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Original Article

Transcranial direct current stimulation on primary sensorimotor area has no effect in patients with drug-naïve restless legs syndrome: a proof-of-concept clinical trial

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ABSTRACT

Objective: To evaluate the efficacy of transcranial direct current stimulation (tDCS) in people with drug-naïve restless legs syndrome (RLS).
Methods: A two-week, double-blind, randomized, sham-controlled trial was performed. Thirty-three females with RLS were recruited. Participants received five sessions of tDCS using cathodal, anodal or sham stimulation. They were assessed at baseline (T0), three days (T1) and 13 days (T2) after the end of tDCS. Primary outcomes included the International RLS Group Rating Scale (IRLS) and the Clinical Global Impressions-Improvement (CGI-I). Secondary outcomes included the Patient Global Impression scale, the Pittsburgh Sleep Quality Index, the Medical Outcome Study sleep subscales, and the Beck Depression Inventory. Objective neurophysiological changes were assessed using event-related desynchronization/synchronization (ERD/ERS) of electroencephalography.
Results: The changes in the IRLS scores, as well as the responder rate in the CGI-I scale, did not differ significantly among the groups. There was also no significant difference in any of the secondary outcome measures and ERD/ERS among the groups.
Conclusions: Transcranial direct current stimulation with electrodes on the sensorimotor areas showed no significant effect in people with drug-naïve RLS.

1. Introduction

Restless legs syndrome (RLS) is a chronic sensorimotor neurological disorder, with a prevalence that ranges from 5.0 to 14.3% [1]. Treatment should be considered for people with RLS symptoms that seriously impair quality of life, daytime functioning, social functioning or sleep. Dopamine agonists are effective, well tolerated, and can be used as a first-line therapy in the treatment of moderate-to-severe RLS. However, while dopamine agonists confer many benefits, drug-emergent problems such as dopamine dysregulation syndrome and augmentation may limit their use for long-term therapy [2].

RLS is currently viewed as a network dysfunction, encompassing different areas involved in somatosensory perception and motor function [3]. Transcranial magnetic stimulation (TMS) and electroencephalography (EEG) studies suggest that dysfunction in inhibitory cortical control and a coexisting alteration in sensorimotor integration may be involved in the pathophysiology of RLS [4]. Magnetic resonance imaging (MRI) studies have also indicated alterations in the sensorimotor cortices and related white matter tracts in RLS [5–7]. Thus, RLS is a disorder of the sensorimotor network involving structures that are involved in somatosensory perception as well as the generation of movement [8], in which sensorimotor control at the cortical level may play an important role [4]. In short, people with RLS seem to have altered cortical excitability in their sensorimotor network.

Transcranial direct current stimulation (tDCS) is a non-invasive method of brain stimulation that can induce long-lasting and polarity-specific changes in the excitability of the cortex in humans. Anodal stimulation increases cortical excitability

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during and after stimulation, while cathodal stimulation leads to a decrease in excitability within the cortex [9]. Transcranial direct current stimulation has been investigated as a potential treatment tool by modulating cortical excitability in various diseases such as depression, chronic pain, stroke, and Parkinson's disease [10–12].

In addition to an alteration in cortical excitability, particularly in the sensorimotor areas, pinprick hyperalgesia, tactile hypoesthesia, and paradoxical heat sensation in people with RLS suggest spinal or supraspinal central sensitization as a pathophysiology of RLS [13]. Thus, it seems reasonable to suggest that altering this pathological state by using stimulation or modulation techniques in the brain, especially in the sensorimotor cortex, might offer a therapeutic target in RLS.

The aims of the present study were to investigate the efficacy and tolerability of tDCS in treating people with drug-naïve RLS with the following measures: (1) subjective symptoms, using the International Restless Legs Syndrome Study Group Rating Scale (IRLS); (2) clinical improvement, using Clinical Global Impressions-Improvement (CGI-I); and (3) objective neurophysiological evidence of hyperexcitability using event-related desynchronization (ERD) and event-related synchronization (ERS) of EEG. Considering the increased cortical excitability in RLS, inhibition by cathodal stimulation would seem to be appropriate for treatment with tDCS in RLS. However, both cathodal [14–16] and anodal [17,18] stimulation have been studied in chronic pain. Thus, anodal or cathodal stimulation was used in the motor cortex, targeting the lower extremities of people with RLS; the efficacies of both were compared with that of sham stimulation.

2. Methods

2.1. Subjects

The present study was a double-blind, randomized, sham-controlled, three-arm proof-of-concept clinical trial. Drug-naïve females, aged 18–70 years, with a diagnosis of idiopathic RLS were recruited from the community. All participants underwent standardized interviews using a structured sleep questionnaire and had clinical neurological examinations. A neurologist established the diagnosis of RLS in a face-to-face interview, based on the diagnostic criteria for RLS set by the National Institutes of Health workshop, using a validated Korean-language version of the Johns Hopkins Telephone diagnostic questionnaire [19]. The inclusion criteria were: (1) duration of RLS ≥1 year; (2) having symptoms ≥3 times per week; and (3) IRLS score ≥20, indicating severe symptomatology. Exclusion criteria were: (1) significant comorbidities likely to be associated with secondary RLS, such as anemia, pregnancy, chronic kidney disease or peripheral neuropathy; (2) presence of cognitive disorders that prevented participants from describing their symptoms; (3) presence of disorders with symptoms similar to RLS, such as attention deficit hyperactivity disorder, essential tremor, Parkinson's disease, neuroleptic-induced akathisia, congestive heart failure, vascular claudication, neurogenic claudication, myelopathy, and arthritis; (4) those who were taking medications that can affect the central nervous system; and (5) those who had metallic objects in their bodies, such as a pacemaker or internal metallic objects in the brain.

The present study was approved by the Institutional Review Board and was registered with the Clinical Research Information Service of Korea (https://cris.nih.go.kr/cris/en/search/basic_search.jsp, registry no. KCT0000618), which is one of the primary registries in the WHO International Clinical Trials Registry Platform. Written informed consent was obtained from all participants.

2.2. Sample size estimation

Sample size was planned so that a hypothesized difference in IRLS score among the three groups could be detected at a 5% significance level, with 80% power. Based on data from a previous trial [20], the mean change in IRLS score was expected to have an effect size of 0.696. The calculated sample size necessary was eight per group. Assuming a screening failure rate as high as 30%, it was estimated that 11 people should be recruited for each group.

2.3. Study design

The study consisted of three phases: baseline, treatment, and follow-up. The baseline evaluation was performed once a week before treatment (T0). After completing baseline assessments, participants were assigned to receive cathodal, anodal or sham tDCS treatment in a 1:1:1 ratio using a predefined random order, which was generated by a computer. All participants and investigators were blinded to the treatment conditions until the end of the study. During the treatment phase, real (anodal or cathodal) or sham tDCS was administered in five treatment sessions per week (once per day, Monday to Friday) [21]. Follow-up evaluations were made three days (T1) and 13 days (T2) after the end of the fifth treatment sessions.

2.4. Transcranial direct current stimulation

A trained investigator who had no knowledge of the participants' group assignment performed the treatments. During each session, a direct current was transferred using a saline-soaked pair of surface sponge electrodes (5×5 cm^2) and delivered with a specially developed, battery-driven, constant-current stimulator (Phoresor II Auto Model PM850, IOMED, Salt Lake City, UT, USA). Because the aim was to stimulate the primary motor cortex, particularly for the leg areas, the active electrode was placed on the vertex (Cz scalp position of the international 10–20 system), covering the bilateral medial aspect of the primary motor cortex involving the leg areas. An extracephalic location was used for the reference electrode because extracephalic reference electrodes may allow for a robust prediction of cortical modulation with little dependence on the reference electrode location [22–24]. The reference electrode was placed over the suboccipital region, roughly corresponding to the spinous process of the axis. Stimulation was administered at 2 mA between 17:00 and 19:00. The ramp-up and ramp-down periods were over 10 s. In both the real and sham stimulations, the electrodes were attached for a total of 20 min. In the real tDCS groups, 2 mA tDCS was applied for 20 min. Participants in the anodal group received anodal stimulation via the active electrode, and the cathodal stimulation was delivered to the reference electrode. Participants in the cathodal group received cathodal stimulation at the active electrode and anodal stimulation at the reference electrode. For the sham tDCS group, the same montage was used as in the anodal group; however, the current was applied for 30 s, which successfully prevented the participants from distinguishing it from real tDCS [25]. The 30-s stimulation period is insufficient to produce a meaningful change [12,26] but mimics the initial sensation associated with real stimulation [25,27–29]. Since all participants were naïve to tDCS, none of them could have possibly distinguished between the real and the sham tDCS.

2.5. Efficacy assessment

The primary outcomes were assessed independently by two measures: change in symptom severity on IRLS [30] and the responder rate in the CGI-I scale [31]. To assess changes in severity of RLS symptoms, participants were asked to complete the IRLS at T0, T1, and T2. At T1 and T2, a sleep-disorder expert physician assessed CGI-I.

A CGI responder was defined as a participant with a CGI-I score of "very much improved" or "much improved." Secondary outcome measures included: participant global impression, measured using the Patient Global Impression scale (PGI) at T1 and T2; subjective sleep disturbance, measured using the Pittsburgh Sleep Quality Index (PSQI) [32]; The Medical Outcome Study (MOS) sleep subscales [31]; and the depression score, measured using the Korean version of the Beck Depression Inventory version II (BDI-II) [33] at T0 and T2. The PGI responder rate was defined as the proportion of participants with a PGI score of "very much improved" or "much improved."

To assess the acute effects of tDCS during the treatment session, participants were asked to record visual analog scale (VAS) scores and the Subjective Post-Sleep Diary (SPSD) [34] of RLS, which contains eight subscales, from five days before beginning treatment to two days after the end of the treatment session.

2.6. Safety assessment

During the treatment sessions, safety was assessed with regard to type, frequency and severity of adverse effects immediately after individual sessions of tDCS stimulation. The adverse effects recorded were: tingling, itching and burning sensations, pain, headaches, fatigue, difficulties in concentration, and nervousness [35].

2.7. Event-related desynchronization/synchronization using a finger-tapping task

Schober et al. found increased beta ERS in people with RLS, suggesting a higher need for motor-cortical inhibition due to an increased level of excitation by motor-cortex activation and input from neighboring functionally-interrelated cortical areas [36]. Thus, beta ERS was considered as a marker for hyperexcitability and was used as an objective tool with which to assess the effects of tDCS in people with RLS. It was hypothesized that beta ERS would decrease if tDCS reduced the excitability of the sensorimotor cortex in people with RLS.

EEG recordings were made at T0 and T1, with 19 electrodes placed on the scalp in accordance with the international 10–20 system. The reference electrode was set to the linked-mastoid electrodes. Impedance was kept below 5 kΩ, and a band-pass filter was set at 0.1–100 Hz, with a sampling rate of 400 Hz. Two electro-oculogram (EOG) channels (placed on the left and right outer canthi) were added to confirm eyeball movements and to remove EOG artifacts. Participants were seated in a comfortable chair and told to keep their eyes open during the procedure. Commercial software (Presentation® Neurobehavioral Systems, Berkeley, CA, USA) was used to present stimuli on a 17-inch LCD monitor. Participants were told to press a button with their right index finger in response to visual stimuli, a letter "click", and to rest their finger on the switch between the movements. The stimuli were presented for 300 ms and interstimulus intervals were fixed at 5700 ms.

Electroencephalography data were processed using EEGLAB [37] (version 11.0.4.3b operated in a MATLAB environment [MathWorks, Natick, MA, USA]). After transforming EEG data to an average reference, they were filtered digitally using a 0.3–50 Hz band-pass filter. The ERP epochs were extracted from –1500 to +2500 ms after the finger movement onset. Trials containing significant artifacts other than EOG artifacts were detected visually and excluded from further analysis. The EOG artifacts and muscle artifacts were also removed using independent component analysis. Baselines were corrected by subtracting the root-mean-square values of pre-stimulus intervals (–1500 to –500 ms).

The event-related spectral perturbation (ERSP) allowed the spectral power changes of the induced EEG relative to the stimulus from the views of the time-frequency domain to be observed, which supplied more details about ERD/ERS patterns of different types of motor imagery. Event-related spectral perturbation (ERSP) is defined as:

$$ERSP(f,t)=\frac{1}{n}\sum_{k=1}^{n}|F_k(f,t)|^2$$

where n is the number of trails, and $F_k(f,t)$ is the spectral estimation of the kth trial at frequency f and time t [37]. A short-time Fourier transform was used to calculate ERSP. Mean ERSP values were calculated from –1500 to 2500 ms and displayed between 0 and 50 Hz for each task. Mean power changes were computed by averaging over all subjects.

2.8. Statistical analyses

The normal distribution of each data set was verified using the Kolmogorov–Smirnov test. Continuous variables with a normal distribution were analyzed using analysis of variance, while ordinal variables and continuous variables with an abnormal distribution were analyzed using the Kruskal–Wallis test. Treatment effects were assessed using the paired t-test or Wilcoxon's rank-sum test. Discrete variables were analyzed using the Chi-squared test or Fisher's exact test.

For correlation analysis, Pearson's correlation (r) or the Spearman's rank correlation coefficient (ρ) were used. Correct was not made for multiple comparisons because this was an exploratory proof-of-principle study. The SPSS (version 17.0, SPSS Inc., Chicago, IL, USA) and 'R' software (version 3.0.1) were used for statistical analyses.

3. Results

3.1. Demographics and clinical characteristics

In total, 33 people were assigned randomly to the real and sham groups. However, two people, who were randomized to the cathodal (one) and anodal groups (one), did not begin the treatment due to personal reasons (Fig. 1). The demographic characteristics of the remaining 31 people are presented in Table 1.

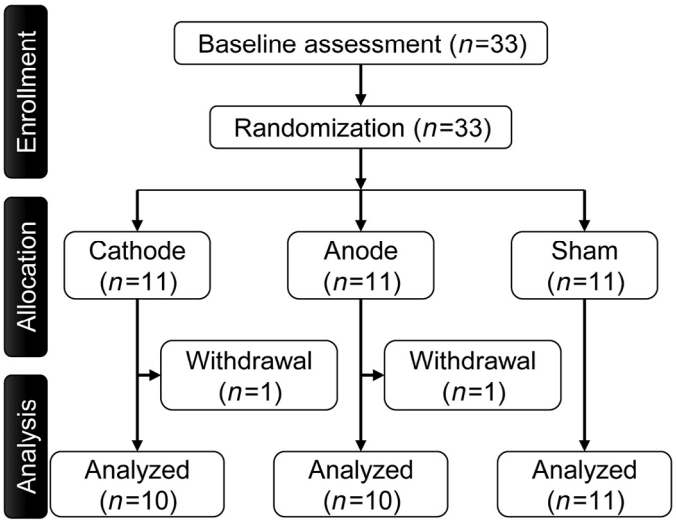

Fig. 1. A flow chart illustrating the study process. Thirty-three people with restless legs syndrome (RLS) were recruited from the community and they were randomized to receive cathodal, anodal or sham tDCS treatment in a 1:1:1 ratio after baseline assessment. Two withdrew (one from the cathodal group, the other from the anodal group) and did not receive tDCS treatment due to personal reasons. A total of 31 participants received five tDCS treatments for 5 days, with raters and subjects blind to the treatment group assignment.

Table 1
The demographics and clinical characteristics of the people with restless legs syndrome.

n	Cathode 10	Anode 10	Sham 11	Total 31	*p*-value
Age (y), mean (±SD)	47.3 (±11.0)	44.1 (±13.4)	46.0 (±10.1)	45.8 (±11.2)	0.715
Age at onset of RLS (y), mean (±SD)	31.6 (±15.4)	31.8 (±14.9)	30.4 (±18.0)	31.2 (±15.7)	0.836
Late-onset RLS, *n* (%)	3 (30)	1 (10)	3 (27)	7 (22)	0.507
Duration of RLS (y), mean (±SD)	15.7 (±16.3)	12.3 (±9.7)	15.6 (±10.5)	14.6 (±12.1)	0.544
Presence of family history, *n* (%)	6 (60)	7 (70)	7 (64)	20 (63)	0.894
IRLS, mean (±SD)	29.7 (±3.6)	27.3 (±3.5)	29.0 (±5.6)	28.7 (±4.3)	0.392
JHRLS, median (IQR)	1.5 (1.0, 3.0)	1.0 (1.0, 2.0)	2.0 (1.0, 2.5)	2.0 (1.0, 3.0)	0.652
ISI, median (IQR)	17.0 (13.8, 22.5)	15.0 (14.0, 18.5)	20.0 (18.0, 21.5)	18.0 (14.0, 21.5)	0.305
BDI, median (IQR)	22.5 (15.3, 31.0)	17.0 (10.0, 20.8)	14.0 (11.5, 23.0)	17.0 (12.5, 26.0)	0.411
HADS anxiety, median (IQR)	7.5 (4.3, 12.3)	6.5 (4.3, 7.8)	8.0 (5.5, 9.5)	7.0 (4.5, 10.0)	0.781
HADS depression, median (IQR)	9.5 (5.5, 12.8)	7.5 (5.5, 9.8)	9.0 (6.5, 11.0)	9.0 (5.5, 12.0)	0.833
PSQI, median (IQR)	12.5 (9.3, 15.8)	11.5 (10.0, 13.5)	14.0 (13.0, 15.5)	13.0 (10.0, 15.0)	0.185
Ferritin (ng/mL), mean (±SD)	94.3 (±58.1)	62.5 (±51.9)	73.2 (±34.9)	76.5 (±49.0)	0.650

Abbreviations: BDI, Beck depression index; HADS, Hospital Anxiety Depression scale; IQR, interquartile range; IRLS, International Restless Legs Syndrome Study Group Rating Scale; ISI, insomnia severity index; JHRLS, Johns Hopkin's RLS severity scale; *n*, number; PSQI, Pittsburgh Sleep Quality Index; RLS, restless legs syndrome; SD, standard deviation; y, years.

3.2. Primary outcome measures

The participants' IRLS scores were significantly lower at T1 and T2 (17.8 ± 5.6 and 17.9 ± 7.8, respectively) than at T0 (28.7 ± 4.3, $p < 0.01$ for both periods). Figure 2 shows the changes in three groups' IRLS scores at T1 and T2. However, the mean reduction in IRLS from baseline to T1 and T2 did not differ among the cathodal, anodal, and sham groups (–13.4 ± 1.1 vs –8.8 ± 1.6 vs –12.0 ± 3.2, $p = 0.377$; –11.0 ± 2.7 vs –10.0 ± 2.6 vs –12.0 ± 3.5, $p = 0.897$, respectively). The changes in the IRLS at T1 correlated negatively with the IRLS at T0 ($r = -0.429$ and $p = 0.016$) (Fig. 3).

The percentages of IRLS responders at T1 and T2 were 16% and 29%, respectively, while the percentages of CGI responders at T1 and T2 were 45% and 32%, respectively. Table 2 shows the numbers of IRLS and CGI responders in each group at T1 and T2, which did not significantly differ.

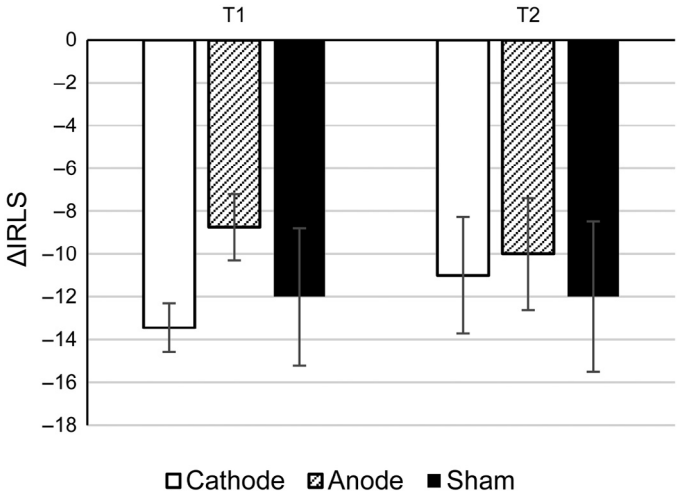

Fig. 2. Changes in the International Restless Legs Syndrome Study Group Rating Scale at T1 and T2. The mean changes in the International RLS Severity rating scale (IRLS) scores of the cathode (white bars), anode (hatched bars) and sham (black bars) groups at T1 (–13.4 ± 1.1 vs –8.8 ± 1.6 vs –12 ± 3.2) and T2 (–11.0 ± 2.7 vs –10.0 ± 2.6 vs –12.0 ± 3.5) from baseline (T0) did not differ significantly among the groups ($p = 0.377$ and $p = 0.897$, respectively). The lines on the bars represent the standard deviations of the changes in the IRLS.

3.3. Event-related desynchronization/synchronization

Figure 4A shows the averaged ERSP plot at the C3 location for all of the participants. Three distinct signals were focused on: alpha ERD (10–12 Hz, –500 to 100 ms), beta ERD (15–21 Hz, 400–

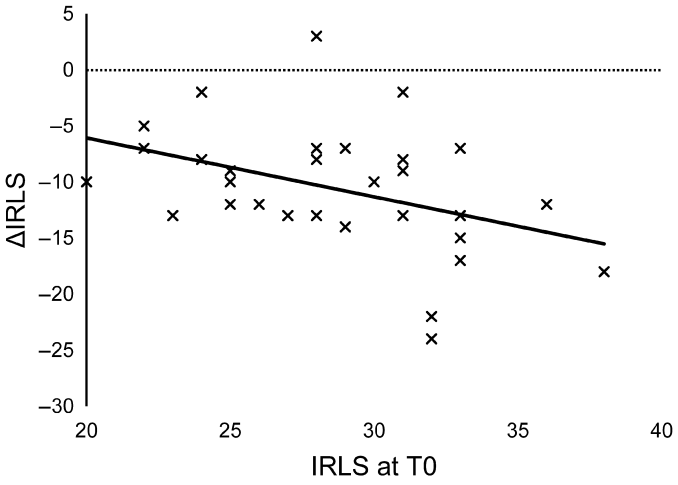

Fig. 3. The correlation between change in the International Restless Legs Syndrome Study Group Rating Scale at T1 and IRLS at T0. This figure shows a significant negative correlation between change in the International Restless Legs Syndrome Study Group Rating Scale (ΔIRLS) at T1 and IRLS at T0 ($r = -0.429$ and $p = 0.016$).

Table 2
Percentages of clinical responders in terms of IRLS, CGI-I, and PGI at different time points.

	Cathode *n* (%)	Anode *n* (%)	Sham *n* (%)	Chi-squared	*p*-value
IRLS responder at T1	2 (20%)	1 (10%)	2 (18%)	0.423	0.810
IRLS responder at T2	3 (30%)	3 (30%)	3 (27%)	0.026	0.987
CGI-I responder at T1	5 (45%)	2 (20%)	7 (63%)	4.073	0.131
CGI-I responder at T2	4 (36%)	3 (30%)	4 (36%)	0.123	0.940
PGI responder at T1	1 (9%)	2 (20%)	4 (36%)	2.424	0.298
PGI responder at T2	2 (18%)	3 (30%)	3 (27%)	0.436	0.804

Abbreviations: CGI-I, Clinician's Global Impression-Improvement scale; IRLS, International RLS Severity rating scale; *n*, number of participants; %, percentage of clinical responders among each group; PGI, Patient Global Impression scale; T1, 3 days after the treatment; T2, 13 days after the treatment.

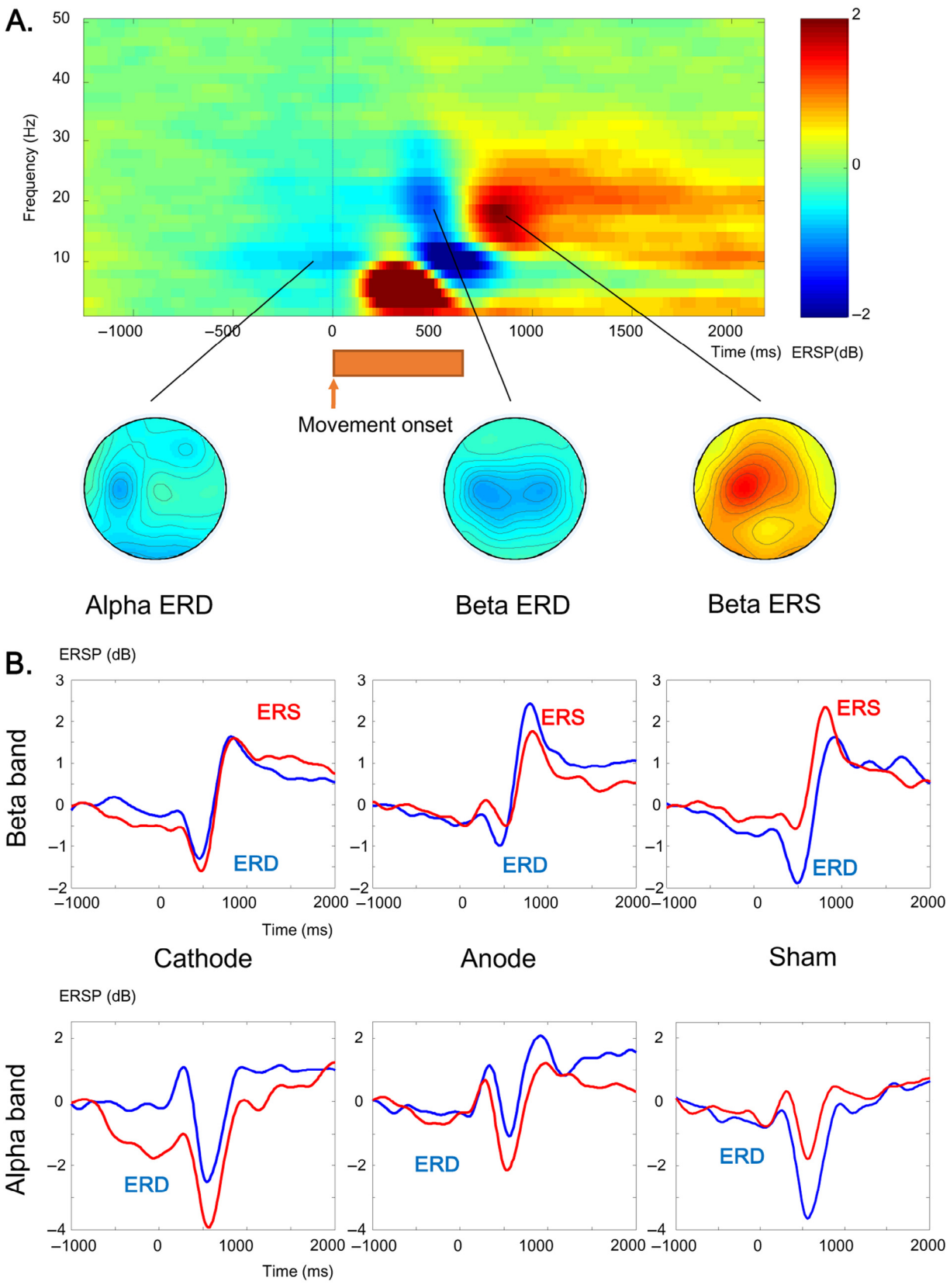

Fig. 4. The event-related spectral perturbation plot (C3) of the participants with restless legs syndrome. A. Mean event-related spectral perturbation (ERSP) values were calculated from –1500 ms to 2500 ms and displayed between 0 and 50 Hz for each task. The mean power changes were computed by averaging over all subjects. Baselines were corrected by subtracting the root-mean-square values of prestimulus intervals (–1500 to –500 ms). Time '0 ms' represents the onset time of finger movement. Alpha event-related desynchronization (ERD) can be seen at a frequency of 10–12 Hz and time of –500 to 100 ms. Beta ERD can be seen at frequency of 15–21 Hz and time of 400 to 600 ms. Beta event-related synchronization (ERS) can be seen at frequency of 15–21 Hz and time of 750 to 1000 ms. The topographic plots of alpha ERD, beta ERD, and beta ERS are shown below. B. Movement ERD and ERS at alpha/beta bands did not differ significantly between baseline (blue) and post-treatment periods (red). No significant differences in ERD or ERS were observed among the groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

600 ms), and beta ERS (15–21 Hz, 750–1000 ms). In all groups, Beta ERD followed by beta ERS were clearly evoked after finger movement. However, these signals did not differ between baseline and post-treatment periods or among the groups (Fig. 4B). Repeated measures with analysis of variance (ANOVA) demonstrated no significant effect of tDCS on alpha ERD, beta ERD, or beta ERS among the three groups (degrees of freedom [dF] = 2, F = 2.157, $p = 0.135$, dF = 2, F = 0.782, $p = 0.467$, and, dF = 2, F = 0.422, $p = 0.660$, respectively), between pretreatment and post-treatment (dF = 1, F = 0.358, $p = 0.554$, dF = 1, F = 0.046, $p = 0.832$, and dF = 1, F = 0.179, $p = 0.676$, respectively), or in 'group × treatment' interaction (dF = 2, F = 0.785, $p = 0.466$, dF = 2, F = 0.012, $p = 0.988$, and dF = 2, F = 1.032, $p = 0.369$, respectively).

3.4. Secondary outcome measures

The overall PGI responder rate at both T1 and T2 was 39%. The number of PGI responders at T1 and T2 did not differ among the three groups (Table 2). The PSQI and BDI-II at T2 (10 [7.25, 11.0] and 12.5 [8.25, 22.5], respectively) were significantly reduced after treatment versus before treatment (13 [10, 15], $p < 0.001$ and 17 [10.5, 26.5], $p = 0.019$, respectively). However, changes in PSQI and BDI-II did not differ among the three groups ($p = 0.065$ and 0.658, respectively). Medical Outcome Study (MOS) subscales also showed significant changes after treatment in all treatment groups, but did not differ among the three groups.

The acute effect of tDCS during the treatment session was also assessed using VAS and SPSD. The VAS scores of participants with RLS improved gradually during tDCS treatment (Supplementary Fig. S1); for example, the mean VAS score on day 5 (3.2 ± 2.6) was significantly reduced relative to day 1 (5.7 ± 2.3, $p = 0.025$). The change in VAS scores between day 1 and day 5 did not differ significantly among the groups. Although the two domains of "quantity of sleep" and "rested in the morning" improved significantly after tDCS treatment, none of the eight SPSD domains differed among the groups (Supplementary Table S1).

3.5. Adverse effects

No participants requested that stimulation be terminated due to adverse effects, and none needed any medical intervention during or after the tDCS. Among the participants, 43.8% experienced some adverse effects. An itching sensation was the most common adverse effect (22%), followed by pain (13%), fatigue (9%), a tingling sensation (6%), a burning sensation (6%), and headache (6%). No participant reported nervousness or difficulty in concentrating. During the second day of treatment, there was one episode of severe fatigue in a participant from the anodal group, which gradually became less severe and resulted in full recovery by the fourth day of treatment. There was no difference in the number of participants with any kind of adverse effect among the cathodal, anodal, and sham groups (36.4% vs 60% vs 36.4%, respectively; $p = 0.458$).

4. Discussion

To the authors' knowledge this is the first reported study to investigate electrical brain stimulation as a possible treatment modality for RLS. As a result, even though the mean IRLS decreased significantly three days and 13 days after the treatment, real treatment did not show any significant difference from sham treatment on primary/secondary outcomes and objective neurophysiological evidence of cortical excitability.

Based on the pathophysiology of a hyperexcitable sensorimotor cortex in people with RLS, two specific tDCS montages, known to have analgesic effects for chronic pain disorders, were investigated [38]: (1) excitability-enhancing (anodal) tDCS delivered over the primary motor cortex, and (2) excitability-diminishing (cathodal) tDCS over the somatosensory cortex. In addition, to deliver more localized stimulation, extracephalic reference electrodes were used [23]. Although an attempt was made to stimulate the leg area, by placing the electrode at Cz, this might have failed to induce polarity changes because the leg area is located more deeply compared to the cortical areas of other body parts such as arms, hands and face. The anodal stimulation used in the present study has also been studied elsewhere [18,39–41], and this montage is known to stimulate the motor cortex, thus activating the lateral thalamic area, which, in turn, inhibits the thalamic sensory neurons that are involved in the transmission of nociceptive signals from the periphery [38]. Cathodal stimulation can reduce the excitability of the somatosensory cortex by activating the motor cortex connected to the primary somatosensory cortex via cortico-cortical pathways [38]. In addition, an animal study has demonstrated increased striatal dopamine levels after cathodal stimulation [42]. However, neither of these two montages seemed to be effective in the stimulation protocol of the present study. Therefore, the present study suggests that hyperexcitability of the somatosensory cortex might be an epiphenomenon rather than primary cause of RLS.

Other studies have demonstrated that stimulation of the prefrontal cortex is associated with modulation of a large neuronal network related to the limbic system, including the cingulate gyrus and parahippocampal areas [43,44], and that tDCS stimulation of the prefrontal dorsolateral cortex increases the pain threshold in healthy subjects [45] and relieves chronic pain [46]. Moreover, previous studies have shown prefrontal dysfunctions [47] or increased activity [48] in RLS, suggesting that tDCS with electrodes located in the frontal area may play a role in treating people with RLS. In this regard, stimulation of the prefrontal cortex would be worth trying in a future study.

Efficacy was only assessed up to two weeks after tDCS treatment because the present study was a proof-of-concept trial. It has been reported that tDCS treatment can change the rate of action potential firing, resulting in an immediate effect, and may involve N-methyl-D-aspartate receptor-dependent mechanisms, leading to long-term effects [49]. A number of previous tDCS studies on depression and various pain disorders have assessed its efficacy after more than one month and up to 24 weeks after treatment [16,18,21,50–53]. Therefore, the possibility of long-term effects of tDCS in people with RLS cannot be ruled out, even though the short-term effects were not shown in the present study.

The present study's results showed that beta ERD/ERS were not affected by tDCS treatment. Although the immediate effect on these activities were not checked, the immediate effects of tDCS using VAS and SPSD were assessed, all of which did not show any significant differences among the groups. In contrast to the present study's results, a recent brain-computer interface study in healthy subjects revealed that tDCS increased beta ERD immediately after treatment [54], suggesting an immediate effect on these activities. Therefore, the lack of any changes of ERD/ERS after tDCS in the present study seems to stem from either no effect or different treatment protocols.

Another reason for the negative results in the present study might be a strong placebo effect of tDCS stimulation. The placebo effect is known to activate both dopamine and endogenous opioid peptides in the nucleus accumbens [55], which are related to treating RLS. Indeed, large placebo effects have been reported in people with RLS [56]. A recent study showed that the placebo effect is especially strong in those who are female, drug-naïve and have severe RLS, all of which were participant characteristics in the present study [57]. As in a previous study [57], these results also suggest that the baseline IRLS score seems to affect the strength of the placebo effect,

by showing that baseline IRLS scores have a negative correlation with the change in IRLS at T1. These factors may contribute to large placebo effects (–10.9 ± 5.8 at T1 and –11.0 ± 8.2 at T2) with the sham treatment. However, as objective neurophysiological parameters were also assessed, such as ERD/ERS of EEG, which showed no significant difference among groups, a placebo effect alone cannot be explained for the negative result.

This proof-of-concept study of tDCS in people with RLS has shown that the specific protocol based on the pathophysiology of hyperexcitable somatosensory cortex was ineffective. Furthermore, the small sample size of the present study precluded us from making any firm conclusions. Therefore, further studies of tDCS with larger numbers of participants and different tDCS parameters such as electrode location, session duration, number of sessions, and the duration of the follow-up period should be encouraged.

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Conflict of interest

None of the authors has indicated any financial conflict of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.07.032.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.sleep.2014.07.032.

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