Neurological Sciences (2019) 40:1821–1827
https://doi.org/10.1007/s10072-019-03912-5

ORIGINAL ARTICLE

The neuromodulatory effect of tDCS in patients affected by functional motor symptoms: an exploratory study

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Received: 11 December 2018 / Accepted: 22 April 2019 / Published online: 1 May 2019

Abstract

Background Recent studies have shown how emotional and cognitive factors might combine together to determine the onset and maintenance of functional motor symptoms (FMS). Nevertheless, no studies have assessed whether brain circuits involved in regulation and processing of emotions and attention might be influenced by neuromodulation. The purpose of this study was to evaluate the effect of a single anodic tDCS session over the right posterior parietal cortex in subjects with FMS and in healthy individuals.

Materials and methods Nine patients and seven healthy subjects underwent two sessions of tDCS (real and sham), in a randomized order. At the end of each session, all participants underwent the heart beat detection task (interoceptive sensitivity) and the Posner paradigm (spatial attention).

Results After sham stimulation, patients with FMS showed significantly lower interoceptive sensitivity and greater cueing effect for reaction times at the Posner paradigm than healthy controls. There was a significant improvement between the levels of interoceptive sensitivity after real and sham stimulation in the whole group of participants and in the group of patients with FMS.

Conclusions Our study provides first indications for a neuromodulatory effect of a single anodic tDCS session over the right posterior parietal cortex on interoceptive sensitivity in subjects with FMS.

Keywords Neuromodulation · Transcranial direct-current stimulation · Functional motor symptoms · Conversion disorders

Introduction

Functional motor symptoms (FMS), which include abnormal movements (e.g., tremor, parkinsonism and dystonia) and weakness, are part of a broad spectrum of functional symptoms that are commonly diagnosed in neurological practice. Patients affected by FMS have levels of disability, distress, and healthcare usage that equal, and in some cases surpass, patients with neurodegenerative disease, yet their etiopathological mechanisms are very poorly understood [1].

Recent studies have shown how emotional (alexithymia, interoceptive sensitivity) and cognitive (attention) factors might combine together to determine the onset and maintenance of FMS [2–4]. In addition, functional neuroimaging studies have provided preliminary evidence that brain circuits involved in regulation and processing of emotions and attention (e.g., limbic system and posterior parietal cortex) might be differentially activated in individuals affected by FMS [5]. Nevertheless, no studies have assessed whether the over mentioned brain circuits might be influenced or modified by the effect of neuromodulation.

Transcranial direct-current stimulation (tDCS) is a non-invasive neuro-stimulation technique based on a weak electric stimulation (1–2 mA for 5 to 30 min) able to modulate neural activity. The increase or decrease in neuronal excitability causes an alteration of the cerebral function that can be

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exploited to improve our knowledge of the functioning of the central nervous system or eventually for therapeutic purposes [6]. Positive stimulation (anodic tDCS) results in a depolarization of the neuronal membrane potential that facilitates the start of spontaneous action potentials (excitatory effect). Negative stimulation (cathodic tDCS) leads to a hyperpolarization with inhibitory effect on the excitability. The effects persist according to the duration of the stimulation: a 10-min session generates 1-h long effects [7].

Given its mechanism of action, the therapeutic efficacy of tDCS has been proposed for a wide range of psychiatric and neurologic conditions, such as Major Depressive Disorder, Schizophrenia, and memory problems [8–10]. A recent review by Lefaucheur et al. underlined a probable efficacy of anodal tDCS for fibromyalgia, depression, and craving/addiction [11]. Some evidences have been shown also for complex regional pain syndrome and chronic pain more widely [12].

The main purpose of this exploratory study was to evaluate the neuromodulatory effect of a single anodic tDCS session over the right posterior parietal cortex in subjects with FMS and in age and gender-matched healthy individuals. Recent models of human posterior parietal cortex have variously emphasized its role in spatial perception and attention, visuomotor control, interoceptive, and exteroceptive attention [13]. We decided to use anodal stimulation to enhance activity in the posterior parietal cortex, since activity in this brain region has been previously found to be modified in patients with FMS [5]. As outcome measures, we decided to choose the heart beat detection task as a measure of interoceptive sensitivity (already shown to be reduced in patients with FMS) [3] and the Posner paradigm for the assessment of spatial attention, given its role in the pathogenesis of FMS.

Materials and methods

Subjects

Eleven consecutive right-handed patients with a diagnosis of FMS were recruited from the outpatient unit of the San Paolo Hospital in Milan, Italy. Patients were included only in the case of a clinically established diagnosis of FMS according to Fahn and Williams criteria [14]. The diagnosis was made by a neurologist and a psychiatrist based on clinical presentation and appropriate investigations. A sample of seven right-handed age-matched and sex-matched healthy subjects was recruited among members of the hospital staff and their relatives. Patients and healthy controls gave written, informed consent. Institutional ethics approval was obtained, and the experiment was conducted in accordance with the Declaration of Helsinki.

Exclusion criteria

Exclusion criteria for all subjects were (i) age less than 18 years; (ii) inability to communicate with the researcher or complete questionnaires due to language difficulties, severe learning disabilities, or dementia; (iii) any other serious neurological or medical disease; and (iv) the presence of an overlap between functional and organic movement disorders.

Assessment

The presence of depressive and anxiety symptoms was evaluated at baseline (prior the first tDCS session) respectively with the Hamilton Rating Scale for Depression (HAM-D) [15] and the Hamilton Rating Scale for Anxiety (HAM-A) [16]. The self-assessment questionnaires 20-item Toronto Alexithymia Scale (TAS-20) [17] and Self-Objectification Questionnaire (SOQ) [18] were also administered at baseline.

tDCS

All participants underwent two sessions of tDCS (one real and one sham) in a randomized order. The second session was set at least 2 days after the first one, in order to avoid carry-over effect.

tDCS was administered through a battery-driven, constant current stimulator (Newronika, Milan, Italy) using a pair of saline-soaked sponge rubber electrodes. Stimulation was applied over the right PPC (at 1.5 mA intensity for 20 min). Electrode size of the anode was 25 cm^2 (leading to 0.06 mA/cm2 current density in the real tDCS conditions), while the size of the supraorbital reference electrode/cathode was 35 cm^2 (leading to 0.04 mA/cm^2 current density in the real tDCS conditions). To allow a double-blinded study design, where both the experimenter and participant were blinded for the sham (control) condition, the latter was performed in the same way as active stimulation but with the instrument set in the "study mode": An initial 30-s real stimulation ensured that participants felt the itching or tingling sensation at the beginning of the stimulation.

Outcome measures: heart beat detection task and Posner paradigm

At the end of each tDCS session, all participants underwent the following outcome measures, in counterbalanced order:

- Heart beat detection task. Patients and healthy subjects took part in a single 15-min testing session. Heart rate was recorded with a Polar wrist worn heart rate monitor (model RS 800 CX). Participants were seated, with their wrists gently resting on the band for the heart rate monitor, which was located on a table in front of them. They were asked to silently count their own heartbeats by concentrating on their heart activity. During heart beat counting, participants were instructed to count their heartbeats by concentrating on bodily feelings without taking their own pulse or trying other physical manipulations. A 3-min baseline heart beat recording was performed after which the perception task was performed three times, for time intervals lasting 25, 45, and 65 s. In between one interval time and the next one, the subject rested for 30 s so that the testing followed this sequence: perception (25 s)–rest (30 s)–perception (45 s)–rest (30 s)–perception (65 s) [19].

- Posner paradigm. In order to test effect of tDCS on arousal or exogenous attention, an external cueing visual paradigm [20, 21] was administered, including 60 trials. At the beginning of each trial, a fixation cross appeared for 2000 ms on the center of the screen. Then, two rectangles appeared at the left and right of the fixation cross and, after a further random range of 200–700 ms, one of the two perimeters blinked for 200 ms (cue). After 100 ms, a small square appeared inside one of the two shapes (target). Subjects had to indicate as quickly and accurately as possible where the target appeared by pressing the left or right index finger one of the assigned keys on a qwerty keyboard: "F" when the target appeared to the left and "J" when to the right. Catch trials in which no target appeared were also included (12 trials). Accuracy (ACC) and response time (RTs) were then collected (Fig. 1). Cueing effect, considered an index of covert orienting attention, was computed as difference between invalid and valid cue trials in accuracy and reaction times for correct response.

After completion of the two tDCS sessions, patients and controls completed a questionnaire for possible adverse reactions during or after tDCS. No adverse reactions were reported. In addition, they were asked which stimulation condition they had perceived as (i) the weakest and (ii) the strongest (if they answered to have perceived differences in the first place). Finally, we checked if individuals became aware of the sham stimulation and could guess it correctly. Fifty percent of the subjects did not recognize the placebo session correctly when asked at the end of the experiment.

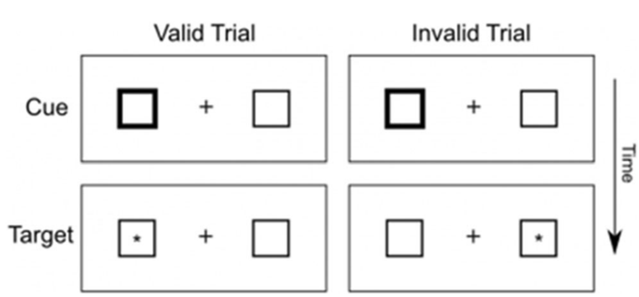

Fig. 1 The Posner paradigm

Statistical analysis

The collected data was exported to Microsoft Excel 2014®. Statistical analysis was performed using Statistical Package for Social Science (SPSS V.24). The variables were first tested for normality using the Shapiro–Wilks test. The variables that were not normally distributed ($p < 0.05$) were log10-transformed. For continuous data, a one-way analysis of variance (ANOVA) was used to test for differences across the groups. The χ^2 test was used for categorical data. ANOVA for repeated measures was used for comparisons between real and sham interoceptive sensitivity. The accuracy of heartbeat perception (termed interoceptive sensitivity, IS) was calculated as the mean score of three heartbeat perception interval according to the following transformation: 1/3 ∑ [(1 − (|recorded heartbeats − counted heartbeats| / recorded heartbeats)] [19]. Using this formula, the IS score can vary between 0 and 1, with higher scores indicating smaller differences between recorded and perceived heartbeats (i.e., more accuracy, or higher IS).

Correlations between values of interoceptive sensitivity and demographic and psychometric variables were calculated with Spearman bivariate correlation. The confidence interval considered for statistical significance was 5% ($p < 0.05$).

Results

Nine patients with FMS (eight out of nine women [88.9%], average age 48.22 years [SD 17.54]) and seven healthy controls (six out of seven women [85.7%], average age 44.86 years [SD 18.76]) were included in the analysis. Two patients were excluded as outliers since they scored more than 2 SD above the groups mean on the heart beat detection task, and there were cues that they did not follow instructions during the task. A lower level of education in patients was the only sociodemographic difference observed between the two groups (F [1] = 6.112, p = 0.013). Patients with FMS presented the following symptoms: 1/9 (11.1%) functional tremor, 1/9 (11.1%) functional dystonia, 2/9 (22.2%) functional myoclonus, 4/9 (44.4%) functional weakness, and 1/9 (11.1%) functional weakness associated to functional gait disturbances.

When examined, three patients were taking selective serotonin uptake inhibitors and four were taking benzodiazepines. None of the patients were on antipsychotic drugs. None of the healthy controls were taking psychotropic medications. For sociodemographic variables and clinical scale scores, see Table 1.

Patients with FMS obtained significantly higher scores than healthy controls both at HAM-D (F [1,14] = 5.077, p = 0.041) and at HAM-A (F [1,14] = 4.588, p = 0.048) scales.

Table 1 Socio-demographic variables and clinical scales scores. *SD* standard deviation, *FMS* functional motor symptoms, *HS* healthy subjects, *TAS-20* Toronto Alexithymia Scale, *HAM-D* Hamilton Rating Scale for Depression, *HAM-A* Hamilton Rating Scale for Anxiety, *BAQ* Body Awareness Questionnaire, *SOQ* Self-Objectification Questionnaire

	Patients with FMS ($N = 9$)	HS ($N = 7$)	p
Gender, female, n (%)	8 (88.9)	6 (85.7)	0.849
Age, years (SD)	48.22 (17.548)	44.86 (18.765)	0.717
Marital status	1 (11.1)	3 (42.9)	0.220
Single	7 (77.8)	3 (42.9)	
Married	0 (11.1)	1 (14.3)	
Divorced	1 (0.0)	0 (0.0)	
Widowed			
n (%)			
Educational level, years (SD)	8 (88.9)	2 (28.6)	*0.013*
13 years	1 (11.1)	5 (71.4)	
18 years			
n (%)			
Employment,	0 (0.0)	0 (0.0)	0.197
Unemployed	5 (55.5)	6 (85.7)	
Student/employed	4 (44.4)	1 (14.3)	
Retired			
n (%)			
TAS-20, mean score (SD)	39.44 (10.91)	35.29 (3.95)	0.356
TAS-20 < 51, n (%)	8 (88.9)	7 (100.0)	
TAS-20 52–60, n (%)	0 (0.0)	0 (0.0)	
TAS-20 > 61, n (%)	1 (11.1)	0 (0.0)	
HAM-D, mean score (SD)	14.67 (9.27)	5.14 (7.03)	*0.041*
HAM-A, mean score (SD)	11.78 (7.95)	4.14 (5.70)	*0.048*
BAQ, mean score (SD)	63.56 (21.33)	75.71 (23.65)	0.299
SOQ, mean score (SD)	− 11.33 (13.60)	− 14.14 (8.07)	0.637

Patients showed lower levels of interoceptive sensitivity than healthy controls [F [1,12] = 15.875, $p = 0.002$)] and greater cueing effect computed on reaction times in the Posner paradigm [(F [1,14] = 13.565, $p = 0.001$)] after sham stimulation. No differences between patients and controls were found after sham stimulation in terms of accuracy at the Posner paradigm (Table 2).

Our data showed a significant difference between the levels of interoceptive sensitivity after real and sham stimulation ($F = 21.87$, $p = 0.001$) in the whole group of participants. When considering the two groups separately, this difference only remained significant in patients with FMS ($F = 13.62$, $p = 0.001$) (Table 3, Fig. 2). With respect to the visual task, we did not find any significant difference between the performance after the real and the one after the sham stimulation, both in the group as a whole and in the two groups considered separately (Table 4).

After the real stimulation, we found a negative correlation between interoceptive sensitivity and (i) TAS-20 total score ($p = 0.024$, $\rho = -0.597$); (ii) HAM-D total score ($p = 0.015$, $\rho = -0.633$); and (iii) HAM-A total score ($p = 0.029$, $\rho = -0.582$). In the same condition, we also found a positive correlation between interoceptive sensitivity and the SOQ total score ($p = 0.010$, $\rho = 0.659$). No significant correlations were observed between visual attention and psychometric scales after real stimulation. No significant correlations were observed between interoceptive sensitivity or visual attention and psychometric scales after sham stimulation.

Table 2 Mean scores of interoceptive sensitivity and cueing effect (invalid-valid trials) for reaction times and accuracy at the Posner paradigm after sham tDCS stimulation. *tDCS* transcranial direct-current stimulation, *SD* standard deviation, *FMS* functional motor symptoms, *HS* healthy subjects

	Patients with FMS ($N = 9$)	HS ($N = 7$)	p
Interoceptive sensitivity post tDCS sham (SD)	0.466 (0.132)	0.697 (0.078)	*0.002*
Cueing effect (invalid-valid trials) for reaction times at the Posner paradigm post tDCS sham (SD)	143.70 (68,725)	41.81 (48.618)	*0.001*
Cueing effect (invalid-valid trials) for accuracy at the Posner paradigm post tDCS sham (SD)	− 0.04 (0,081)	− 0.04 (0.062)	0.654

Table 3 Mean scores of interoceptive sensitivity after sham and after real tDCS stimulation. *tDCS* transcranial direct-current stimulation, *FMS* functional motor symptoms, *HS* healthy subjects, *SD* standard deviation

	Interoceptive sensitivity post tDCS sham (SD)	Interoceptive sensitivity post tDCS real (SD)	*p*
Patients with FMS ($N = 9$)	0.466 (0.132)	0.672 (0.151)	*0.001*
HS ($N = 7$)	0.697 (0.078)	0.810 (0.072)	0.231
Group as a whole	0.544 (0.111)	0.724 (0.083)	*0.001*

Discussion

Here, we evaluated the neuromodulatory effect of a single anodic tDCS session over the right posterior parietal cortex in subjects with FMS and in age and gender-matched healthy individuals, using the heart beat detection task and the Posner paradigm as outcome measures.

Interoceptive sensitivity

In this study, we first replicated our previous results showing that patients affected by FMS have lower interoceptive sensitivity than healthy controls [3]. We further showed that interoceptive sensitivity might be influenced by a single anodic tDCS session over the right posterior parietal cortex in the FMS group but not in the healthy control subjects. Several complex neurobiological mechanisms that are still not well understood seem to be involved in the neuromodulatory effect of tDCS. A recent review suggested a cascade of events at the cellular and molecular levels including modulation of glutamatergic, GABAergic, dopaminergic, serotonergic, and cholinergic activity [22].

Given the role of interoceptive sensitivity in the pathophysiology of FMS and given the neuromodulatory effect of tDCS in patients with FMS (in terms of improvement of the performance on the heart beat detection task), we might also hypothesize a possible therapeutic effect of tDCS for FMS. Despite a steady growth of evidence to support transcranial magnetic stimulation (TMS) as a treatment for functional neurological disorders over the past decade [23–25], no study has been conducted to explore the therapeutic effect of tDCS in patients with conversion disorders. Overall, TMS has been shown to be a highly effective treatment for FMS. Nevertheless, it is hard to interpret data from uncontrolled case series, especially when methodologic reporting is not optimal, as the majority of available studies. In addition, given that one of the possible mechanism of action of TMS in FMS is the placebo effect, these results must be interpreted with particular caution. Future studies are needed to better investigate the role of tDCS in patients with FMS, both in terms of understanding etiological mechanisms and in terms of treatment implications.

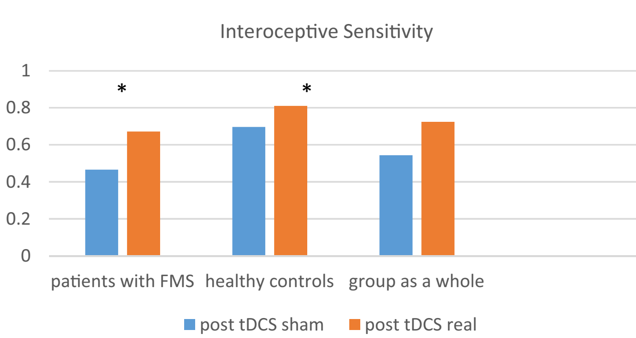

Fig. 2 Mean scores of interoceptive sensitivity after sham and after real tDCS stimulation. RT reaction time, tDCS transcranial direct-current stimulation, FMS functional motor symptoms, HS healthy subjects, SD standard deviation. * = $p < 0.05$

Spatial attention

The crucial role of attention in the aetiopathology of FMS has already been shown [26]. Clinical examination in patients with FMS reveals the role of self-directed attention in developing these symptoms: When their attention is distracted, patients affected by FMS are significantly less symptomatic [26]. On the same line, it is not difficult to provoke new symptoms and worsen the ones present during clinical examination, via enhancing self-directed attention. This phenomenon has been examined experimentally, with evidence that duration of direct visual attention towards the body during movement (e.g., looking directly at the affected limb) is significantly higher in patients affected by FMS than in patients affected by organic neurological disorders [27]. To the best of our knowledge, no previous studies have assessed spatial attention in patients affected by FMS. According to several studies, the posterior parietal cortex plays a central role in visual attention control [28].

In addition, Matthias et al. established a connection between interoceptive sensitivity and attentive performance: Healthy controls with higher levels of interoceptive sensitivity reported significantly higher scores to the visual attention task [29]. Thus, authors have hypothesized that the perception of the signals coming from within body is crucial for the processing of exogenous visual stimuli and that the processing pathways of these two different types of stimulation may be partially shared.

On these assumptions, we evaluated whether there was a significant difference between the attentional capacities of healthy controls and FMS patients and whether a single

Table 4 Mean scores of cueing effect (invalid-valid trails) for reaction times and accuracy at the Posner paradigm after sham and after real tDCS stimulation. *RT* reaction time, *tDCS* transcranial direct-current stimulation, *FMS* functional motor symptoms, *HS* healthy subjects, *SD* standard deviation

	Cueing effect (invalid-valid trials) for reaction times at the Posner paradigm post tDCS sham (SD)	Cueing effect (invalid-valid trials) for reaction times at the Posner paradigm post tDCS real (SD)	*p*	Cueing effect (invalid-valid trials) for accuracy at the Posner paradigm post tDCS sham (SD)	Cueing effect (invalid-valid trials) for accuracy at the Posner paradigm post tDCS real (SD)	*p*
Patients with FMS ($N = 9$)	143.70 (68.72)	121.38 (67.15)	0.543	− 0.04 (0.081)	− 0.05 (0.071)	0.432
HS ($N = 7$)	41.81 (48.61)	45.18 (32.37)	0.231	− 0.04 (0.062)	− 0.01 (0.030)	0.653
Group as a whole	100.54 (54.12)	86.55 (44.43)	0.645	− 0.04 (0.075)	− 0.03 (0.064)	0.431

anodic tDCS session over the right posterior parietal cortex might influence the spatial attention in the two groups. As hypothesized, our results showed that patients with FMS had greater cueing effect than healthy controls at the Posner paradigm, namely they were more influenced by exogenous cues than controls. This is in line with previous clinical and research studies which have found that patients with FMS present increased attention to exteroceptive signals about the state of the body, i.e., visual or tactile signals [30], but reduced attention to signals arising from within the body, namely to interoceptive signals [3]. According to our previous study, we hypothesized that patients with FMS may dedicate great attention to their bodily symptoms as perceived from the outside, because they have limited ability to perceive the internal states of the body and vice versa. This in line with previous research, showing patients with somatoform disorders to have reduced interoceptive sensitivity [31] and showing that improvements in cardiac awareness have been linked with reduction of distress associated with somatic symptoms in these disorders [32].

However, our data did not show an effect of tDCS on spatial attention, either in patients with FMS and in controls. This might be due to the small number of subjects included. Further studies on bigger samples are needed to better clarify this aspect.

The first limitation of this study resides in the small sample size. Second, the choice of the TAS-20 scale might be criticized: Although this is the most widely used instrument for assessing alexithymia, the use of a self-reported scale might be not appropriate, as alexithymic patients are not very self-reflective. Third, the design of our study, a cross-sectional one, does not allow direct interpretation of causality. Fourth, we did not perform a baseline assessment of interoceptive sensitivity and spatial attention.

Conclusions

Our study provides preliminary indications for a neuromodulatory effect of a single anodic tDCS session over the right posterior parietal cortex on interoceptive sensitivity in subjects with FMS. Further studies are needed to confirm this data and to explore the possible application of tDCS on patients affected by FMS also from a therapeutic angle.

Author contributions Authors' role

1. Drafting/revising the manuscript for content, including medical writing for content
2. Study concept or design
3. Analysis or interpretation of data
4. Acquisition of data
5. Statistical analysis
6. Study supervision or coordination

Funding No role of the funding source.

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflicts of interest.

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