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FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN  
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## Masterproef

The effects of bihemispheric anodal transcranial direct current stimulation on multi-limb coordination in multiple sclerosis

Promotor :  
Prof. dr. Raf MEESEN

Copromotor :  
Mevrouw John Ferdin Daphnie LEENUS

Daan Vanvlijmen

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

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## **PREFACE**

In the first place, I want to thank my promotor Prof. Raf L.J. Meesen and copromotor Dra. Daphnie J.F. Leenus for the firm teamwork, the critical views, the endless feedback and invaluable help these past two years. I've learned a great deal about the captivating challenges that research has to offer and through their guidance I successfully delivered this master thesis.

Secondly, I want to manifest my appreciation to Prof. Bart Van Wijmeersch, the 'Rehabilitation and MS centre of Overpelt' and all the subjects that participated for their cooperation, goodwill and dedication. Without their voluntarily efforts this experiment had not taken place.

Finally, I want to render my thanks to my friends and family, and specially my partner Denise, for their advises and unconditional support.

Gratitudel!



## FRAMEWORK

Since a few decades non-invasive brain stimulation techniques have been attracting attention in neuro-rehabilitation and neuro-behavioural research. Because of the growing amount of evidence, with beneficial transcranial direct current stimulation (tDCS) effects in a variety of neurological disorders, the research domain is rapidly expanding. Hereby multiple sclerosis (MS) is shifting to the forefront and becoming a particular interesting research field to explore the potentials of tDCS. This experiment was conducted at the 'Rehabilitation and MS centre of Overpelt' in cooperation with the 'Rehabilitation Research Centre REVAL' instituted at the University Hasselt. This research is part of a broader study that investigates the effects of tDCS in the MS population. Under the lead of Prof. Dr. Raf L.J. Meesen and Dra. Daphnie J.F. Leenus my personal domain was confined to help investigating the effects of tDCS on multi-limb coordination in patients with multiple sclerosis. The inability to execute complex movements fluently is namely experienced as one of the most disabling aspects from the onset of MS. During complex movements some constraints emerge for the processing brain areas (Swinnen et al., 1997). Even with these constraints, healthy subjects are capable to execute complex motions with great efficiency. It is well documented in the literature that tDCS can alter cortical excitability (Nitsche and Paulus, 2000, 2001) and interhemispheric connectivity (Paulus, 2011; Polania et al., 2011). Therefore tDCS is presenting as a promising tool to suppress the motor constraints, by increasing corticomotor excitability and interhemispheric communication, and improve motor coordination in MS patients. From this point of view, we formed the research question: 'Does tDCS have beneficial effects on multi-limb coordination in patients with MS?'.

In exception of the data-acquisition, I made contributions to each aspect of the experiment. During the design and experimental procedures I was involved in discussions and instructed to scan the literature for the effects of bihemispheric and consecutive tDCS stimulations. Before patient recruitment began I designed an Excel template that selected the appropriate MS patients, based on inclusion criteria, from the patients list of the 'Rehabilitation and MS centre of Overpelt'. Moreover I created the patient information brochure and recruited thirty MS patients for the experiments by phone. Because the planning of this experiment coincided with my internship and exams, I was not able to help with the data-acquisition. Nevertheless I aided in a similar data-acquisition of the pilot study last year. For the data-analysis I started with the raw data and developed an Excel template to re-order the data. From that point I independently, with guidance of prof. Raf Meesen, analysed and interpreted the data via the SPSS applications. Finally, I solely wrote this master thesis to the best of my academic writing abilities.

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## MANUSCRIPT

### The effects of bihemispheric anodal transcranial direct current stimulation on multi-limb coordination in multiple sclerosis

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#### Conflict of interest

The authors declare no competing financial interests.

## **Abstract**

Motor coordination is the ability to integrate and unite complex movements, consisting out of a wide variety of joint and muscles combinations, to fluently execute well planned motor tasks. In patients with multiple sclerosis, the inability to fluently execute complex motions is experienced as one of the most disabling aspects of the disease. The scope of neuro-rehabilitation research is constantly evolving and various interventions have the ability to improve motor control. Thanks to beneficial effects in a variety of neurological conditions, transcranial direct current stimulation (tDCS) is shifting to the forefront, in MS motor research, as a possible alternative or additional therapy to improve motor control. Only studies that address the effects of tDCS on multi-limb coordination are rare, and moreover, to our knowledge, they are non-existing in the MS population. For this reason, the effects of bihemispheric anodal tDCS, over the primary motor cortices, on multi-limb coordination were examined, in a sham-controlled double-blinded crossover design, by means of a multi-limb coordination task in MS subjects. 'Accuracy' (number of trials responded on time) and 'speed' (time till correct) were the outcome measurements for the multi-limb coordination task. Our results indicate that bihemispheric anodal tDCS has no significant effect on multi-limb coordination in MS subjects. We did detect a higher level of difficulty, in MS subjects, for 3-limb movements compared to healthy subjects. Therefore more research is needed to identify the value of tDCS in motor rehabilitation, and more specific on multi-limb coordination, in patients with multiple sclerosis.

**Keywords:** tDCS; multi-limb coordination; motor control; interhemispheric connectivity

## 1. Introduction

Multiple sclerosis (MS) is a chronic progressive autoimmune disease that mainly affects young adults with an estimated prevalence of 88 per 100 000 inhabitants in Europe (Pugliatti et al., 2006). MS pathology is characterized by the inflammation and destruction of myelin in the central nervous system. Typical clinical signs of MS are visual disturbance, loss of sensation, muscle weakness, bladder dysfunction, fatigue,... as well as motor deficits and more specifically incoordination of complex movements (Adams et al., 2000). These coordination problems are often mentioned as one of the most disabling aspects in the early stage of the disease because of their tremendous impact on the quality of life (Kurtzke et al., 1972; Adams et al., 2000; Paltamaa et al., 2007; Kern et al., 2011). Motor coordination is the ability to integrate and unite complex movements, consisting out of a wide variety of joint and muscles combinations, to fluently execute well planned motor tasks. Many daily activities, like driving a car or texting during walking, contain complicated motor tasks. Therefore impaired motor coordination, as seen in multiple sclerosis, has a deplorable impact on daily living activities. During the execution of complex coordination movements, constraints for the processing brain areas emerge (Swinnen et al., 1997). The first is the egocentric constrain, which refers to the preference of simultaneous activation of homologue muscle groups and brain areas, often resulting in mirror-symmetric motions (Swinnen et al., 1997). The second is defined as the allocentric constraint that addresses a general preference to move non-homologous limbs in the same direction in extrinsic space (Swinnen et al., 1997). According to literature the allocentric constraint is subordinate to the egocentric (Swinnen et al., 1998; Park et al., 2001; Meesen et al., 2008). Furthermore it is stated that these basic constraints occur most prominent during the fulfilment of multiple limbs tasks (Swinnen et al., 1998; Park et al., 2001; Meesen et al., 2005; 2006; 2008). To elucidate, during the implementation of a multi-limb coordination task a subject is intrinsically more driven to move, for example, both hands or feet in the same direction than one hand and one foot. In general even with these constraints, a healthy subject, is still able to perform complex motions with great efficiency and little effort. Beside other brain regions such as the cerebellum, pre-supplementary motor area, supplementary motor area, dorsolateral prefrontal cortex, cingulate motor cortex, premotor cortex and primary cortex (M1), the corpus callosum (CC) is an important brain structure for multi-limb coordination (Swinnen and Wenderoth, 2004; Fling et al., 2008). The CC is the main connection between the hemispheres, it connects homologous brain regions, and thereby it is partly responsible, via intrahemispheric and

interhemispheric inhibition and facilitation processes, for multi-limb coordination. Thus it plays an important role in the organization of complex commands involving the precise timing of information transfers between sides (Bloom and Hynd, 2005; Llufrui et al., 2012). In addition to other neurological disorders, MS affects the corpus callosum in an early stage of the disease. It is widely indicated in the literature that from the onset of the MS disease the functioning of CC is being impaired (Larson et al., 2002; Coombs et al., 2004; Hasan et al., 2005; Audoin et al., 2007; Bonzano et al., 2008; 2011; Llufrui et al., 2012). Therefore experimental designs that affect the corpus callosum are particularly interesting for MS motor coordination research. It is known that exercise therapy, in both healthy and patient populations, produces beneficial effects and has the ability to improve motor coordination by optimizing motor control and inhibition (Swinnen and Carson, 2002; Latimer-Cheung et al., 2013). Recently non-invasive brain stimulation techniques and more specific transcranial direct current stimulation (tDCS) has been attracting attention as a possible alternative or as additional therapy in neuro-rehabilitation research. Conversely with the growing amount of tDCS studies in the healthy population and several neurological disorders, including stroke (Fregni et al., 2005), chronic pain (Fregni et al., 2007), as well as Parkinson disease (Wu et al., 2008) research in the multiple sclerosis population is still scarce. Hitherto it is shown that anodal tDCS, over the motor cortex, has the ability to improve motor performance by enhancing cortical excitability (Nitsche and Paulus, 2000, 2001; Nitsche et al., 2005; Stagg and Nitsche, 2011). Recently, Gomes-Osman et al. (2013) stated that bihemispheric anodal tDCS applied over the corticomotor hand area had a positive influence on bimanual skilled hand performance in healthy subjects. Additionally, Polania et al. (2011) indicated that transcranial direct current stimulation induces significant intra-hemispheric and inter-hemispheric connectivity (Paulus, 2011). Herewith indirectly making the link between the corpus callosum and the tDCS intervention. Since the primary motor cortex is an essential brain region during complex motor tasks and excitability can be augmented by tDCS, it presents itself as an applicable stimulation site. Furthermore it is plausible that through transcallosal connectivity between the M1's, intra- and interhemispheric communication can improve and thus diminish the impact of the motor constraints. Therefore the current study aimed to explore the effects of anodal tDCS on multi-limb coordination in the MS population. More concrete, we hypothesized that bihemispheric anodal tDCS, over the primary motor cortices, suppresses motor constraints and consequently improves multi-limb coordination in patients with multiple sclerosis.

## **2. Materials and Methods**

### **2.1 Subjects**

MS patients were recruited from a list provided by the 'Rehabilitation and MS centre of Overpelt'. Inclusion criteria were: EDSS score between 1.5 and 4.5, allocation of EDSS score within the previous year, no cognitive deficits and no MS disease exacerbations in the last six months. After contact by phone and a group acquaintance session, 20 patients enrolled in the study. Five of them were excluded based on TMS/tDCS contra-indications (Wassermann, 1998). Two subjects dropped out for the following reasons; non-availability and sickness (figure 1). In total 13 patients (9 woman and 4 men), aged between 24 and 69 (mean age: 49 years; standard deviation:  $\pm 11,78$ ) with a mean EDSS score of  $\pm 2,58$  (standard deviation: 0,78) completed the study (see table A, for detailed subject characteristics). After approval by the local ethical committee of the University of Hasselt for the experiment, each participant signed a written informed consent according to the Declaration of Helsinki.

### **2.2 experimental design**

The experiment was conducted on the basis of a double blinded crossover design. All 13 subjects received active tDCS (atDCS) or sham tDCS (stDCS) as intervention over two pseudo-randomised counterbalanced sessions. The sessions were identical, with the exception of the intervention and spaced at least 48 hours to ensure wash-out effects. Each session subjects had to perform a sequence of the same multi-limb coordination task (see figure 2). The sequence started with a 5-minute familiarization block to ensure that all the subjects fully understood the goal of the task. Next a 10-minute test block was used as baseline, followed by two test batteries each containing three 10-minute test blocks. In the test batteries patients received each test block a 10-minute atDCS or stDCS intervention. Within the session the interventions were kept equal. Finally a 10-minute retention block was done.

### **2.3 transcranial direct current stimulation**

TDCS is an application that passes low-intensity (1-2mA), monophasic electrical current through the scalp via surface electrodes. This weak current has the ability to alter brain excitability via membrane

polarisation (Paulus, 2011; Stagg and Nitsche, 2011). During anodal stimulation the resting membrane depolarises, meaning that anodal tDCS can increase cortical excitability (Nitsche and Paulus, 2001; Stagg and Nitsche, 2011). Although the underlying mechanisms aren't entirely understood, the literature states that it is a safe intervention causing no serious adverse effects (Brunoni et al., 2011; Stagg and Nitsche, 2011).

### 2.3.2 active tDCS

In this experiment we investigated the effects of tDCS on multi-limb coordination. Therefore a bihemispheric anodal electrode set up was used (derived from the method used by Gomes-Osman and Field-Fote (2013)). Over both primary motor cortices a, 25cm<sup>2</sup> sponges with, rubber anodal electrode was placed. The primary motor cortices were located via head measurements and an ECG-cap (spot C3 and C4). One 50cm<sup>2</sup> sponge, with rubber cathodal electrode was placed and centred at the supraorbital region. The cathode size was increased, to minimize possible side effects under it and, to make it functionally more inert (Nitsche et al., 2007; Cuypers et al., 2013). The sponges were soaked with saline ([NaCl] 0,9%) and an electrophysiological gel was used to optimize conduction through the scalp. Patients received six times a 10-minute atDCS (Newronika HDC stimulator) at an intensity of 1,5mA (0,06mA/cm<sup>2</sup>), within the safety measures (Brunoni et al., 2011; Stagg and Nitsche, 2011). The current ramp up and down, at the start and end of the stimulation, was set to thirty seconds.

### 2.3.2 sham tDCS

All conditions for stDCS were identical to those of atDCS, with the exception that after thirty seconds of ramp up, to 1,5mA, the current was ramped down again and ended. By means of this procedure we could simulate the effects, a light tingling sensation for twenty seconds (or less), of atDCS and retain the patients blinded for the intervention (Paulus, 2011).

## 2.4 Motor task

Via a multi-limb task (MLT) the effects of tDCS on complex motor coordination in MS patients was examined. Subjects were instructed to sit in front of computer screen and place their hands and feet, in rest, on four capacitive switches (Pepperl Fuchs CBN5-F46-E2, sampling frequency: 1000 Hz, Mannheim, Germany)(see figure 3A). On the computer screen four grey squares, in a two above two

order, each corresponding with one capacitive switch and thus one limb were shown (see figure 3B). If the extremity was in contact with the sensor the corresponding square turned white. When all four grey squares turned white, the subject was in position to start the task (see figure 3B). After two seconds the squares turned randomly blue in different combinations. Eight different limb combinations were tested, two homolateral, two heterolateral and four 3-limb combinations (see figure 3C), based on the motor constraints in the experiments of Swinnen et al. (1997). In conformity with the visual stimulus (one of the eight combinations) the patients had to lift the corresponding limbs as fast and accurate as possible from the sensors. For example, if the upper left square and the lower right square turned blue (see figure 3B), the patient should raise their left hand and right foot. But if the subject did not react on the visual stimulus, by lifting any limb, within 1000ms the squares turned white again and a new random limb combination was presented on the computer screen. If the subjects did react, within 1000ms, the trial continued until the correct combination of limbs was raised. There was no visual feedback of which limb was correctly nor incorrectly lifted during performance (note: during the familiarization session the feedback was turned on). Each of the eight limb combinations were fully at random tested for ten times per test block. Meaning that in total the subject had to perform 80 trials per test block. To assess performance on the MLT 'number of non-responded trials' and 'time until correct' were measured for each trial.

## **2.5 Data analysis**

For the statistical analysis advanced linear applications (SPSS 20, SPSS Inc., Chicago Il) were utilized. From the MLT outcomes three research measurements were defined; 'speed', 'accuracy' and 'accuracy rate'. First, 'speed' was defined as the mean time (total time [ms] divided by the number of trials that were answered on time) needed to lift the correct limb combination. Second, 'accuracy' was recorded as the number of trials a limb combination was not answered on time (>1000ms). Third, 'accuracy rate' was calculated (the number trials not answered on time (>1000ms) divided by the total number of trials) as the ratio non-answering trials on total trials, to compare the coordination patterns mutually. The eight different limb combinations were classified under three coordination patterns. The labelling in the homolateral (combination 1: left hand + left foot; combination 2: right hand + right foot), heterolateral (combination 1: left hand + right foot; combination 2: right hand + left foot) and 3-limb (combination 1: left hand + left foot + right foot; combination 2: left foot + right foot + right hand;



combination 3: right foot + right hand + left hand; combination 4: right hand + left hand + left foot) groups was based on the number of involved limbs and the movement constraints (Swinnen et al., 1997). Due to a small sample size, the effects of the intervention (atDCS vs. stDCS), on 'speed', 'accuracy' and 'accuracy rate' were analysed by the non-parametric 'Related-Samples Wilcoxon Signed Rank Test'. For the same reason the mutual comparison between the homolateral, heterolateral and 3-limb patterns was also done with the 'Related-Samples Wilcoxon Signed Rank Test'. The significance level was set at  $p < 0.05$ .

### **3. Results**

The corresponding p-values of this section are outlined in table B and table C.

Baseline performance was compared between groups (atDCS vs. stDCS) for each research measurement (speed, accuracy, accuracy rate) in each coordination pattern (homolateral, heterolateral, 3-limbs). No significant differences between atDCS and stDCS were established at baseline (all,  $p > 0,05$ ).

#### **3.1 Speed**

There was no significant effect found for stDCS vs. atDCS in any of the three coordination patterns for the research measurement 'speed' (all,  $p > 0,05$ ). There was a significant difference for 'speed' between the three coordination patterns. The heterolateral and 3-limb conditions significantly differed from the homolateral condition ( $p = 0,000$  and  $p = 0,000$ ), but the heterolateral and 3-limb did not differed mutually ( $p > 0.05$ ). This observation was also present when stDCS and atDCS were separately compared for homolateral, heterolateral and 3-limb conditions.

#### **3.2 Accuracy**

There was a significant difference established in the 3-limb coordination pattern between stDCS and atDCS ( $p = 0,043$ ), but not in the other two coordination patterns ( $p > 0.05$ ). Therefore a deeper analysis, baseline-test battery 1, baseline-test battery 2 and baseline-retention, was done between stDCS and atDCS. This deeper analysis did not reveal any significant effects of stDCS vs. atDCS (all,  $p > 0,05$ ) between the different test blocks.

#### **3.3 Accuracy rate**

There was a significant difference for 'accuracy rate' between the three coordination patterns. The heterolateral and 3-limb conditions significantly differed from the homolateral condition ( $p = 0,000$  and  $p = 0,000$ ), but the heterolateral and 3-limb did not differed mutually ( $p > 0.05$ ). This observation was also present when stDCS and atDCS were separately compared for homolateral, heterolateral and 3-limb conditions.

#### 4. Discussion

To our knowledge this is the first study that aimed to probe the effects of atDCS on multi-limb coordination in the multiple sclerosis population. In line with previous research, in healthy and patient populations, we expected that bihemispheric atDCS would ameliorate multi-limb coordination (Gomes-Osman and Field-Fote, 2013). In contrast with this theorem, this experiment did not disclose a significant difference for 'speed' and 'accuracy' for atDCS compared to stDCS on the performance of the MLT. Most tDCS motor research is based on simple motor tasks. Only recently evidence was brought to the front, by Kaminski et al. (2013) and Saucedo Marquez et al. (2013), that the effects of tDCS are depending on task complexity. From this point of view, the utilization of a complex multi-limb coordination task may offer an explication for lacking tDCS effects. The literature is in consensus that tDCS can alter cortical excitability (Nitsche and Paulus, 2000, 2001) and improve intra- and interhemispheric communication (Paulus, 2011; Polania et al., 2011). Still, the underlying neurophysiological mechanisms of tDCS aren't fully understood (Stagg and Nitsche, 2011). By which it is thinkable, given that MS is a neuro-inflammatory disorder, that the central nervous system of patients with MS responds in a different way on tDCS stimulation compared to healthy subjects.

By comparing 'speed' and 'accuracy rate' between the three coordination patterns we were able to determine which coordination pattern was harder to perform. We established that 'speed' and 'accuracy rate' were equal in heterolateral and 3-limb patterns, but higher compared to the homolateral patterns. Systematically patients needed more time and reacted less on time for the heterolateral and 3-limb trials. Hence we can presume that these two coordination patterns were encountered as more difficult to complete. A finding that is in contrast with the current available literature in the healthy population. Boisgontier et al. (2014) recently documented in a healthy population, using the same task, that the heterolateral coordination patterns are the most demanding, based on error rates and reaction times, followed by the 3-limb and the homolateral patterns. An explanation for this rank can be found in the number of engaged limbs and the movement constraints in each coordination pattern. During the execution of a 3-limb movement the subject has to inhibit three constraints. Since the egocentric constraint is stronger and superior to the allocentric, the subject has to inhibit the egocentric in the first place, secondly the allocentric and third the heterolateral constraint (Meesen et al., 2006; Boisgontier et al., 2014). For example, a subject is commissioned to move the right hand

and both feet. To impede left hand movement, the egocentric constraint of the right hand, the allocentric constraint of the left foot and the heterolateral constraint of the right foot have to be suppressed. Thus to prevent the movement of the fourth limb, during a 3-limb task, three constraints have to be conquered. In light of these statements the higher complexity of the heterolateral compared to the 3-limb patterns, can be clarified by the necessity to simultaneously inhibit two limbs from the egocentric and allocentric constraint in contrast to one. In consequence the homolateral coordination patterns are perceived as easiest because only two egocentric constraints have to be inhibited. Subsequently it is reported that bilateral symmetric (homolateral) movements are performed more precise and consistent than asymmetrical (heterolateral) movements (Swinnen and Carson, 2002). From this perspective our aberrant results can be interpreted. Given that the experiment was realised in an MS population, and not with healthy subjects, the rank of coordination patterns, as mentioned above, can vary. It is plausible for MS subjects, that the suppression of three constraints, during 3-limb coordination, is difficult and forms a threshold. Meaning that from the moment a complex motion contains more than three constraints no distinction, based on 'speed' and 'accuracy rate', can be made with the heterolateral condition. Thus it seems that in the MS population the 3-limb patterns move up in the rank and converge with the heterolateral coordination patterns.

Our study comprises some potential limitations and findings should be interpreted with caution for the following reasons. First of all, this experiment was accomplished with a relatively small sample size and therefore findings should not be generalised. Secondly, due to the tDCS set up it is possible that we did not exclusively stimulate the primary motor cortex. Thirdly, during the performance of the MLT patients were pushed, by a time limit (1000ms), to react as fast as possible. Based on a pilot study, with healthy volunteers, it is conceivable that this time limit was too short for patients with MS, whereby 'speed' can be underestimated and 'accuracy' overestimated. Finally, because of lacking literature in the MS population, experimental procedures were designed solely based on studies with healthy subjects.

## **5. Conclusion**

In conclusion, we summarize that active transcranial direct current stimulation did not have a significant effect on multi-limb coordination in patients with multiple sclerosis. The experiment did detect a higher arduousness level, in MS subjects, for 3-limb movements compared to healthy subjects. Further research is needed to identify the value of tDCS in motor rehabilitation, and more specific on multi limb coordination, in patients with multiple sclerosis.

**Acknowledgments**

Special thanks to Prof. Dr. B. Van Wijmeersch and the 'Rehabilitation and MS center of Overpelt' for the cooperation.

**Conflict of interest**

The authors declare no competing financial interests.

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## Table captions

**Table A:** represent the characteristics of the 13 MS patients that completed the study. Nine females and 4 men with: a mean age of 48 years, EDSS scores determined within the previous year, a mean EDSS score of 2,58 and all with the type relapsing-remitting MS (RRMS).

**Table B:** describes the p-values of the 'Related-Samples Wilcoxon Signed Rank Test' for the homolateral, heterolateral and 3-limb condition, between sham and active tDCS, via the outcome measurements 'speed' and 'accuracy'. In 'accuracy' of the 3-limb condition a significant difference between active and sham tDCS was established. But in the deeper analysis, between test blocks, of the 3-limb pattern no significant effect was detected in 'accuracy' between sham and active tDCS.

**Table C:** displays the p-values of the 'Related-Samples Wilcoxon Signed Rank Test' for 'speed' and 'accuracy rate' in the homolateral vs. heterolateral vs. 3-limb comparison. A significant difference was found between the homolateral and heterolateral, the homolateral and 3-limb conditions, but not between heterolateral and 3-limb conditions. These tangible effects were similar for active and sham tDCS.

**Table 1**  
Patient characteristics

ID.	Sexe	Age	EDSS	EDSS date	First symptom	Diagnosis	MS type
1	F	49	2	22/11/2013	Oct-2000	Nov-2000	RRMS
2	F	38	3	2/12/2013	Nov-2009	Nov-2010	RRMS
3	M	35	3	6/02/2014	/	/	RRMS
4	M	60	4	25/11/2013	Jan-2007	Jul-2012	RRMS
5	F	46	2	4/02/2014	Jan-2005	May-2009	RRMS
6	F	69	2	24/01/2014	Dec-1986	Jan-1987	RRMS
7	F	24	2,5	2/12/2013	/	/	RRMS
8	M	61	2,5	16/09/2013	Jan-2000	Mar-2009	RRMS
9	M	59	1,5	21/06/2013	Jan-2006	Mar-2006	RRMS
10	F	46	4	13/12/2013	Jan-2004	Jan-2006	RRMS
11	F	47	3	30/08/2013	Jan-2000	Oct-2000	RRMS
12	F	57	2,5	14/10/2013	Jan-1993	May-2011	RRMS
13	F	45	1,5	31/07/2013	Mar-2006	Dec-2009	RRMS

M, male; F, female; EDSS, Expanded Disability Scale Score; RRMS, Relapsing Remitting Multiple Sclerosis.  
F/M ratio: 9/4; Mean age: 48; Standard deviation age: 11,78; Mean EDSS: 2,58; EDSS standard deviation: 0,78.

**Table 2**

P-values for sham vs. active tDCS for 'speed' and 'accuracy' in the homolateral, heterolateral and 3-limb patterns  
P-values for sham vs. active tDCS for 'accuracy' in the 3-limb pattern, baseline vs. baseline, baseline vs. battery 1, baseline vs. battery 2, baseline vs. retention

**stDCS vs. atDCS**

	Homolateral pattern	Heterolateral pattern	3-limb pattern
Speed	0,917	0,807	0,861
Accuracy	0,637	0,050	<b>0,043*</b>

	Baseline vs. Baseline	Baseline vs. Battery 1	Baseline vs. Battery 2	Baseline vs. Retention
Accuracy 3-limb	0,125	0,060	0,162	0,752

\* = p < 0,05

**Table 3**

P-values for homolateral vs. heterolateral vs. 3-limb patterns, for 'speed' and 'accuracy rate'

**Homo vs. Hetero vs. 3-limb**

		Homo vs. Hetero	Homo vs. 3-limb	Hetero vs. 3-limb
Speed	stDCS + atDCS	<b>0,000*</b>	<b>0,000*</b>	0,534
	stDCS	<b>0,001*</b>	<b>0,001*</b>	0,600
	atDCS	<b>0,002*</b>	<b>0,002*</b>	0,807
Accuracy rate	stDCS + atDCS	<b>0,000*</b>	<b>0,000*</b>	0,620
	stDCS	<b>0,001*</b>	<b>0,002*</b>	0,780
	atDCS	<b>0,001*</b>	<b>0,001*</b>	0,727

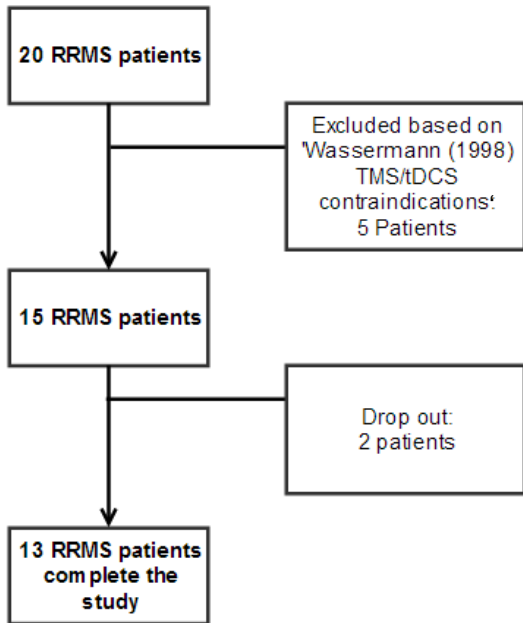
\* = p < 0,05

## Figure captions

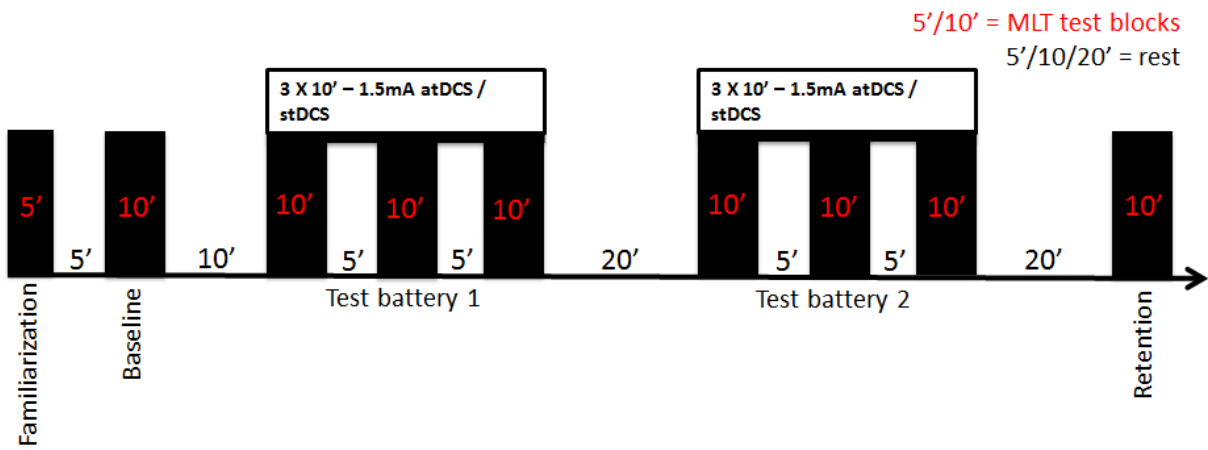
**Figure 1:** Patients flowchart: 20 subjects enrolled in the study, five were excluded based on the 'Wassermann (1998) TMS/tDCS contraindications'. Two subjects did not complete the study and dropped out.

**Figure 2:** Experimental design, session representation: After a short MLT familiarization block (5 minutes), motor performance was measured at baseline (10 minutes). Next two test batteries with each 3 MLT test blocks (10 minutes) were executed. Finally a retention block (10 minutes) was completed. During the test batteries either atDCS or stDCS was administered, the intervention stayed unchanged within the session.

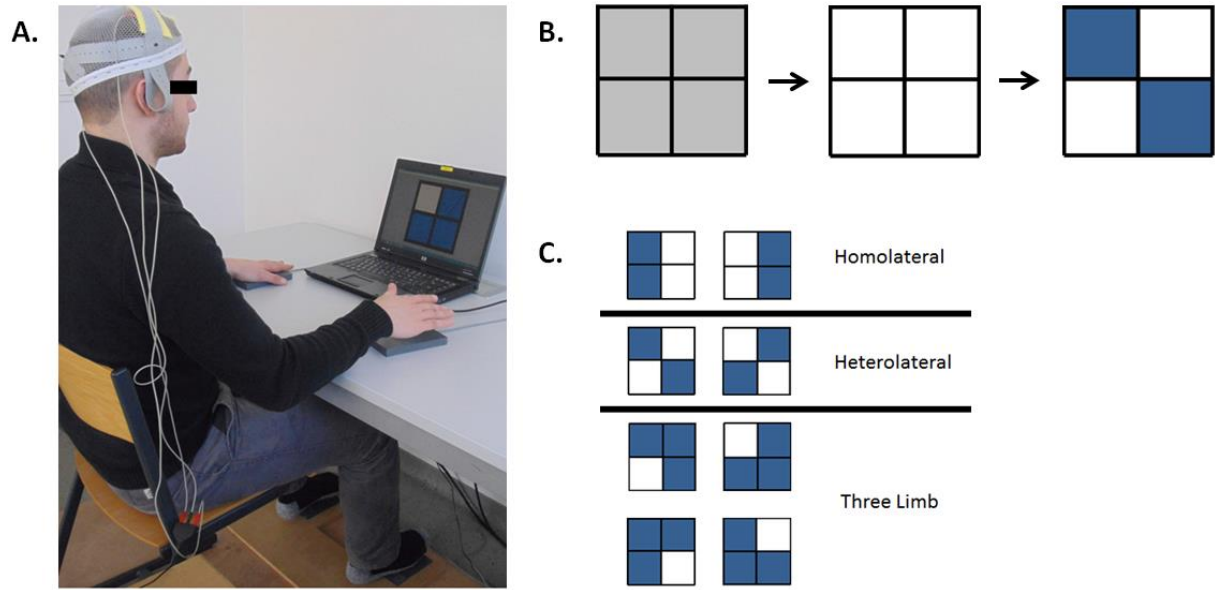
**Figure 3:** Representation of the multi-limb task and movement combinations: **A.** The experimental set up and subject reacting to a 3-limb combination. **B.** The four sensors were presented as four squares. The four grey squares indicated that the four limbs were not resting on the sensors. Once the limbs were in contact with the sensors the four squares turned white, the subject is now ready to start the task. The squares turned randomly blue, in this example a heterolateral combination was requested. **C.** The eight visual representations of the different movement combinations, two homolateral, two heterolateral and four 3-limb combinations.



**Figure 1**  
Patients flowchart



**Figure 2**  
Experimental design, session representation



**Figure 3**  
Representation of the multi-limb task and movement combinations







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**The effects of bihemispheric anodal transcranial direct current stimulation on multi-limb coordination in multiple sclerosis**

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen**

Jaar: **2014**

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