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RESEARCH ARTICLE

The effects of bifrontal anodal transcranial direct current stimulation (tDCS) on sleepiness and vigilance in partially sleep-deprived subjects: A multidimensional study

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Summary

In recent years, transcranial electrical stimulation techniques have demonstrated their ability to modulate our levels of sleepiness and vigilance. However, the outcomes differ among the specific aspects considered (physiological, behavioural or subjective). This study aimed to observe the effects of bifrontal anodal transcranial direct current stimulation. Specifically, we tested the ability of this stimulation protocol to reduce sleepiness and increase vigilance in partially sleep-deprived healthy participants. Twenty-three subjects underwent a within-subject sham-controlled stimulation protocol. We compared sleepiness and vigilance levels before and after the two stimulation conditions (active versus sham) by using behavioural (reaction-time task), subjective (self-report scales) and physiological (sleep-onset latency and electroencephalogram power [$n = 20$] during the Maintenance of Wakefulness Test) measures. We showed the efficacy of the active stimulation in reducing physiological sleepiness and preventing vigilance drop compared with the sham stimulation. Consistently, we observed a reduction of perceived sleepiness following the active stimulation for both self-report scales. However, the stimulation effect on subjective measures was not statistically significant probably due to the underpowered sample size for these measures, and to the possible influence of motivational and environmental factors. Our findings confirm the ability of this technique to influence vigilance and sleepiness, pointing out the potential for new treatment developments based on transcranial electrical stimulation.

KEYWORDS

diurnal sleepiness, neurobehavioural performance, sleep deprivation, sleepiness, transcranial electrical stimulation

1 | INTRODUCTION

Daytime sleepiness represents one of the biggest challenges in our increasingly sleepless society. Sleepiness does not reflect a unitary phenomenon as: (a) it is influenced by multiple internal and environmental factors; and (b) it underlies a wide range of subjective and objective outcomes (Cluydts et al., 2002). Vigilance, defined as the ability to sustain attention over extended periods of time (Parasuraman & Davies, 1977), represents the tonic component of attention and is closely related to sleepiness. In accordance with the two-process model of sleep–wake regulation, sleepiness and vigilance are both dependent on the interaction between the homeostatic and circadian processes (Borbély, 1982).

In recent years, the investigation of the effects of transcranial direct current stimulation (tDCS) on sleepiness and vigilance levels has gained increasing attention (Annarumma et al., 2018). The most widely used protocols of tDCS involve the application of a low-intensity (0.1–2.0 mA) current stimulation through the skull by anode and cathode electrodes placed over target regions on the scalp (Fertonani & Miniussi, 2017). Conceptionally, anodal stimulation moves the resting membrane potential closer to the depolarization threshold and activates the underlying cortical area, whereas cathodal stimulation leads to the opposite inhibitory effect (Stagg & Nitsche, 2011).

Although the exact mechanisms of action of these techniques are still debated, their ability to affect the sleep/arousal pattern is consistently attributed to the modulation of the "top-down" cortico-thalamic pathway of sleep regulation (Frase et al., 2016; Krone et al., 2017). As the anterior cortical regions are the first to exhibit the distinctive electroencephalogram (EEG) activity of sleep-onset processes (i.e. slowing of EEG, intensification of frontal alpha and reduction of frontal theta; Gorgoni et al., 2019; Marzano et al., 2013; Werth et al., 1996), they represent the main target areas of transcranial electrical stimulation (tES) aimed at influencing the electrophysiological correlates of the wake–sleep transition (Frase et al., 2016). Further, prefrontal regions play a pivotal role in the alerting network functioning (Langner & Eickhoff, 2013). Hence, tES protocols aimed at increasing or decreasing the neuronal excitability of these regions may also influence the cortical component of the vigilance control system (Dalong et al., 2020).

Several protocols have been implemented for using tES to promote sleep propensity and accelerate the sleep-onset process (D'Atri et al., 2015; D'Atri et al., 2016; D'Atri et al., 2017, 2019; Kirov et al., 2009; Xie et al., 2021). A complementary line of research tried to investigate the effectiveness of tES as a countermeasure for excessive sleepiness and vigilance decrement (Brunyé et al., 2019). In pioneering studies, the application of anodal tDCS targeting specific areas of the prefrontal cortex was able to prevent the typical vigilance reduction across time-on-task (Nelson et al., 2014) and to mitigate sleep-deprivation-induced vigilance drop more efficiently than caffeine (McIntire et al., 2014). A more recent study confirmed these results by examining the effects of active tDCS over the frontal areas on the behavioural and electrophysiological functioning of distinct vigilance components (Luna et al., 2020). Along the same vein, Cheng et al. found an attenuation of the subjective drowsiness and fatigue following sleep deprivation (Cheng et al., 2021). Studies on patients with idiopathic (Galbiati et al., 2016) or organic hypersomnia (Frase et al., 2015) also described the efficacy of similar stimulation protocols in reducing diurnal sleepiness as well as increasing attentional performance in a clinical population. However, they did not explore the electrophysiological pattern underlying the observed results.

Taken together, these results suggest that different tES protocols could be effective sleepiness countermeasures. However, their effects on the electrophysiological pattern have been poorly investigated and warrant further studies. To our knowledge, tES studies aimed to reduce sleepiness or increase vigilance that have simultaneously considered subjective, behavioural and electrophysiological measures are still lacking.

Thus, the present study aimed to explore the effects of bifrontal anodal tDCS on a sample of healthy subjects, in which elevated levels of diurnal sleepiness were experimentally induced through partial sleep deprivation before the laboratory sessions. We adopted a within-subjects sham-controlled design to determine the effects of the active stimulation by using: (1) EEG recordings during the execution of the Maintenance of Wakefulness Test (MWT); (2) Psychomotor Vigilance Task (PVT) to assess behavioural sleepiness; and (3) self-reported questionnaires to evaluate subjective drowsiness.

We hypothesized that the active stimulation could globally reduce the diurnal sleepiness experienced by the sleep-deprived participants, as reflected by prevention of early EEG signs of sleepiness, reduction of vigilance drops during the sustained attentional task, and lower self-rated sleepiness scores, differently from sham stimulation.

2 | METHODS

2.1 | Participants

Twenty-three healthy subjects (12 males and 11 females) aged between 24 and 37 years (mean age 29.73 ± 3.44 years) took part in the study. From the originally recruited sample, three subjects were excluded from the EEG power analyses due to the occurrence of technical problems (i.e. scarce EEG signal quality due to artefacts). The final sample considered for the EEG power analyses was composed of 20 subjects (11 males and nine females) aged between 26 and 37 years (mean age 30.35 ± 3.23 years).

All participants met the following inclusion criteria as assessed by a clinical interview: no excessive daytime sleepiness (total score on the Epworth Sleepiness Scale ≤ 10); medication-free; no presence or history of epilepsy; no neurological or psychiatric disorder; no intracranial metal implants; no daytime nap habits or any sleep disorders; no excessive consumption of neuroactive drugs or caffeine.

All participants provided written informed consent to the experimental procedure and could withdraw from the study at any moment.

The study was approved by the Institutional Ethics Committee of the Department of Psychology of the University of Rome Sapienza (Prot. n. 0000942) and was conducted in accordance with the Declaration of Helsinki.

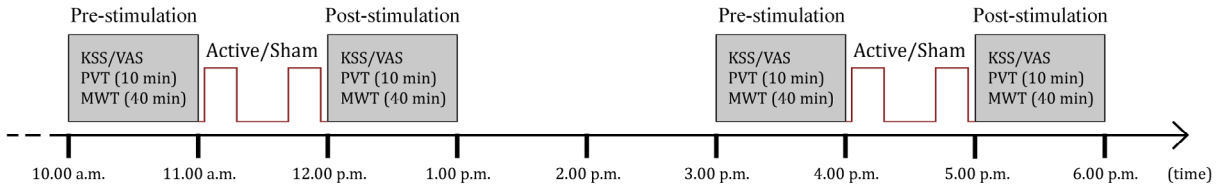

FIGURE 1 Study design. Experimental design and timeline of the two experimental sessions (Active and Sham). KSS, Karolinska Sleepiness Scale; MWT, Maintenance of Wakefulness Test; PVT, Psychomotor Vigilance Task; VAS, Visual Analogic Scale

2.2 | Experimental design

Participants were asked to keep regular sleep–wake schedules during the week before the experimental session, and to fill out a daily sleep log to control their compliance. All subjects underwent a partial sleep deprivation protocol at home (maximum 4 hr of sleep from 01:00 hours to 05:00 hours) during the night before the experimental day, monitored by sleep logs and actigraphic recordings (AMI, MicroMini Motionlogger, USA). Specifically, we checked the sleep logs and actigraphic data the following morning to verify the subjects' adherence to the deprivation protocol and define their inclusion/exclusion in the study, without further storing the acquired data.

The intake of any kind of neuroactive drugs, including coffee, tea and chocolate, or intense physical training was not allowed before the experimental session.

Our single-day experimental protocol consisted of two consecutive within-subjects sessions: one active condition (anodal tDCS) and one sham condition, separated by an interval of at least 2 hr. The order in which the real and sham stimulations were delivered in each session was randomized and balanced across subjects (i.e. 12 subjects started with real stimulation and 11 subjects with sham). As regard the subgroup of subjects considered for the EEG data analyses, 10 participants started with real and 10 with sham stimulation.

We used a single-blind protocol in which the participants were blinded to the stimulation type, whereas the experimenter who administered the stimulation was aware. Anyway, the experimenters were blinded to the specific condition during the scoring procedure.

Subjects came to the laboratory at 08.00 hours, and electrodes were fixed on their head in about 2 hr.

Each session lasted 3 hr and included an identical timeline: (a) a pre-stimulation assessment; (b) the stimulation protocol (active or sham); (c) a post-stimulation assessment (Figure 1). The pre- and post-stimulation assessment included subjective (self-reported questionnaires), behavioural (reaction-timed task) and objective (EEG recording) measures.

2.3 | Materials

2.3.1 | Electrical stimulation

The tDCS equipment consisted of a battery-driven stimulator system (BrainSTIM, EMS Medical, Italy) and conductive-rubber square electrodes (25 cm^2, 5 × 5 cm) placed in sponges saturated with high-conductivity gel. In line with the aims of the study and earlier similar protocols (Frase et al., 2015, 2016; Frase et al., 2019), the anodes (positively charged electrodes) were individually applied bilaterally at frontal locations (F3 and F4 of the international 10–10 system), and the cathodes (reference electrodes) at temporo-occipital positions (Y-cable split for stimulation and reference electrodes). A constant current (1.5 mA stimulator output) was delivered through a repetitive stimulation protocol: two consecutive blocks of 15 min with a 20 min inter-stimulation interval (30 s fade-in/fade-out).

In the sham session, the stimulation setting was the same as the tDCS condition, but the current was reduced to zero after 30 s in order to maintain the same physical sensation at the beginning of the real stimulation. Participants reported no adverse effects of the stimulations and no perceived differences between the active and sham conditions, as verified by a post-experiment debriefing.

We used an open-source software package (SimNIBS 2.1; Saturnino et al., 2015) to generate computational modelling of the distribution of the electric field strength over the cortex yielded by the adopted stimulation protocol (Figure 2).

2.3.2 | EEG recordings

BrainAmp MR plus system (Brain Products GmbH, Gilching, Germany) and Brain Vision Recorder (Version 1.10, Brain Products GmbH, Gilching, Germany) software were used to amplify and record the signals. EEG signals were recorded with a sampling rate of 250 Hz (0.1-μV steps resolution). A high-pass filter with a time constant of 1 s and a 70-Hz low-pass filter were applied to raw EEG data (phase shift-free Butterworth filters).

There were 26 unipolar electrodes (sintered Ag–AgCl) mounted at Fz, Cz, Pz, Oz, F7, F8, Fc1, Fc2, Fc5, Fc6, Fp1, Fp2, C3, C4, Cp1, Cp2, Cp5, Cp6, P3, P4, P7, P8, O1, O2, T7 and T8, according to the international 10–10 system.

The ground electrode was placed at Fpz (fronto-polar location), and the EEG signals were referenced online to the averaged mastoids (A1 and A2). Horizontal eye movements were detected by recording electrooculogram (EOG). The submental electromyogram (EMG) was also recorded for the offline artefacts detection and sleep scoring. Electrodes impedance was < 5 kΩ (EEG) and < 15 kΩ (EOG, EMG).

The EEG data were digitally stored for further offline analyses.

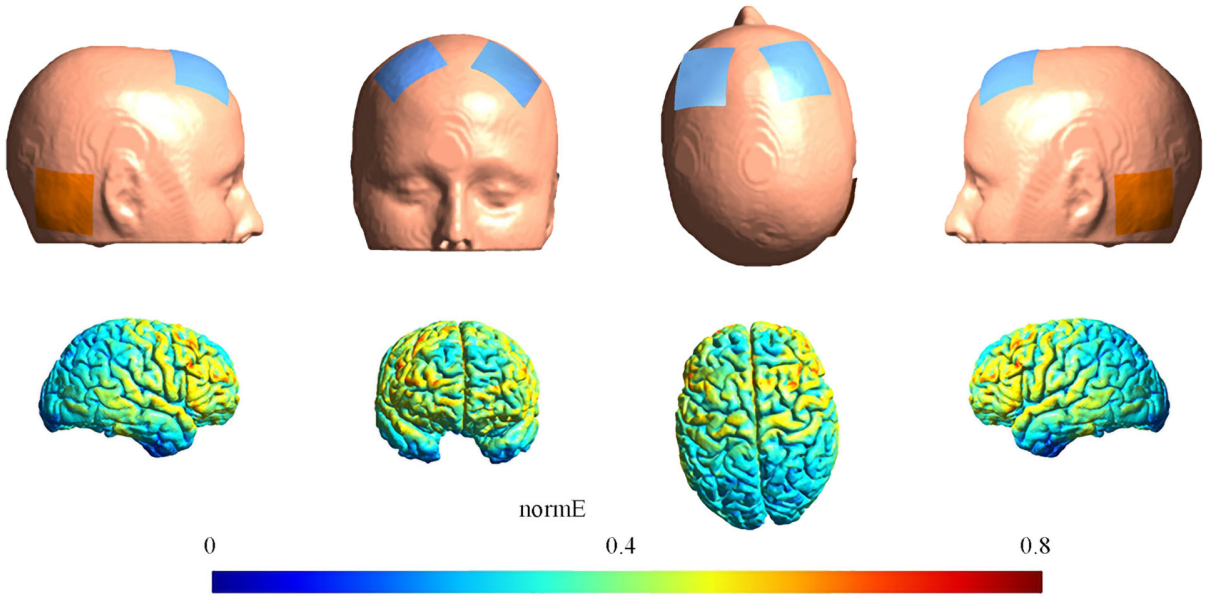

FIGURE 2 SimNIBS simulation of transcranial direct current stimulation (tDCS) study set up. Computational modelling (SimNIBS) of the electric field strength generated by tDCS bifrontal montages with 5 × 5 cm electrodes centred over F4 and F3

2.3.3 | Maintenance of Wakefulness Test

The EEG signal was recorded while subjects underwent four successive trials of MWT (40-min protocol) in an electrically shielded, soundproof and temperature-controlled room. The MWT was chosen in line with the aim to evaluate the effects of the stimulation on the subject's ability to counteract the accumulating homeostatic drive for sleep during wakefulness.

The MWT protocol observed the following American Academy of Sleep Medicine recommendations (Littner et al., 2005).

1. The first trial started at least 3 hr after the subject's wake-up time.
2. The trials were performed at intervals of at least 2 hr.
3. The room was maximally insulated from external light and the light source was positioned out of field of vision. The subject was seated comfortably, with the back and head supported by a pillow.
4. Instructions to the participant consisted of the following: "Please sit still and remain awake for as long as possible." Participants were not allowed to use extraordinary measures to stay awake, such as slapping the face or singing.
5. Naps and the use of neuroactive drugs before and during MWT were not allowed. Light breakfast is recommended at least 1 hr before the first trial, and a light lunch is recommended immediately after the second trial.
6. Trials were ended after 40 min if no sleep occurs or after unequivocal sleep onset (first appearance of a *K*-complex or spindle), identified by a sleep expert who continuously monitored the EEG recordings.

2.3.4 | Psychomotor Vigilance Task

The PVT is a well-established behavioural measure to assess sustained attention and objective levels of sleepiness, very sensitive to the effects of sleep loss and without learning effect (Reifman et al., 2018). We used a 10-min version of PC-PVT software (Khitrov et al., 2014). Participants were asked to click the left mouse button as quickly as possible every time a counter appears at random intervals.

2.3.5 | Sleepiness questionnaires

Subjective sleepiness was evaluated by the Karolinska Sleepiness Scale (KSS; Åkerstedt & Gillberg, 1990) and by the Visual Analogic Scale for Global Vigor (VAS-gv; Monk, 1989).

The KSS is a self-report measure to assess subjective levels of state-like sleepiness. Subjects were asked to rate their sleepiness level on a nine-point rating scale, ranging from 1 ("Extremely alert") up to 9 ("Extremely sleepy").

The VAS-gv is a continuous measure of subjective vigilance, which takes into account the scores from four subscales (alert, sleepy, weary and effort) to obtain a global vigour score between 0 and 40. Subjects indicated their current state (from "Not at all" to "Very much") by placing a mark on a 10-cm line for each scale. In accordance with the purposes of the study, we selectively considered the "sleepiness" scale (VAS-sleepiness).

2.4 | Data analysis

2.4.1 | Quantitative EEG analysis

The EEG signals were offline high-pass filtered with the time constant of 0.3 s and low-pass filtered at 30 Hz. Ocular and/or muscle artefacts in the EEG recordings were rejected by off-line visual inspection of 2-s epochs.

Power spectra of the artefact-free epochs were computed by a Fast Fourier Transform (FFT) routine for the 26 scalp

locations in the 0.5–29-Hz range (1-Hz bin resolution except for the 0.5–1-Hz bin) and then averaged across epochs (periodogram: 2 s).

The spectral power values for the adjacent frequency bins were then averaged across the traditional EEG bands: δ (1–4 Hz), θ (5–7 Hz), α (8–12 Hz), $\beta 1$ (13–15 Hz) and $\beta 2$ (16–24 Hz).

2.4.2 | Statistical analysis

Data analysis was performed using the software package MATLAB 7.13 (The Math Works, MA, USA) and its statistics toolbox.

The physiological sleepiness measures were: (1) EEG power spectra (μV^2); and (2) sleep-onset latency (SOL, s), which was either the time interval from the "start" of the MWT trial to the end of the 40 min or to the appearance of a *K*-complex/spindle. One of the most reliable measures of PVT (median Reaction Time, RT, ms) was considered as behavioural outcomes. Scores from the two self-rating sleepiness scales (KSS, VAS) were used as subjective parameters. Raw data were log transformed (Log_{10}) to approximately conform to normality.

Stimulation-related variations in physiological, behavioural and subjective measures were calculated for each variable of interest as difference scores between pre- and post-stimulation (Post minus Pre, Δ), and for both experimental conditions (ΔActive, ΔSham). The difference scores for each sleepiness variable were compared by two-way mixed-effects analysis of variance (ANOVA) with *Stimulation* (Active versus Sham) and *Circadian phase of active stimulation* ($Active_{a.m.}$ versus $Active_{p.m.}$) as within- and between-subject factors, respectively.

In order to better describe the relationship between the effects of active stimulation (i.e. pre–post changes during the active condition) on EEG spectral power and the other sleepiness outcomes, we calculated the Pearson correlations coefficients between ΔActive EEG and ΔActive SOL, PVT-RT, KSS and VAS.

The False Discovery Rate (FDR; Benjamini & Yekutieli, 2001) on EEG data was applied to correct for multiple comparisons in ANOVA models ($p_{FDRcorrected} \leq 0.05$), and the post hoc planned tests were carried out by *t*-tests for significant effects ($p \leq 0.05$).

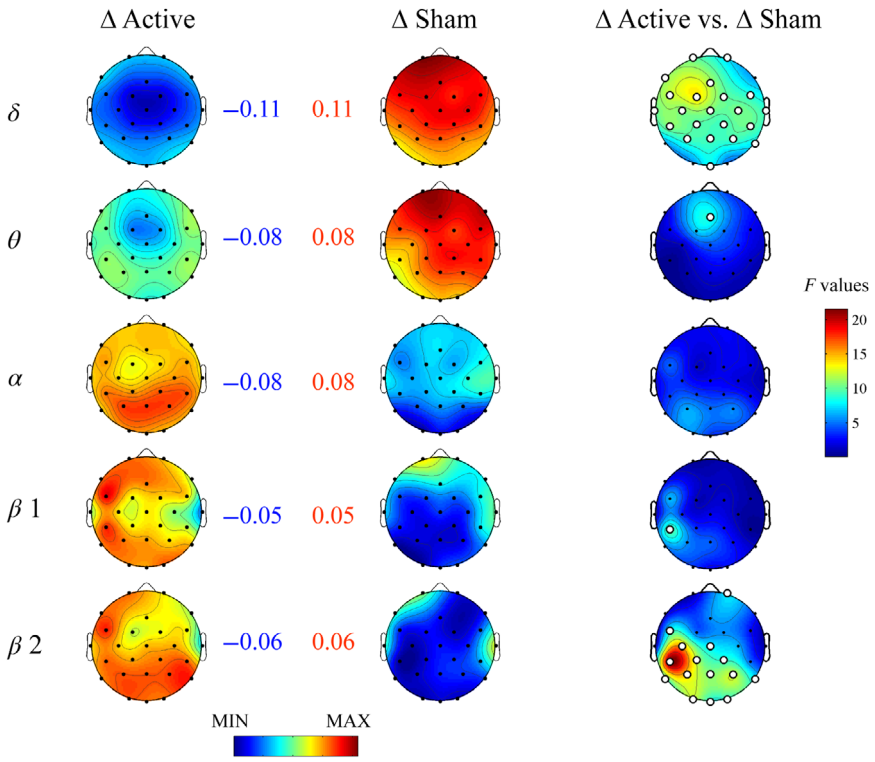

FIGURE 3 Effects of transcranial direct current stimulation (tDCS) protocol on electrophysiological correlates of sleepiness. Topographic maps of the Post–Pre stimulation (Δ) electroencephalogram (EEG) power spectra (log-transformed μV^2) during the Active (first column) and Sham (second column) condition, and statistical maps (*F*-values) of Stimulation effect (ΔActive versus ΔSham) assessed by mixed analysis of variances (third column). The topographic maps are scaled symmetrically according to the absolute maximal value of the spectral power considering the two experimental conditions within each frequency band. The absolute maximal value within each frequency band is also reported close to the corresponding maps. Maps are plotted for the following frequency bands: δ (1–4 Hz), θ (5–7 Hz), α (8–12 Hz), $\beta 1$ (13–15 Hz) and $\beta 2$ (16–24 Hz). Values are colour coded and plotted at the corresponding position on the planar projection of the scalp surface, and are interpolated (biharmonic spline) between electrodes. The statistical maps are scaled symmetrically according to the absolute maximal *F*-value across all frequency bands. White dots represent significant statistical differences, according to the False Discovery Rate (FDR) correction (adj $p \leq 0.015$)

3 | RESULTS

3.1 | Effects of tDCS protocol on sleepiness measures

3.1.1 | Electrophysiological correlates of sleepiness

EEG power spectra

The topography of EEG power changes induced by the two stimulation protocols – defined as the difference in spectral power between pre- and post-stimulation (ΔActive, ΔSham) for each frequency band and derivation – and the results of the statistical comparisons are shown in Figure 3.

The active condition is characterized by a post-stimulation decrease of the slower frequency bands (δ and θ) over the fronto-central regions, and a slight increase of the higher frequency bands over the occipital (α and β2) and central (β1) regions. Otherwise, in the sham condition we observe a strong enhancement of the slower frequency bands (especially over the fronto-central areas), and a slight decrease of the α (occipital areas) and β1 (posterior regions) and β2 (fronto-centro-parietal regions) rhythms.

The results of the *Stimulation* (Active versus Sham) × *Circadian phase of active stimulation* ($Active_{a.m.}$ versus $Active_{p.m.}$) mixed ANOVAs at each scalp location and frequency band showed no significant interaction or *Circadian phase of active stimulation* effects ($p_{FDRcorrected} > 0.826$ and $p_{FDRcorrected} > 0.203$, respectively). Instead, a significant main effect of the *Stimulation* factor (alpha level after FDR correction: $p = 0.015$; Figure 3) was found for δ (C3, C4, Cp1, Cp2, Cp5, Cp6, Cz, F7, Fc1, Fc2, Fc5, Fc6, Fp1, Fp2, Fz, Oz, P3, P4, P8, Pz, T7, T8), θ (Fz), β1 (Cp5) and β2 frequency

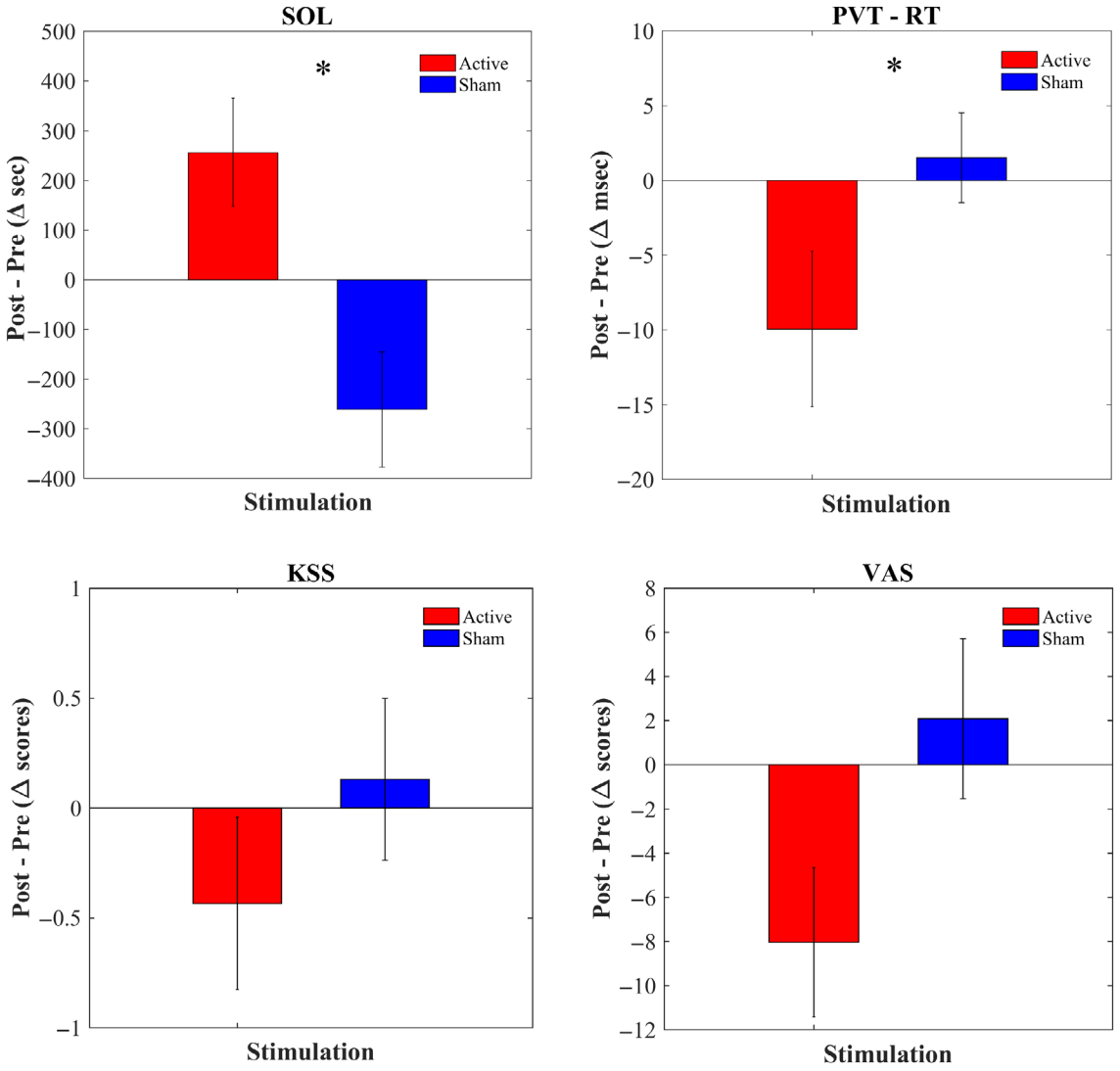

FIGURE 4 Effects of transcranial direct current stimulation (tDCS) protocol on sleep-onset latency (SOL), behavioural and subjective sleepiness. Means and standard errors (SE) of ΔActive (red) and ΔSham (blue) condition for the following variables (raw data): SOL (s); Psychomotor Vigilance Task-Reaction Time (PVT-RT; ms); Karolinska Sleepiness Scale (KSS) and Visual Analogic Scale (VAS; scores). Asterisks indicate statistical significance of the Stimulation effect resulting from mixed analysis of variances: *$p \leq 0.05$

TABLE 1 Mixed ANOVAs results

					Stimulation		Circadian phase of active stimulation		Interaction	
	Stimulation	Circadian phase of active stimulation	Mean	SE	*F*-value	*p*	*F*-value	*p*	*F*-value	*p*
SOL (s)	ΔActive	$Active_{a.m.}$	0.0866	0.067	7.961	0.010*	3.245	0.086	5.007	0.036*
		$Active_{p.m.}$	0.1211	0.099						
		Total	0.1031	0.057						
	ΔSham	$Active_{a.m.}$	0.0442	0.054						
		$Active_{p.m.}$	−0.2459	0.062						
		Total	−0.0946	0.050						
PVT-RT (ms)	ΔActive	$Active_{a.m.}$	0.0013	0.008	6.658	0.017*	0.472	0.499	13.672	0.001**
		$Active_{p.m.}$	−0.0271	0.010						
		Total	−0.0123	0.007						
	ΔSham	$Active_{a.m.}$	−0.0055	0.005						
		$Active_{p.m.}$	0.0110	0.006						
		Total	0.0024	0.004						
KSS (scores)	ΔActive	$Active_{a.m.}$	−0.0720	0.033	0.897	0.354	1.293	0.268	0.649	0.430
		$Active_{p.m.}$	0.0138	0.056						
		Total	−0.0310	0.032						
	ΔSham	$Active_{a.m.}$	−0.0007	0.025						
		$Active_{p.m.}$	0.0195	0.057						
		Total	0.0090	0.029						
VAS (scores)	ΔActive	$Active_{a.m.}$	−0.1394	0.049	2.966	0.100	0.573	0.457	1.625	0.216
		$Active_{p.m.}$	−0.0365	0.054						
		Total	−0.0902	0.037						
	ΔSham	$Active_{a.m.}$	0.0380	0.035						
		$Active_{p.m.}$	−0.0100	0.057						
		Total	0.0151	0.033						

Note: Descriptive statistics (Mean and SE for log-transformed data) and summary of mixed ANOVAs results for comparison between subjects receiving Active stimulation during morning ($Active_{a.m.}$) or afternoon ($Active_{p.m.}$) circadian phase (between-subjects factor) at Active (ΔActive) and Sham (ΔSham) condition (within-subjects factor).

Abbreviations: KSS, Karolinska Sleepiness Scale; PVT-RT, Psychomotor Vigilance Task-Reaction Time; SOL, Sleep-Onset Latency; VAS, Visual Analogic Scale.

*$p \leq 0.05$. **$p \leq 0.001$.

bands (C3, Cp1, Cp2, Cp5, Cz, Fc5, Fp2, O1, O2, Oz, P3, P4, P7, P8, Pz) ($F_{1,18} \geq 7.275$, $p \leq 0.015$; all data and statistical results are reported in Table S1).

Sleep-onset latency

Results of mixed ANOVA on ΔSOL showed no effect of the *Circadian phase in the active stimulation* ($F_{1,21} = 3.245$, $p = 0.086$), but a significant main effect of the *Stimulation* ($F_{1,21} = 7.961$, $p = 0.010$; Figure 4), and a significant interaction between the two factors ($F_{1,21} = 5.007$, $p = 0.036$). These effects are in the direction of: (a) increased SOL following the active stimulation compared with its decrement observed after sham; and (b) significant changes in the group of subjects who received the active stimulation in the afternoon ($t = 2.604$, $p = 0.026$) than the morning ($t = 0.779$, $p = 0.453$; Table 1).

3.1.2 | Behavioural sleepiness

Results of mixed ANOVA on ΔPVT-RT showed no effect of the *Circadian phase of active stimulation* ($F_{1,21} = 0.472$, $p = 0.499$) factor, a significant main effect of the *Stimulation* ($F_{1,21} = 6.658$, $p = 0.017$) factor (Figure 4) and a significant interaction among them ($F_{1,21} = 13.672$, $p = 0.001$; Table 1). Specifically, we found a decrement of PVT-RT following the active stimulation significantly different from their slight increment after sham. Further, planned post hoc tests showed a significant PVT-RT reduction compared with the sham-related increment only for the $Active_{p.m.}$ group ($t = -4.057$, $p = 0.002$), while no significant difference was found for subjects who received active stimulation in the morning ($t = 0.868$, $p = 0.404$).

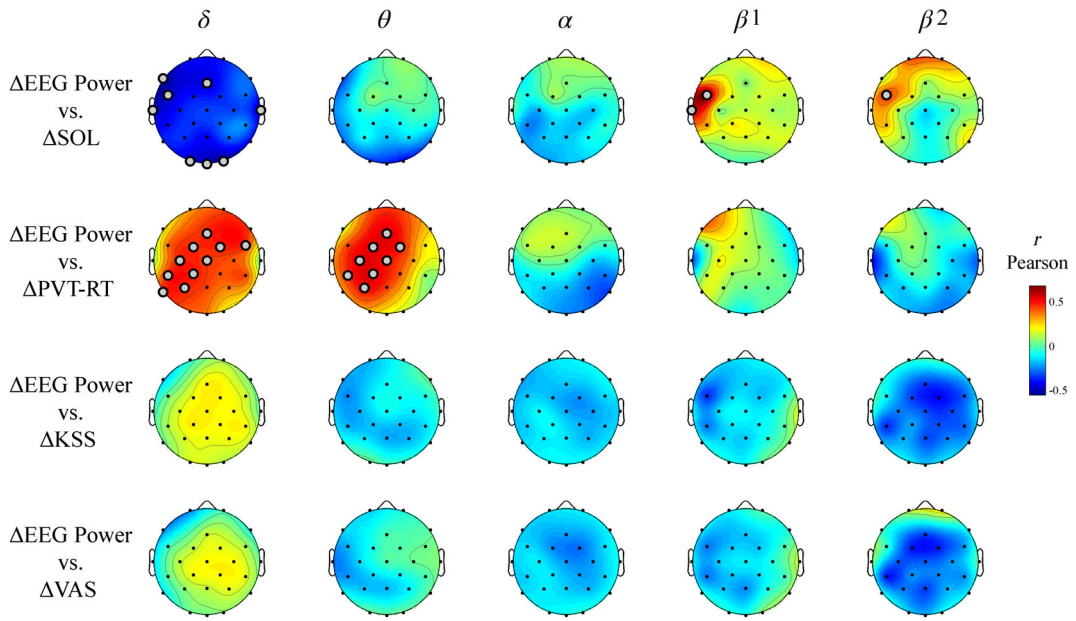

FIGURE 5 Correlation between stimulation effects on different sleepiness measures. Topographic distribution of the Pearson correlation coefficients between Post–Pre stimulation (Δ) electroencephalogram (EEG) power spectra (ΔEEG Power) and ΔSOL (first row), ΔPVT-RT (second row), ΔKSS (third row) and ΔVAS (fourth row) during the Active condition (all data were log-transformed). Values are expressed in terms of *r*-values: positive *r*-values indicate positive correlations and vice versa. Grey dots represent significant correlations ($p \leq 0.05$). KSS, Karolinska Sleepiness Scale; PVT-RT, Psychomotor Vigilance Task-Reaction Time; SOL, Sleep-Onset Latency; VAS, Visual Analogic Scale

3.1.3 | Subjective sleepiness

Results of mixed ANOVA on subjective sleepiness scores on both scales (ΔKSS, ΔVAS) showed neither interaction effect (KSS: $F_{1,21} = 0.649$, $p = 0.430$; VAS: $F_{1,21} = 1.625$, $p = 0.216$) nor significant main effect of *Stimulation* (KSS: $F_{1,21} = 0.897$, $p = 0.354$; VAS: $F_{1,21} = 2.966$, $p = 0.100$; Figure 4) or *Circadian phase of active stimulation* (KSS: $F_{1,21} = 1.293$, $p = 0.268$; VAS: $F_{1,21} = 0.573$, $p = 0.457$; Table 1).

3.2 | Correlation between stimulation effects on different sleepiness measures

The correlation (Pearson *r* coefficient) between changes in cortical pattern (ΔEEG Power) and changes in sleep latency (ΔSOL), behavioural sleepiness (ΔPVT-RT) and subjective sleepiness scales (ΔKSS and ΔVAS) in the active condition is depicted in Figure 5. No correlation was significant after the FDR correction for multiple comparisons. However, considering the canonical alpha level ($\alpha = 0.05$), we report negative correlations between ΔSOL and ΔEEG Power for δ (F7, Fc5, Fz, O1, O2, Oz, T7, T8; $r \leq -0.463$, $p \leq 0.040$), and positive correlations between ΔSOL and ΔEEG Power for β1 (Fc5, T7) and β2 (Fc5; $r \geq 0.456$, $p \leq 0.043$). Further, also ΔPVT-RT and ΔEEG Power are positively correlated for the following frequency bands: δ (C3, Cp1, Cp5, Cz, Fc1, Fc2, Fc6, Fz, P3, P7) and θ (C3, Cp1, Cp5, Cz, Fc1, Fc2, Fz, P3; $r \geq 0.449$, $p \leq 0.047$; all statistical results are reported in Tables S2–S5).

4 | DISCUSSION

The present study aimed to assess the effects of bifrontal anodal tDCS on different outcomes of sleepiness and vigilance among partially sleep-deprived subjects. To this end, we adopted a multidimensional approach using distinct sleepiness measures (i.e. EEG recordings during MWT, a behavioural vigilance task, subjective sleepiness questionnaires).

For the first time, we showed the topographic EEG correlates of physiological sleepiness reduction following the application of bifrontal anodal stimulation. We also found a simultaneous increase in behavioural vigilance and no stimulation effect regarding self-reported sleepiness. Taken together, these results substantiate the current literature on the effects of frontal anodal stimulation on vigilance increment (Annarumma et al., 2018), and support the hypothesis of separate mechanisms underlying different aspects of sleepiness and vigilance (Cluydts et al., 2002).

Sleep drive evaluated by separate trials of MWT (before and after real and sham stimulation) allowed for assessing both macrostructural (the amount of time to fall asleep) and quantitative (spatiotemporal EEG patterns) aspects of objective sleepiness.

Many studies have consistently shown that sleep deprivation accelerates and deepens the EEG changes that characterize the sleep onset as a consequence of the increased homeostatic sleep pressure (Borbély et al., 1981, 1982 Gorgoni et al., 2019; Guerrero & Achermann, 2019).

The active stimulation significantly improves the subject's ability to maintain wakefulness (longer sleep latency), reflecting its power to

contrast the sleep pressure resulting from previous deprivation. This evidence was particularly strong among subjects who received the active stimulation during the afternoon session, when sleepiness levels were probably higher likely due to the circadian influence. It should also be noted that the sham stimulation per se showed a drowsiness-increasing effect, with participants falling asleep faster post- versus pre-sham stimulation ($t = 2.244$, $p = 0.035$). This finding probably reflects the physiological increase of sleepiness in a context that strongly facilitates the sleep propensity (i.e. sitting in a chair for 2 × 15 min in a comfortable position with eyes closed; Johns, 2002). Consistently, we also observed the exacerbation of the early physiological signs of sleep onset following the sham condition (i.e. increase of frontal θ and decrease of occipital α) and a significant increase of subjective sleepiness in our previous study using a comparable protocol of transcranial stimulation (D'Atri et al., 2017).

In parallel, anodal tDCS provoked a net gain of cortical arousal, as reflected by the localized increase of rapid and desynchronized EEG rhythms (β1 and β2 frequency bands), and the spread decrease in slow EEG frequencies (δ and θ). Conversely, the sham-related EEG pattern showed the frontal increase of the distinctive markers of sleep propensity (i.e. δ) and somnolence (i.e. θ; Finelli et al., 2000), and the simultaneous reduction of higher frequency bands (i.e. β1 and β2).

From a topographical standpoint, the anterior EEG synchronization following sham condition is consistent with the well-known sensitivity of the frontal cortical areas to exhibit the earliest signs of the physiological need for sleep (De Gennaro et al., 2007; Finelli et al., 2000; Gorgoni et al., 2019; Vyazovskiy et al., 2011), especially after a period of sleep deprivation (Gorgoni et al., 2020). On the other hand, the presence of a complementary electrophysiological pattern after anodal tDCS reflects the ability of the active stimulation protocol to counteract the physiological process of sleep onset and boost the physiological levels of cortical arousal. Indeed, fast EEG frequencies are traditionally considered physiological indices of cortical arousal and motor/cognitive activation (Merker, 2013).

We can also observe a consistent correlation between the two aspects of objective sleepiness assessed by MWT. In particular, we found an association between the longer sleep latency following active tDCS and the stimulation-related (a) decrement of slow EEG frequencies (i.e. δ) and (b) increment of rapid EEG frequencies (i.e. β1 and β2).

In this vein, the bifrontal montage represents an undoubted advantage for several reasons. Firstly, as demonstrated in previous studies (Frase et al., 2016), concurrent stimulation to both hemispheres maximizes the effects as they are equally involved in falling asleep. Secondly, this specific type of montage (bifrontal tDCS with temporo-occipital references) may have engendered the additional stimulation of deep brain structures involved in the initiation of the typical EEG synchronization of falling asleep (e.g. thalamus and hippocampus; Magnin et al., 2010; Sarasso et al., 2014). Also, we chose the repetitive stimulation protocol in light of its enhanced effects over time (Monte-Silva et al., 2013) and with the ultimate goal of preserving the effects for the entire duration of the post-stimulation assessment (approximately 1 hr).

From a behavioural viewpoint, we selected PVT to assess sustained attention over time as it represents one of the most reliable instruments to test vigilance decrement in sleep-deprived subjects (Reifman et al., 2018). Consistently with our hypotheses, the performance on this RT task was better after anodal tDCS relative to sham. Such results corroborate evidence found in previous studies showing the reduction of the attentional drop during long and monotonous tasks following the administration of anodal stimulation over the prefrontal cortex (McIntire et al., 2014; Nelson et al., 2014). Here, we replicated these findings by also providing the electrophysiological correlates of the stimulation outcome. Notably, the behavioural effect was observed only in the subgroup receiving the active stimulation during the afternoon session. We can speculate that the additive effect of the physiological decrease of alertness during the post-prandial circadian phases and the cumulative sleep loss in the afternoon (Bermudez et al., 2016) could have exacerbated the excitatory effects of tDCS on vigilance performance. Thus, the floor effect in the morning session could have attenuated the great sensitivity to both homeostatic and circadian factors of the PVT (Wright Jr et al., 2002).

Further, we observed a positive correlation between the reduction of RTs on PVT and the cortical decrement of δ/θ EEG power, consistently with the activating effect of stimulation and with the results of previous research (Bernardi et al., 2015; Gorgoni et al., 2014; Nir et al., 2017). Such results may suggest a possible causal relation between the modulation of the local EEG activity by tDCS and the secondary changes in behavioural outcomes.

Concerning subjective results, we can appreciate—from a descriptive standpoint—a numerical reduction of the perceived sleepiness following the active stimulation for both self-reported scales (KSS and VAS) and their slight increase after sham, according to our expectations. It is worth noting that the absence of significant variations in subjective sleepiness between the two stimulation conditions could be ascribable to underpowered analyses. Indeed, the sample sizes needed to reach the appropriate power value (≥ 0.8) based on our study design and the current effect sizes (η_p^2: 0.041 [KSS]; 0.124 [VAS]) are $n = 80$ and $n = 43$, respectively, for KSS and VAS scale (G*Power 3.1.9.4; Faul et al., 2007). Further, the lack of significant effects on subjective measures is not surprising if we consider the hypothesis of separate aetiological mechanisms underlying subjective and objective sleepiness (Cluydts et al., 2002). Specifically, subjective sleepiness represents a phenomenon reflecting both sleep and situational wake drive (De Valck & Cluydts, 2003; Kim & Young, 2005), differently from the objective outcomes of the same construct. For example, the degree of perceived sleepiness was shown to be affected by environmental and motivational factors, such as external incentives or desired outcomes (Horne, 2010).

The main limitation of the current repetitive tDCS protocol is represented by the short distance between the two stimulation protocols (about 4 hr). Indeed, although the early effects on neuronal and synaptic excitability last up to 3 hr, the later after-effects can last for over 24 hr (Monte-Silva et al., 2013). However, the long-lasting changes would seem relevant for enduring alterations of cerebral functions underlying learning and memory formation

(Agboada et al., 2020), and therefore are not directly involved in the cortical state of arousal and excitability. In any case, the exact mechanisms explaining the long-lasting consequences of tES on the human frontal cortex are yet to be explored, and standardized guidelines on the amount of time to ensure the total wash-out are still absent.

Further, stimulation was delivered immediately before and after the sleepiness evaluation, and then its effects were inferred by comparing pre- and post-stimulation assessment. Future studies should perform online stimulation protocols (Yavari et al., 2018) to observe the direct impact of tDCS on neuronal excitability during the execution of the MWT and PVT. We should also consider that the absence of data storing related to actigraphy and sleep logs (used for the compliance check) prevented the possibility of exploring any potential correlation between the effects of the stimulation and the qualitative/qualitative variables related to previous sleep.

Another major limitation of this study protocol is represented by the single-blind design (i.e. the experimenter was aware of the type of stimulation during the tDCS administration). Indeed, even though we adopted some precautions (e.g. making the initial sensations of the two stimulation types similar, as also revealed by the final debriefing interview), we cannot exclude some external bias due to the absence of a double-blind protocol.

5 | CONCLUSIONS

In conclusion, we confirmed that anodal tDCS over the frontal cortical regions could represent a useful tool to prevent the increase sleep propensity and vigilance decline in subjects experiencing heightened levels of diurnal sleepiness. Although our results are preliminary and referred to healthy subjects, follow-on studies on clinical samples or within ecological settings might help pave the way for understanding the efficacy of tES protocols as alertness-enhancing tools in different work or daily life contexts.

AUTHOR CONTRIBUTIONS

Substantial contributions to the conception and design of the work: Valentina Alfonsi, Aurora D'Atri and Luigi De Gennaro. Participants enrolment, acquisition and analysis of data: Valentina Alfonsi, Francesco Giacinti, Ludovica Annarumma, Federico Salfi, Giulia Amicucci and Domenico Corigliano. Interpretation of data: Valentina Alfonsi, Aurora D'Atri, Serena Scarpelli, Maurizio Gorgoni and Luigi De Gennaro. Writing of the manuscript with comments from all authors: Valentina Alfonsi, Aurora D'Atri, Serena Scarpelli, Maurizio Gorgoni and Luigi De Gennaro.

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CONFLICT OF INTEREST

None of the authors has potential conflicts of interest to be disclosed.

DATA AVAILABILITY STATEMENT

The dataset supporting the results of this study is available upon request.

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