Brain Stimulation 12 (2019) 674–683

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Differential effects of bifrontal tDCS on arousal and sleep duration in insomnia patients and healthy controls

Lukas Frase [a, h], Peter Selhausen [a], Lukas Krone [a], Sulamith Tsodor [a], Friederike Jahn [a], Bernd Feige [a], Jonathan G. Maier [a], Florian Mainberger [a], Hannah Piosczyk [a], Marion Kuhn [a], Stefan Klöppel [b], Annette Sterr [c], Chiara Baglioni [a], Kai Spiegelhalder [a], Dieter Riemann [a], Michael A. Nitsche [d, e, f], Christoph Nissen [a, g, *]

[a] Department of Psychiatry and Psychotherapy, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Germany
[b] University Hospital of Old Age Psychiatry and Psychotherapy, Bern, Switzerland
[c] Department of Psychology, University of Surrey, UK
[d] Department of Clinical Neurophysiology, University Medical Center Göttingen, Germany
[e] Leibniz Research Centre for Working Environment and Human Factors, Dortmund, Germany
[f] Department of Neurology, University Medical Hospital Bergmannsheil, Bochum, Germany
[g] University Hospital of Psychiatry and Psychotherapy, Bern, Switzerland
[h] Center for NeuroModulation, Faculty of Medciine, University of Freiburg, Germany

ARTICLE INFO

Article history:
Received 19 July 2018
Received in revised form
28 December 2018
Accepted 2 January 2019
Available online 4 January 2019

Keywords:
Non-invasive
Brain stimulation
Hyperarousal
Electrosleep
EEG

ABSTRACT

Background: Arousal and sleep represent basic domains of behavior, and alterations are of high clinical importance.
Objective/hypothesis: The aim of this study was to further elucidate the neurobiology of insomnia disorder (ID) and the potential for new treatment developments, based on the modulation of cortical activity through the non-invasive brain stimulation technique transcranial direct current stimulation (tDCS). Specifically, we tested the hypotheses that bi-frontal anodal tDCS shortens and cathodal tDCS prolongs total sleep time in patients with ID, compared to sham stimulation. Furthermore, we tested for differences in indices of arousal between ID patients and healthy controls and explored their potential impact on tDCS effects.
Methods: Nineteen ID patients underwent a within-subject repeated-measures sleep laboratory study with adaptation, baseline and three experimental nights. Bifrontal anodal, cathodal and sham tDCS was delivered in a counterbalanced order immediately prior to sleep. Wake EEG was recorded prior to and after tDCS as well as on the following morning. Subsequently, we compared patients with ID to a healthy control group from an earlier dataset.
Results: Against our hypothesis, we did not observe any tDCS effects on sleep continuity or sleep architecture in patients with ID. Further analyses of nights without stimulation demonstrated significantly increased levels of arousal in ID patients compared to healthy controls, as indexed by subjective reports, reduced total sleep time, increased wake after sleep onset and increased high frequency EEG power during wakefulness and NREM sleep. Of note, indices of increased arousal predicted the lack of effect of tDCS in ID patients.
Conclusions: Our study characterizes for the first time differential effects of tDCS on sleep in patients with ID and healthy controls, presumably related to persistent hyperarousal in ID. These findings suggest that adapted tDCS protocols need to be developed to modulate arousal and sleep dependent on baseline arousal levels.

Introduction

Insomnia disorder (ID) is a prevalent health problem leading to reduced quality of life [1], adverse health outcomes [2–4] and a

* Corresponding author. Medical Center – University of Freiburg, Department of Psychiatry and Psychotherapy, Hauptstr. 5, 79104 Freiburg, Germany.
E-mail address: christoph.nissen@upd.ch (C. Nissen).

https://doi.org/10.1016/j.brs.2019.01.001
1935-861X/

relevant economic burden [5]. Current first-line treatments include cognitive behavior therapy and, for short-term treatment, pharmacotherapy [6–8]. Still, only about half of the patients achieve long-term remission, indicating the need for additional research [9]. The current study was designed to further elucidate the neurobiology of ID and the potential for novel treatments based on the modulation of cortical activity through the non-invasive brain stimulation technique transcranial direct current stimulation (tDCS).

Recent concepts of the pathophysiology of ID highlight the importance of persistent (24 h) hyperarousal, as indexed by psychological, endocrine, immunological, electrophysiological and neuroimaging studies (for overview [9,10]). Particularly, patients with ID demonstrate elevated cortical arousal during non rapid eye movement (NREM) sleep, as indicated by increased electroencephalographic (EEG) power in high frequency bands [11] and a lack of decline in glucose metabolism in thalamo-cortical arousal systems from waking to NREM sleep in comparison to controls [12,13]. More specifically, alterations in ID include widespread wake EEG signatures of hyperarousal, including in the prefrontal cortex [14], in which deactivation is critically important for reduced consciousness and persistent sleep [15]. However, it remains unclear whether cortical hyperarousal in ID represents a pathophysiological mechanism and potential treatment target or a mere epiphenomenon of subcortical activity changes.

Standard models of sleep-wake regulation delineate an ascending reticular activating system (ARAS), that originates in the brain stem and activates the thalamus and cortex via *bottom-up* pathways during wakefulness [16,17]. Current pharmacological treatments for clinical conditions of disturbed arousal or sleep modify relevant neurotransmitter systems of the ARAS with some success, but limited efficiency and relevant adverse effects [6].

Other neuroanatomical [18] and neurophysiological [19] studies in animals have described descending cortico-thalamic pathways that are critically important for synchronized cortico-thalamo-cortical slow oscillations as a prerequisite for decreased arousal and sleep [20]. These *top-down* pathways complement bottom-up pathways of sleep-wake regulation and might represent a treatment target for non-invasive brain stimulation techniques in humans [21].

The brain stimulation technique transcranial direct current stimulation (tDCS) provides the opportunity to non-invasively modulate cortical excitability and, following the described top-down perspective, to target cortico-thalamic pathways of sleep-wake regulation, with anodal tDCS leading to increased and cathodal tDCS leading to decreased cortical excitability [22,23]. We recently demonstrated that repetitive bilateral anodal tDCS to the prefrontal cortex prior to sleep significantly increases cortical arousal during wakefulness (high frequency EEG power) and decreases total sleep time (TST) compared to cathodal and sham stimulation in healthy humans [24]. In the same study, cathodal stimulation appeared to decrease cortical arousal during wakefulness (high frequency EEG power), but did not prolong TST, potentially due to ceiling effects in healthy controls [24].

The current study translated this line of research to patients with ID and aimed to provide proof-of-concept that local cortical activity changes through tDCS can modulate arousal and sleep in ID. Specifically, we tested the hypotheses that bi-frontal anodal tDCS shortens and cathodal tDCS prolongs TST in patients with ID, compared to sham stimulation. Furthermore, we tested for differences in indices of arousal between ID patients and healthy controls from our earlier dataset [24] and explored their potential impact on tDCS effects. The rationale behind this analysis is that further elucidating differential tDCS effects on indices of arousal and sleep in patients and controls might inform about distinct mechanisms of sleep-wake regulation and guide future treatment developments.

Material and methods

Participants

Nineteen patients with ID according to DSM-5 criteria [25] (13 females, 6 males, age 43.8 ± 15.1 years, age range 20–60 years) participated in the study. Patients were diagnosed according to ICD-10 criteria, based on subjective sleep disturbances, by an experienced psychiatrist and sleep practitioner and recruited at the sleep laboratory of the University Medical Center Freiburg. Other mental, physical or sleep disorders were excluded based on a clinical examination, routine blood test, structured psychiatric interview [26], and polysomnography (apnea-hypopnea-index >5/h and periodic limb movements with arousal index >5/h excluded). All patients were right handed and non-smokers. They did not consume caffeine, alcohol or CNS-active medication two weeks prior to and during the study, and were eligible for tDCS according to standard safety criteria [27]. The data set of ID patients was compared to an earlier data set of 19 healthy controls with the same eligibility criteria besides the diagnosis of ID [24]. The study was conducted in accordance with the Declaration of Helsinki, approved by the Ethics Committee of the University Medical Center Freiburg (271/12), and registered in the German Register for Clinical Studies (www.germanctr.de, DRKS00004299). All patients provided written informed consent prior to participation.

Study design

The current study design in ID patients followed the study design in healthy participants reported earlier [24]. All participants maintained a regular sleep-wake schedule two weeks prior to and during the study as monitored by sleep diaries [28] and actigraphy (Actiwatches®, Cambridge Neurotechnology). Subjective ratings for depressive symptoms (Beck Depression Inventory, BDI [29]), stress (Perceived Stress Questionnaire, PSQ-20 [30]), sleep quality (Pittsburgh Sleep Quality Index, PSQI [31]) and daytime sleepiness (Epworth Sleepiness Scale, ESS [32]) were assessed at baseline.

All participants underwent a within-subject, repeated-measures protocol across five nights in the sleep laboratory (Fig. 1). After an adaptation and baseline night, three experimental nights with polysomnographic monitoring were recorded from 11:00 p.m. to 7:00 a.m. Prior to the experimental nights, tDCS was administered between 10:00 p.m. and 10:46 p.m. according to the experimental protocol in a counterbalanced order (anodal, cathodal or sham stimulation) with one week interval to prevent carry-over effects. Resting state EEGs were recorded prior to (T0) and after (T1) the stimulation protocol in the evening and in the following morning (T2). Sleep questionnaires were completed in the evening prior to and in the morning after each experimental night to assess subjective sleep quality and quantity (Schlaffragebogen-A, SF-A [33]). Neuropsychological tests were conducted at 8:30 p.m. prior to and 8:00 a.m. after the experimental nights (Test for Attentional Performance, TAP [34]).

Transcranial direct current stimulation (tDCS)

This study used the same tDCS protocol as described in detail in our previous study in healthy controls [24]. Participants were seated in a quiet sleep laboratory with eyes open, using a standardized resting state instruction. In brief, tDCS was delivered by a battery-driven, micro-processor-controlled CE-certified constant current stimulator (neuroConn GmbH, Illmenau, Germany) and comprised bi-frontal target electrodes (5 × 7 cm, FP1/FP2) and bi-parietal return electrodes (10 × 10 cm, P3/P4). The selected size of the return electrodes has previously been shown to be functionally

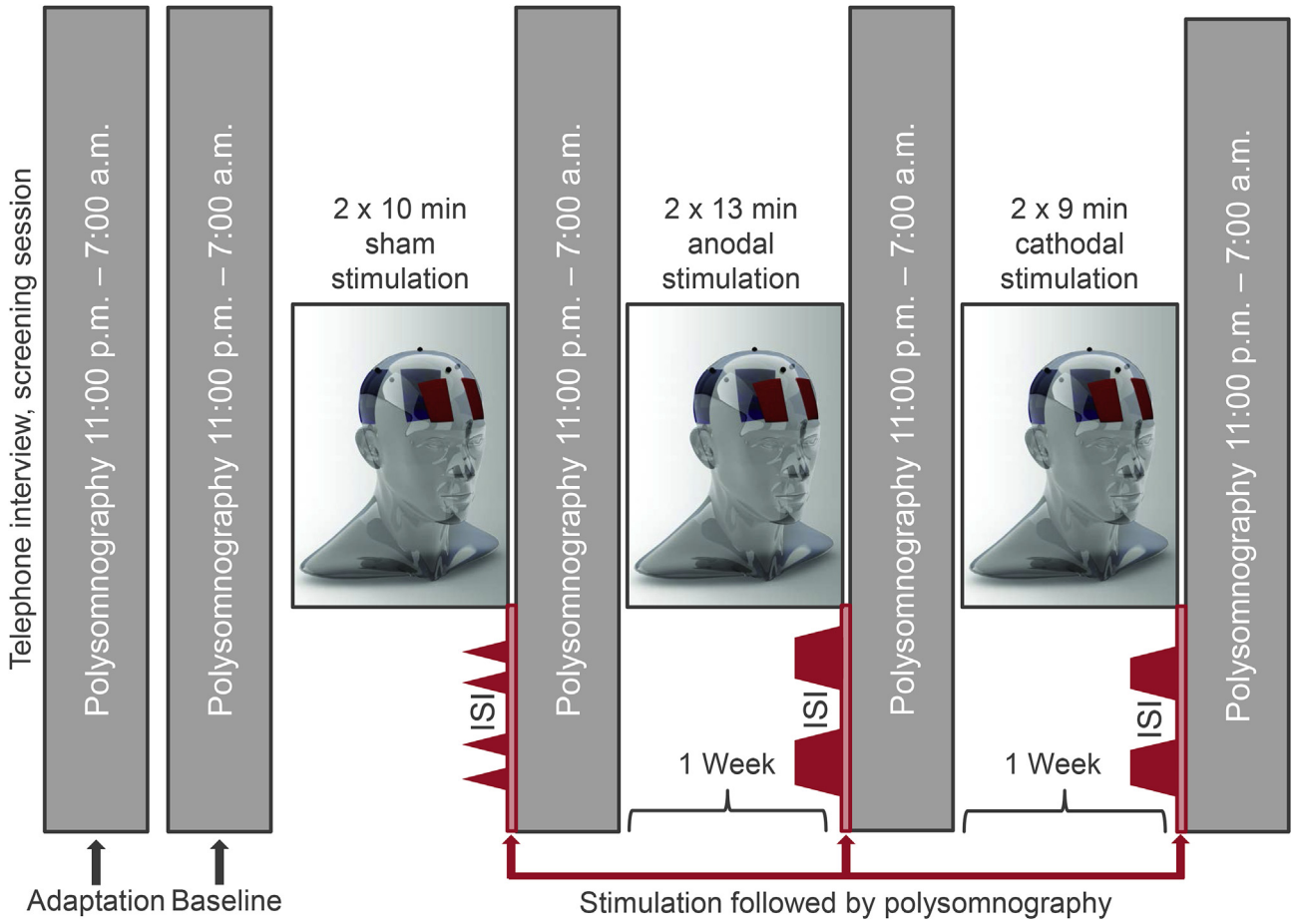

Fig. 1. Study design. Adaption, baseline and three experimental nights with tDCS starting at 10:00 p.m. and ending prior to polysomnography from 11:00 p.m. to 07:00 a.m.; stimulation protocols with electrode positioning over the prefrontal and parieto-occipital cortex: I. Sham stimulation: 2 blocks of 11 min tDCS with the stimulator fading in and out at the beginning and end of each 11 min period with 20 min interval between sham stimulation blocks (inter-stimulation interval, ISI). II. Anodal stimulation: 2 blocks of 13 min with fade-in/fade-out and 20 min ISI. III. Cathodal stimulation: 2 blocks of 9 min with fade-in/fade-out and 20 min ISI. Stimulation protocols were implemented in a counterbalanced order (Fig. from Ref. [24]).

inert to the cortex [35]. A constant current of 1 mA over each electrode was applied (2 mA stimulator output, Y-cable split for stimulation and reference electrodes) using an optimized repetitive stimulation protocol for each condition [36,37] with 2 × 13 min of anodal and 2 × 9 min of cathodal stimulation with 20 min inter-stimulation intervals (Fig. 1). The chosen tDCS protocols have been demonstrated to induce lasting aftereffects up to several hours. To achieve comparable aftereffects, optimal stimulation durations need to be slightly different between polarities [36,37]. A fade-in/fade-out design (30 s each) was used to decrease potential skin sensations during the beginning and end of the stimulation [38]. The sham condition mimicked these sensations by implementing a 30s fade-in current until 1 mA was reached with an immediate 30s fade-out at the beginning and end of each sham stimulation period. The sham procedure has been repeatedly shown to keep participants blind for the stimulation conditions [39]. In accordance with this notion, participants of the current study were not able to discern between the tDCS conditions when asked in the mornings following the experimental nights. As listed in Tab. S1 (Supplements), most participants described skin sensations during the stimulations, including sham stimulation, and some described headache, pain and unspecific somatic reactions, without any differences between the tDCS conditions.

Polysomnography

Polysomnography was recorded from 11:00 p.m. to 7:00 a.m. according to standard procedures as described previously [24]. All recordings included an EEG (C3-A2), electrooculogram, submental electromyogram and an electrocardiogram. Polysomnographic recordings were visually scored off-line according to standard criteria [40] by experienced raters who were blind towards the experimental conditions. The following polysomnographic parameters of sleep continuity and architecture were assessed: sleep onset latency (SOL), defined as the period between turning the lights off and the first 30 s epoch of stage 2 sleep (N2), slow wave sleep (SWS/N3) or rapid eye movement (REM) sleep; total sleep time (TST), defined as the time spent in stage 1 or 2 sleep, slow wave sleep (SWS) or REM sleep; sleep efficiency (SE), defined as the ratio of TST to time in bed × 100%; wake after sleep onset (WASO), defined as the time spent awake during the sleep period time; number of sleep stage changes; number of wake periods; arousal index (AI), defined as the number of arousals per hour of sleep for TST; percentages of stage 2 sleep, SWS and REM sleep referred to TST; REM sleep latency (REML), defined as the period between sleep onset and the occurrence of the first 30 s epoch of REM sleep; number of REM sleep cycles per night; eye movement epochs (EOGS), defined

as the number of 3-s mini-epochs including rapid eye movements during REM sleep; REM density, defined as the ratio of 3-s REM sleep mini-epochs including rapid eye movements referred to the total number of REM sleep mini-epochs × 100%.

EEG spectral analysis

Sleep EEG spectral analysis was carried out to assess power spectra during NREM sleep as described previously [24,41]. The main analysis was performed on the C3-A2 derivation in 30-s epochs for which sleep stages had been determined. Spectral estimates for each epoch were obtained by averaging of 22 overlapping FFT windows (512 data points, 2.56 s) covering a 30-s epoch to obtain the spectral power within that epoch, resulting in a spectral resolution of 0.39 Hz. A Welch taper was applied to each FFT window after demeaning and detrending the data in that window. The spectral power values were then log-transformed (base e) and continuously stored on disk. All subsequent steps including statistical analysis were performed on these logarithmic values, which have a more symmetrical distribution of errors as compared to raw spectral power. Rejection of artefacts mainly connected to low EEG spectral frequencies (e.g., EOG) or high EEG spectral frequencies (e.g., EMG) was conducted by an automatic, data-driven method. The total and gamma band log power of each epoch was related to the corresponding median-filtered value (the median of values in the 5 min preceding and 5 min following the epoch), and an epoch was excluded if the deviation was larger than the difference between the median and the first quartile of all median-filtered values across the night [41]. The log spectra of the remaining epochs were averaged across all NREM sleep epochs. Spectral band power was calculated for the following frequency ranges: delta 0.1–3.5 Hz (delta1 0.1–1.5 Hz; delta2 1.5–3.5 Hz); theta 3.5–8 Hz; alpha 8–12 Hz; sigma 12–16 Hz (sigma1 12–14 Hz; sigma2 14–16 Hz); beta 16–24 Hz; and gamma 24–50 Hz.

Wake EEG recordings

Following the procedures described previously [24], 5 min resting state EEGs (C3-A2) were recorded prior to stimulation [T0], immediately after the stimulation [T1] and on the following morning [T2] to assess indices of cortical arousal during wakefulness. Patients were seated in a quiet sleep laboratory with eyes closed, using a standardized resting state instruction ('Please sit upright, think of nothing in particular, stay awake and relax, please also relax your chewing muscles'). EEG recordings were visually scored off-line by experienced raters according to standard criteria to exclude possible sleep stages (C3-A2 derivation, 30 s epochs). EEG spectral power was calculated for single frequency bins for each EEG measurement according to the procedures described for polysomnographic recordings. Each 5 min EEG trace was visually inspected and technical or movement artifacts were marked. Then, data were segmented into windows of 2.56 s overlapping by half (i.e., steps of 1.28 s) avoiding regions from 5 s prior to the start to 5 s after the end of each marked artifact as well as any 30 s epoch scored as non-wake.

Statistical analyses

Descriptive values are given as means and standard deviations. To test for polysomnographic differences between the experimental tDCS conditions, repeated-measures analyses of variance (ANOVAs) with the within-subject factor Condition (anodal stimulation, cathodal stimulation, sham stimulation) were conducted. Total sleep time (TST) was used as the primary outcome parameter. Other analyses were secondary analyses. To further explore possible regional effects, ANOVAs with the within-subject factor Condition (anodal stimulation, cathodal stimulation, sham stimulation) were conducted for all EEG spectral power frequency bands and each EEG electrode (C3, C4, CZ, FZ, OZ) individually. To explore tDCS effects on resting state EEG, the repeated-measures factor Testsection (T0, T1, T2) was added.

ANCOVAs with the within-subject factor Condition, the between subject factor Group (insomnia, controls) and the covariate Age were used for comparisons of clinical and physiological data and stimulation effects between ID patients and controls from an earlier data set [24]. For the estimation of effect sizes, partial ETA square (η_p^2) values were calculated (low: <0.06; medium: ≥ 0.06 and < 0.14; large: ≥ 0.14). Post-hoc contrasts were calculated in case of significant main effects or interactions. The level of significance was set at $p < 0.05$ (two-tailed). All analyses were conducted with the statistical software R (R version 3.1.2, The R Foundation for Statistical Computing).

Results

TDCS effects in patients with insomnia disorder

Polysomnography and NREM EEG spectral analysis

In contrast to our primary hypothesis, neither anodal nor cathodal tDCS modified TST in patients with ID. Polysomnographic findings are listed in Table 1 and visualized in Fig. 2. Further analyses did not demonstrate any significant tDCS effect on sleep continuity or sleep architecture (for all analyses, $p > 0.1$). In our main analysis, EEG spectral power during NREM sleep did not differ between the stimulation conditions (Fig. 2). In a second exploratory step exploring possible regional effects, uncorrected single ANOVAs with the within-subject factor Condition (anodal stimulation, cathodal stimulation, sham stimulation) were conducted for all EEG spectral power frequency bands and each EEG electrode (C3, C4, CZ, FZ, OZ) individually. We found a significant condition effect only for frontal delta1 spectral power (Fz; $p = 0.036$), with anodal and cathodal stimulation being followed by slightly decreased spectral power, compared to sham. All other analyses showed no condition effect (all $p > 0.05$).

To control for age differences, we conducted repeated-measures ANOVAs with the within-subject factor Condition (anodal stimulation, cathodal stimulation, sham stimulation) and the covariate Age. No significant interaction was detected. To control for circadian effects, all participants were assessed with the Munich ChronoType Questionnaire (MCTQ [42]) and stated a regular preferred bedtime between 11–11.30 p.m. and 7–7.20 a.m. In addition, actigraphy demonstrated a regular sleep rhythm, with sleep onset at 11.48 p.m. ± 47 min, a total sleep time of 375 ± 54 min and a regular SOL of 13 ± 12 min. Sleep diaries demonstrated similar results for subjective sleep parameters, with only a slight overestimation of SOL (mean 25 min).

Subjective sleep and neurophysiological parameters

Subjective sleep and neurophysiological parameters are listed in Table 1. The analysis did not reveal any differences between the stimulation conditions.

Wake EEG spectral analysis

In a first analysis of EEG power differences between conditions at a single frequency, we calculated false discovery rate (FDR) corrected significances, obtained using the Benjamini-Hochberg step-up procedure as a correct assessment of the significance of multiple tests. This approach did not reveal any significant condition effect in ID patients. In a second exploratory analysis, we used uncorrected ANOVAs to further explore tDCS effects on EEG power

Table 1
Polysomnography, subjective sleep parameters and alertness following tDCS in patients with insomnia disorder (ID).

	Sham stimulation	Anodal stimulation	Cathodal stimulation	*F*	*p*	$pETA^2$
Polysomnography						
Sleep continuity						
Sleep onset latency, min	19.0 ± 18.3	20.3 ± 14.9	23.9 ± 22.8	1.9	.160	.097
Total sleep time, min	389.6 ± 58.3	396.3 ± 43.6	393.2 ± 38.7	.2	.819	.011
Sleep efficiency, %	81.1 ± 12.2	82.7 ± 9.0	81.7 ± 8.0	.3	.772	.014
WASO, min	53.4 ± 41.0	51.1 ± 32.9	51.5 ± 32.8	<.1	.956	.003
Stage changes	166.4 ± 40.0	161.3 ± 46.6	166.4 ± 57.2	.2	.796	.013
Wake periods	27.4 ± 14.3	27.5 ± 11.0	32.0 ± 16.6	3.3	.050	.154
Arousal Index (TST)	14.6 ± 6.4	17.1 ± 10.2	14.5 ± 6.5	1.5	.242	.076
Sleep architecture, %total sleep time						
Stage 2 sleep	59.3 ± 9.5	60.9 ± 11.0	61.8 ± 8.8	1.0	.385	.052
Slow wave sleep	7.3 ± 8.4	6.0 ± 8.3	5.1 ± 6.5	1.8	.173	.093
REM sleep	21.8 ± 4.8	20.6 ± 6.0	21.5 ± 6.9	.4	.693	.020
REM sleep parameters						
REM latency, min	78.4 ± 26.4	91.3 ± 62.8	85.7 ± 40.1	.7	.449	.039
REM sleep cycles	3.6 ± 0.8	3.7 ± 1.0	3.6 ± 0.7	.1	.860	.005
EOGS	311.7 ± 142.6	287.0 ± 99.5	325.1 ± 141.4	1.1	.335	.059
REM density	18.3 ± 6.3	17.8 ± 4.3	19.2 ± 5.6	.7	.506	.037
Subjective sleep parameters (SFA)						
Sleep onset latency, min	35.8 ± 32.6	36.1 ± 32.2	31.4 ± 26.2	.2	.805	.013
Total sleep time, min	369.7 ± 87.1	375.8 ± 75.8	377.8 ± 61.4	.2	.862	.009
Sleep efficiency, %	82.1 ± 15.3	83.7 ± 12.8	85.1 ± 11.7	.4	.648	.025
Wake time, min	40.8 ± 39.8	34.4 ± 29.0	34.6 ± 36.6	.4	.708	.020
Alertness (TAP)						
Tonic Improvement, %	.4 ± 8.2	.1 ± 6.5	1.0 ± 9.1	<.1	.931	.003
Phasic Improvement, %	2.8 ± 7.8	1.5 ± 8.8	1.0 ± 9.1	.3	.747	.017

Means ± SDs. WASO, wake after sleep onset; TST, total sleep time; REM, rapid eye movement; EOGS, number of 3-s mini-epochs including REMs during REM sleep; SFA, Schlaffragebogen-A. ANOVAs with the factor Condition (sham, anodal, cathodal stimulation). $pETA^2$, partial eta square.

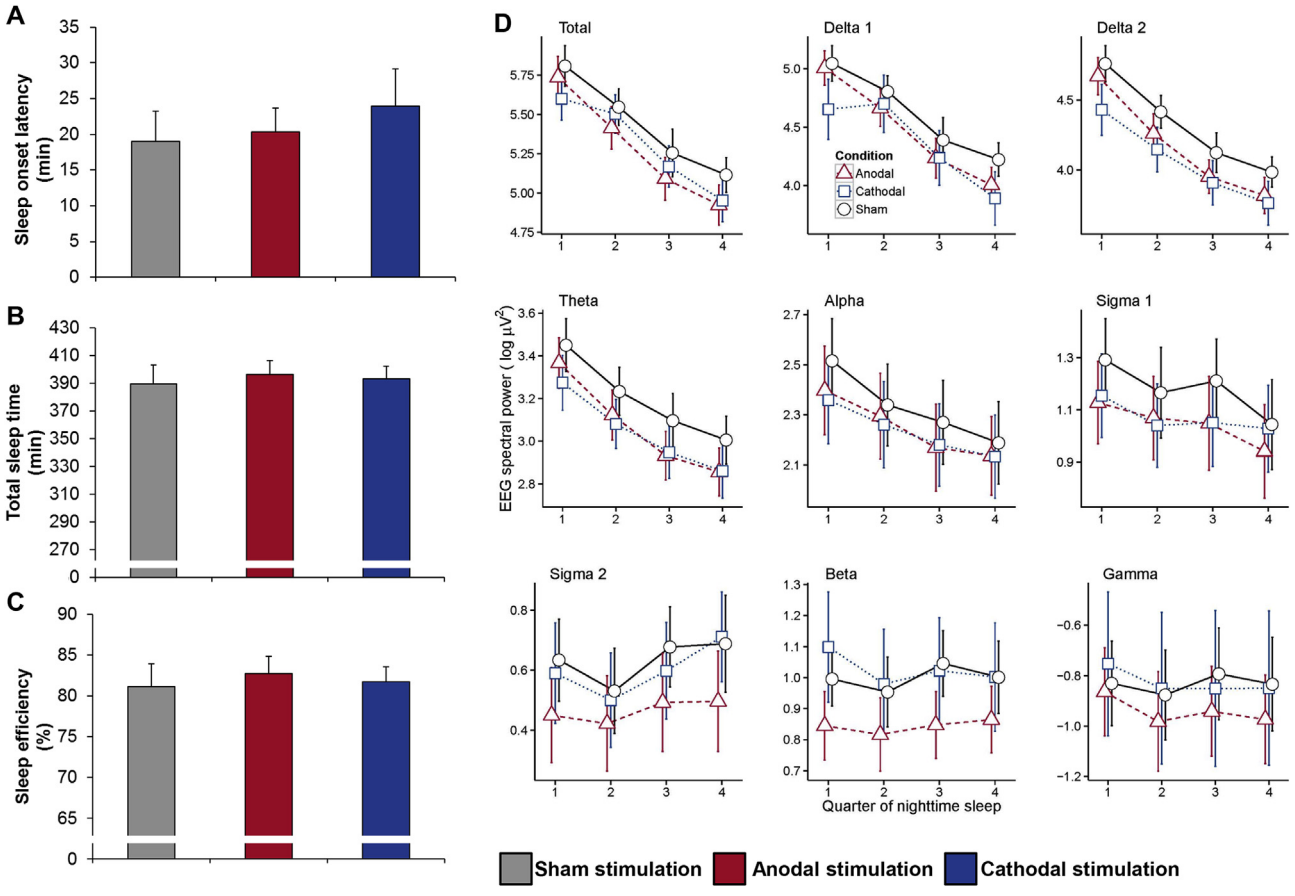

Fig. 2. tDCS effects on sleep continuity and architecture in patients with insomnia. A-C. Polysomnography. In contrast to our primary hypotheses neither bi-frontal cathodal nor anodal stimulation modified total sleep time (TST) in patients with ID. Further exploratory analyses did not demonstrate any significant effect on any other parameter of sleep continuity or sleep architecture, including sleep efficiency and sleep onset latency. D. NREM EEG spectral analysis. EEG spectral power values of NREM sleep for single quarters of nighttime sleep for total power and the following frequency ranges: delta 0.1–3.5 Hz (delta1 0.1–1.5 Hz; delta2 1.5–3.5 Hz); theta 3.5–8 Hz; alpha 8–12 Hz; sigma 12–16 Hz (sigma1 12–14 Hz; sigma2 14–16 Hz); beta 16–24 Hz; and gamma 24–50 Hz. EEG spectral power did not significantly differ between the conditions. Means ± SEs.

spectra. The results are visualized in Fig. 3. We first analyzed short-term effects of tDCS from T0 to T1 for all three conditions separately, demonstrating isolated, but significant changes in EEG spectral power for few frequency bins following cathodal and sham stimulation without a clear pattern. We then again conducted ANOVAs with the repeated-measures factors Testsection (T0, T2) and Condition (anodal stimulation, cathodal stimulation, and sham stimulation) showing no significant effects.

Comparison of ID patients and healthy controls

In a subsequent step, we compared the data from patients with ID to a healthy control group from an earlier dataset [24]. Clinical characteristics for patients and controls are listed in Table 2. Both groups showed a similar sex distribution, but patients were significantly younger. We therefore used age as a covariate for all subsequent analyses.

Sleep parameters without stimulation

Sleep parameters without stimulation (sham condition) for patients with ID and controls are listed in Table 2 and depicted in Fig. 4. As expected by design, patients reported a significantly worse subjective sleep quality (PSQI) and quantity (SFA) than controls. In addition, patients reported significantly higher cognitive arousal (PSAS). Patients showed a significantly reduced TST compared to controls in the sham stimulation night (mean difference 23 min) and significantly increased WASO.

For EEG NREM sleep spectral analysis, we calculated false discovery rate (FDR) corrected significances, obtained using the Benjamini-Hochberg step-up procedure as a correct assessment of the significance of multiple tests. This approach did not reveal any significant differences. In a second exploratory analysis, we used uncorrected ANOVAs to further explore tDCS effects on EEG power spectra. Here, we observed a significant main effect for the factor group on EEG spectral power values during NREM sleep, with significantly higher gamma power in patients compared to controls, consistent with the notion of increased arousal during NREM sleep in patients with ID (Fig. 4 A–D).

Baseline wake EEG

To identify potential group differences of arousal levels during wakefulness, we investigated wake EEG spectral power values at baseline prior to the stimulation protocol (T0) (sham condition) at single frequencies. We calculated false discovery rate (FDR) corrected significances, obtained using the Benjamini-Hochberg step-up procedure as a correct assessment of the significance of multiple tests. This approach did not reveal any significant differences. In a second exploratory analysis, we used uncorrected ANOVAs to further explore tDCS effects on EEG power spectra. This analysis demonstrated elevated power in patients compared to controls,

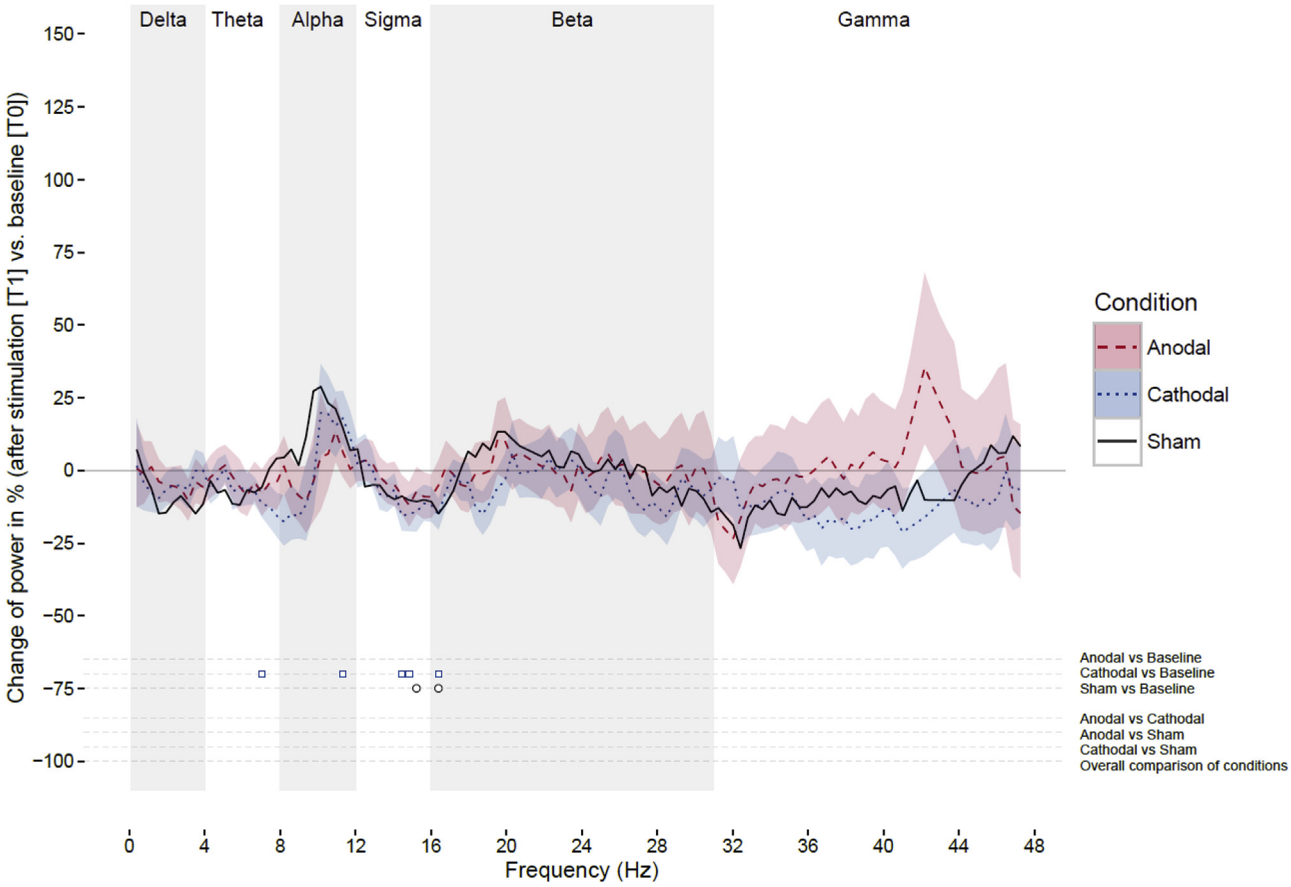

Fig. 3. tDCS effects on wake EEG spectral power in patients with insomnia. Wake EEG spectral power changes from baseline to after the stimulation protocol (%) for the following frequency ranges: delta 0.1–3.5 Hz; theta 3.5–8 Hz; alpha 8–12 Hz; sigma 12–16 Hz; beta 16–24 Hz; and gamma 24–50 Hz. We used uncorrected ANOVAs to explore tDCS effects on bin-wise EEG power spectra between baseline (T0) and immediately after stimulation (T1), denoting no significant group differences. Further uncorrected explorative analyses revealed differences for single, unconnected frequency bins following cathodal stimulation compared to baseline (squares) as well as following sham stimulation compared to baseline (circles). Highlighted areas indicate the SEs.

Table 2
Comparison of clinical and sleep parameters of patients with insomnia disorder (ID) and healthy controls.

	Healthy controls (n = 19)	Patients with ID (n = 19)	*F*	*p*	$pETA^2$
Clinical parameters					
Sex, male/female	6/13	6/13			
Age, years	53.7 ± 6.9	43.8 ± 15.1	6.7	***0.014***	0.158
BMI, kg/m^2	23.9 ± 2.2	23.4 ± 3.4	0.2	0.626	0.007
IQ	101.5 ± 12.5	105.0 ± 11.9	0.8	0.386	0.021
BDI	4.5 ± 3.0	6.4 ± 4.9	2.1	0.160	0.054
PSQ-20	46.8 ± 5.1	45.3 ± 3.5	1.2	0.289	0.031
Subjective sleep parameters					
PSQI	4.5 ± 2.3	9.4 ± 2.9	27.2	***<0.001***	0.437
ESS	6.7 ± 3.3	10.0 ± 5.0	3.3	0.078	0.086
PSAS – somatic arousal	10.0 ± 2.1	11.6 ± 2.3	1.0	0.325	0.028
PSAS – cognitive arousal	12.5 ± 2.2	18.2 ± 6.3	6.3	**0.017**	0.152
Sleep onset latency, min (SFA)	18.8 ± 13.6	39.0 ± 31.7	9.7	***0.004***	0.226
Wake time, min (SFA)	18.2 ± 22.5	34.7 ± 37.2	5.7	***0.023***	0.147
Total sleep time, min (SFA)	418.1 ± 39.0	371.4 ± 84.8	7.4	***0.010***	0.184
Sleep efficiency, % (SFA)	91.8 ± 6.7	82.7 ± 14.0	11.5	***0.002***	0.259
Polysomnographic sleep parameters					
Sleep continuity					
Sleep onset latency, min	13.2 ± 6.7	19.0 ± 18.3	.5	.474	.015
Total sleep time, min	412.6 ± 27.7	389.6 ± 58.3	7.5	***.010***	.176
Sleep efficiency, %	86.3 ± 6.0	81.1 ± 12.2	8.3	***.007***	.192
Wake time, min	63.0 ± 28.7	86.8 ± 58.3	8.1	***.007***	.188
Stage changes	174.2 ± 64.4	166.4 ± 40.0	.3	.560	.010
Wake periods	30.3 ± 12.4	27.4 ± 14.3	<.1	.939	<.001
Arousal Index	16.0 ± 6.1	14.6 ± 6.4	.3	.578	.009
Sleep architecture, %total sleep time					
Stage 2 sleep	60.4 ± 7.8	59.3 ± 9.5	.2	.678	.005
Slow wave sleep	4.6 ± 6.9	7.3 ± 8.4	<.1	.995	.000
REM sleep	22.1 ± 5.6	21.8 ± 4.8	.2	.644	.006
REM sleep parameters					
REM latency, min	79.5 ± 50.5	78.4 ± 26.4	<.1	.890	.001
REM sleep cycles	3.7 ± 1.0	3.6 ± 1.1	1.3	.265	.035
EOGS	276.9 ± 121.5	311.7 ± 142.6	.5	.491	.014
REM density, %	15.2 ± 4.9	18.2 ± 6.3	4.2	***.048***	.107
EEG spectral power (NREM sleep)					
Delta	5.08 ± .57	5.16 ± .56	.1	.714	.004
Theta	3.33 ± .65	3.39 ± .53	<.1	.865	.001
Alpha	2.48 ± .79	2.43 ± .68	.3	.591	.009
Sigma	1.38 ± .57	1.54 ± .63	.1	.802	.002
Beta	.65 ± .54	1.03 ± .39	6.8	***.014***	.166
Gamma	−2.15 ± .68	−1.27 ± .54	23.1	***<.001***	.405

Means ± SDs. BMI, body mass index; IQ, intelligence quotient; BDI, beck depression inventory; PSQ-20, perceived stress questionnaire; PSQI, Pittsburgh sleep quality index; ESS, Epworth sleepiness scale; PSAS, pre sleep arousal scale; SFA, Schlaffragebogen-A (sleep questionnaire); (N)REM, (non) rapid eye movement; EOGS, number of 3-s mini-epochs including REMs during REM sleep; EEG, electroencephalogram. ANCOVAs with the factor Group (healthy controls, patients) and the covariate Age. F, p, and $pETA^2$ (partial eta square) for group effects. Significant results are given in bold.

which reached statistical significance mainly for frequency bins in the higher gamma spectrum (Fig. 4 E).

Delineation of differential tDCS effects in patients with ID and controls and potential mechanisms

To further explore whether persistent hyperarousal in patients with ID might modify tDCS effects on arousal and sleep, we directly compared the stimulation effects from this study in ID patients to those in healthy controls from an earlier dataset [24]. We restricted this analysis to significant sleep parameters of our prior study (total sleep time, sleep efficiency, wake time after sleep onset). In a first step, we directly compared total sleep time, sleep efficiency and WASO between patients and controls in the sham, anodal and cathodal stimulation night (Table 3). ANCOVAs with the factor Group (patients, controls) and the covariate Age demonstrated significantly higher TST and SE as well as significantly reduced WASO following sham and cathodal stimulation in controls compared to patients. For anodal stimulation, TST, SE and WASO did not differ between the groups.

Next, to further investigate differential tDCS effects in patients and controls, we calculated and compared difference values between the stimulation conditions across the groups (Table 3). This analysis revealed significant group effects, with a significantly stronger decrease of TST following anodal compared to cathodal or sham stimulation in healthy controls, but not in ID patients. No such effects were detected for cathodal stimulation (TST, SE). WASO differences showed no significant group effects.

We finally explored whether hyperarousal in patients with ID as indexed by higher EEG power values in high frequencies under baseline resting-state conditions might influence the susceptibility to tDCS. This analysis demonstrated significant negative correlations for all frequencies >42.6 Hz (all $p < 0.05$) with higher wake EEG power at baseline prior to anodal stimulation correlating with a lower power increase following stimulation, suggesting that elevated baseline arousal levels might prevent arousal-inducing effects of anodal stimulation (Fig. 4 F).

Discussion

In contrast to our primary hypothesis, the current tDCS protocol did not modify sleep in patients with ID. Yet our study characterizes for the first time differential effects of tDCS in patients with ID and healthy controls, presumably related to persistent hyperarousal in ID. These findings suggest that adapted tDCS protocols need to be

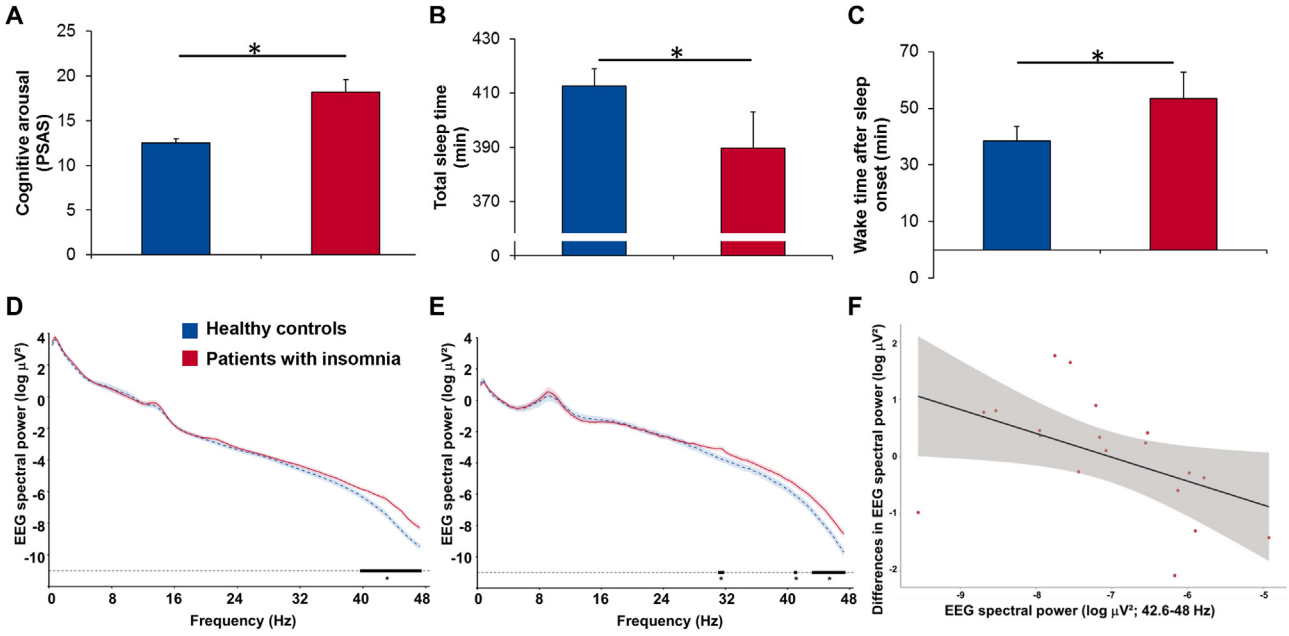

Fig. 4. Hyperarousal in patients with insomnia compared to healthy controls. A. Subjective Data. Cognitive arousal, as reported in the Pre-Sleep Arousal Scale (PSAS), was significantly higher in ID patients than in controls. Means ± SEs. B. Polysomnography (sham condition). Total sleep time was significantly lower in ID patients than in controls. Means ± SEs. C. Polysomnography (sham condition). Wake time after sleep onset was significantly higher in ID patients than in controls. Means ± SEs. D. NREM sleep EEG spectral analysis in ID patients and healthy controls (sham condition). Significant group differences were detected for frequency bins >40 Hz with spectral power being significantly higher in ID patients than in controls. Highlighted areas indicate the standard error of the mean. E. Wake EEG spectral analysis (sham condition) during baseline (T0). Differences between groups reached the significance level mainly for high frequency gamma power ($F > 10$, $p < 0.01$). Highlighted areas indicate the standard error of the mean. F. Correlation between baseline wake EEG spectral power prior to anodal stimulation and differences following stimulation compared to baseline level. This analysis demonstrated significant negative correlations for all frequencies >42.6 Hz (all $p < 0.05$) with higher wake EEG power at baseline prior to anodal stimulation correlating with a lower power increase following stimulation, suggesting that elevated baseline arousal levels might prevent arousal-inducing effects of anodal stimulation.

Table 3
Differential tDCS effects in patients with insomnia disorder (ID) and healthy controls.

	Healthy controls ($n = 19$)	Patients with ID ($n = 19$)	F	p	$pETA^2$
Total sleep time, min					
Sham stimulation	412.6 ± 27.7	389.6 ± 58.3	7.5	**.010**	.176
Anodal stimulation	387.4 ± 44.5	396.3 ± 43.6	<0.1	.943	.000
Cathodal stimulation	414.0 ± 28.3	393.2 ± 38.7	6.8	**.013**	.163
Difference Sham vs. Anodal	25.1 ± 48.5	6.7 ± 51.4	4.9	**.034**	.122
Difference Sham vs. Cathodal	−1.5 ± 26.2	−3.6 ± 46.3	0.6	.447	.017
Difference Cathodal vs. Anodal	26.6 ± 39.5	−3.1 ± 39.7	4.2	**.049**	.106
Sleep efficiency, %					
Sham stimulation	86.3 ± 6.0	81.1 ± 12.2	8.1	**.007**	.188
Anodal stimulation	81.0 ± 9.3	82.7 ± 9.0	<0.1	.958	.000
Cathodal stimulation	86.3 ± 5.7	81.7 ± 8.0	7.9	**.008**	.184
Difference Sham vs. Anodal	5.3 ± 9.7	−1.6 ± 11.2	5.5	**.025**	.136
Difference Sham vs. Cathodal	.0 ± 5.2	-.6 ± 9.4	0.7	.404	.020
Difference Cathodal vs. Anodal	5.3 ± 7.8	−1.0 ± 8.2	5.0	**.031**	.126
WASO, min					
Sham stimulation	38.6 ± 21.4	53.4 ± 41.0	9.2	**.001**	.344
Anodal stimulation	53.8 ± 39.9	51.1 ± 32.9	2.4	.110	.119
Cathodal stimulation	42.0 ± 20.6	51.5 ± 32.8	5.8	**.007**	.247
Difference Sham vs. Anodal	−15.2 ± 37.4	2.3 ± 30.8	1.7	.193	.090
Difference Sham vs. Cathodal	−3.4 ± 23.4	1.9 ± 43.5	.5	.606	.028
Difference Cathodal vs. Anodal	−11.8 ± 35.8	.4 ± 31.0	.6	.547	.034

Means ± SDs. ANCOVAs with the factor Group (controls, patients) and the Covariate Age. $pETA^2$, partial eta square. Significant effects are given in bold.

developed to modulate arousal and sleep dependent on baseline arousal levels.

The absence of tDCS effects on polysomnographic parameters in patients with ID observed in the current study stands in line with several ineffective attempts to induce 'electro-sleep' in the 1970s and early 1980s. At that time, there had been single reports on an improvement of self-reported insomnia symptoms [43,44], but polysomnographic studies did not observe any effects [45,46] – presumably, at least in part, related to small and inhomogeneous samples with various comorbidities and poorly refined tDCS protocols without prolonged after-effects applied several hours prior to sleep [47]. In contrast, the current study investigated a well-defined sample of ID patients without comorbidities, and the stimulation protocol had induced a significant, long-lasting, polarity and location specific effect in healthy controls [24]. Particularly, anodal in comparison with sham and cathodal stimulation

protocol had led to increased levels of arousal during wakefulness as indexed by resting-state EEG markers and a reduction of TST of about 25 min in healthy humans [24]– an effect that was not present in the current study in patients with ID. Further direct comparisons revealed significantly different tDCS effects in patients and controls, with significantly stronger arousal-inducing effects of anodal tDCS in controls than in patients with ID.

Two observations lead us to propose persistent hyperarousal processes in patients with ID as a potential mechanism preventing the arousal-inducing effect of anodal tDCS observed in controls. First, the current sample of ID patients demonstrated indices of significantly increased arousal in comparison to the control sample, including increased subjective wake time, reduced polysomnographic TST, and increased power values of high EEG frequencies during resting-state and NREM sleep (experimental nights without stimulation). These findings corroborate prior reports on markers of hyperarousal in ID [9,10]. As a possible limitation, it is to note that differences in high-frequency EEG activity might be influenced by macro-sleep-architectural phenomena, such as body movements or arousal. Second, the extent of hyperarousal as assessed by EEG power values in high frequency bins during resting state EEGs prior to the stimulation predicted the lack of effect of anodal tDCS on resting state EEG in patients with ID. In other words, participants with indices of high arousal levels at baseline were those who showed the lowest effect of anodal tDCS. Together, this pattern of results is consistent with the notion that patients with ID show elevated arousal levels that prevent further arousal-inducing effects of tDCS. Interestingly, similar results of resistance to arousal induction have been reported for stress-related acute sleep disruption in patients with ID compared to healthy controls [48]. This excludes an alternative hypothesis according to which it might have been easier to induce arousal in participants with elevated baseline arousal levels and rather argues for a ceiling effect regarding arousal levels.

The cathodal stimulation protocol did not reduce markers of arousal and did not prolong sleep in patients with ID, paralleling our finding in controls [24]. Whereas we used the, according to our knowledge, currently best described cathodal stimulation protocol to induce long-lasting decreases in cortical excitability [36], it is still possible that the induced electrical field was too weak to 'override' arousal processes in healthy participants and patients with ID [10]. In addition, cathodal stimulation protocols frequently produce far less robust results than anodal stimulation in neurocognitive studies [49,50]. Future studies are needed that aim to develop stimulation protocols that reduce arousal and increase total sleep time to a clinically relevant extent.

It is interesting to note that our anodal tDCS protocol lead to an insomnia-like phenotype in healthy controls based on resting-state EEG, polysomnography and NREM sleep EEG spectral analysis parameters. This observation supports the idea that increased levels of arousal in the prefrontal cortex might play a major role in the pathophysiology of ID [10], and that bi-frontal anodal tDCS in healthy humans, and maybe also in animals, could be used as an experimental model of ID, e.g. in studies investigating the effects of novel treatments.

Another current approach uses either transcranial slow-oscillating tDCS or *alternating* current stimulation (tACS) to generate oscillation-like potential fields in sleep specific frequencies, e.g. slow waves [21]. For instance in a pivotal study, 0.75 Hz slow-oscillating tDCS during early NREM sleep enhanced cortical slow oscillations and slow spindle activity in the frontal cortex [51]. While this study only induced brief periods of slow oscillations (seconds), a recent study reported that slow (0.75 Hz) oscillatory transcranial direct current stimulation during the first stage 2 episode of non-rapid eye movement sleep increased the duration of stage 3 sleep by 33 min and decreased stage 1 by 22 min in the following night, but only in six patients with ID [52]. When applied during wakefulness, frontal oscillating anodal tDCS at 5 Hz has been demonstrated to increase subjective sleepiness and slow-frequency EEG activity [53,54]. Further studies are needed to replicate these effects. Additional studies are needed to clarify whether tDCS or tACS induced changes in sleep modulate sleep-related brain functions, such as memory consolidation [55,56].

The Research Domain Criteria (RDoC) concept of 'arousal and sleep' proposes a continuum between states of increased and decreased arousal as one of five major research domains, with potential clinical relevance in both directions, i.e. the therapeutic increase and decrease of arousal [57]. For instance, we recently provided preliminary evidence for a beneficial effect of the described anodal stimulation protocol in increasing arousal in a patient with chronic and treatment resistant hypersomnia following reanimation [58]. Further studies are needed to refine the stimulation protocols and to translate these concepts to clinical conditions characterized by decreased or increased arousal levels across neuropsychiatric disorders. Future studies are also needed to investigate effects in other age groups and to unravel underlying neural mechanisms.

In summary, tDCS did not alter sleep continuity and architecture in ID patients. Particularly, persistent hyperarousal in patients with ID might prevent arousal-promoting effects of bifrontal anodal tDCS demonstrated in healthy controls. Further studies are needed to refine tDCS protocols to modulate arousal and sleep.

Disclosures

The described work was supported by intramural funds of the University Medical Center Freiburg, Department of Clinical Psychology and Psychophysiology. This research did not receive any further specific grant from funding agencies in the public, commercial, or not-for-profit sectors. MAN is in the Advisory Board of Neuroelectrics and has received funding by the framework of the EU Research and Innovation program Horizon 2020 (686764-LUMINOUS). None of the other authors declare any conflict of interest.

Acknowledgments

The authors wish to thank the sleep laboratory staff at the Department of Psychiatry and Psychotherapy, Freiburg, for their help in conducting the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.01.001.

References

[1] Kyle SD, Morgan K, Espie CA. Insomnia and health-related quality of life. Sleep Med Rev 2010;14(1):69–82.
[2] Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord 2011;135(1–3):10–9.
[3] Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the risk of acute myocardial infarction: a population study. Circulation 2011;124(19):2073–81.
[4] Meng L, Zheng Y, Hui R. The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. Hypertens Res 2013;36(11):985–95.
[5] Léger D, Bayon V (6). Societal Costs of Insomnia, vol. 14; 2010. https://doi.org/10.1016/j.smrv.2010.01.003. Available from:, http://www.ncbi.nlm.nih.gov/pubmed/20359916.

[6] Riemann D, Nissen C. Sleep and psychotropic drugs. In: Morin CM, Espie CA, editors. Oxford handbook of sleep and sleep disorders. Oxford: Oxford University Press; 2012. p. 190–222.
[7] Riemann D, Baum E, Cohrs S, Crönlein T, Hajak G, Hertenstein E, et al. S3-Leitlinie nicht erholsamer schlaf/schlafstörungen. Somnologie 2017;21(1):2–44.
[8] Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG, et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res 2017;26(6):675–700.
[9] Riemann D, Nissen C, Palagini L, Otte A, Perlis ML, Spiegelhalder K. The neurobiology, investigation, and treatment of chronic insomnia. Lancet Neurol 2015;14(5):547–58.
[10] Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep Med Rev 2010;14(1):19–31.
[11] Spiegelhalder K, Regen W, Feige B, Holz J, Piosczyk H, Baglioni C, et al. Increased EEG sigma and beta power during NREM sleep in primary insomnia. Biol Psychol 2012;91(3):329–33.
[12] Nofzinger EA, Buysse DJ, Miewald JM, Meltzer CC, Price JC, Sembrat RC, et al. Human regional cerebral glucose metabolism during non-rapid eye movement sleep in relation to waking. Brain 2002;125(Pt 5):1105–15.
[13] Kay DB, Karim HT, Soehner AM, Hasler BP, Wilckens KA, James JA, et al. Sleep-wake differences in relative regional cerebral metabolic rate for glucose among patients with insomnia compared with good sleepers. Sleep 2016;39(10):1779–94.
[14] Colombo MA, Ramautar JR, Wei Y, Gomez-Herrero G, Stoffers D, Wassing R, et al. Wake high-density electroencephalographic spatiospectral signatures of insomnia. Sleep 2016;39(5):1015–27.
[15] Massimini M, Huber R, Ferrarelli F, Hill S, Tononi G. The sleep slow oscillation as a traveling wave. J Neurosci 2004;24(31):6862–70.
[16] Jones BE. Arousal systems. Front Biosci 2003;(8):438–51.
[17] Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature 2005;437(7063):1257–63.
[18] Timofeev I, Grenier F, Bazhenov M, Sejnowski TJ, Steriade M. Origin of slow cortical oscillations in deafferented cortical slabs. Cerebr Cortex 2000;10(12):1185–99.
[19] Steriade M. Grouping of brain rhythms in corticothalamic systems. Neuroscience 2006;137(4):1087–106.
[20] Steriade M. Corticothalamic resonance, states of vigilance and mentation. Neuroscience 2000;101(2).
[21] Krone L, Frase L, Piosczyk H, Selhausen P, Zittel S, Jahn F, et al. Top-down control of arousal and sleep: fundamentals and clinical implications. Sleep Med Rev 2017;31:17–24.
[22] Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. Modulation of cortical excitability by weak direct current stimulation–technical, safety and functional aspects. Suppl Clin neurophysiol 2003;56:255–76.
[23] Nitsche MA, Seeber A, Frommann K, Klein CC, Rochford C, Nitsche MS, et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J Physiol (Lond) 2005;568(Pt 1):291–303.
[24] Frase L, Piosczyk H, Zittel S, Jahn F, Selhausen P, Krone L, et al. Modulation of total sleep time by transcranial direct current stimulation (tDCS). Neuropsychopharmacology 2016;41(10):2577–86.
[25] American Psychiatric Association, editor. Diagnostic and statistical manual of mental disorders: DSM-5. Washington, DC: American Psychiatric Publishing; 2013.
[26] Robins LN, Wing J, Wittchen HU, Helzer JE, Babor TF, Burke J, et al. The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatr 1988;45(12):1069–77.
[27] Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clin Neurophysiol 2003;114(11):2220.
[28] Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep 2012;35(2):287–302.
[29] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatr 1961;4:561–71.
[30] Levenstein S, Prantera C, Varvo V, Scribano ML, Berto E, Luzi C, et al. Development of the Perceived Stress Questionnaire: a new tool for psychosomatic research. J Psychosom Res 1993;37(1):19–32.
[31] Buysse DJ, Reynolds 3rd CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193–213.
[32] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14(6):540–5.
[33] Görtelmeyer R. Schlaffragebogen SF-A und SF-B. In: Weyer G, editor. Internationale Skalen für Psychiatrie. fifth ed. Göttingen: Beltz Test; 2005.
[34] Zimmermann P, Fimm B. Testbatterie zur Aufmerksamkeitsleistung (TAP). Germany: Würselen; 2007. Psytest.
[35] Nitsche MA, Doemkes S, Karaköse T, Antal A, Liebetanz D, Lang N, et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. J Neurophysiol 2007;97(4):3109–17.
[36] Monte-Silva K, Kuo M-F, Liebetanz D, Paulus W, Nitsche MA. Shaping the optimal repetition interval for cathodal transcranial direct current stimulation (tDCS). J Neurophysiol 2010;103(4):1735–40.
[37] Monte-Silva K, Kuo M-F, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimul 2013;6(3):424–32.
[38] Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul 2008;1(3):206–23.
[39] Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol 2006;117(4):845–50.
[40] Iber C. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.
[41] Feige B, Voderholzer U, Riemann D, Dittmann R, Hohagen F, Berger M. Fluoxetine and sleep EEG: effects of a single dose, subchronic treatment, and discontinuation in healthy subjects. Neuropsychopharmacology 2002;26(2):246–58.
[42] Roenneberg T, Wirz-Justice A, Merrow M. Life between clocks: daily temporal patterns of human chronotypes. J Biol Rhythm 2003;18(1):80–90.
[43] Hearst ED, Cloninger CR, Crews EL, Cadoret RJ. Electrosleep therapy—a double-blind trial. Arch Gen Psychiatr 1974;30:463–6.
[44] Cartwright RD, Weiss M. The effects of electrosleep on insomnia revisited. J Nerv Ment Dis 1975;161(2):134–7.
[45] Frankel BL, Buchbinder R, Snyder F. Ineffectiveness of electrosleep in chronic primary insomnia. Arch Gen Psychiatr 1973;29(4):563–8.
[46] Coursey RD, Frankel BL, Gaarder KR, Mott DE. A comparison of relaxation techniques with electrosleep therapy for chronic, sleep-onset insomnia a sleep-EEG study. Biofeedback Self Regul 1980;5(1):57–73.
[47] von Richthofen CL, Mellor CS. Cerebral electrotherapy: methodological problems in assessing its therapeutic effectiveness. Psychol Bull 1979;86(6):1264–71.
[48] Gehrman PR, Hall M, Barilla H, Buysse D, Perlis M, Gooneratne N, et al. Stress reactivity in insomnia. Behav Sleep Med 2016;14(1):23–33.
[49] Jamil A, Batsikadze G, Kuo H-I, Labruna L, Hasan A, Paulus W, et al. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. J Physiol (Lond) 2017;595(4):1273–88.
[50] Strube W, Bunse T, Nitsche MA, Nikolaeva A, Palm U, Padberg F, et al. Bidirectional variability in motor cortex excitability modulation following 1 mA transcranial direct current stimulation in healthy participants. Phys Rep 2016;4(15).
[51] Marshall L, Helgadóttir H, Mölle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature 2006;444(7119):610–3.
[52] Saebipour MR, Joghataei MT, Yoonessi A, Sadeghniiat-Haghighi K, Khalighinejad N, Khademi S. Slow oscillating transcranial direct current stimulation during sleep has a sleep-stabilizing effect in chronic insomnia: a pilot study. J Sleep Res 2015;24(5):518–25.
[53] D'Atri A, Simoni E de, Gorgoni M, Ferrara M, Ferlazzo F, Rossini PM, et al. Electrical stimulation of the frontal cortex enhances slow-frequency EEG activity and sleepiness. Neuroscience 2016;324:119–30.
[54] D'Atri A, Romano C, Gorgoni M, Scarpelli S, Alfonsi V, Ferrara M, et al. Bilateral 5 Hz transcranial alternating current stimulation on fronto-temporal areas modulates resting-state EEG. Sci Rep 2017;7(1):15672.
[55] Eggert T, Dorn H, Sauter C, Nitsche MA, Bajbouj M, Danker-Hopfe H. No effects of slow oscillatory transcranial direct current stimulation (tDCS) on sleep-dependent memory consolidation in healthy elderly subjects. Brain Stimul 2013;6(6):938–45.
[56] Sahlem GL, Badran BW, Halford JJ, Williams NR, Korte JE, Leslie K, et al. Oscillating square wave transcranial direct current stimulation (tDCS) delivered during slow wave sleep does not improve declarative memory more than sham: a randomized sham controlled crossover study. Brain Stimul 2015;8(3):528–34.
[57] Insel TR. The NIMH research domain criteria (RDoC) project: precision medicine for psychiatry. Am J Psychiatry 2014;171(4):395–7.
[58] Frase L, Maier JG, Zittel S, Freyer T, Riemann D, Normann C, et al. Bifrontal anodal transcranial direct current stimulation (tDCS) improves daytime vigilance and sleepiness in a patient with organic hypersomnia following reanimation. Brain Stimul 2015;8(4):844–6.