2014•2015

FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN

master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

The effect of consecutive bihemispheric transcranial direct current stimulation on unimanual motor learning in multiple sclerosis

Promotor :
Prof. dr. Raf MEESEN

Copromotor :
Mevrouw John Ferdin Daphnie LEENUS

Talissa Vanaken

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

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KNOWLEDGE IN ACTION

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Written according to the guidelines of 'Clinical Neurophysiology':
http://www.elsevier.com/journals/clinical-neurophysiology/1388-2457/guide-for-authors

Acknowledgement

This master thesis could not have been accomplished without the support of various people. In this opportunity, I wish to offer my sincere gratitude to those who contributed to this research. First, I would like to express my great appreciation to the University of Hasselt and in particular my promotor Prof. Dr. Raf Meesen and co-promotor Dra. Daphnie J.F. Leenus for providing a continuous support, a constructive critical attitude and guidance throughout the entire course of this research. In addition, I extend my sincere thanks to Prof. Bart Van Wijmeersch and the Rehabilitation and MS Centre of Overpelt. Furthermore, I would like to thank Mr. Jan Kuppens who assisted in the recruitment of the subjects. Likewise, a special gratitude goes to all the subjects for their willingness to participate in this study. Without their great endeavor, this research could not have been completed. I would also like to give a special note of gratitude to Prof. Herbert Thijs. Without his statistical expertise, we would not have been able to finalize the data-analysis. Moreover, I would like to thank my parents for giving me the opportunity to attain my master's degree. In particular, I would like to offer a special gratitude to my mother for her unimaginable caring support on any moment of any day. Also, I would like to express my thankfulness to my brother for his encouraging support and the distracting sportive activities which we performed together. Last but not least, I thank my partner, Dimitri, for providing valuable advice and for standing behind me during the entire process of this research.

Maaseik, June 2015 V.T.

Research context

Over the last decades transcranial direct current stimulation (tDCS) has become a promising adjuvant instrument in the domain of neuro-rehabilitation. This non-invasive brain stimulation technique has the potential to modulate the corticospinal excitability of the human motor cortex (Nitsche & Paulus, 2000). Furthermore, it is able to facilitate unimanual motor function in healthy individuals (Goodwill, Reynolds, Daly, & Kidgell, 2013; Matsuo et al., 2011) and individuals with neurological disorders such as stroke (F. Hummel et al., 2005; F. C. Hummel et al., 2006) and Parkinson's Disease (Fregni et al., 2006). Interestingly, it has been proven that a bihemispheric combination of anodal tDCS and cathodal tDCS induces an additive effect on unimanual motor learning compared to a unihemispheric tDCS montage (Karok & Witney, 2013; Mordillo-Mateos et al., 2012; Vines, Cerruti, & Schlaug, 2008). However, investigations of tDCS in a population with multiple sclerosis (MS) remain scarce. To date no research has investigated the effect of this bihemispheric tDCS montage on unimanual motor learning in MS patients. Therefore, the following research question was proposed for this study: "Does consecutive bihemispheric tDCS have a beneficial effect on unimanual motor learning in MS patients?".

This research is situated within the Ph.D. project of Dra. Daphnie J.F. Leenus, entitled "Does tDCS improve the motor functions and abilities of neurodegenerative patients?". Within this project the effect of tDCS has been investigated on three different types of motor tasks: a multi limb coordination task, a switching task and a circuit task. This dissertation investigated the effect of consecutive bihemispheric tDCS on motor learning during a circuit task in MS patients. My personal contribution during this research process consisted of the installation of the programs, the setting of the tasks based on a pilot study of healthy volunteers and writing a programming-manual of the tasks. I also contributed to the determination of the method of stimulation, in particular the stimulation area and the bihemispheric electrode montage based on a literature search. I helped with the experiment at the 'Rehabilitation and MS Centre of Overpelt. Because the data-analysis of the circuit task could not have been analyzed by myself due to complex statistical analyses not incorporated in our education, this has been conducted by Prof. Dr. Herbert Thijs. I independently analyzed the secondary outcome measures and accomplished the academic writing of this master thesis under supervision of Prof. Dr. Raf Meesen and Dra. Daphnie J.L.

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Highlights

- Bihemispheric tDCS seemed to have an additive effect on unimanual motor learning in both healthy and stroke population, however its effect in MS is unknown.
- We investigated the effect of a single session of consecutive bihemispheric tDCS over the primary motor cortex (M1) on the total time parameter in a circuit task in MS patients.
- Bihemispheric tDCS over M1 induces an inferior improvement in total time performance of the circuit task in MS patients compared to sham tDCS.

Abstract

Objective: The present study investigated the effect of consecutive bihemispheric tDCS over the primary motor cortex (M1) on unimanual motor learning in MS patients.

Methods: Twelve MS patients participated in a pseudo-randomized, sham controlled, double blinded cross-over design. The motor learning of the non-dominant hand was evaluated during a circuit task before, during and 20 minutes after bihemispheric or sham tDCS. The 'total time', defined as the time needed to finish a complex circuit, was measured. Anodal tDCS was applied over the non-dominant M1 region and cathodal tDCS was applied over the dominant M1 region. The consecutive stimulation was conducted by two test batteries of 30 minutes, each divided in 3 repetitions of 10 minutes of tDCS.

Results: Data-analysis indicated that the total time performance significantly improved in both bihemispheric tDCS and sham tDCS. However, a significant difference was established between both stimulation conditions, indicating that sham tDCS led to a superior positive evolution in total time performance compared to bihemispheric tDCS. However, a significant difference in total time performance was observed at baseline.

Conclusion: The current study suggests that consecutive bihemispheric tDCS on M1 induces a significant inferior improvement on unimanual motor learning in MS patients. However, the results should be interpreted carefully due to a significant difference at baseline.

Keywords: tDCS, multiple sclerosis, primary motor cortex, motor learning, motor function, interhemispheric inhibition

1 Introduction

Multiple sclerosis (MS) is a common neurological disorder with a prevalence rate of 87.9 per 100,000 habitants in Flanders (Pugliatti et al., 2006; van Ooteghem, D'Hooghe, Vlietinck, & Carton, 1994). It involves a chronic autoimmune inflammatory disease in which the immune system destructs the myelin sheath of the neurons in the central nervous system. Damage of the neurons causes a delayed conduction of the nerve signals leading to various clinical manifestations including deficits in motor function (Compston & Coles, 2002). Therefore, motor activities will be performed slower and less accurate (Longstaff & Heath, 2006; Tomassini et al., 2012). Interestingly, over the past decades new brain stimulation therapies such as transcranial direct current stimulation (tDCS) have been established in the domain of neuro-rehabilitation.

TDCS is a non-invasive brain stimulation technique in which low amplitudes of electrical direct currents are applied to specific regions of the cerebral cortex by using external scalp electrodes. Moreover, given its polarity-dependent characteristics, it has the potential to modulate the corticospinal excitability in a specific direction. In particular, anodal tDCS induces a facilitation of the corticospinal excitability, while cathodal tDCS is able to decrease the corticospinal excitability (Nitsche & Paulus, 2000). An enhancement of the cortical excitability of M1 produced by anodal tDCS seems to be related to implicit motor learning (Nitsche et al., 2003). The underlying mechanism of motor learning is presumed to rely on the neurotransmitter γ-amino butyric acid (GABA), which affects the plasticity of the motor cortex. Interestingly, tDCS over M1 can reduce the concentration of GABA in the motor cortex (Orban de Xivry et al., 2011; Stagg et al., 2009) whereupon strengthening of the synaptic connection will be induced as a result of a mechanism related to long term potentiation (LTP), the cellular basis of learning (Stagg & Nitsche, 2011).

Until now, tDCS has already been applied to facilitate motor function in healthy young individuals (Boggio et al., 2006; Matsuo et al., 2011; Schambra et al., 2011), in an elderly population (Goodwill et al., 2013; F. C. Hummel et al., 2010; Zimerman et al., 2013) and patients with neurodegenerative diseases such as Parkinson's Disease (Fregni et al., 2006) and stroke (Fregni et al., 2005; F. Hummel et al., 2005; F. C. Hummel et al., 2006; Lefebvre, Laloux, et al., 2012; Lefebvre et al., 2014). Unfortunately, research investigating the influence of tDCS on motor performance in a MS population is limited. However, it is supposed that tDCS has the ability to modulate the corticospinal excitability in M1 in MS. Hence, tDCS could have the potential to affect motor function and facilitate motor recovery in MS patients (Cuypers et al., 2013). Evidence suggests that MS patients are still able to learn new motor skills with training because of preserved brain plasticity (Tomassini et al., 2011). Furthermore, through fMRI an imbalance in the interhemispheric interaction has been observed in MS patients during the performance of a unimanual motor task. In a healthy population, the ipsilateral motor cortex should be inhibited while the contralateral motor cortex should be activated when performing a unimanual motor task. In a MS population, a similar cortical activation is observed in the contralateral motor cortex, whereas a reduced inhibition in the homologue ipsilateral motor region is detected. This interhemispheric imbalance is supposed to be associated to atrophy in the corpus callosum (CC), the principal tract connecting both hemispheres (Manson, Palace, Frank, & Matthews, 2006; Manson et al., 2008).

Similarly, a compromised interhemispheric interaction is observed in stroke patients during unimanual motor performance (Murase, Duque, Mazzocchio, & Cohen, 2004).

Interestingly, a bihemispheric tDCS montage seems to have an additive effect on unimanual motor performance compared to unihemispheric tDCS in healthy subjects (Karok & Witney, 2013; Mordillo-Mateos et al., 2012; Vines et al., 2008). Furthermore, superior beneficial results were also demonstrated in stroke patients when placing the anodal electrode over the M1 region ipsilesional to the executive hand and a cathodal electrode over the contralateral M1 region. This suggests that bihemispheric tDCS could rebalance the deregulated interhemispheric interaction (Lefebvre et al., 2015; Lefebvre, Laloux, et al., 2012; Lefebvre et al., 2014; Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010). Therefore, bihemispheric tDCS seemed to be the pre-eminent application to induce a superior level on unimanual motor performance. Hence, we assume that bihemispheric tDCS applied to a MS population would elicit improvements in unimanual motor function. In addition to this, Bastani et al. proposed that the lasting effect could be prolonged by means of repeated shorter anodal tDCS applications instead of a single long application (Bastani & Jaberzadeh, 2014; Monte-Silva et al., 2013).

Remarkably, up to date there are no studies evaluating the effect of bihemispheric tDCS application on unimanual motor learning in a MS population as an attempt to rebalance the interhemispheric dysregulation. The aim of this study was to evaluate the influence of a consecutive bihemispheric tDCS intervention on unimanual motor training in MS patients. Therefore, we hypothesized that consecutive bihemispheric tDCS over M1 would induce a superior level of unimanual motor performance in a MS population compared to sham tDCS.

2 Methods

2.1 Participants

Twelve MS patients participated in this study (9 female, 3 male; aged 24 to 69 years; mean age: 47.92 ± 12.25 years) identified by relapsing-remitting MS (RMMS). Expanded Disability Status Scale (EDSS) ranged between 1.5 and 4.0 (mean EDSS: 2.58 ± 0.85). The patients were recruited at the Rehabilitation and MS Centre of Overpelt. They were included based on several inclusion and exclusion criteria. Inclusion in this study required an EDSS score between 1.5 and 4.5; ≥18 years and no exacerbation in the previous three months. Furthermore, the subjects were screened for contra-indications to rTMS/tDCS (Auvichayapat & Auvichayapat, 2011; Wassermann, 1998). Initially, twenty MS patients entered this study of which five patients were excluded based on the exclusion criteria and three patients discontinued the study because of sickness and unavailability. The Edinburgh Handedness Inventory (Oldfield, 1971) was used to asses for handedness. Eleven patients were right-handed (mean lateralization quotient (LQ; 81.18 ± 23.11), one patient was extremely left-handed (LQ: -100). Furthermore, patients were asked which hand they experienced as the most motor impaired. Neurocognitive functions were assessed using the Symbol Digit Modality Test (SDMT; mean score 37.08 ± 11.07). Three MS patients achieved a score more than -2 standard deviations below the normative data in healthy adults (Centofani, 1975). Table 1 summarizes the detailed patient characteristics. Before participating in this study, all the subjects signed a written informed consent. The study was conducted in accordance to the Declaration of Helsinki and was approved by the Local Ethics Committee of the University of Hasselt.

Table 1
Patient characteristics

ID	Sex	Age	MS type	EDSS	LQ	MMIH	SDMT	Normative SDMT
1	F	47	RRMS	3	100	R	27	46.8 ± 8.4
2	M	35	RRMS	3	- 100	R	26	51.1 ± 8.1
3	M	60	RRMS	4	100	R	44	41.5 ± 8.6
4	F	46	RRMS	2	29.4	L	42	46.8 ± 8.4
5	F	45	RRMS	1,5	80	R	61	46.8 ± 8.4
6	F	38	RRMS	3	86.7	L	43	51.1 ± 8.1
7	M	59	RRMS	1,5	80	R	39	41.5 ± 8.6
8	F	46	RRMS	4	47.4	L	46	46.8 ± 8.4
9	F	69	RRMS	2	100	R	22	37.4 ± 11.4
10	F	24	RRMS	2,5	89.5	L	37	55.2 ± 7.5
11	F	57	RRMS	2,5	100	L	28	41.5 ± 8.6
12	F	49	RRMS	2	80	R	30	46.8 ± 8.4

F = female; M = male; EDSS = Expanded Disability Severity Scale; LQ = lateralization quotient; RRMS = relapsing-remitting multiple sclerosis; MMIH: Most motor impaired hand; SDMT = Symbol Digit Modalities Test.

2.2 Experimental design

The study was a pseudo-randomized, sham controlled, double blinded cross-over design. Each patient received bihemispheric tDCS or sham tDCS, in which the order of the two experimental sessions was counterbalanced. Both sessions were separated by a washout period of at least 48 hours based on the method of the preliminary studies of Bastani and Jaberzadeh (Bastani & Jaberzadeh, 2013, 2014) (Fig.1). Each session was conducted in the following manner: 1) a 'familiarization' block to become habituated to the circuit task (5'); 2) the 'baseline' including the performance of the circuit task without stimulation (10'); 3) The 'first test battery', comprising a total of 30 minutes of training the circuit task, was divided in 3 repetitions of 10 minutes of training and 5 minutes of rest in-between (10'-5'-10'-5'-10'); 4) the 'second test battery' followed the same procedure as the first test battery (10'-5'-10-'5'-10'). During the two test batteries, the subjects were receiving bihemispheric or sham tDCS, while simultaneously performing the circuit task with the non-dominant hand. At last, the 'retention block' was conducted which consisted of the performance of the circuit task with the non-dominant hand without stimulation (10') (Fig.2).

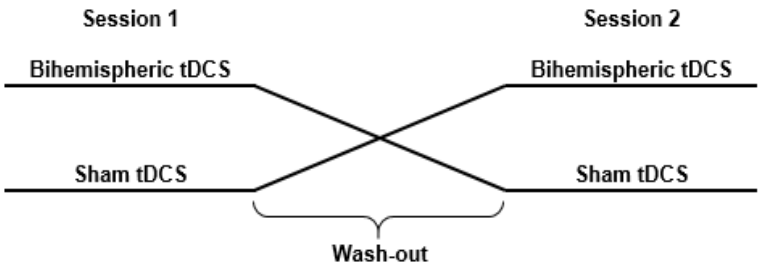


Fig. 1. Cross-over design
Both sessions were separated by a washout period of at least 48 hours.

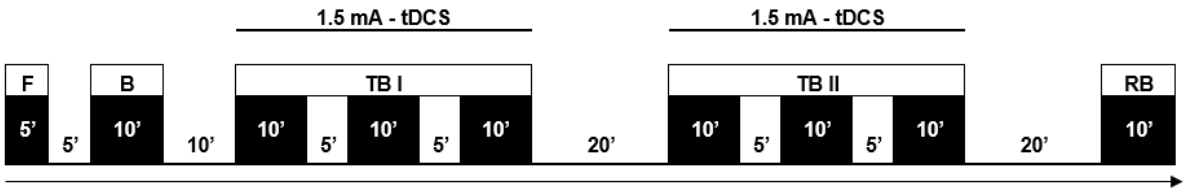


Fig. 2. Experimental design
F = Familiarization; B = Baseline; TB I = Test battery 1; TB II: Test battery 2; RB: Retention Block.

2.3 Transcranial direct current stimulation (tDCS)

Subjects received consecutive bihemispheric tDCS (HDCstim, Newronika, Italy) or sham tDCS, randomly separated over two experimental sessions. Two saline-soaked ([NaCl] 0.9%) sponge electrodes (35 cm^2, current density: 0.04 mA/cm^2) covered with an electrophysiological gel, were bilaterally placed over the left and the right M1. The localization of both M1 regions was determined according to the International 10/20 Electroencephalogram (EEG) System, in which position C3 and C4 corresponds to respectively the left M1 and the right M1 region (DaSilva, Volz, Bikson, & Fregni, 2011) (Fig. 3). The anode electrode was placed over M1 contralateral to the non-dominant hand and the cathode electrode over M1 ipsilateral to the non-dominant hand. TDCS was repetitively applied during the two test batteries of the experimental design using a current intensity of 1.5 mA (Fig. 2). A current intensity between 1-2 mA is considered to be safe (Brunoni et al., 2011; Nitsche et al., 2008). Sham tDCS was conducted with the same electrode montage as in the bihemispheric tDCS condition but the stimulation was only ramped-up for the first 30 seconds, after which the stimulation was turned off. This mimics the initial tDCS associated sensations in order to blind the subject to the stimulation condition (Gandiga, Hummel, & Cohen, 2006; Paulus, 2011).

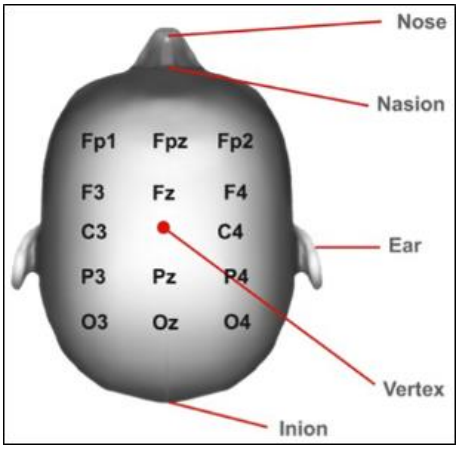


Fig 3. C3/C4 (left/right M1) location of the 10/20 EEG System (DaSilva et al., 2011).

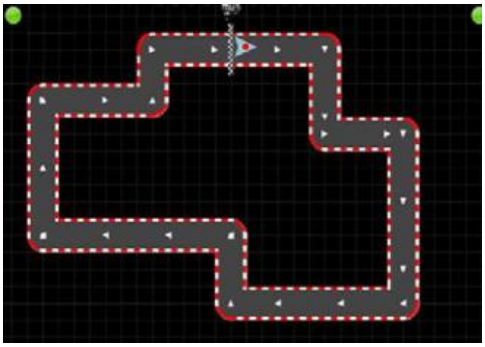


Fig. 4. Circuit task: illustration of one circuit (Lefebvre, Dricot, Gradkowski, Laloux, & Vandermeeren, 2012).

2.4 Circuit task

The circuit task is a complex visuomotor learning task, in which both speed and accuracy are taken into account to evaluate motor learning. The circuit task has been described previously by Lefebvre et al. (Lefebvre, Dricot, et al., 2012; Lefebvre, Laloux, et al., 2012) (Fig. 4). The subjects were seated upright in an armless chair in front of a computer screen. They were instructed to navigate the computer mouse on the desk with their non-dominant hand to move the cursor as accurately and quickly as possible along ten different circuits, displayed on the computer screen. Patients were given 30 seconds to finish

each circuit alternating with 30 seconds of rest. During rest, a feedback video of the previous performance of each circuit was presented. In this manuscript, the speed represented as 'total time' was measured. 'Total time' is defined by the time needed to finish a complex circuit. The accuracy of the task performance is subjected to the master thesis of a colleague student.

2.5 Visual analogue scales

The visual analogue scale (VAS) for the level of fatigue (0 = highest level of fatigue; 10 = no fatigue) and attention (0 = no attention; 10 = highest level of attention) were administered to evaluate whether a confounding influence existed on motor learning of the subjects. During each session, the level of fatigue and attention were evaluated six times: before baseline (VAS 1); after the first test battery (VAS 2); before and after the second test battery (VAS 3 and VAS 4) and before and after the retention block (VAS 5 and VAS 6). The VAS for pain, stress and illness were assessed by a colleague student in a different master thesis.

2.6 Statistical analysis

2.6.1 Primary outcome measures

The statistical analysis of the primary outcome measure 'total time' has been conducted by CenStat. Total time is defined as the amount of time needed to finish each circuit within the provided time of 30 seconds. A p-value ≤ 0.05 was considered to be statistically significant.

2.6.2 Secondary outcome measures

The analysis of the data was accomplished using IBM SPSS Statistics 22.0. To observe the evolution of the parameters attention and fatigue, the Friedman Anova Test was performed. This non-parametric test included all six VAS time points (VAS 1-6) for each parameter, separately for the active tDCS and the sham condition. Furthermore, the Wilcoxon Signed Rank Test was used to perform multiple pairwise comparisons between each combination of the six VAS time points for fatigue and attention. This was also performed separately for the active tDCS and the sham condition. The level of significance was set at 5%, a p-value (two tailed) ≤ 0.05 was considered to be statistically significant. Post-hoc correction for multiple comparisons was carried out using the Bonferroni correction. Additionally, to evaluate for differences in the parameters attention and fatigue at each VAS time point between both stimulation conditions, the Wilcoxon Signed Rank Test was used.

3 Results

3.1 Primary outcome measures

Baseline values significantly differed for total time between bihemispheric tDCS and sham tDCS (Tot_time_b $p < 0.0001$). Remarkably, at baseline the bihemispheric tDCS group performed better (mean total time: ± 22 sec.) in comparison to the sham group (mean total time: ± 23.5 sec.). A significant positive evolution in total time was established for both stimulation conditions at the end of the session in comparison to the baseline (TIME $p < 0.0001$). A significant difference in total time was observed between bihemispheric tDCS group and sham tDCS (STIM $p < 0.0014$), indicating that the sham tDCS group improved superiorly towards the bihemispheric stimulation group in total time. The evolution in time was influenced by the total time at baseline (TIME*tot_time_b $p < 0.0001$). The total time needed to finish a circuit at baseline differed between both stimulation conditions (Tot_time_b*STIM $p < 0.0001$). The interaction between time and stimulation demonstrated no significant effect (TIME*STIM $p = 0.2935$) (Fig. 5). Table 2 demonstrates the data-analysis of the mean total time.

Table 2
Data-analysis of mean total time.

Effect	p-value
TIME	<.0001*
STIM	0.0014*
TIME*STIM	0.2935
Tot_time_b	<.0001*
TIME*tot_time_b	<.0001*
Tot_time_b*STIM	<.0001*

*indicates p-value ≤ 0.05

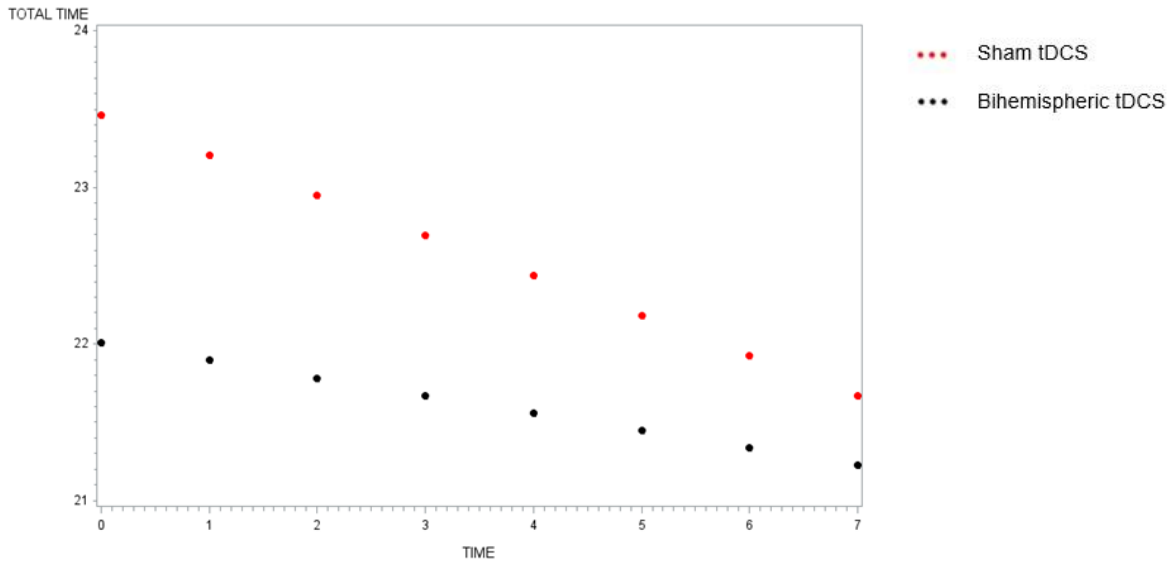


Fig. 5. Graphical representation of the evolution in mean total time (all circuits) during both sessions (sham/bihemispheric tDCS).

3.2 Secondary outcome measures

3.2.1 *Bihemispheric tDCS*

The Friedman Anova Test demonstrated no significant changes for VAS for attention ($p = 0.090$) and VAS for fatigue ($p = 0.707$) between the 6 VAS time points (VAS 1-6). In contrast, the Wilcoxon Signed Rank test showed a significant difference for the pairwise comparisons in the VAS for attention between VAS 1+2 ($p = 0.040$), VAS 1+4 ($p = 0.043$) and VAS 4+5 ($p = 0.012$), in which a significant decline is observed between VAS 1+2 (mean: 5.28; 4.85) and VAS 1+4 (mean: 5.38; 4.53). On the contrary the comparison between VAS 4+5 (mean: 4.53; 5.47) improved significantly. The remaining pairwise comparisons revealed no significant differences in level of attention ($p > 0.05$). Likewise, the pairwise comparisons for the level of fatigue did not reveal any significant differences ($p > 0.05$) (Fig. 6). A detailed presentation of the mean VAS scores and p-values are summarized in respectively table 3 and table 4A. However, post-hoc analysis indicated no significant changes for the level of attention and fatigue in the bihemispheric tDCS condition (all, $p > 0.0033$ after Bonferroni correction).

3.2.2 *Sham tDCS*

The Friedman Anova Test revealed significant differences for VAS for fatigue ($p = 0.050$) but not for VAS for attention ($p = 0.193$) between the six VAS time points (VAS1-6). However, the Wilcoxon Signed Rank Test for the pairwise comparisons obtained a significant decrease between VAS 1+4 (mean: 6.35; 5.30) for VAS for attention ($p = 0.044$) and between VAS 5+6 (mean: 5.59; 4.80) for VAS for fatigue ($p = 0.009$). All other pairwise comparisons for the level of attention and fatigue did not differ significantly ($p > 0.05$) (Fig. 6). A detailed presentation of the mean VAS scores and p-values are summarized in respectively table 3 and table 4A. However, post-hoc analysis indicated no significant changes for the level of attention and fatigue in the sham tDCS condition (all, $p > 0.0033$ after Bonferroni correction).

3.2.3 *Bihemispheric tDCS vs. sham tDCS*

The Wilcoxon Signed Rank Test showed only a significant difference in attention between both stimulation conditions at the time point of VAS 1 and at the time point of VAS 2. Neither significant differences were obtained for attention between the time point of VAS 3, VAS 4, VAS 5 and VAS 6, nor for fatigue between all the six VAS time points (Table 4B).

Table 3
Visual analogue scale. Data summarizes the mean ± SD for the six VAS time points between both stimulation conditions.

A. mean ± SD VAS for attention

	VAS 1	VAS 2	VAS 3	VAS 4	VAS 5	VAS 6
Bihemispheric tDCS	5.38 ± 2.15	4.85 ± 1.94	5.06 ± 2.07	4.53 ± 1.86	5.47 ± 2.27	5.17 ± 2.59
Sham tDCS	6.35 ± 2.00	5.88 ± 2.12	5.57 ± 2.40	5.30 ± 2.61	5.72 ± 2.31	5.43 ± 2.61

B. mean ± SD VAS for fatigue

	VAS 1	VAS 2	VAS 3	VAS 4	VAS 5	VAS 6
Bihemispheric tDCS	4.64 ± 2.07	4.63 ± 2.29	4.82 ± 2.32	4.63 ± 2.48	5.10 ± 2.31	4.83 ± 3.08
Sham tDCS	5.89 ± 2.50	5.43 ± 2.46	5.58 ± 2.37	5.01 ± 2.77	5.59 ± 2.44	4.80 ± 2.80

Table 4
P-values for VAS for attention and fatigue.
A. Between the six VAS time points separately for each parameter.

	Bihemispheric tDCS		Sham tDCS	
	Attention	**Fatigue**	**Attention**	**Fatigue**
VAS 1+2+3+4+5+6	p = 0,090	p = 0,707	p = 0,193	p = 0,050*
VAS 1+2	p = 0,040*	p = 0,715	p = 0,089	p = 0,531
VAS 1+3	p = 0,176	p = 0,807	p = 0,275	p = 0,458
VAS 1+4	p = 0,043*	p = 0,864	p = 0,044*	p = 0,195
VAS 1+5	p = 0,713	p = 0,256	p = 0,105	p = 0,837
VAS 1+6	p = 0,849	p = 0,748	p = 0,064	p = 0,107
VAS 2+3	p = 0,624	p = 0,604	p = 0,432	p = 0,607
VAS 2+4	p = 0,413	p = 0,435	p = 0,206	p = 0,436
VAS 2+5	p = 0,144	p = 0,480	p = 0,258	p = 0,718
VAS 2+6	p = 0,557	p = 0,814	p = 0,287	p = 0,067
VAS 3+4	p = 0,106	p = 0,457	p = 0,465	p = 0,226
VAS 3+5	p = 0,426	p = 0,577	p = 0,848	p = 0,879
VAS 3+6	p = 0,782	p = 0,943	p = 0,346	p = 0,055
VAS 4+5	p = 0,012*	p = 0,183	p = 0,240	p = 0,065
VAS 4+6	p = 0,240	p = 0,501	p = 0,752	p = 0,197
VAS 5+6	p = 0,717	p = 0,846	p = 0,435	p = 0,009*

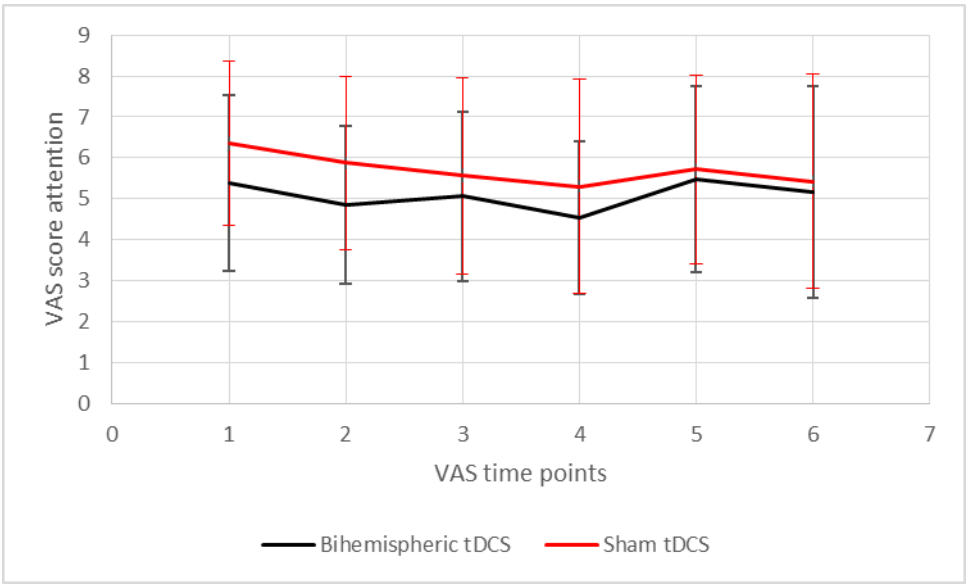
*****indicates p-value ≤ 0.05; VAS 1+2+3+4+5+6: Friedman Anova; 15 pairwise comparisons: Wilcoxon Signed Rank Test, no significant differences for the level of attention and fatigue after Bonferroni correction (all ≤ 0.0033).

B. At the same VAS time points between bihemispheric tDCS and sham tDCS.

	Attention	Fatigue
VAS 1	0.050*	0.118
VAS 2	0.010*	0.081
VAS 3	0.275	0.233
VAS 4	0.233	0.400
VAS 5	0.865	0.481
VAS 6	0.492	0.831

*****indicates p-value ≤ 0.05; Wilcoxon Signed Rank Test

A.



B.

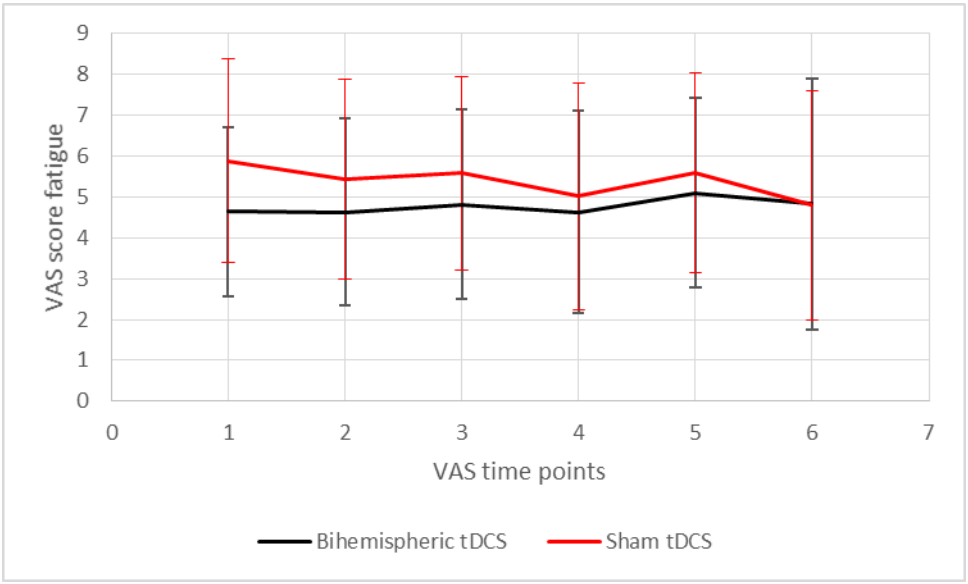


Fig. 6. Illustration of the evolution in mean VAS scores (A) for attention; (B) for fatigue for bihemispheric tDCS and sham tDCS.

4 Discussion

This current study aimed to investigate whether consecutive bihemispheric tDCS could influence unimanual motor learning in a MS population. Both bihemispheric tDCS and sham tDCS significantly improved in total time performance. However, the results revealed a superior improvement in the sham condition in comparison to bihemispheric tDCS. These results could be due to several factors. Therefore, the undermentioned potential reasons need to be taken into consideration.

4.1 Baseline differences

Noteworthy, a significant difference in baseline was established between both stimulation conditions, whereas the bihemispheric tDCS group performed better compared to the sham tDCS group. Several causes could be responsible for the presence of the different baseline values between both groups. Firstly, it could be due to the relatively small sample size, whereupon potential outliers in task performance may interfere with the results. Secondly, because both stimulation conditions were performed on different days and different moments (morning versus afternoon), it could be possible that psychophysical data such as the level of fatigue, attention, pain, motivation or other confounding factors vary between both stimulation conditions. In this study the level of fatigue and attention has been analyzed. A significant difference in attention during the first and second epochs has been found between both stimulation groups. Thirdly, the experiment was conducted during summertime in the MS Centre of Overpelt in an experimental room without air-conditioning. At this respect, it is worth noting that MS patients could perceive an aggravation of their symptoms when exposed to warm environmental temperatures (Simmons, Ponsonby, van der Mei, & Sheridan, 2004). In an explorative study of Flensner et al., it has been documented that 58% of the MS patients reported to be heat sensitive which induced worsening of the symptoms such as difficulties in concentration, paresthesia or an increased level of fatigue or pain. Moreover, 70% of heat sensitive MS patients reported to prefer a room temperature below 20°C (Flensner, Ek, Soderhamn, & Landtblom, 2011). Therefore, it is not inconceivable that it may have influenced the results of the present study due to inconsistent room temperatures. It is important to note that data-analysis showed that the evolution in total time was influenced by the mean total time score at baseline. The bihemispheric tDCS group performed better at baseline, but improved inferiorly in comparison to the sham tDCS group. Therefore, on the one hand we could speculate that the active tDCS condition had an inferior effect on motor learning. On the other hand did the bihemispheric group perform better at baseline, it could be speculated that this was the reason for a smaller growth-potential due to a possible ceiling effect in motor learning. However, these findings should be interpreted very cautiously.

4.2 Bihemispheric tDCS

In the present study we preferred to use a bihemispheric electrode montage, applying anodal tDCS over the non-dominant hemisphere and cathodal tDCS over the dominant hemisphere while simultaneously training a unimanual motor task with the non-dominant hand. This method of electrode placement has been demonstrated to induce an additive effect on unimanual motor learning compared to

unihemispheric tDCS in healthy subjects (Karok & Witney, 2013; Mordillo-Mateos et al., 2012; Vines et al., 2008). Additionally, in neurological diseases such as stroke and MS, an interference in interhemispheric inhibition during unimanual movements is observed (Manson et al., 2006; Manson et al., 2008; Murase et al., 2004). Furthermore, it has been proposed that bihemispheric tDCS induces a superior improvement in unimanual motor performance in stroke patients, likely by restoring the interhemispheric imbalance (Lefebvre et al., 2015; Lefebvre, Laloux, et al., 2012; Lefebvre et al., 2014; Lindenberg et al., 2010). Therefore, we expected that bihemispheric tDCS applied to a MS population would superiorly improve the unimanual motor function. Nevertheless, the current study demonstrated an inferior effect on motor learning in the bihemispheric tDCS intervention compared to the sham condition. These findings could be explained by several hypotheses. First, although beneficial results of bihemispheric tDCS were reported in healthy subjects and stroke patients (Karok & Witney, 2013; Lindenberg et al., 2010; Mordillo-Mateos et al., 2012; Vines et al., 2008), it is not clear whether these findings are transferable to a MS population. In fact, in MS multiple lesions affect the brain or the spinal cord at different locations (Compston & Coles, 2002), whereas stroke is characterized by a focal brain lesion (Sacco et al., 2013). Moreover, a discrepancy is seen in the response to inhibitory stimulation in severe stroke patients. In this regard, evidence shows that suppressive stimulation to the contralesional M1 aggravated the function of the paretic upper limb in severe stroke patients (Ackerley, Stinear, Barber, & Byblow, 2010; Bradnam, Stinear, Barber, & Byblow, 2012). Furthermore, it has been observed that the paretic upper limb function improved in mildly impaired stroke patients by applying cathodal tDCS to the contralesional M1 region but deteriorated in moderate to severely impaired stroke patients (Bradnam et al., 2012). Therefore, given the multifocal lesions in the CNS in MS (Compston & Coles, 2002) it could be speculated that inhibitory stimulation might have an deleterious influence on the motor learning effect in MS patients dependent on the extent of the lesions. In addition, Ferrucci et al. investigated the effect of bilateral anodal tDCS on the fatigue level and found that 65% of the MS patient improved due to tDCS while 35% did not respond to the stimulation (Ferrucci et al., 2014). Furthermore, in a study of Saiote et al., the effect of anodal tDCS over the dorsolateral prefrontal cortex (DLPFC) was investigated on the fatigue level in MS patients. Although the results were not altered by tDCS, they did find a correlation between the response to tDCS and the lesion load in the prefrontal cortex. Patients with a higher lesion load responded positively to tDCS (Saiote et al., 2014). Therefore, in attempt to restore the interhemispheric imbalance, the protocol of applying cathodal or bihemispheric tDCS must be tailored individually to MS patients. At last, in this manuscript only the total time of the task performance was investigated. Therefore, bihemispheric tDCS could possibly elicit another effect on the accuracy of the motor performance, which has been analyzed by a colleague student.

4.3 Stimulation protocol

To date, the stimulation protocols used in the MS population are not consistent. Based on the evolution in total time, the current study demonstrated that bihemispheric tDCS improved inferiorly on unimanual motor learning compared to sham. In this respect, based on previous tDCS studies in a MS population (Ferrucci et al., 2014; Mori et al., 2010; Mori et al., 2013; Tecchio et al., 2014), it could be hypothesized that multiple sessions on several consecutive days are required to obtain a beneficial effect of the

stimulation. In studies of Ferrucci et al. and Mori et al., they conducted tDCS for five consecutive days to investigate the influence respectively on fatigue score and tactile sensation in MS population. They found a significant beneficial effect after five days of stimulation (Ferrucci et al., 2014; Mori et al., 2013). In another study of Mori et al., a significant difference was observed after the third day of stimulation on neuropathic pain in MS (Mori et al., 2013). This study evaluated for a summation effect in a single session by conducting repetitive short tDCS applications instead of a continuous long tDCS application (Bastani & Jaberzadeh, 2014; Monte-Silva et al., 2013). Furthermore, a diversity in current intensity is applied ranging from 1 mA - 2 mA (Cuypers et al., 2013; Ferrucci et al., 2014; Meesen, Thijs, Leenus, & Cuypers, 2014; Mori et al., 2010; Mori et al., 2013; Saiote et al., 2014; Tecchio et al., 2014). Although 1 mA anodal tDCS seemed to be sufficient to upregulate the corticospinal excitability in M1 (Cuypers et al., 2013), it might be not sufficient to induce neurobehavioral changes in motor performance in MS patients (Meesen et al., 2014). Contrarily, tDCS applied in a healthy population with 1 mA intensity revealed significant effects on unimanual motor task performance (Matsuo et al., 2011; Schambra et al., 2011). It could be speculated that MS patients are less sensitive to tDCS and have a higher intensity threshold. Therefore, we opt for an intensity of 1.5 mA for both cathodal and anodal stimulation. However, it could be hypothesized that this current intensity would be too high for cathodal stimulation and need to be adjusted to a MS population. It might have induced an inhibitory effect on their motor learning.

4.4 Limitations and future research

This study contains some limitiations. Therefore, the results should be interpreted carefully. First of all, the study has been conducted with a relatively small sample size. Secondly, one person was extremely left handed while the other patients were weak or extremely right handed. A greater trainability has been observed in healthy individuals with strong right hand dominance compared to weak hand preference or strong left hand dominance (Walker & Henneberg, 2007). Possibly, this could influence the results. Thirdly, although a consistent protocol has been used to localize and to apply the electrodes over M1 (DaSilva et al., 2011), an inconsistent electrode montage could have been occurred because this was conducted by several investigators. At last, as mentioned before, the experiment has been performed during summer which possibly could affect the results.

This is the first study evaluating the effect of bihemispheric tDCS in a MS population, by applying cathodal tDCS on the ipsilateral M1 region and anodal tDCS on the homologue M1 region contralateral to the non-dominant hand. To confirm that cathodal stimulation could induce an inhibitory effect on motor learning in MS patients, future research in larger sample sizes is required. Furthermore, the corticospinal excitability and brain activation has not been investigated, which might be necessary to complement in future studies in order to understand the underlying mechanism. Likewise, given the complexity of MS symptomatology, it could be recommended that future research has to consider to evaluate a wide range of factors which could confound the results in a MS population. At last, an adequate stimulation protocol tailored to the MS population is necessary to optimize the efficacy of tDCS in a MS population.

5 Conclusion

In summary, in contrast to our hypothesis, the results indicate that consecutive bihemispheric tDCS induces an inferior improvement in unimanual motor learning in a MS population compared to sham stimulation. However, the results should be interpreted carefully. More research is required to investigate the impact of bihemispheric tDCS on neurophysiological and neurobehavioral characteristics in a MS population.

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