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A single session of 1 mA anodal tDCS-supported motor training does not improve motor performance in patients with multiple sclerosis

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Abstract.
Purpose: To assess the effects of atDCS on motor performance in patients with multiple sclerosis (MS). Previously, anodal transcranial direct current stimulation (atDCS) has been shown to improve motor performance in healthy subjects and neurodegenerative populations. However, the effect of atDCS on motor performance is not examined in MS.
Methods: In the current study, a sham controlled double-blind crossover design was used to evaluate the effect of 20 minutes of 1 mA atDCS or sham tDCS (stDCS) on a unimanual motor sequence-training task, consisting of sequential finger presses on a computer keyboard with the most impaired hand. Patients received stimulation (atDCS or stDCS) during motor training. tDCS was applied over the primary motor cortex contralateral to the most impaired hand. Motor performance was assessed immediately before, during and 30 minutes after stimulation.
Results: Although we need to be careful with the interpretation of the data due to lack of power, our results showed no significant effect of atDCS on motor performance.
Conclusions: Our findings indicate that atDCS-supported motor training was not able to improve motor performance more than sham-supported motor training. Possibly, the effects of atDCS are mediated by specific MS-related characteristics. Furthermore, increasing atDCS intensity and offering multiple stimulation sessions might be necessary to optimize motor performance resulting from atDCS-supported motor training.

Keywords: Multiple sclerosis, transcranial direct current stimulation, tDCS, neural rehabilitation, motor training

1. Introduction

Recently, transcranial direct current stimulation (tDCS) has been applied for improving motor function in healthy subjects and patient populations. Studies in stroke (Hummel et al., 2006, 2005; Madhavan, Weber, and Stinear, 2011; Tanaka et al., 2011), Parkinson's disease (Fregni et al., 2006) and healthy aging (Hummel et al., 2010) showed that a single session of anodal tDCS (atDCS) over the primary motor cortex (M1) was sufficient to improve motor performance, reaction time (Fregni et al., 2006; Hummel et al., 2006), pinch force (Hummel et al., 2006; Tanaka et al., 2011), motor control (Hummel et al., 2005; Madhavan et al., 2011), and

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motor learning (Fritsch et al., 2010; Galea and Celnik, 2009; Tecchio et al., 2010) significantly.

Although the underlying mechanisms of tDCS remain largely unclear, previous reports (Nitsche and Paulus, 2000, 2001) revealed that a single-session of direct current stimulation induced sustained (up to 90 minutes) and polarity-dependent cortical excitability changes. Furthermore, atDCS is presumed to influence the resting membrane potential during stimulation; and to modulate GABAergic and glutamatergic synapses within the cortex after stimulation (Stagg and Nitsche, 2011). There is strong evidence that motor training combined with atDCS applied on the primary motor cortex (M1) improves motor performance (Kantak, Mummidisetty, and Stinear, 2012; Lefebvre et al., 2012; Nitsche et al., 2003; Reis and Fritsch, 2011; Reis et al., 2009; Zimerman et al., 2012).

Until now, there is no evidence that the combination of motor training and atDCS improves motor performance in patients with MS. MS is an inflammatory disease in which the myelin sheaths around the axons of the brain and spinal cord are damaged, leading to a disturbed signal transfer between central and peripheral regions. Despite of this dysfunctional signal transfer, evidence from a recent magnetic resonance imaging (MRI) study (Tomassini et al., 2011) confirmed that the potential to learn new motor skills is preserved in MS patients, provided that the potential for functional reorganization remains relatively unimpaired (Schoonheim, Geurts, and Barkhof, 2010).

The aim of the current study was to evaluate the effect of a single atDCS session combined with a unimanual sequence-training task on motor performance in patients with mild to moderate MS. We hypothesize that atDCS-supported motor training leads to superior motor performance as compared to sham-supported motor training.

2. Experimental procedures

2.1. Subjects

Thirty-one patients with MS (9 men and 22 women) aged 27 to 65 years (mean ± SD: 48.16 ± 10.13 years) participated in this double-blinded crossover design (see Table 1 for patient characteristics). Expanded Disability Status Scale (EDSS) scores ranged between 1.5 and 6.5 (mean ± SD 3.15 ± 1.22). Patients were recruited at REVAL Research Institute in Diepenbeek and the Multiple Sclerosis and Rehabilitation Hospital in Overpelt. Experimental procedures were approved by the Ethical Committee of the University of Hasselt according to the Declaration of Helsinki. All patients gave their written consent prior to the study. Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). Twenty-nine patients were right-handed (mean LQ ± SD = 89.43 ± 18.74) and two were left-handed (mean LQ ± SD = −58.35 ± 58.90). Patients showed no cognitive deficits (score ≥26 on the Montreal Cognitive Assessment Test, mean ± SD: 28.00 ± 1.34) and exhibited stable MS, showing no relapse for at least 3 months prior to the study. Before inclusion, patients were screened for other pathologies associated with peripheral and/or central sensory dysfunction, psychotropic or antiepileptic medication intake and contra-indications for tDCS.

2.2. Experimental design

Prior to the experiment, the Nine-hole Peg Test was administered to assess motor performance of each hand separately to determine the most impaired hand (called the 'intervention hand'). The mean time required to perform the test was 25.16 (±7.20 SD) seconds for the intervention hand and 21.53 (±5.38 SD) seconds for the least impaired hand ($p < 0.0001$; paired t-test). Subsequently, patients moved on to a double-blind (both the experimenter applying the stimulation and the patient were blinded for the intervention) crossover procedure. In two pseudo-randomized, counterbalanced sessions separated by at least a week, patients received either atDCS or sham tDCS (stDCS) on M1 contralateral to the intervention hand while performing a unimanual sequence-training task.

2.3. Motor training

Patients were instructed to perform a unimanual sequence-training task (Cuypers et al., 2013) consisting of sequential finger presses using the intervention hand (see Fig. 1). They were seated in front of a computer screen and were instructed to press the key corresponding to the number on the screen with one of the four fingers (2nd–5th) as quickly and as accurately as possible. In a single session patients performed a total of 26 blocks. Motor performance was measured prior (baseline, 3 blocks), during training (20 blocks) and 30 minutes after the end of the train-

Table 1
Patient characteristics

ID	Age	Sex	First symptom	Diagnosis	MS Type	Visual	Brainstem	Pyramidal	Cerebellar	Sensory	Bladder/Bowell	Mental	Edss
1	51	F	Aug-97	Oct-02	SPMS	0	0	2	2	2	3	1	4.5
2	32	M	Jan-04	May-04	RRMS	0	2	2	2	2	0	0	3
3	57	M	Dec-06	Jun-07	RRMS	0	0	1	1	3	1	0	3
4	60	F	Jan-94	Jan-94	SPMS	0	0	1	1	2	1	0	2
5	58	M	Jan-92	Jan-92	RRMS	1	0	3	3	2	1	2	4
6	34	F	Nov-09	Nov-10	RRMS	0	0	1	2	2	1	0	2.5
7	27	F	Jun-09	Jul-09	RRMS	0	0	1	1	2	0	1	2
8	61	M	Jan-00	Jul-01	SPMS	0	0	2	2	2	1	0	3
9	51	F	Nov-89	Nov-89	SPMS	0	2	2	3	3	1	1	4
10	44	F	Jan-89	Feb-89	RRMS	0	0	2	2	2	1	1	3
11	52	F	Aug-00	Sep-00	RRMS	1	0	1	2	2	1	1	2.5
12	42	F	Jan-03	Feb-03	RRMS	1	0	2	2	2	1	1	3
13	60	F	Jan-00	Jan-01	SPMS	0	1	2	2	2	1	2	5.5
14	58	F	Aug-07	Mar-09	RRMS	0	1	2	1	2	1	0	2.5
15	48	F	Sep-05	Sep-05	RRMS	0	0	2	1	2	1	1	2.5
16	46	F	Oct-00	Nov-00	RRMS	0	0	2	1	1	1	1	2
17	54	F	Jan-80	Jan-87	SPMS	0	2	2	3	3	1	0	6.5
18	61	F	Jan-69	Jan-83	SPMS	0	0	2	2	2	1	1	3
19	38	F	Jan-09	Oct-10	RRMS	0	1	2	1	1	1	1	2
20	65	M	Jan-01	Jan-02	PPMS	0	1	0	1	1	2	2	2.5
21	49	M	Jan-88	Jan-08	RRMS	0	0	3	2	2	1	1	3.5
22	55	F	Feb-08	Feb-08	RRMS	0	1	1	1	2	1	0	2
23	45	F	Apr-88	Apr-98	SPMS	0	2	3	3	2	1	1	4
24	43	F	Jan-05	May-09	RRMS	0	1	2	1	0	1	1	2
25	41	M	Jan-06	Jan-07	SPMS	0	1	2	3	3	1	0	4
26	54	F	Dec-04	Dec-04	RRMS	0	1	2	1	2	1	1	2.5
27	43	M	Jul-07	Jul-07	RRMS	0	1	1	0	2	0	0	2
28	28	M	Jan-12	May-12	RRMS	0	0	1	1	0	0	0	1.5
29	55	F	Jan-98	Feb-98	PPMS	0	1	3	2	3	1	0	6
30	43	F	Sep-08	Mar-10	RRMS	0	0	3	1	2	0	1	3.5
31	38	F	Jan-04	Feb-04	RRMS	0	1	3	1	2	1	1	3.5

ing (post-intervention, 3 blocks). In a single block, sequences were initiated in 30-second time frame. Each block was terminated after completion of the last sequence. Patients were instructed to perform as many correct sequences as possible; therefore the amount of sequences provided during each block depended on the speed of the patient. Each time a key was pressed a black dot appeared beneath the corresponding number. No feedback about the correctness of the performance was provided. The sequences were pseudo-randomized and counterbalanced over the sessions and had the same level of difficulty. The sequences were [4 2 1 3 4 2 3 2] and [2 4 3 1 2 3 2 4] (1 = index finger, 2 = middle finger, 3 = ring finger and 4 = little finger).

2.4. Non-invasive cortical stimulation

During motor training patients received either atDCS (HDCstim, Newronika, Italy) or stDCS on M1 contralateral to the intervention hand. The anode (surface 25 cm^2) was centered on the cortical representation field (hotspot) of the First Dorsal Interosseous (FDI) as determined by transcranial magnetic stimulation (TMS). The cathode (surface 50 cm^2) was fixed on the contralateral supraorbital region. By increasing the size of the cathode this electrode will become functionally inert (Nitsche et al., 2007). Stimulation was delivered with a current intensity of 1 mA for 20 min. In the stDCS condition the same current intensity was delivered but only during the first 12 seconds.

2.5. Psychophysical assessment

In each session visual analogue scales (VAS) were provided to assess the level of attention, fatigue, and pain/discomfort during the experiment. In addition, sleep duration and sleep quality (VAS) was also assessed.

2.6. Data analysis

Advanced linear models applications (SAS 9.2, SAS institute Inc., Cary, NC) were used for statistical analysis. Prior to analysis, scores for the compound

Fig. 1. Subjects were instructed to perform an 8-element finger sequence with the dominant hand by pressing different keys, each corresponding to one of the four fingers (2nd–5th).

measures [percentage correct sequences/mean inter tap interval (ITI) and percentage correct key presses/mean ITI], were normalized (%) to baseline for each subject separately.

To evaluate the effect of tDCS during motor training over time, a mixed model including fixed effects for condition (atDCS vs. stDCS), time (20 training blocks) and their interaction, was used to estimate the rate of change (i.e. slope-analysis) of motor performance. More specifically, the following parameters were tested: percentage correct sequences/mean ITI, percentage correct key presses/mean ITI, percentage correct sequences, percentage correct key presses, mean ITI, and mean number of correct sequences in the performance interval.

To reveal the effect of tDCS-induced motor training on motor performance at post-intervention, paired *t*-tests were applied to evaluate the evolution of motor performance within conditions and between conditions. In addition, a power analysis was performed on the current data to calculate the minimum sample size required to detect an effect of a given size. The significance level was set at $p < 0.05$.

3. Results

3.1. Baseline performance

At baseline, paired *t*-tests revealed no significant differences in performance between the different stimulation conditions for none of the parameters (all, $p > 0.05$). The results for each parameter are illustrated in Fig. 2.

3.2. Motor performance during tDCS-supported training

The slope analysis revealed no significant effects for condition and for the interaction between condition and time during motor training for none of the parameters (all, $p > 0.05$), indicating that atDCS did not significantly contribute to motor performance. With respect to the effect of time, the slope analysis revealed significant effects for percentage correct sequences/mean ITI ($p < 0.001$), percentage correct key presses/mean ITI ($p < 0.001$), percentage correct sequences ($p < 0.001$), percentage correct key presses ($p < 0.045$), and mean ITI ($p < 0.001$). The mean number of correct sequences in the performance interval did not significantly change over time ($p > 0.05$).

3.3. Motor performance at post-intervention

3.3.1. Effects of atDCS on motor performance

At post-intervention, no significant differences in motor performance between the atDCS and stDCS condition were found, indicating that there was no additional effect of the intervention over time. (all, $p > 0.05$). For the parameter mean number of correct sequences in the performance interval, a marginal trend was found for the atDCS condition ($p = 0.077$).

A power analysis showed insufficient power for all parameters (see Table 2).

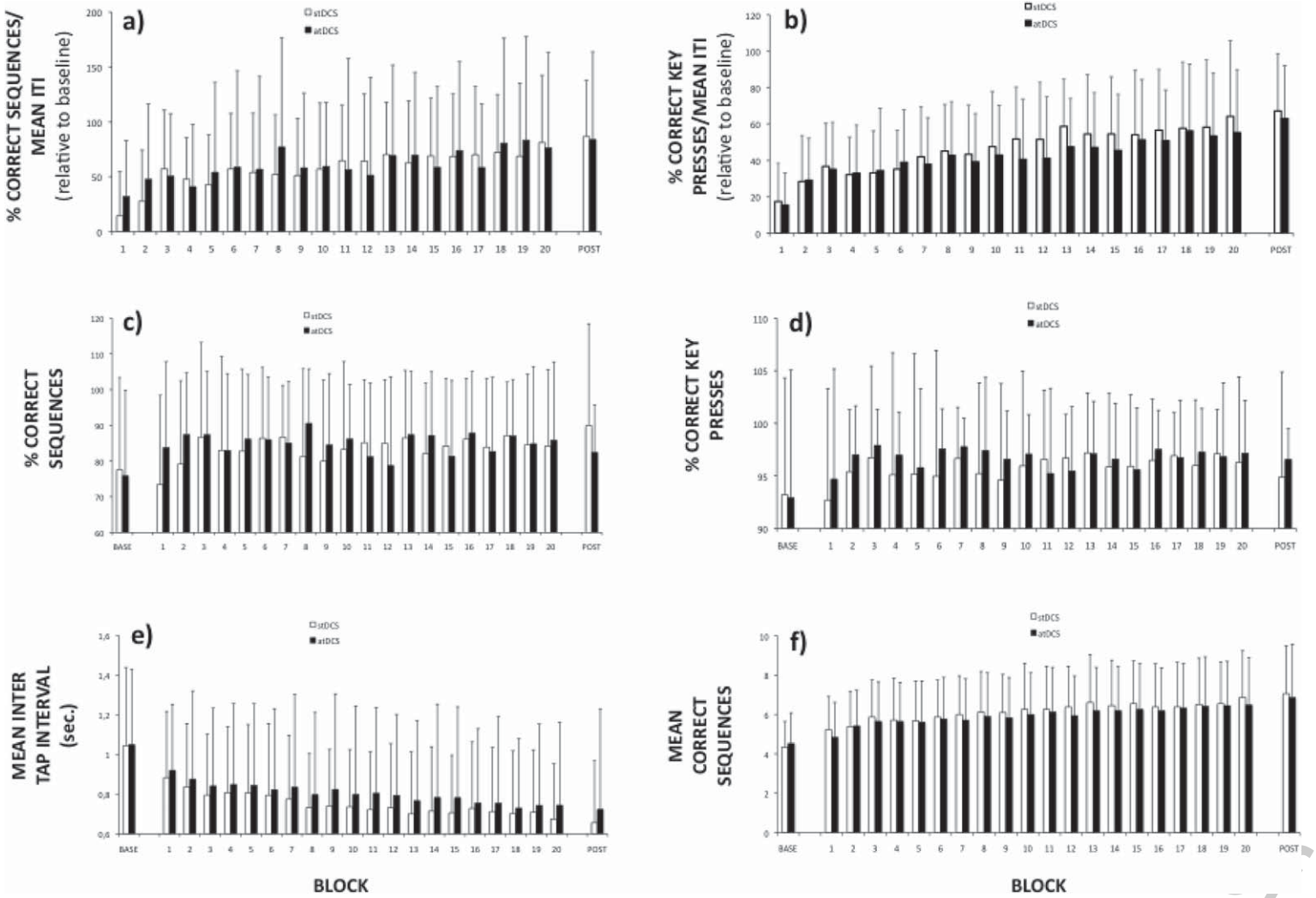

Fig. 2. Evolution of the percentage correct sequences/mean inter tap interval (ITI) (a), percentage correct key presses /mean ITI (b) during tDCS-supported motor training and at post-intervention (relative to baseline) for the atDCS and stDCS condition. The evolution of the percentage correct sequences (c), percentage correct key presses (d), Mean inter tap interval (e) and mean number of correct sequences in the performance interval (f) are shown at baseline, during tDCS-supported motor training, and at post-intervention for the atDCS and stDCS. Mean value and standard deviation for atDCS (black bars) and stDCS (white bars) are shown for each block.

Table 2
Power analysis

Parameter	Power (%)	Subjects required for a power of 80%
Percentage correct sequences/mean ITI	17.7	211
Percentage correct key presses/mean ITI	11.8	386
Percentage correct sequences	12.1	368
Percentage correct key presses	5	89000
Mean ITI	6	1554
Mean number of correct sequences in the performance interval	42.5	73

Table 3
Psychophysical assessment. The amount of sleep (±SD) is reported. Visual analog scales scores (±SD) are shown for sleep quality (1 = bad sleep quality; 10 = excellent sleep quality), attention (1 = no attention; 10 = highest level of attention), fatigue (1 = highest level of fatigue; 10 = no fatigue) and pain/discomfort (1 = no pain/discomfort; 10 = maximal level of pain/discomfort)

Condition	Sleep (hours)	Visual Analog Scale Score			
		Sleep quality	Attention	Fatigue	Pain/discomfort
atDCS	7.61 (1.63)	7.10 (2.04)	8.16 (1.32)	3.06 (2.82)	0.84 (1.98)
stDCS	7.63 (1.08)	6.90 (2.19)	7.97 (1.50)	2.93 (2.70)	0.70 (1.70)

3.3.2. Overall training effects

The following parameters improved after motor training (at post-intervention) for the atDCS condition: percentage correct sequences/mean ITI ($p < 0.0001$), percentage correct key presses/mean ITI ($p < 0.0001$), mean ITI ($p < 0.0001$), mean number of correct sequences in the performance interval ($p < 0.0001$)

For the stDCS condition, the percentage correct sequences/mean ITI ($p < 0.0001$), percentage correct key presses/mean ITI ($p < 0.0001$), percentage correct sequences ($p = 0.010$), mean ITI ($p < 0.0001$), mean number of correct sequences in the performance interval ($p < 0.0001$) improved after motor training.

All other parameters did not change significantly (all, $p > 0.05$).

3.4. Psychophysical assessment

Paired sample *t*-tests revealed no significant differences for the level of attention, fatigue, pain/discomfort, sleep duration and sleep quality (all, $p > 0.05$; see Table 3).

4. Discussion

The present study is the first to address the question whether a single session of anodal tDCS stimulation on M1 contralateral to the target hand was able to improve motor performance in MS patients. Based on the findings reported in other neurodegenerative populations (Fregni et al., 2006; Hummel et al., 2005; 2006; Madhavan et al., 2011; Tanaka et al., 2011), we hypothesized that atDCS-supported training will lead to superior motor performance as compared to sham-supported training.

Our results indicated that atDCS-supported motor training was not able to improve motor performance more than sham-supported motor training. This result is in contrast with findings in stroke (Hummel et al., 2005; 2006; Madhavan et al., 2011; Tanaka et al., 2011) and healthy aging (Hummel et al., 2010) indicating that a single session of tDCS during motor training was sufficient to significantly improve motor performance as compared to sham-supported motor training. Our results can be explained in several ways.

Firstly, we have to be aware that the statistical power in this study was low, making the interpretation of the current results difficult. Although the statistical analysis did not reveal any significant effect of the intervention for the different parameters, we cannot conclude that there was no effect (due to lack of power). According to the power analysis more subjects are required to reach acceptable statistical power (80%).

Secondly, it is possible that performance improvements are limited (Morgen et al., 2004) or occur slower in MS patients. In this respect, Hatzitaki et al. (2006) reported that visuo-motor learning occurred at a lesser extent in patients with MS as compared to healthy controls (Hatzitaki, Koudouni, and Orologas, 2006). Additionally, it was reported that motor performance in MS patients was highly variable. This variability could be attributed to the widespread and unpredictable nature of demyelization of the central nervous

system affecting motor performance in MS (Hatzitaki et al., 2006). Additionally, Casadio et al. (2008) showed that MS patients achieved close-to-normal motor function by performing a greater proportion of micro-adjustments to compensate for partly incorrect descending commands (Casadio, Sanguineti, Morasso, and Solaro, 2008). Although we chose to train the most impaired hand from a therapeutically point of view, it might be argued that (based on symptom severity) more variability would be expected when training this hand. However, as we did not train and/or collected sequence-training data of the least impaired hand in the current study, we cannot discuss this issue. Based on the findings mentioned above, we can assume that if individual motor performance variability is too high, as a result of MS, the contribution of atDCS-induced motor performance might be washed out.

Third, nonetheless a recent study of our group reported that 20 min of 1 mA atDCS is sufficient to increase corticospinal excitability in a comparable group (age, symptoms, EDSS) of MS patients (Cuypers et al., in press), it might be possible that atDCS induces excitability changes on the cortical level in absence of sufficient signal transfer to the peripheral level. As mentioned earlier it is reported that the signal transfer between central and peripheral regions is disturbed. Studies using TMS showed significant correlations between disability and TMS abnormalities in MS patients (Kale, Agaoglu, Onder, and Tanik, 2009; Sahota et al., 2005; Thickbroom, Byrnes, Archer, Kermode, and Mastaglia, 2005). More specifically, parameters such as MEP amplitude, MEP latency and central motor conduction time were abnormal as compared to healthy controls.

A fourth explanation is that tDCS intensity might be too low to induce atDCS-supported training effects in a single session. Recently, our group (Cuypers et al., 2013) reported that stimulation intensity plays an important role in obtaining the desired results. Furthermore, it was reported that 20 minutes of atDCS-supported motor training at 1.5 mA significantly improved online and offline motor performance in healthy subjects as compared to sham-supported motor training. Between atDCS-supported motor training at 1 mA and sham no significant differences were reported.

Fifth, it might be reasonable that a single session was not sufficient to obtain the desired therapeutic result and that multiple sessions are required. Recently, Mori et al. (2012) evaluated the effect of atDCS on tactile sensation in MS. Although they did not found any beneficial effects after the first stimulation session, they reported that a 5-day course of atDCS was sufficient to ameliorate tactile sensory loss with long-lasting beneficial effects (Mori et al., 2012). In line with this finding, Reis et al. (2009) found that atDCS enhanced skill acquisition in healthy subjects after 5 consecutive atDCS-supported motor training sessions (Reis et al., 2009). Interestingly, they reported no differences in online skill acquisition between the atDCS and the stDCS conditions. Instead, the atDCS-supported learning effect was mediated by beneficial offline effects referred to as 'motor consolidation'.

In summary, our findings indicate that atDCS-supported motor training was not able to improve motor performance more than sham-supported motor training. Possibly, effects of atDCS are mediated by specific MS-related characteristics. Furthermore, increased atDCS intensity and multiple stimulation sessions might be necessary to optimize motor performance resulting from atDCS-supported motor training.

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