, and poor quality or insufficient sleep would increase the intensity of AEs, whereas they would be reduced by exercise. However, regarding the specific effect of smoking on skin erythema, we

hypothesized that tobacco use would decrease skin erythema via an impaired vasodilatory response. Based on our previous results (32), we expected that repeated stimulations would not increase the incidence of adverse effects.

METHODS

STUDY SAMPLES

This study utilized samples from two studies. The first study was conducted using tDCS and the second study using tRNS. In the rest of the article, we will refer to these as "tDCS study" and "tRNS study", respectively.

The first sample (tDCS study) was gathered as part of the Optimizing Transcranial Electrical Stimulation for Clinical Applications: Systemic Effects in Healthy Volunteers (sOptES) Study, in which a total of 82 Caucasian male volunteers (age mean [SD] = 28.9[5.7]) were recruited from the North Savo region of Finland; its aim was to examine the physiological effects of tDCS. Detailed characteristics of the sample can be found in *Supplementary Table 1*. The participants received either tDCS or sham stimulation in a double-blind setting. They received stimulation for five consecutive days. In this study, only the data from the first and the last day were used – the former to compare with the tRNS data, and the latter to examine the exacerbation of possible adverse effects of tDCS with time. The distributions of the samples are presented in *Supplementary Figures 1-3*.

The second sample (tRNS study) was gathered as part of the Optimizing Transcranial Electrical Stimulation for Clinical Applications: Impulsivity and Risk-Taking as Potential Treatment Targets for Psychiatric Disorders (OptES-iTreat) study, in which a total of 60 male and female participants (age mean [SD] = males: 25.8[4.5], females: 27.6[7.2]) were recruited from the North Savo region of Finland; its aim was to determine the effects of tRNS on impulsivity and risk-taking. Detailed characteristics of the sample can be found in Supplementary Table 2. The participants received both tRNS and sham stimulation in two separate sessions in a double-blind, crossover setting, with a minimum of one week between the two sessions. As the participants' experiences of adverse effects may differ depending on the novelty of the testing/stimulation situation, we only used the data from the first testing session to maintain comparability with the tDCS study. The distributions of the sample are presented in *Figure 1*.

Participants with a history of substance dependence/abuse were excluded in the tDCS study; otherwise, there were no exclusion criteria related to psychiatric illness in either study. All participants provided written informed consent after a full explanation of the study. Both study protocols were approved by the Ethics Committee of the North Savo Hospital District and conformed to the Declaration of Helsinki.

Inclusion criteria for the tDCS study were male sex, age of 18 to 40 years at the time of recruitment, right-handedness (i.e. belonging to the 1st to 10th right decile according to the Edinburgh Handedness Questionnaire (33)) and not having previously received tDCS. The inclusion criteria for tRNS Study were age from 18 to 50 years at the time of recruitment and right-handedness (i.e. belonging to the 1st to 10th right decile according to the Edinburgh Handedness Questionnaire (33)).

The exclusion criteria for both studies were metal implants inside the skull or eye, severe skin lesions in the electrode placement areas, a pacemaker, a history of epilepsy or previous seizures and a history of intracerebral bleeding during the previous six months. The tDCS study had an additional two exclusion criteria that related to the specific aims of that study: a history of any endocrinological condition (i.e. any physician-defined E00-E32 diagnosis according to the International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10) (34)) and a self-reported history of substance dependence/abuse during the past six months.

EXPERIMENTAL PROCEDURE

Before the experiments, the participants were instructed to abstain from alcohol consumption for 12 hours and to have consumed, at most, 2 doses (e.g. two 33 cl doses of beer or two 4 cl doses of hard liquor) during the preceding 24 hours, to abstain from products containing caffeine for 3 hours, and to abstain from smoking and heavy exercise for one hour prior to the experiment. In the tDCS study, the participants were randomly assigned to a 5-day period of tDCS or sham stimulation, while in the tRNS study they were randomized to receive either tRNS or sham stimulation in the first of the two sessions, with the other stimulation form delivered in the latter session. Information about potential influencing factors, including age, smoking history and alcohol use were collected prior to the stimulation sessions. Self-assessment of the quality and duration of the preceding night's sleep was also collected.

In both studies, each participant received a 20-minute stimulation session with 15 seconds of ramping up and down using a neuroConn DC-Stimulator (neuroConn GmbH,

Ilmenau, Germany). The 5×5 cm2 conductive rubber electrodes were inserted inside sponge pads soaked with 12 ml of saline and held in place with elastic straps. Elastic straps were tight enough to keep the sponge in place, while avoiding too much pressure on the skin. In the tDCS study, the anode was placed at site F3 and the cathode at site F4 according to the international 10–20 electroencephalography system. In the tRNS study, the electrodes were placed in the same locations. The sham stimulation consisted of 15 seconds of ramping up and ramping down at the beginning, after which stimulation was discontinued. In the tDCS study, the current was 2mA; in the tRNS study, the current was 2mA peak-to-peak between +1 and -1mA with the high frequency current fluctuating between 101 and 640 Hz (i.e. the "HF-Noise" setting of the neuroConn DC-Stimulator). The current flow for the tRNS protocol was the same, as the maximum stimulation frequency was below 10 kHz and the biological tissues can be treated as purely resistive, and "quasi-static" approximation of the Maxwell equations (35)

In both studies, the participants were shown a non-narrated video of a train during the stimulation to standardize the mental stimulus the patients received. In the tDCS study the participants had no significant tasks before or during the stimulation. On the other hand, in the tRNS study the participants had to complete an extensive package of psychometric tests about risk taking and inhibition before and after the stimulation.

OUTCOME MEASURES

After the stimulation, both the participant and the experimenter filled in a form in which they were asked to provide their estimate of the intensity of various adverse effects on a scale from 0 to 100. The adverse effects inquired in the form were feelings of tiredness, sensations under the stimulation electrodes and skin redness under the electrodes. As only experimenter-reported data on skin redness was available in the tRNS study, experimenter-reported values were used for the tDCS study in order to maintain comparability. Subjective measures for the adverse effects were used, as no objective measures were available.

POTENTIAL PREDICTORS

Alcohol use was measured with AUDIT-C, a short version of Alcohol Use Disorders Identification Test (AUDIT) score, focusing only on the amount of alcohol being consumed (36). It consists of three questions, each with five response options, and the total maximum score is 12. A score of 4 or higher (for men) or 3 or higher (for women) is considered indicative of alcohol abuse. The participants were asked to report how many years, if any, they had smoked, and how many hours of exercise they were getting, on average, each week. In addition, they were asked how many hours they had slept on the night preceding the first stimulation session, and how they would rate the quality of that sleep on a scale of 1 (very good) to 4 (very poor). In addition, as the tRNS study contained both males and females, sex was a variable of interest in that study. The lifestyle variables of interest were chosen based on availability and high frequency of use in clinical practice.

STATISTICAL METHODS

Preliminary analysis

The distribution of all the AE results can be seen in *Figure 1* (tRNS study) and *Supplementary Figures 1-3* (tDCS study). All models were run with R version 3.5.2. The data were initially checked for overdispersion via implementing a generalized linear model (GLM) defined as "Adverse effect ~ Group + Predictor + Group × Predictor", with the Quasi-Poisson distribution as reference for the dependent variable. As all these models showed substantial overdispersion which could lead to biased estimates, a GLM with a negative binomial distribution (with log-link) as reference was thus adopted instead for the main analyses, which is a more robust approach to overcome the undesirable overdispersion consequences of the data.

Main tests

All negative binomial GLM (log-link) were executed in R-CRAN software version 3.5.2 utilizing the package "msme" (37). Since age and stimulation condition could potentially modify the adverse effects (32), these factors were included into all models. A separate model was built for each adverse effect predictor pair, so the final models were defined as "Adverse effect ~ Age + Group + Predictor + Group × Predictor". A separate model for each pair was necessary in order to detect possible effects, as the data did not allow for more comprehensive models to be fitted.

Bonferroni corrections were used to compensate for multiple comparison. The alpha level used was 0.0083 as, at most, six different models were built per adverse effect (sex, hours of exercise, AUDIT-C, years of smoking, sleep duration, sleep quality) and study group.

The interaction term Group × Predictor, as well as the main effect term for the Predictor were the main outcomes of

interest. In addition, the main effect for the stimulation group was used to aid in the interpretation of the main outcomes, but not as an independent outcome.

Additional tests

SPSS 25 was used for all additional tests. In addition to the main tests, Wilcoxon signed ranks test was used to compare intensities of the adverse effects on days 1 and 5 of the tDCS sample. This test was chosen due to the non-normal distribution of the data. As there were 6 tests (3 adverse effects for both sham and active conditions), the alpha level for these tests was also set at 0.0083.

Lastly, we compared the intensity of the adverse effects between the study groups (i.e. active stimulation vs. sham) with Mann-Whitney U-test. As there were 9 of these tests, the alpha level was set to 0.0056.

Power calculations

To determine the sample sizes necessary for future studies, GLMs, with a negative binomial distribution as a reference, were used. In some cases, the dispersion parameter became infinite, implying a Poisson distribution would be more appropriate; in these cases, the analysis was performed with a Poisson likelihood.

After the GLMs had been trained, an analysis of variance was performed on the model, returning the variance explained by each model component. The explained variance and residual deviance for the interaction term were used to calculate the partial eta squared effect size for the interaction.

The partial eta squared effect sizes were then used for a sample size calculation, along with the relevant degrees of freedom of the GLMs, a statistical power of 0.8 and a significance level of 0.05. The returned sample sizes are the total population necessary, to be rounded up to the nearest integer for practical use, and halved for the population for each arm of the study.

RESULTS

The characteristics of the two study samples have been described in *Supplementary Tables 1-2*. In the tDCS study, only one participant in the tDCS group and two participants in the sham stimulation group reported no AEs at Day 1; at Day 5, all participants in the tDCS group reported AEs and only four participants in the sham group reported no AEs. For the tRNS study, seven participants in the tRNS group reported no AEs and nine participants in the sham group reported no AEs.

COMPARISON OF AES BETWEEN ACTIVE AND SHAM GROUPS IN TDCS AND TRNS STUDIES

The only statistically significant difference in AEs between the groups focused on skin redness on day 5 in the tDCS sample ($p<0.001$). Interestingly, sensations under the electrodes in the same sample were significantly milder on day five in the sham group ($p=0.007$), but not in the stimulation group (*Tables 1 and 2*).

PROGRESSION OF THE AES IN THE TDCS STUDY

Data revealed a slightly upwards trend for erythema in the tDCS group, and a slightly downwards trend for sensations of both conditions over time. However, the differences were statistically significant only in the sham group, with respect to sensations under the electrodes (Day 1 mean [SD] = 28.34[22.32], Day 5 = 20.36[22.12]), with the intensity of the adverse effects being lower on day 5 (*Table 1*).

EFFECTS OF LIFESTYLE FACTORS

Alcohol use, smoking, exercise, or the quality or duration of sleep were not associated with AEs in any of the models (*Supplementary Tables 3-5*).

POWER CALCULATIONS

Our power calculations suggested that the sample sizes necessary to detect any potential effects of lifestyles factors on AEs as significant are substantial (*Table 3*). To detect an effect of any studied lifestyle factor on skin redness under the electrodes, sample sizes ranging from 91 to 52825 participants would be required. The numbers are similarly large for feelings of tiredness (115–427174 participants) and sensations under the electrodes (83–23430 participants).

DISCUSSION

We ran retrospective exploratory analyses using two datasets to investigate the possible contribution of lifestyle factors on tDCS and tRNS AEs. Our analyses indicated that lifestyle factors did not contribute to the intensity of AEs following either tDCS or tRNS in the utilized samples, and that substantially larger samples would be needed for future studies on the same topic. Furthermore, in line with previous

research (38), the utilized samples displayed a significant difference in any AE (here, skin redness) only at day 5 in the tDCS Study, suggesting that the stimulation causes very few AEs. The observed AEs could instead represent nocebo or be caused by other factors of the study protocol, such as the elastic straps putting pressure on the head.

COMPARISON WITH THE EXISTING LITERATURE

To the best of our knowledge, there are no publications examining the effects of smoking, alcohol use or exercise habits on the AEs of tDCS and tRNS. Our findings provide direct guidance for the design of potential future studies investigating the same topic, while indicating that any potential effects of lifestyle factors on AEs are very small in nature.

With regard to the effect of cumulative stimulation sessions on tDCS adverse effects, we observed no intensification of adverse effects over repeated daily sessions. This finding is of particular clinical interest, as it indicates that tDCS protocols with a higher number of repeated daily sessions do not appear to increase the likelihood of more intense AEs.

STRENGTHS AND LIMITATIONS

The main strengths of our study are the relatively large number of observations and robust study protocols with a randomized, sham-controlled study design, as well as statistical methods well suited to handle the available data.

Perhaps the strongest limitation of our study is the number of participants, considering the observed minor effects of lifestyle factors on AEs. Nevertheless, we utilized our data to guide future studies by providing estimates for the needed numbers of participants for any studies focusing on the same topic.

Our results regarding repeated stimulation sessions would have been more reliable and better generalizable if we had had a longer intervention of, for example, four weeks. However, a recent meta-analysis (39) only found seven studies that reported adverse effects separately for each day, demonstrating that our retrospective analysis utilizing a 5-day stimulation protocol provides new information.

While the montage we used (i.e. anode on F3 and the cathode on F4 for tDCS) is common in both clinical and experimental tDCS studies, our results concerning tiredness and headache may not apply to other montages. However, sensations under the electrodes and skin redness are considered to be caused by local effects on the skin and should therefore be relatively unaffected by the electrode montage.

AUDIT-C scores and years of smoking reflect long-term use rather than shorter-term effects. Therefore, the results of this study represent chronic, not acute exposure, and future research should examine possible effects linked to acute exposures. Furthermore, caffeine is a commonly used substance with clear neurological effects, but with our current data, we could not investigate its effects, so its effects remain to be clarified.

A review by Brunoni et al. (40) concluded that the frequency of AEs reported was proportional to the extent to which they are sought. In other words, actively using structured questionnaires tends to overestimate the AEs when compared to passive monitoring. Thus, our study is conservative in this respect, and is more likely to have overestimated than underestimated the frequency of AEs.

CONCLUSIONS

Skin redness was more pronounced in the active group when compared to the sham group on day 5 in the tDCS Study. Our data suggests that in order to investigate potential effects of the studied lifestyle factors on AEs, significantly larger sample sizes are required.

Table 1. Comparisons of the intensity of the adverse effects on a scale 0-100 on days 1 and 5 of the tDCS study using Wilcoxon signed rank tests (rows) and a comparison between the study groups using Mann-Whitney U-test (columns).

		Day 1		Day 5		
Adverse effect		**Mean**	**SD**	**Mean**	**SD**	**P-Value**
Redness under the electrodes	Sham	3.12	3.77	1.49	3.36	0.019
	Active	5.54	5.46	5.76	5.31	0.829
	P-value	0.056		**<0.001**		
Feeling of tiredness	Sham	7.43	15.76	7.51	15.95	0.767
	Active	10.98	20.19	8.17	16.54	0.513
	P-value	0.288		0.537		
Sensation under the electrodes	Sham	28.32	22.32	20.36	22.12	**0.007**
	Active	27.10	25.49	24.25	10.18	0.844
	P-value	0.676		0.116		

Notes: SD = Standard Deviation; tDCS = transcranial direct current stimulation. Corrected alpha level = 0.0083 for the Wilcoxon Signed Rank test, 0.0056 for the Mann-Whitney U-test.

Table 2. Comparisons of the intensity of the adverse effects on a scale 0-100 between the study groups of the tRNS study using Mann-Whitney U-test.

Adverse effect		**Mean**	**SD**	**P-Value**
Redness under the electrodes	Sham	5.37	12.8	0.984
	Active	4.83	11.0	
Feeling of tiredness	Sham	18.9	26.6	0.575
	Active	23.8	27.7	
Sensation under the electrodes	Sham	0.53	2.01	0.008
	Active	8.23	16.1	

Notes: SD = Standard Deviation; tRNS = transcranial random noise stimulation. Corrected alpha level = 0.0056.

Table 3. Estimated total sample sizes necessary to detect the potential effects of lifestyle factors on adverse effects of tDCS or tRNS as significant.

		AUDIT	Smoking	Hours of exercise	Quality of sleep	Hours of sleep	Sex
Redness under the electrodes	tDCS	52825	14173	7131	324	3336	
	tRNS	91	493	153	569	606	264
Feeling of tiredness	tDCS	427174	254	142	183	115	
	tRNS	13358	992	3763	4957	661	336
Sensation under the electrodes	tDCS	670	23430	462	997	430	
	tRNS	1295	176	147	10184	210	83

Notes: SD = Standard Deviation; tDCS = transcranial direct current stimulation; tRNS = transcranial random noise stimulation. Corrected alpha level = 0.0056.

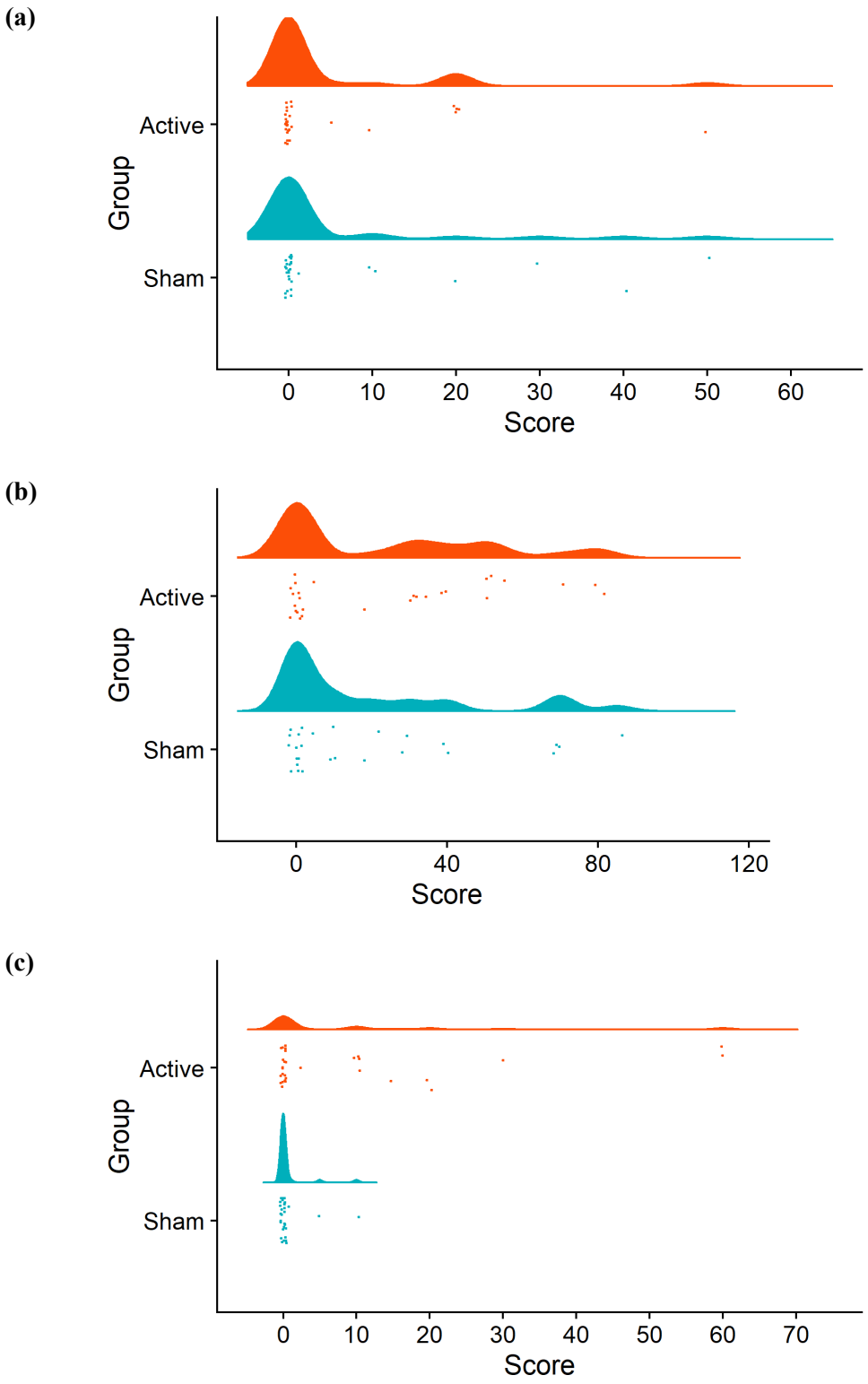


Figure 1. Distribution of adverse effect intensity in the tRNS study for (a) redness under the electrodes, (b) feeling of tiredness, and (c) sensations under the electrodes.

Supplementary Table 1. Characteristics of the tDCS sample.

	Sham		Active	
	Mean	SD	Mean	SD
Age (years)	28.4	5.50	29.3	6.00
BMI	25.3	3.68	25.9	4.10
Education (Years)	15.6	2.58	15.3	2.38
AUDIT-C	3.95	1.58	4.18	1.99
Exercise (h/week)	7.80	5.02	7.99	4.10
Sleep Duration (h/day)	6.88	1.06	6.97	1.03
Sleep Quality	1.92	0.66	1.95	0.61
Smoking (Years)	2.12	4.15	1.95	4.57

Notes: SD = Standard Deviation, BMI = Body Mass Index.
Sleep quality measured on a scale of 1 (Very Good) to 4 (Very Poor).

Supplementary Table 2. Characteristics of the tRNS sample.

	Sham		Active	
	Mean	SD	Mean	SD
Age (years)	27.5	6.80	26.1	5.30
BMI	24.6	4.50	23.6	3.59
Education (Years)	16.4	3.67	15.7	2.78
AUDIT-C	3.73	2.43	4.17	1.64
Exercise (h/week)	7.87	4.15	8.20	3.53
Sleep Duration (h/day)	7.61	1.11	7.51	1.15
Sleep Quality	1.70	0.70	1.77	0.68
Smoking (Years)	1.37	3.33	1.13	3.59
Subjects	14 males, 15 females		15 males, 15 females	

Notes: SD = Standard Deviation, BMI = Body Mass Index.
Sleep quality measured on a scale of 1 (Very Good) to 4 (Very Poor).

Supplementary Table 3. The impact of lifestyle factors on tDCS-induced adverse effects on day 1 as assessed by negative binomial regression. The main effect coefficients represent the listed lifestyle factors and the interaction coefficients are the interactions between lifestyle factors (each inserted separately into the models) and the intervention group.

		Main-effect Coef.		Interaction Coef.		Group Coefficient	
		P-Value	Coef.	P-Value	Coef.	P-Value	Coef.
Redness under the electrodes	Hours of exercise	0.318	-0.06	0.767	0.02	0.62	0.35
	AUDIT-C	0.613	-0.08	0.950	0.01	0.62	0.45
	Years of smoking	0.255	0.12	0.166	0.57	0.17	-7.92
	Sleep Duration	0.825	-0.06	0.664	0.16	0.84	-0.52
	Sleep Quality	0.297	0.48	0.163	-0.88	0.07	2.30
Tiredness	Hours of exercise	0.493	-0.10	0.120	0.52	0.15	-4.04
	AUDIT-C	0.683	0.17	0.842	-0.10	0.69	0.83
	Years of smoking	0.228	-2.20	0.221	2.25	0.29	-6.82
	Sleep Duration	0.281	-0.50	0.492	0.42	0.60	-2.27
	Sleep Quality	0.663	-0.35	0.358	1.09	0.47	-1.74
Sensation under the electrodes	Hours of exercise	0.772	0.01	0.204	-0.07	0.30	0.54
	AUDIT-C	0.300	-0.11	0.304	0.13	0.36	-0.52
	Years of smoking	0.446	0.05	0.297	-0.07	0.38	0.54
	Sleep Duration	0.790	0.04	0.201	-0.33	0.21	2.22
	Sleep Quality	0.069	-0.44	0.398	0.33	0.44	-0.62

Notes: AUDIT-C = The Alcohol Use Disorders Identification Test, short version. Ratio = Risk ratio. Corrected alpha level = 0.0083.

Supplementary Table 4. The impact of lifestyle factors on tDCS-induced adverse effects on day 5 using negative binomial regression. The main effect coefficients represent the listed lifestyle factors and interaction coefficients reflect the interactions between lifestyle factors (each inserted separately into the models) and the intervention group.

		Main-effect model		Interaction model		Group Coefficient	
		P-Value	Coef.	P-Value	Coef.	P-Value	Coef.
Redness under the electrodes	Hours of exercise	0.099	-0.11	0.692	0.04	0.203	1.04
	AUDIT-C	0.511	0.12	0.616	-0.12	0.095	1.76
	Years of smoking	0.424	-0.17	0.328	0.21	0.515	0.91
	Sleep Duration	0.600	-0.15	0.404	-0.36	0.210	4.00
	Sleep Quality	0.051	-1.05	0.069	1.24	0.569	-0.69
Tiredness	Hours of exercise	0.828	-0.04	0.812	1.07	0.782	-0.66
	AUDIT-C	0.975	0.02	0.767	1.19	0.740	-0.83
	Years of smoking	0.583	-0.18	0.126	2.30	0.096	-8.77
	Sleep Duration	0.461	-0.63	0.771	1.37	0.779	-2.26
	Sleep Quality	0.587	-0.75	0.455	3.42	0.465	-2.18
Sensation under the electrodes	Hours of exercise	0.723	-0.01	0.623	0.49	0.319	-0.03
	AUDIT-C	0.347	-0.12	0.471	-0.24	0.716	0.11
	Years of smoking	0.302	-0.11	0.809	-0.01	0.993	0.03
	Sleep Duration	0.198	-0.24	0.634	-0.68	0.726	0.13
	Sleep Quality	0.891	0.04	0.964	0.21	0.750	-0.02

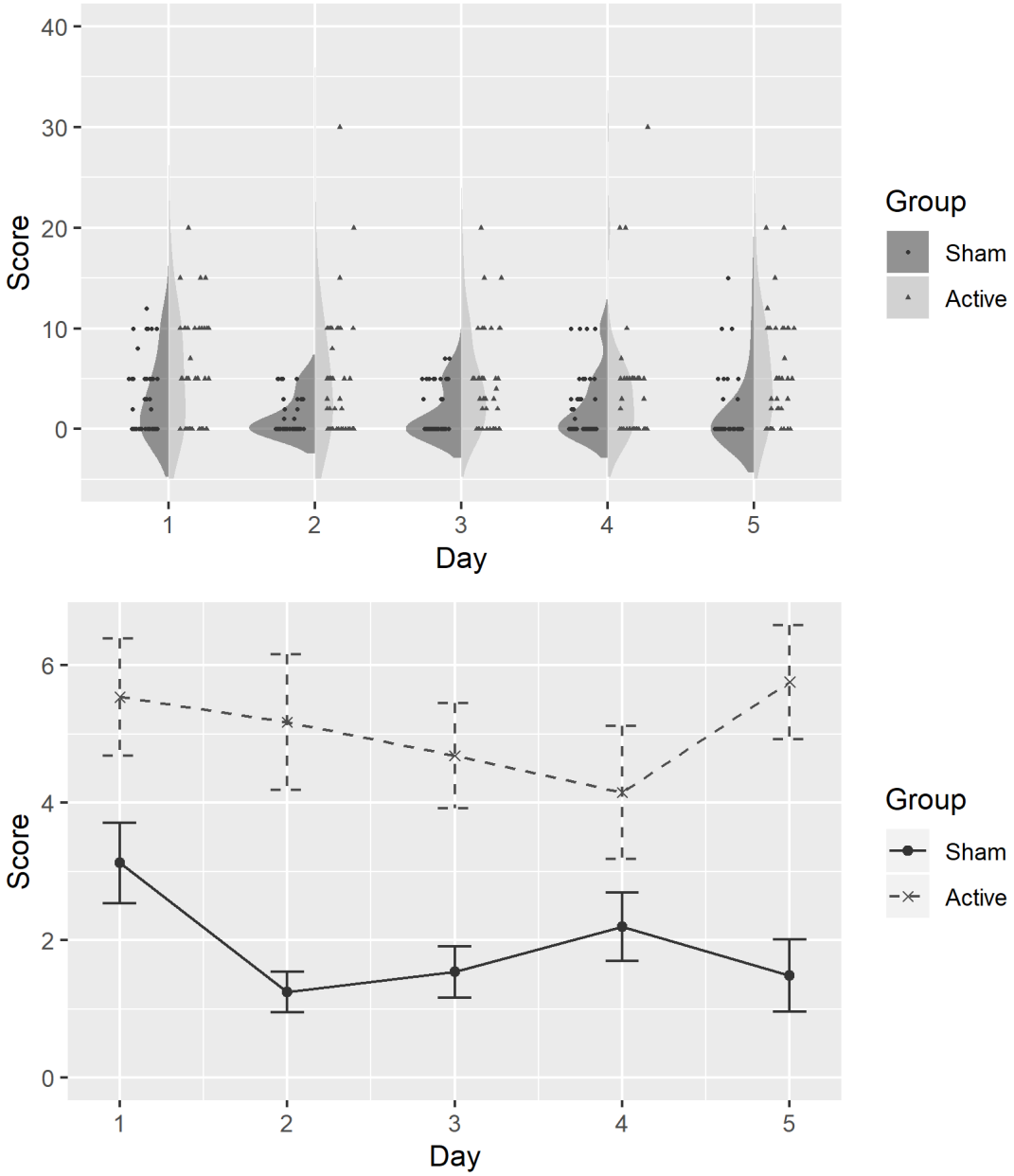
Notes: AUDIT-C = The Alcohol Use Disorders Identification Test, short version. Ratio = Risk Ratio. Corrected alpha level = 0.0083.

Supplementary Table 5. The impact of lifestyle factors on tRNS-induced adverse effects using negative binomial regression. The main effect coefficients represent the listed lifestyle factors and the interaction coefficients describe the interactions between lifestyle factors (each inserted separately into the models) and the intervention group.

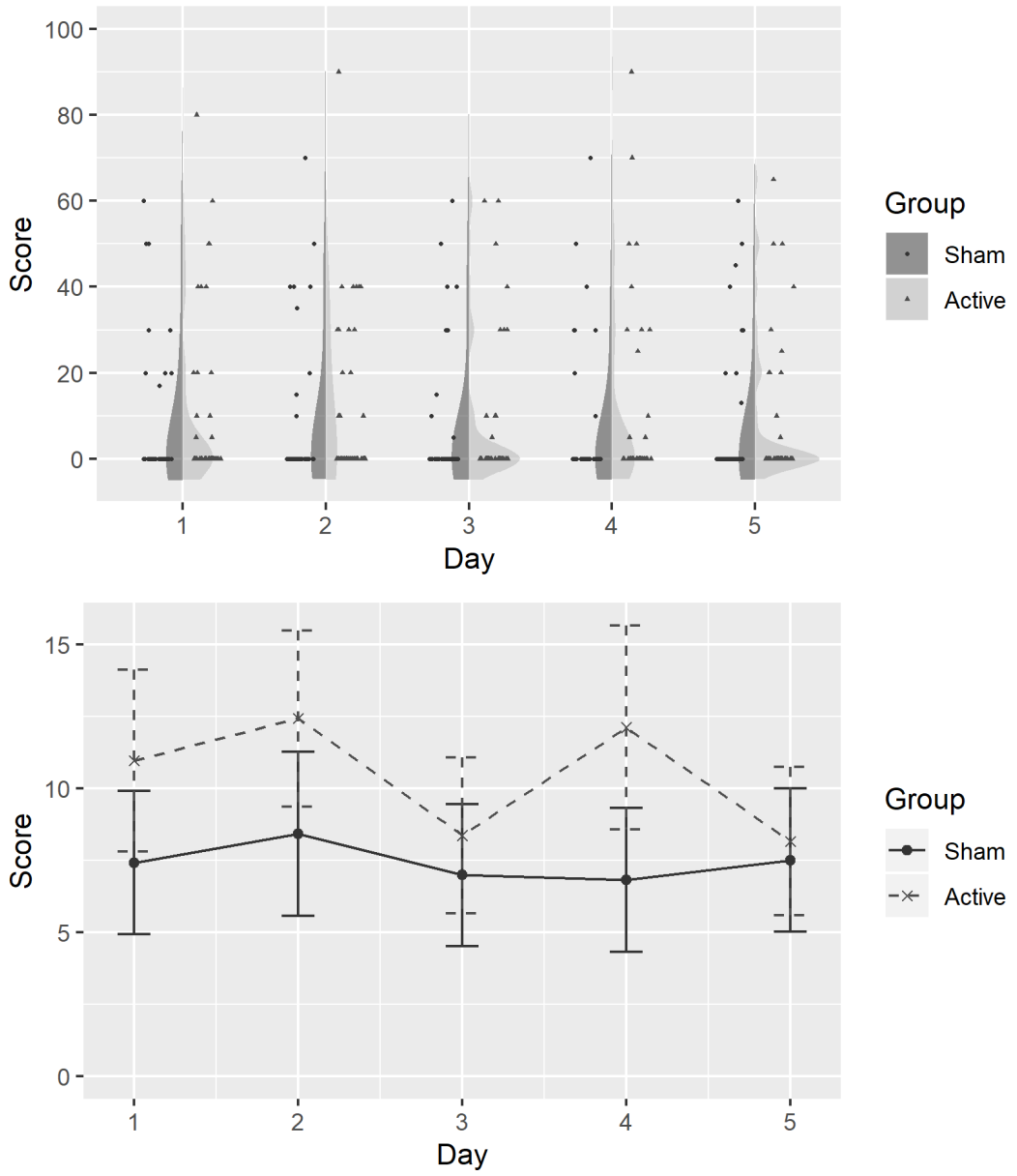
		Main-Effect Coef.		Interaction Coef.		Group coefficient	
		P-Value	Coef.	P-Value	Coef.	P-Value	Coef.
Redness under the electrodes	Sex	0.598	0.70	0.640	-0.81	0.446	0.68
	Hours of exercise	0.529	0.07	0.430	-0.08	0.662	0.89
	AUDIT-C	0.657	0.17	0.047	0.03	0.941	0.11
	Years of smoking	0.645	0.07	0.969	-0.05	0.645	0.32
	Sleep Duration	0.900	-0.31	0.341	0.33	0.639	-2.24
	Sleep Quality	0.712	0.07	0.468	-0.17	0.775	0.50
Tiredness	Sex	0.454	1.51	0.512	-3.11	**0.001**	4.84
	Hours of exercise	0.700	-1.07	0.733	1.13	0.379	-3.01
	AUDIT-C	0.352	0.40	0.937	-0.28	0.117	4.35
	Years of smoking	0.581	0.39	0.786	-0.35	**<0.001**	4.59
	Sleep Duration	0.500	-1.29	0.602	1.58	0.227	-8.00
	Sleep Quality	0.902	1.13	0.859	-0.28	0.286	3.53
Sensation under the electrodes	Sex	0.277	1.15	0.076	1.11	0.534	-1.03
	Hours of exercise	0.070	-0.12	0.065	0.19	0.451	-1.75
	AUDIT-C	0.501	0.13	0.678	-1.89	0.083	6.51
	Years of smoking	0.099	-0.10	0.224	-4.35	0.926	-0.10
	Sleep Duration	0.117	0.10	0.083	-1.26	0.369	8.98
	Sleep Quality	0.470	0.48	0.878	1.50	0.379	-3.22

Notes: AUDIT-C = The Alcohol Use Disorders Identification Test, short version. Ratio = Risk Ratio. Corrected alpha level = 0.0083.

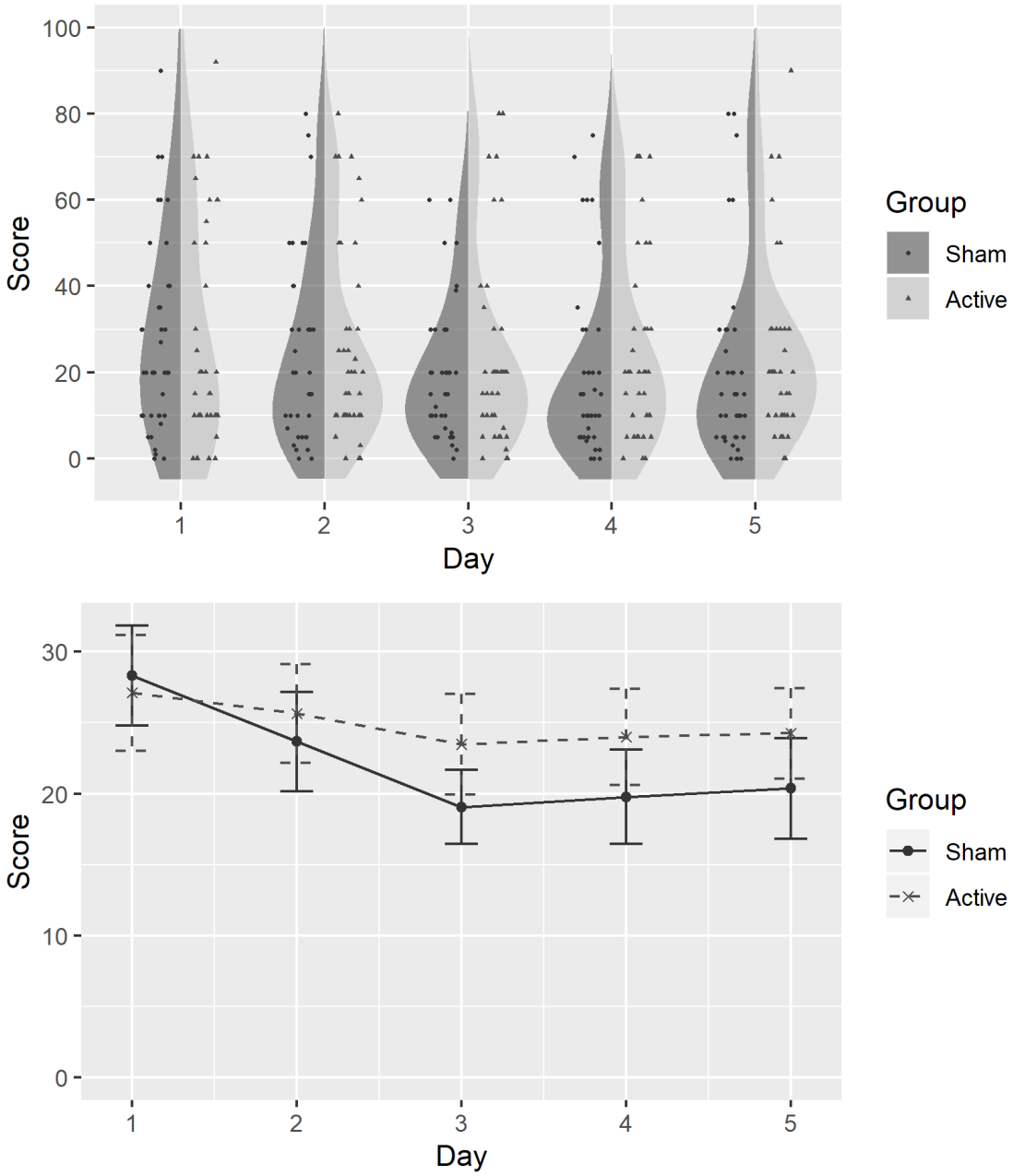
Supplementary Figure 1. Progression of the intensity of redness under the electrodes in the tDCS study.



Supplementary Figure 2. Progression of the intensity of feeling of tiredness in the tDCS study.



Supplementary Figure 3. Progression of the intensity of sensations under the electrodes in the tDCS study.



Conflict of Interest statement

All authors declare that there is no conflict of interest

Running title:

Lifestyle factors and the intensity of tDCS and tRNS adverse effects

Author:

Aaron Kortteenniemi [1], *BM*
Alfredo Ortega-Alonso [2], PhD
Amir-Homayoun Javadi [3,4,5], PhD
Owen Thomas [6,7], PhD
Tommi Tolmunen [1,8], MD,PhD
Tuukka Kotilainen [9], MD
Jan Wikgren [10], PhD
Soili M. Lehto [11,12,13], MD, PhD

[1] Institute of Clinical Medicine/Psychiatry, University of Eastern Finland, P.O. Box 1627, FI-70211 Kuopio, Finland
[2] Department of Public Health Solutions, Finnish Institute for Health and Welfare, Helsinki, Finland
[3] School of Psychology, University of Kent, Canterbury, Kent, England
[4] Institute of Behavioural Neuroscience, Department of Experimental Psychology, University College London, London, United Kingdom
[5] School of Rehabilitation, Tehran University of Medical Sciences, Tehran, Iran
[6] Department of Biostatistics, University of Oslo, Oslo, Norway
[7] Division of Research and Innovation, Akershus University Hospital, Nordbyhagen, Norway
[8] Department of Adolescent Psychiatry, Kuopio University Hospital, P.O. Box 100, FI-70211 Kuopio, Finland
[9] Acute Health Services, Iisalmi Regional Hospital, Iisalmi, Finland
[10] Centre for Interdisciplinary Brain Research, Department of Psychology, University of Jyväskylä, P.O. Box 35, FI-40014 Jyväskylä, Finland
[11] Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[12] R&D department, Division of Mental Health Services, Akershus University Hospital, Lørenskog, Norway
[13] Psychiatry, University of Helsinki and Helsinki University Hospital, Finland. FI-00029, Helsinki, Finland

Correspondence to:

Aaron Kortteenniemi, BM,
Department of Psychiatry, Institute of Clinical Medicine,
University of Eastern Finland,
P.O. Box 1627, FI-70211 Kuopio,
Finland.

Tel. +358 44 5278898
E-mail: *aaronk@studen.uef.fi*

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