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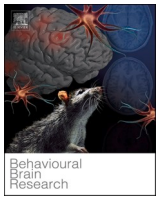

Influence of a placebo tDCS treatment on cybersickness and EEG-neurofeedback success

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ABSTRACT

Virtual Reality (VR) serves as a modern and powerful tool within the domain of neurofeedback (NF). Users can learn how to alter their own brain activation with the help of NF, for example visual feedback. VR can help to make the training more engaging and motivating with its immersive nature. However, cybersickness (CS) poses a serious problem, as it negatively affects up to 80% of all VR users. Especially women seem to be affected. Some studies suggest positive effects of placebo interventions, so that less CS in the users can be detected. Hence, we investigated whether a transcranial direct current stimulation (tDCS) placebo intervention can influence CS symptoms in a VR-based NF training and whether CS affects NF performance. Additionally, we focused on possible sex differences in the development of CS and the NF success. For this purpose, we tested 41 healthy participants in an EEG-NF-training with sensorimotor rhythm (SMR, 12–15 Hz) upregulation and VR feedback. Half of the participants got a placebo tDCS stimulation in advance to the training and were told that the stimulation would prevent them from getting cybersick. The other half received no such treatment. Both groups underwent six NF runs to three minutes each where they were asked to follow a ball along a predefined path in the virtual environment by increasing their SMR. Results showed that women experienced significantly more CS than men regardless of whether they received a placebo intervention or not. Women were also not able to increase their SMR successfully over the six NF runs. Male participants were able to increase their SMR. Also, only participants in the non-placebo group were able to increase their SMR, not those from the placebo group. The tDCS placebo intervention had little to no effect on sickness symptoms in VR, however it hampered the ability to increase SMR power. Also, CS seems to be associated with a worse NF training outcome, especially in women. Strategies to reduce CS inducing factors in VR environments could help participants to benefit more from a VR-based NF training. This should be especially considered in vulnerable groups that are more prone to CS.

1. Introduction

Virtual Reality (VR) offers a seemingly endless possibility of visualizing virtual environments and hence serves a multitude of use-cases ranging from sports, the educative domain up to the medical field [5] and cognitive training tools including neurofeedback (NF) [8]. Here, participants are trained to self-regulate their own brain activation by means of feedback, primarily visually. VR can make the visualization more immersive and engaging, which is important to keep participants motivated throughout the NF training process [14]. The main goal of the present study is to investigate the effects of VR-based feedback on NF training performance and determine whether any potential side effects of VR interaction conflict with this. Furthermore, we investigate whether a placebo-intervention affects potential side effects of VR interaction and consequently NF training performance.

Using VR-based feedback in NF training applications can increase motivation and adherence to training [14]. Generally, many repeated training sessions are necessary to achieve improvements in e.g. cognitive functions by means of NF [8]. Traditional feedback screens show two-dimensional simple moving objects [6,16] such as bars or circles changing their size in relation to changes in brain activation. Participants' motivation turned out to be a correlate of successful NF training performance, i.e., modulating one's own brain activity in a desired direction during NF training [13]. A few studies already showed that VR-based feedback leads to an increased NF performance [3,7]. There is also evidence that VR-based NF training might not be beneficial for all

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NF user groups. For instance, Kober et al. [15] have shown that elderly or neurological patients who are not accustomed to this technique have a certain technological gap that may also affect NF training performance.

Besides its positive immersive and motivating aspects, VR also entails adverse effects of which CS is the most prominent one. This can be described as the development of sickness symptoms, such as nausea, oculomotor problems and disorientation, due to the interaction with a virtual environment. Up to 80% [22] of the VR users experience at least some CS symptoms during the interaction. The most popular theory of the causes of CS is the sensory mismatch. It predicts CS when visual stimuli do not match, e.g. when users are virtually moving through an environment but are in reality remaining in a seated position [22]. The feeling of sickness can interfere with different psychological factors, such as the feeling of presence. It describes the subjective feeling of being present in a virtual environment (for a review see [26]) and is related to NF success [10]. Sex differences in CS symptoms are also frequently mentioned in the literature [25]. Women are more frequently and more intensely affected by CS [4]. This may be due to hormonal differences, less previous gaming experience, or a smaller interpupillary distance [25]. However, there are studies reporting no sex differences at all in CS. Results seem to vary according to exposure time, previous VR experience and so forth [20]. Hence, the potential side-effects of VR-based NF training might have different effects in male and female participants, depending on the VR setting.

Different attempts to reduce sickness symptoms in VR have been made such as reducing passive movements or using a constant navigation speed [1]. When it comes to sickness in general, different placebo interventions have been tried. For different purposes such as Chemotherapy, seasickness in naval recruits and simple motion sickness tests, placebos in form of pills, verbal instructions, acupuncture, overshadowing procedures, and context learning [9,21]. However, this has not yet been investigated in the context of CS and VR, especially in the context of NF training. Hence, in this study we investigated whether a sham treatment of transcranial direct current stimulation (tDCS) results in lower CS during the NF training, when telling the participants the cover-story that they would get an actual tDCS stimulation to prevent CS from happening.

Such a placebo intervention might not only affect CS but also NF training performance. A previous NF study showed that a placebo intervention using sham tDCS hampered the ability to modulate one's own brain activity during NF training and therefore reduced the NF success, when being told that the stimulation increases the training success. This might be ascribed to the strong expectation effects resulting through the placebo [17] leading to increased connectivity in the brain which interfered with the trained brain signals. This arises the question, whether our sham tDCS treatment interferes with the NF and hence results in lower training outcomes or whether the training success would be higher due to possible less CS.

Participants' sex could play a role not only in CS effects but also in placebo effects. Placebo effects seem to work differently when considering the sex of the participants. Previous studies showed that the mechanisms of placebo effects in nausea seem to differ between men and women, as different EEG activity can be shown [9].

In the present study, we investigated whether a placebo intervention can reduce CS symptoms in a VR-based NF training. Furthermore, we also focused on the effects of CS in VR on NF training performance. We expect higher CS to lead to reduced NF training success, defined as the SMR power increase across the six feedback runs. For the NF training, we use an established NF training protocol in which participants should learn to increase their sensorimotor rhythm (SMR, 12–15 Hz) in the EEG while keeping other EEG frequencies constant [8,14]. This NF training protocol turned out to improve cognitive as well as affective functions in patient populations as well as healthy controls [8,16]. NF training success is defined in a linear increase in SMR activity over the training course. If the placebo intervention affects CS symptoms, it might also affect NF training performance. A reduction in CS symptoms might lead to an increased NF training success. Because of the reported sex differences in CS as well as placebo effects, we also focus on sex differences in the present study. We expect that women will show stronger CS symptoms than men and that the placebo intervention has different effects in male and female participants.

2. Material and methods

2.1. Participants

In total, 41 healthy participants were tested in this study. They were pseudo-randomly assigned to one of the two groups (no sham tDCS vs. sham tDCS treatment; see Table 1). Inclusion criteria were an age between 18 and 34 years and the absence of neurological or psychiatric diseases, as well as normal or corrected to normal vision. The upper limit of 34 years was chosen, because CS levels between people below 35 years of age seem to differ from those above 35 years of age [24]. The experiment was double-blinded. The stimulation was performed by student assistants while experimenters were waiting outside the lab. After the stimulation or after passing the time needed for a stimulation, respectively, the experimenters entered the room to start the EEG montage and were not informed by the student assistants whether sham tDCS was applied or not. The student assistants were not informed that the stimulation was only sham. Participants either were told they received real stimulation or did not get any such treatment at all. Groups were stratified by sex, with participants assigned pseudo-randomly so that all groups were of equal size.

All participants gave their written informed consent. The study was approved by the local ethics committee of the University of Graz (GZ. 39/116/63 ex 2020/21), Austria and is in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans (World Medical Association, 2013).

2.2. VR-based NF training

The NF sessions consisted of a baseline and six feedback runs of 3 min each where the participants received visual feedback. For the visualization of the brain activation, the HTC Vive Pro-System was used. The paradigms were created and programmed using the game engine Unity 3D, Version 2018.3.1.4 and for the visualization in the VR system, the SteamVR plugin has been used. To integrate brain activation into the Unity paradigm, the lab streaming layer LSL4Unity plugin, freely available at https://github.com/labstreaminglayer/LSL4Unity, was implemented to stream the incoming EEG data from OpenViBE 2.2.0. The latter is a software for brain computer interfaces and serves as an interface between the incoming signal and the visualization software. It preprocesses the data in real-time and feeds it into the paradigm (see 2.3 EEG data acquisition).

During the VR-based NF training, participants would find themselves in a virtual light-flooded forest environment, containing a ball and multiple cubes (see Fig. 1). Participants were instructed to move the ball

Table 1
Mean values with standard deviations for the questionnaire data for every group. Shown are mean values ± standard deviations.

	Female		Male	
	No Placebo	Placebo	No Placebo	Placebo
N	11	10	10	10
Mean age	23.18 years	21.50 years	24.50 years	26.80 years
SSQ1	16.66 ± 12.56	16.08 ± 23.53	13.84 ± 14.54	14.59 ± 12.52
SSQ2	63.58 ± 32.73	62.83 ± 38.05	28.80 ± 29.08	29.92 ± 17.63
SSQ_Diff	46.92 ± 35.85	46.75 ± 51.26	14.96 ± 21.66	15.33 ± 19.11

Note. SSQ: Simulator Sickness Questionnaire, 1: pre NF training, 2: post NF training.

Fig. 1. : VR-based visual feedback during the NF training.

as far as possible along a predefined path marked by blue cubes, by increasing their sensorimotor rhythm (SMR).

During the baseline run, participants should relax and watch the forest walk paradigm moving by itself and were instructed to not try to influence it. The individual means for SMR (12–15 Hz) for each person were calculated during online data processing based on the data recorded during the baseline run as a threshold for the NF training. Also, Theta (4–8 Hz) and Beta (16–30 Hz) power values were included for artifact control, as Theta is associated with blinking and eye movements, whereas Beta is associated with muscle artifacts [16]. So, the mean plus one standard-deviation were calculated for Theta and Beta thresholds as well to establish the threshold for positive NF in the next runs. Participants were instructed to be physically relaxed, blink as seldom as possible to keep both Theta and Beta as low as possible. Also, participants were instructed to increase SMR by being mentally focused and physically relaxed, as this is the state where SMR shows.

Whenever participants were able to increase their SMR over the individually defined threshold, a ball rolled along a predefined path, collecting blue cubes that mark the path through the virtual forest (see Fig. 1) during the six feedback runs. Each feedback run started at the beginning of the forest environment again and the goal was to get as far as possible each time. The VR camera followed the ball as it moved, so participants had the feeling that they were flying behind it. In a pilot-study, we investigated a speed that was comfortable for the participants. Whenever the SMR level was under the individual threshold, the ball stood still. Additionally, whenever the participants produced too many artifacts, i.e. Theta (eye blinks/movements etc.) or Beta (facial movements etc.) were over the predefined individual levels, the ball turned red.

We also included the *Consensus on the reporting and experimental design of clinical and cognitive-behavioural NF studies* (CRED-nf) checklist, which was developed to improve the reporting and experimental design standards of NF studies, in the Supplementary material (Supplementary Material A), referring to where in our paper which relevant information on the design can be found [23].

2.3. EEG data acquisition

Electroencephalography (EEG) data was recorded with the gUSBamp RESEARCH EEG-amplifier from g.tec medical engineering with a sampling rate of 256 Hz. Signal was measured via 16 sintered Ag/AgCl passive ring electrodes placed according to the 10–20 system F3, Fz, F4, C3, Cz, C4, CPz, P3, Pz, P4, O1, and O2, as well as three EOG electrodes, reference electrodes placed left and right mastoid and a ground electrode.

A conductive, liquid gel was used for an ideal impedance and signal quality (ABRALYT). All electrodes where directly referenced against left mastoid. The ground electrode was placed at FPz, a further reference channel was placed at the right mastoid to allow the calculation of a linked mastoid reference during offline data analysis. Impedances of references and head electrodes were held below 5 kΩ and electrooculogram (EOG) electrodes below 10 kΩ. Cz was used to give feedback as SMR primarily shows over the sensorimotor areas.

2.3.1. EEG data analysis

2.3.1.1. Real-time data preprocessing. During the NF training, EEG data was preprocessed in real-time with OpenViBE. Data was recorded and in a first step, the three frequency bands of interest Theta (4–7 Hz), Beta (16–30) and SMR (12–15) were extracted and time-based echoing with 1 sec epoch duration and 0.5 sec. epoch intervals was applied. Data was exponentiated by two to get power values, then, data was averaged. Afterwards, a moving epoch average followed and data was logarithmized and exported to Unity (see Supplementary Material B).

2.3.1.2. Offline data preprocessing. Offline data analysis was performed using the Brain Vision Analyzer software (version 2.2, Brain Products GmbH, Munich, Germany). At first, a notch filter of 50 Hz was applied, as well as a low cutoff filter of 0.01 and a high cutoff filter of 100 Hz were used to eliminate low frequencies such as large drifts, as well as high frequencies. Afterwards, we excluded big muscle artifacts, heavy drifts and the like during a manual raw data inspection. Data was then referenced to the linked mastoid reference to rule out hemisphere effects, as the left mastoid was the primary reference electrode. In a next step, blinks and eye movement components were eliminated using a semi-automatic independent component analysis (ICA). Lastly, a second semi-automatic data inspection followed to exclude additional remaining artifacts that survived the other preprocessing steps (Criteria for rejection: maximum allowed voltage step of 50μV/ms, maximum allowed difference between values in a segment was 200 μV, amplitudes ± 120 μV, lowest allowed activity in 100 ms intervals was 0.5 μV, artifacts were marked 200 ms before and after emergence).

In the next steps, power in the range of the frequency bands SMR (12–15 Hz), Mid-Beta (15–21 Hz), High-Beta (21–35 Hz) and Theta (4–8 Hz) were extracted in the BrainVision Analyzer using complex demodulation. Data was segmented into 1 s intervals and segments with artifacts were removed.

We additionally calculated and analyzed the coherence of resting-state EEG, see Supplementary Material F.

2.4. Sham tDCS intervention

Preceding the NF training, half of the participants received sham transcranial direct current stimulation (tDCS). For this, we used the one-channel stimulator DC-STIMULATOR PLUS (neuroCare Group GmbH, Germany). Two electrodes (3 cm×5 cm) were soaked with 0.9% NaCl solution. The anode was placed at F3 and the cathode was placed at C4, according to the 10–20 system.

To make the experience of the sham tDCS as realistic as possible, at the first second to 1 mA (current density of 0.06 μA/cm^2) was applicated in a ramp-like fashion, comparable to a real stimulation protocol, and switched off afterwards [17]. The stimulation lasted 3 min. The experimenters and participants were blinded and consequently not aware, that it was only sham stimulation. These parameters for the sham stimulation were chosen based on previous reports [17]. Participants receiving the sham stimulation were told, that it would decrease the probability of feeling cybersick during subsequent VR interaction. More precisely, the instruction given to the placebo group was the following:

min. You can simply sit relaxed during that time.".

After the stimulation, both EEG and VR were placed on the participant's head. The other half of the participants just conducted the training without any preceding sham stimulation and information on CS.

2.5. Procedure

When participants arrived in the laboratory, they were asked to fill out the first set of questionnaires on the computer, using LimeSurvey. Then, the sham tDCS stimulation followed with blinded experimenters who did not know only sham stimulation was given. Next, the EEG montage followed, and ECG electrodes were placed, and the VR system was put on and participants were told to adjust the interpupillary distance (IPR) on a wheel on the goggles.

When everything was in place, resting EEGs with open and closed eyes for 2 min each were recorded. The baseline for the NF training followed and afterwards the NF was explained to the participants. Six NF runs to 3 min each followed. In between each run, the Fast Motion Sickness Scale (FMS) was verbally presented to the participants, so they would not have to put down the goggles each time. After training, another resting EEG with opened and closed eyes followed and the VR, EEG and ECG was put off. Participants could put off some of the paste in their face and had to fill out the second set of the questionnaire. Afterwards, they had the possibility to wash their hair in the lab. Participants either got 20 € as an incentive or a confirmation of participation for psychology students.

2.6. Questionnaires

To investigate the subjective experience of the participants during the training, they had to fill out several questionnaires before and after the training in line with the CRED-nf checklist [23]. Some of the questionnaires are not relevant for this specific research question, more on them can be found in the Supplementary Material C. Here, the Simulator Sickness Questionnaire (SSQ) is explained in more detail.

2.6.1. Simulator sickness questionnaire (SSQ; Kennedy, 1993)

Participants rated 16 different physiological symptoms on the three subscales nausea, disorientation and oculomotor problems via a four-point Likert scale [12]. Response options to listed symptoms were from Not at all (0), Mild (1), Moderate (2), to Severe (3). The higher the scores, the higher the sickness. The questionnaire was given twice, once before and once after training. Kennedy et al. [12] proposed a specific formula to calculate the total score and the scores of the subscales. Raw values are added up and multiplied by a weighting factor which varies for all the subscales and the total score. We calculated our SSQ scores according to this formula.

2.7. Electrocardiography (ECG)

The ECG of every participant was additionally recorded with an eMotion Faros 180° (BioSign GmbH). However, as it is not relevant for the present study, it will not further be reported here.

2.8. Statistical analyses

Statistical analyses were performed using RStudio (2022.07.2+576) using R (freely available at http://cran.r-project.org.). The lmer4 and lmerTest packages were used (available online at: http://CRAN.R-project.org/package=lme4). The script is also available as markdown file in the Supplementary Material H. The significance level of $p < .05$ was used in the analyses.

To investigate whether the placebo intervention had effects on the development of CS, we calculated a 2×2 ANOVA, with CS as dependent variable, and sex (male/female) and placebo (yes/no) as factors. For CS as dependent variable, we calculated the difference $SSQ_{post\ NF\ training}$ - $SSQ_{pre\ training}$ (SSQ_Diff). Positive values indicating an increase of CS.

To investigate the NF performance (changes in SMR power across six NF runs) of the different groups (male vs. female participants, participants receiving tDCS placebo intervention vs. participants receiving no placebo and the six feedback runs), a linear mixed model with three fixed factors (sex, placebo, feedback runs) was calculated for the dependent variable SMR power over electrode position Cz (Type I Sum-of-Squares Analysis of Variance with Satterthwaite's method). In order to enable a better interpretation of the results we split the factor runs in two groups, one for the first training half (first three runs) and one for the second training half (runs four to six). The factor subjects was included in the model as crossed random effect. As post-tests for significant interaction effects, separate linear mixed effect model analyses per group were performed. The same method was used for Theta and Beta frequency bands (in line with CRED-nf checklist, [23]), here, calculation and results can be found in the Supplementary Material G.

To check for associations between individual NF training performance and CS, we calculated correlations for all four groups between SSQ difference values (difference SSQpost NF training - SSQpre training) and the individual SMR power regression slopes across the six feedback runs. The slopes were determined using a regression with SMR power as the criterion variable and feedback run number as the predictor variable. A positive regression slope indicates a linear increase in SMR power across the six feedback runs which is associated with successful NF performance, while a negative regression slope indicates a decrease in SMR power across feedback runs, which is associated with unsuccessful training.

Also, we added additional statistical analyses with the other questionnaires in the Supplementary Material D and E.

3. Results

3.1. Effects of placebo on cybersickness

Table 1 shows mean CS values per group and time point. The results of the 2×2 ANOVA with CS as dependent variable and sex and placebo as factors showed a group difference for sex (see Fig. 2B), with higher CS increase for women ($\overline{X} = 46.84 \pm 42.72$) compared to men ($\overline{X} = 15.15 \pm 19.88$). For F-statistics see Table 2.

3.2. NF performance

A linear mixed effect model for the dependent variable SMR (see Table 2) power showed a significant main effect for runs, with higher values in the second half ($\overline{X} = 1.93 \pm 1.91$) compared to the first half ($\overline{X} = 1.76 \pm 1.38$). Also, there is an interaction effect for placebo and feedback runs. Post-tests showed that only participants in the no placebo group could increase their SMR ($F(1,103 = 5.78$, $p = .018$, $\eta_p^2 = .06$). Finally, there was a significant interaction effect of sex and feedback runs and post-tests showed an increase in SMR power only in men with higher power values during the second half of the training ($\overline{X} = 1.93 \pm 2.03$) compared to the first half ($\overline{X} = 1.59 \pm 0.95$; $F(1,98) = 5.21$, $p = .025$, $\eta_p^2 = .05$). Fig. 2A shows the changes in SMR power across the NF runs separately for each group.

3.3. Relationship between CS and NF performance

All groups showed a negative association between CS and the individual SMR power regression slopes, however they were not statistically significant (see Table 2). A negative correlation indicates that an increase in CS during the NF training is associated with a poorer NF performance. For a more detailed correlation matrix see Supplementary Material D.

4. Discussion

In the present study, we focused on CS in a VR-based NF training task. CS symptoms were not affected by a placebo tDCS intervention. However, the intervention overall hampered the ability to increase SMR power during the NF-training. Also, we found overall sex differences in

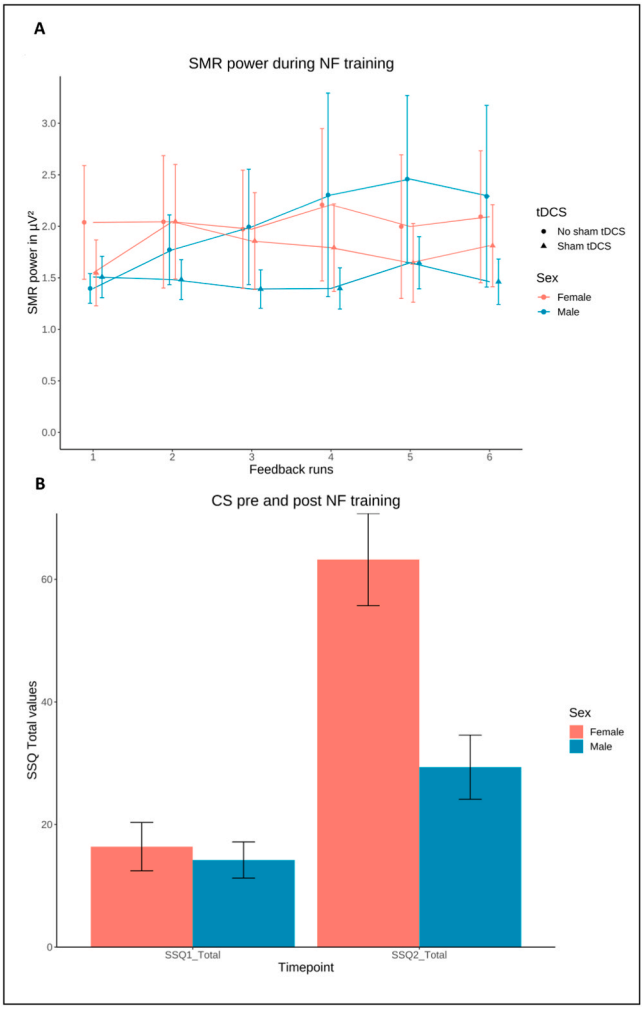

Fig. 2. : A. NF training performance per group. Line graph showing the SMR power for all four groups over the six feedback runs. Error bars represent standard error. **B.** CS pre and post NF training for men and women.

Table 2
Results of the statistical analyses.

2×2 ANOVA: SSQ_Diff as dependent variable and sex and placebo as factors					
Factors	df	*F*	*p*	η_p^2	sig.
Placebo	1,37	0.00	.952		
Sex	1,37	8.65	.006	.19	**
Placebo*sex	1,37	0.00	.980		
Linear Mixed Effects Model: SMR power as dependent variable and sex, runs and tdcs as factors					
Placebo	1,37	0.68	.417		
Runs	1,201	4.62	.033	.02	*
Sex	1,37	0.10	.755		
Placebo*runs	1,201	5.09	.025	.03	*
Placebo*sex	1,37	0.08	.784		
runs*sex	1,201	4.47	.036	.02	*
Placebo*runs*sex	1,201	1.96	.164		
Correlation of SSQ_Diff and individual SMR power regression slopes for each group					
	r	*p*			
Female no placebo	–.35	.288			
Female placebo	–.26	.464			
Male no placebo	–.30	.402			
Male placebo	–.48	.163			

Note. * $p < .05$, ** $p < .01$.

CS symptoms and NF training performance with a worse outcome for female participants. Male participants showed lower CS symptoms and only male participants were able to increase their SMR activity during the NF training.

Sham tDCS as a placebo intervention did not affect CS symptoms in a VR-based NF training task. Prior VR studies used different attempts to reduce sickness symptoms in VR by manipulating technological factors such as navigation speed, field of view, etc. [1]. In the present study, we used a placebo intervention by applying sham tDCS and telling the participants a cover story about its sickness reducing effects. Placebo interventions were also used in prior studies to reduce sickness symptoms in general, not specifically in VR. Some of those interventions were successfully reducing sickness symptoms, using different placebos such as pills or acupuncture [9,21]. It is likely that the credibility of the cover story for the placebo intervention was not high enough in the present study when it comes to the reduction of CS. Our instruction suggested only a reduction and slower appearance of CS symptoms and gave examples on possible symptoms, which could make participants more aware on such symptoms, making the intervention less successful. The missing placebo effect on CS can also be attributed to the fact that the time between the sham tDCS stimulation and the actual NF training was quite long, about 30 min (see limitations). However, a review on placebos and sickness [21] found effects when placebos were given 10 min before the treatment or task, but also when the placebo was given an hour or even a day before. This suggests that the placebo was not convincing enough to the participants concerning the reduction of CS or made the participants more aware of the sickness symptoms. This can be the case since the tDCS treatment was not described powerful enough, but only to reduce symptoms. Previous studies on placebo effects added instructional sheets with information on the placebo, with more detailed description why the placebo would be helpful [21]. So, for further studies in this field, creating a more convincing set up and description of the used placebo would be of a great advantage. Also, research on placebo showed a wide variety of effectivity depending on the type of placebo that was given. Participants are more likely to experience higher placebo effects, when, among others, the price of the placebo is high, and the dosage increased and go even as far as the color of prescribed pills. Further, placebos seem to work more, when given by physicians or someone wearing a white lab coat [18]. In our study, sham tDCS was applied by research assistants who did not wear a white lab coat or some other socially conventioned symbol of scientific or medical authority. In comparison to the NF training duration including the EEG montage, the three-minute-long placebo treatment might have been too short to leave a greater impact on the participants concerning CS. In that case, it could have been beneficial to again remember the participants about the placebo right before the training and repeat the instruction that they will feel less cybersick due to the treatment half an hour ago. In research settings like ours one could add to the cover story that the longer time between treatment and training would be necessary to give an effect with experimenters wearing white lab coats like physicians to create a more clinic-like and convincing impression.

We selected the placebo intervention following one of our previous studies in which we successfully applied sham tDCS to influence NF performance [17]. And although we did not find decreases of CS due to the placebo, we could replicate the findings by Kober et al. [17] that only the participants in the no placebo group could successfully increase their SMR power, but not the placebo group. There, the cover story differed to ours, as participants were told the intervention would help them in achieving a better NF training performance instead of focusing on CS, as we did. However, the outcome is comparable, as it led to a worse NF training outcome due to unspecific effects. Those effects are said to be driving factors during the training process, as they can for example lead to raised expectancies in the participants which can distract from the training [17]. Nevertheless, there are NF studies including sham feedback where the fed back signal is not the own brain activation but those from other participants. Results can be comparable

to NF training with real feedback [3]. Here, placebo seems quite effective for the NF process. In such study designs the placebo is mostly not specifically verbalized and participants do not know they get no real feedback. Hence, no specific expectations are triggered in the participants that could distract from the training process. When it comes to NF performance, the type of placebo seems to play a crucial role and needs to be investigated further.

Although our placebo intervention did not work to reduce CS in VR, we could replicate a general finding that women showed stronger CS symptoms in VR than men. In our sample, women showed a mean SSQ increase of more than 40 SSQ-points during VR interaction. Previous literature supports our findings concerning sex differences in the development of CS [4]. Especially with the usage of HMD, such differences seem apparent, as VR goggles are mostly adjusted for a male interpupillary distance (IPD), which is why women mostly cannot properly adjust the image quality, which increases the probability of CS [25]. However, some studies did not find such sex differences concerning CS [20]. In this literature it is encouraged to deliver more specific information about the VR environments to interpret such effects. There, it could be shown that the development of CS and also connected sex differences can be assigned to a multifactorial reasoning, such as age of the participants, exposure time in the virtual environment or the familiarity with the presented content. Within the duration of ten minutes, virtual environments are mostly agreeable for male as well as female participants in a similar way. Exposure times for a longer duration, such as 20 min, leads to a greater gap between groups concerning the development of CS. In our study, the NF training lasted about 30 min with breaks, which is relatively long and could account for the sex differences in our sample. Also, the amount of interaction with the virtual environment and speed and amount of movement during the VR task plays a great role when it comes to CS [20]. In our study, the participants in fact did not have to physically engage with the environment, which in itself would be only very little CS inducing. However, they were passively moving ("flying") in the virtual environment while comfortably sitting in a chair, which triggers incompatibility of physical resting and visual movement which is one of the main factors resulting in sickness [22]. Interestingly, another factor that plays a big role in the efficacy of placebo treatments is, whether participants have already had experience with nausea in the domain of study interest. Hence the literature on sickness and placebo proposes, to integrate a baseline session, where participants will get in touch with the sickness-inducing task to get an idea of potential sickness and will afterwards get the placebo, before the actual experiment, to get an idea of how it is going to feel and why one would get sick in that very environment.

In our study, women not only experienced more sickness but also were not able to successfully increase their SMR during the NF training. Only male participants showed an increase in SMR power over the six feedback runs. There are no studies investigating the influence of CS on the NF performance so far, however, studies on VR and CS could find small, yet negative associations with cognitive performance [19] and visual attention [2]. Both cognitive focus and visual attention are necessary for a good NF performance [11,7] which could explain the worse NF performance of women. Here, shorter feedback durations or breaks with closed eyes to reduce the feeling of sickness could help working against the development of sickness and secure a better NF training performance for more vulnerable participant groups. Consequently, this should be the topic of further research projects.

5. Limitations

Within the study design there were several limitations which should be considered in future studies. Firstly, a relatively long time passed between the placebo tDCS treatment and the actual NF training (about 30 min. delay). Here, the time might have been too long for proper placebo effects against CS to develop, especially as the cover story was only told once right before the treatment and was not repeated before the NF training start and hence could have been too little convincing for the participants. Further, for the instructions one should avoid being too vague to achieve a more specific experience for the participants. In order to validate the tDCS treatment, it is also necessary to ask validation questions at the end of the experiment to check whether the participants believed in a real treatment or not. This should also be taken into account in future studies.

Additionally, all our participants got their real brain signal fed back during the NF training and we did not include any sham NF group. However, in line with CRED-nf checklist [23] it is suggested to include such groups to being able to differentiate NF training effects from possible placebo effects.

Finally, we investigated CS only with the SSQ questionnaire. Including objective sickness measures, such as electrodermal activity (EDA) would be of importance to get a better understanding for the development and processes of CS.

6. Conclusions

In our study, we showed that women seem to profit less from VR-based NF training compared to men, which might be attributable to a higher proneness to develop CS. To tackle this problem, exposure times should be held shorter, and more breaks should be added to the experiments where participants could close their eyes to relax and decrease possible CS symptoms. Also, one could introduce an extra session where participants could get to know the VR-system, as experience can also lower the development of sickness. For the placebo treatment the persuasiveness could be increased by including baseline sessions to introduce the task and treatment, explaining the placebo mechanism on an example. This could help to prevent CS more properly. However, as the placebo intervention led to a worse NF performance, a detailed report is of utmost importance.

CRediT authorship contribution statement

Guilherme Wood: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Silvia Erika Kober:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Lisa Maria Berger:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Data Availability

Data that support the findings of this study are uploaded as Supplementary Material.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbr.2024.114917.

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