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Effects of Transcutaneous Spinal Direct Current Stimulation in Idiopathic Restless Legs Patients

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ABSTRACT

Background: Transcutaneous spinal direct current stimulation (tsDCS) is a new non-invasive technique to modulate spinal cord activity. The pathophysiological concept of primary RLS proposes increased spinal excitability.
Objective: This pilot study used tsDCS to reduce pathologically enhanced spinal excitability in RLS patients and to thereby ameliorate clinical symptoms.
Methods: 20 patients with idiopathic RLS and 14 healthy subjects participated in this double-blinded, placebo-controlled study. All participants received one session of cathodal, anodal and sham stimulation of the thoracic spinal cord for 15 min (2.5 mA) each, in randomized order during their symptomatic phase in the evening. The soleus Hoffmann-reflex with Hmax/Mmax-ratio and seven different H2/H1-ratios (of two H-reflex responses to double stimuli) were measured. The RLS symptoms were assessed by a visual analogue scale (VAS). All parameters were measured before and twice after tsDCS.
Results: RLS patients showed increased H2/H1-ratios during their symptomatic phase in the evening. Application of anodal stimulation led to a decreased H2/H1-ratio for 0.2 and 0.3 s interstimulus intervals in patients. Furthermore, application of anodal and cathodal stimulation led to a reduction in restless legs symptoms on the VAS, whereas application of sham stimulation had no effects on either the VAS or on the H2/H1-ratio in patients. VAS changes did not correlate with changes of H2/H1-ratios.
Conclusions: This is the first tsDCS study in idiopathic RLS, which resulted in short-lasting clinical improvement. Furthermore, our results support the pathophysiological concept of spinal cord hyperexcitability in primary RLS and provide the basis for a new non-pharmacological treatment tool.

Introduction

The pathophysiological concept of restless legs syndrome (RLS) hypothesizes an increased spinal excitability in RLS patients [1–6]. Rijsman and co-workers [7] describe increased H2/H1-ratios (measured from two H-reflex-responses to double stimuli with different interstimulus intervals) for the interstimulus intervals of 0.4, 0.3 and 0.2 s in eight patients with RLS and one patient with Periodic Limb Movement Disorder (PLMD). This disorder is characterized by periodic limb movements (PLM) in sleep > 15/h, reduced sleep quality and the exclusion of a clinical RLS or another secondary cause.

Currently licensed dopaminergic therapy in RLS is complicated by the phenomenon of augmentation [8–11] as well as by constraining side effects of dopaminergic medication, such as impulse control disorders and weight gain [12,13]. Therefore, non-pharmacological therapeutic tools offering additional efficacy and fewer side effects may improve the therapeutical repertoire.

Anodal transcranial direct current stimulation (tDCS) of the motor cortex is a well-established non-pharmacological method to alleviate chronic pain [14–17]. A few recently published studies indicate that transcutaneous spinal direct current stimulation (tsDCS) may be a non-invasive, painless way to reduce spinal cord excitability [18–21].

Our study assessed whether the application of tsDCS could become a suitable new therapeutic tool in the treatment of RLS

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patients. We especially asked if the application of anodal tsDCS is suited to reduce the severity of restless legs symptoms and if this potential alleviation is associated with inhibitory effects on spinal pathways, as measured by decreased H2/H1-ratios for the double stimulus intervals of 0.2, 0.3 and 0.4 s.

Methods

Participants

20 patients with primary idiopathic RLS (mean age: 56.2 ± 14.9 years, 15 female, 5 male, International Restless Legs Severity Scale (IRLSS) score: 27) from the movement disorders outpatient ward at the Department of Clinical Neurophysiology at the University Medical Center in Göttingen participated. Fourteen of the 20 patients received H-reflex-measurements (mean age 53.4 ± 13.6 years, 9 female, 5 male, Table 1). The diagnosis of RLS was based on the four essential criteria defined by the International Restless Legs Syndrome Study Group [22,23]. For inclusion in the study all patients were classified as having RLS by experts (WP, CGB) in the field of RLS. All patients were also scored again on the IRLSS at the beginning of the study to assess general symptom severity. Secondary RLS (e.g. due to low ferritin, iron or B-vitamins) was excluded by neurological examination, blood tests and normal peripheral sensory and motor nerve conduction velocities. All patients had stopped their RLS medication or other CNS-affecting medication for at least five drug half-lives prior to the intervention. Since the patients mainly took low doses of medication, no tapering was required. During this off-medication period, patients took 100 mg of L-DOPA in the evening at bedtime. L-DOPA was stopped at least 24 h before and thus also more than 5 half-lives prior to the experiments [2].

The control group consisted of 14 gender- and age-matched healthy subjects (age: 52.8 ± 14.1 years, 9 female, 5 male) without CNS-affecting medication, any central or PNS disorder in their history or a family history of RLS. The controls showed a normal neurological status.

All participants gave their written informed consent. The study was approved by the ethics committee of the University of Göttingen and conforms to the standards of the Declaration of Helsinki.

Transcutaneous spinal direct current stimulation (tsDCS)

TsDCS was conducted using a protocol similar to that of tsDCS studies published recently [18,21] to allow for methodological comparability [24]. The center of the electrode determining the polarity was placed over the thoracic spinal cord about 2 cm left paravertebrally and longitudinally to the Th11 level, and the return electrode was positioned over the right supraclavicular region. Both equally sized stimulation electrodes (Krauth*Timmermann Derma-Flex, 5 cm×9 cm) were coated with EEG paste. A current strength of 2.5 mA was applied for 900 s via a Neuro Conn DC Stimulator, which resulted in a current density of 0.056 mA/cm^2 and a total delivered charge of 0.05 C/cm^2.

Sham tsDCS was achieved by turning off the stimulator after 40 s. Similar to numerous previous studies using transcranial DCS (tDCS) [16,17], the participants felt the same tingling sensation at the beginning of the stimulation [14] and, therefore, could not distinguish verum from sham stimulation, when asked after the intervention.

Visual analogue scale (VAS)

Patients were asked to rate their instantaneous restless legs symptom severity in the legs on the VAS from 0 (no symptoms) to 100 (worst symptoms ever) at all three time points (Experimental procedures, Fig. 1).

H-reflex tests

The soleus Hoffmann-reflex was measured by stimulating the tibial nerve in the popliteal fossa and recording the answers from surface electrodes on the soleus muscle. H-reflex measurements

Table 1
Demographic data of idiopathic RLS patients.

Patient	Gender	Age at onset (years)	Duration (years)	IRLSS	Family history	RLS medication with total daily dose (mg)	Years of drug use at study entry	Hours off medication prior to the assessment
1	F	30	30	28	Yes	Ropinirole 0.5	3	30
2	F	16	6	8	Yes	None	–	–
3	F	28	20	38	Yes	Ropinirole 0.5	2	30
4	M	37	6	21	Yes	Pramipexole 0.72	2.5	60
5	F	58	6	40	Unknown	Rotigotine 3	3/12	35
6	F	40	21	28	Yes	Pramipexole 0.36	6	60
7	F	46	25	22	Yes	Ropinirole 3/	4	30
						Tilidine + Naloxone 50 + 4, only 1/week	3	30
8	F	18	44	31	No	Ropinirole 3/	1/12	30
						Tilidine + Naloxone 100 + 4	1/12	30
9	F	35	10	33	Yes	Pramipexole 0.18	3	60
10	M	48	3	31	Unknown	Trazodone n a/	1½	30
						Rotigotine 3	1/12	35
11	F	58	6	23	Yes	Trazodone 25	1/12	30
12	M	32	20	24	Yes	L-DOPA 100	1	24
25	M	48	20	33	Yes	L-DOPA 100	8	24
26	M	10	27	37	Yes	Rotigotine 2/	1/12	35
						Tilidine 50	1/12	30
27	F	49	26	23	Yes	Ropinirole 2	7	30
30	F	44	25	30	Yes	Ropinirole 1.5/	2	30
						L-DOPA 100, only 2/week	10	24
31	F	63	15	27	Yes	Tilidine + Naloxone 50 + 4/	3	30
						Pregabalin 75	7	30
32	F	39	30	26	Yes	Rotigotine 2	½	35
33	F	34	18	21	Yes	Ropinirole 2/	3	30
						Tilidine + Naloxone 50 + 4	3	30
34	F	32	1,5	16	Yes	None	–	–