Anodal transcranial direct current stimulation of motor cortex does not ameliorate spasticity in multiple sclerosis

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Abstract.
Purpose: To assess whether anodal transcranial direct current stimulation (tDCS) is effective in modulating lower limb spasticity in MS patients. Previously, anodal tDCS has been shown to improve motor deficits in several neurological diseases and, recently, it has been proposed as effective in decreasing spasticity after stroke. However, the effect of anodal tDCS on spasticity is not examined in MS.
Methods: We performed a single-centre randomized, double-blind, sham-controlled study to investigate efficacy of anodal vs sham tDCS in 20 relapsing-remitting MS patients. Ten patients received anodal tDCS stimulation to the primary motor cortex of the more affected side, 20 minutes/day for 5 consecutive days. Ten patients received sham tDCS stimulation. Spasticity was assessed by using the modified Ashworth scale (MAS), the self-scoring MSSS-88 (Multiple Sclerosis Spasticity Scale) and Multiple Sclerosis Walking Scale (MSWS-12) at baseline and at the end of protocol stimulation.
Results: No side effects were detected during either anodal tDCS or sham. In both groups, there was no significant improvement in MAS, MSSS-88 and MSWS-12 scores. Moreover the comparison between anodal tDCS and sham showed no difference.
Conclusions: Five-daily sessions of anodal tDCS to the primary motor cortex does do not improve lower limb spasticity in MS patients.

Keywords: Multiple sclerosis, anodal transcranial direct current stimulation, lower limb spasticity

1. Introduction

Spasticity is one of the most common disabling multiple sclerosis (MS) symptoms and occurs in 40–84% of MS-patients, with an increasing severity as the disease progressed (Rizzo et al., 2004). Spasticity can be defined as a velocity dependent increase in muscle tone following hyperexcitability of the stretch reflex secondary to lesion of the corticospinal tract (Lance, 1980; Young et al., 1994). Animal models suggested that spasticity may occur because of changes in supraspinal drive and secondary changes at cellular level in the spinal cord below the lesion (Bareyre et al., 2004; Raineteau et al., 2001). Several studies have suggested that clinical disability in multiple sclerosis, including spasticity, occurs when synaptic long term potentiation (LTP) fails (Weiss et al., 2014, Centonze et al., 2007, Mori et al., 2010, Nielsen et al., 1996) as consequence of progression of neuronal damage without any compensation by adaptive LTP mechanism (Nisticò et al., 2014). Moreover, LTP deficit has been demonstrated in experimental autoimmune encephalomyelitis experimental model at cortical level (Di Filippo et al., 2014)

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This may indicate that technique able to alter brain excitability may be of great interest in rehabilitation of spasticity providing non-pharmacological strategies for spasticity management. Repetitive transcranial magnetic stimulation (rTMS) has already been shown to ameliorate clinical and neurophysiological measures of spasticity (Mori et al., 2010, 2011; Centonze et al., 2007). Transcranial direct current stimulation (tDCS) is another simple, non-invasive technique that can induce sustained excitability changes in relatively restricted human brain areas (Stagg et al., 2011) and on lumbar spinal network in healthy subject (Roche et al., 2011) modulating spontaneous neuronal firing rates, synaptic and non-synaptic plasticity (Nietsche et al., 2003). Anodal tDCS, that promotes LTP, could boost brain plasticity and improve the spasticity. Recently, anodal tDCS has been applied in multiple sclerosis to improve chronic pain (Mori et al., 2010), tactile sensory deficit (Mori et al., 2013), strength (Cuypers et al., 2013) and fatigue (Ferrucci et al., 2014; Saiote et al., 2014; Tecchio et al., 2014). No studies have investigated whether anodal tDCS improves spasticity in multiple sclerosis, information on its benefits or failure might give patients with MS a new treatment option (Gunduz et al., 2014).

2. Methods

2.1. Patients

We studied 20 remitting patients with MS and spasticity affecting predominantly or exclusively one lower limb (Table 1). This choice was based on clinical assessments of spasticity through rating scale, but not on statistical analysis. We focused our attention on lower limb spasticity because this clinical condition significantly impacts the quality of life. All patients were naïve about the procedure and give written informed consent to the study, which was approved by the local institutional ethical committee. Inclusion criteria were a diagnosis of relapsing-remitting multiple sclerosis (RRMS) according to McDonalds revised criteria (Polman et al., 2011), with lower limb spasticity and no radiological and/or clinical evidence of disease activity in the previous two months, defined by the absence of contrast enhancement at the brain and cervical spine MRI. Expanded Disability Status Scale (EDSS) score was comprised between 3 and 6. The score between 3 and 6 is based primarily on gait

Table 1
Demographic and clinical baseline features between tDCS and SHAM patients

	tDCS (n = 10)	SHAM (n = 10)	p values
Age, years (±SD)	43,3 ± 7,5	40,3 ± 4,5	p = 0,3
Gender, M/F (%)	2/8 (20/80)	3/7 (30/70)	p = 0,6
Disease duration, years (±SD)	7,0 ± 3,1	7,8 ± 1,9	p = 0,5
EDSS score	3,6 ± 0,9	3,8 ± 0,9	p = 0,5
Limb stimulated, left/right (%)	6/4 (60/40)	5/5 (50/50)	p = 0,6
MAS score (left)	3,1 ± 2,2	2,9 ± 2,4	p = 0,9
MAS score (right)	2,3 ± 1,9	3,1 ± 1,9	p = 0,3
Medication			
Interferon 1-beta, n (%)	5 (50%)	4 (40%)	p = 0,6
Glatiramer Acetate, n (%)	5 (50%)	6 (60%)	p = 0,6

M = male; F = female; EDSS = Expanded Disability Status Scale; MAS = Modified Ashworth Scale.

dysfunction that is the main function affected by lower limb spasticity. Although the need to treat spasticity increases as the disease progress, we believed that a potential benefit of anodal tDCS could be easily detectable when patients are still ambulatory. Remission was defined as a stable clinical condition on the basis of a complete neurological examination and the patients report. Antispastic medication was suspended at least 3 months before the beginning of the study because they were ineffective. Immunomodulatory therapy and physiotherapy were not modified during the study and 2 months before. Exclusion criteria were symptoms or signs suggestive of a superimposed peripheral neuropathy, cognitive deficits and/or psychiatric disorders, history of epilepsy or seizures, pregnancy or mental devices in the head. The study was performed according to the declaration of Helsinki.

2.2. Experimental design

Patients were randomized to five-daily session of either anodal tDCS (n = 10) or sham tDCS (n = 10). Both anodal tDCS and sham tDCS were applied by using a battery-driven constant-current stimulator (Eldith-NeuroConn GmbH, Ilmenau, Germany). The same stimulation protocol was used in previous studies, showing beneficial effect on sensory deficit and tactile sensation in multiple sclerosis patients (Mori et al., 2010, 2013). In both group the intervention is equal for all aspects than the current delivery duration. Anodal tDCS (2 mA intensity for 20 min once a day for five consecutive days) was transferred by a pair of saline-soaked surface sponge electrodes (35 cm^2)

positioned on the primary motor cortex (anode) of the more affected limb and over the contralateral supraorbital area (cathode). For sham tDCS, the current was ramped up to 2 mA and slowly decreased over 30 s to ensure the typical initial tingling sensation. Electrodes were placed on the hot spot of the affected side where abductor halluces muscle MEPs were easily obtained in the primary motor cortex. In the case of the hot spot could not be defined on the motor cortex of the affected side, it could be acquired by the same position of hot spot of the unaffected side to apply the anodal electrode. TMS was performed using a high power magnetic stimulator (MagProX100, Medtronic, Denmark) connected with a figure-of-eight coil (90 mm) to stimulate selectively the leg area of the chosen hemisphere. Resting motor threshold was defined as the minimum stimulus intensity that produced a liminal MEP (50μV in at least 5 of 10 trials) at rest. The stimulation intensity was set to 120% of RMT when RMT was <80% of maximum stimulator output (MSO), or at 100% of MSO when the RMT was >80%. MEP was obtained from abductor halluces muscle. Each site was stimulated 4 times at 1-cm intervals with a minimum of 10 s between stimulation.

The treating physician, who was aware of group allocation because she had to set up the stimulation protocol, was instructed not to talk to both the patients and assessing physicians about the stimulation procedure. Modified Ashworth Spasticity scale (MAS) (Bohannon et al., 1987), Multiple Sclerosis Spasticity Scale (MSSS-88) (Hobart et al., 2006) and Multiple sclerosis walking scale (MSWS-12) (Hobart et al., 2003) were evaluated by two neurologists who were unaware of group allocation, on the first day of treatment before the session stimulation beginning and immediately after the last stimulation session, on five day of stimulation.

3. Data analysis

For two-group comparison (anodal tDCS versus SHAM patients), Mann-Whitney U-test was performed for non-parametric variables and independent samples *t*-test for parametric variables. $\chi2$ was used to compare gender distribution and medication between two groups. We applied a mixed model ANOVA with Time (two levels: baseline and 5 days) as within subject factors and Intervention (two levels: real tDCS vs SHAM group) as between subject factor. One-

way repeated-measures analyses of variance (ANOVA) was used to compare the effect of real tDCS and SHAM protocol on MAS, MSSS-88 and MSWS-12 scores at different times of evaluation (within-subject comparison). Moreover the direct comparison between the two groups (real tDCS vs SHAM group) was performed by using unpaired *t*-test. Data were analyzed using software (SPSS v. 19.0 for Windows; SPSS Inc.). Data are presented as mean ± SD. The significance level was set as $p < 0,05$.

4. Results

Demographics and clinical baseline characteristics in patients treated with real or sham stimulation TDCS are shown in Table 1. To evaluate *Time by Intervention* interaction we applied a mixed model ANOVA, that did not show any significant interaction for all three scales (MAS, $F = (1, 18) = 1.461$, $p = 0.242$; MSSS-88, $F = (1, 18) = 0.056$, $p = 0.816$; MSWS-12, $F = (1, 18) = 0.046$, $p = 0.833$). One-way ANOVA revealed no significant change of clinical scores both for anodal tDCS (MAS, $F = (1, 18) = 0.03$, $p = 0.86$; MSSS-88, $F = (1, 18) = 0.013$, $p = 0.91$; MSWS-12, $F = (1, 18) = 0.74$, $p = 0.79$) and SHAM patients (MAS, $F = (1, 18) = 0.286$, $p = 0.6$; MSSS-88, $F = (1, 18) = 0.015$, $p = 0.905$; MSWS-12, $F = (1,18) = 0.036$, $p = 0.852$) at different time of evaluation. At baseline and after five days of stimulation, *t*-test revealed no significant differences between the two groups: baseline [MAS: $t(18) = -0.747$, $p = 0.5$; MSSS-88: $t(18) = 0.490$, $p = 0.6$; MSWS-12: $t(18) = 0.346$, $p = 0.7$], after five days of stimulation [MAS: $t(18) = -0.483$, $p = 0.6$; MSSS-88: $t(18) = 0.549$, $p = 0.6$; MSWS-12: $t(18) = 0.300$, $p = 0.8$], Table 2.

Table 2

Differences between tDCS and SHAM patients in clinical and functional outcome

	tDCS (n = 10)	SHAM (n = 10)	p values
MAS baseline (±SD)	4,3 ± 1,6	4,7 ± 1,2	p = 0,5
MAS 5 days (±SD)	4,1 ± 1,5	4,4 ± 1,3	p = 0,6
MSSS-88 baseline (±SD)	207 ± 76,9	188 ± 95,5	p = 0,6
MSSS-88 5 days (±SD)	203,1 ± 74,4	183 ± 88,8	p = 0,6
MSWS-12 baseline (±SD)	44 ± 13,1	42 ± 12,7	p = 0,7
MSWS-12 5 days (±SD)	42,5 ± 11,6	41 ± 10,7	p = 0,8

MAS = Modified Ashworth Scale; MSSS-88 = Multiple Sclerosis Spasticity Scale; MSWS-12 = Multiple Sclerosis Walking Scale.

5. Discussion

The present study is the first one to address whether anodal tDCS is effective in modulating lower limb spasticity in MS patient The results of anodal tDCS for the treatment of fatigue, tactile sensory deficit, pain and motor performance were assessed in several studies and showed conflicting results (Mori et al., 2010, 2013; Cuypers et al., 2013; Ferrucci et al., 2014; Saiote et al., 2014; Tecchio et al., 2014). Studies regarding anodal tDCS application in spasticity are very limited and it has been studied only in stroke patients (Hummel et al., 2005; Sohn et al., 2013) showing promising results in post-stroke recovery. MS spasticity is commonly believed to follow the exaggerated activation of the stretch reflex secondary to the lesion of the upper motoneuron of the corticospinal tract as a result of loss of adaptive plasticity changes of brain activity. To promote the individual's potential for recovery in MS by exploiting adaptive plasticity is a major component of MS management. Unfortunately, our results indicate that anodal tDCS is not able to improve MS spasticity more than sham stimulation. Our results are in contrast with those obtained using rTMS protocol in the management of multiple sclerosis spasticity (Mori et al., 2010; Centonze et al., 2007) but they could be explained in several ways. While rTMS can generate strong circuits capable to depolarize neurons, tDCS differs from transcranial magnetic stimulation techniques as it does not trigger action potential but alters brain activity rather by influencing ion channels and gradients and hence the resting membrane potential (Fregni et al., 2007). In demyelinated axon there is an increase of passive nodal capacitance necessary to maintain resting membrane potential. Then it is conceivable that is necessary a higher current to modify membrane potential (Bostock et al., 1978). This pathological process could be responsible of tDCS failure given that its major effect is the shift in resting membrane potential of pre- and post- synaptic neurons (Nitsche et al., 2003). In addition, it is increasingly clear that both form of synaptic plasticity, LTP and LTD, are altered in MS due to synaptic dysfunctions involving glutamatergic and GABAergic neurotransmission (Nisticò et al., 2014). The loss of these mechanisms results in increased axonal damage and a lower numbers of synaptic connections and could be responsible of the unresponsiveness to anodal tDCS protocol. In fact, we applied anodal tDCS in a real-world clinical setting, including patients who

are moving to a more progressive phase and progressive structural damage limits functional reorganization (Schoonheim et al., 2010; Vuciv et al., 2012).On the other hand, it might be possible that anodal tDCS induces excitability changes on the cortical level in absence of a sufficient signal transfer to the peripheral level (Meesen et al., 2014) due to the alteration of signal transfer between central and peripheral regions in multiple sclerosis (Kale et al., 2009; Thickbroom et al., 2005). Although anodal tDCS induces effects on spinal network excitability, there is a lack of evidence in modulating Sol H reflex that is a reliable electrophysiological measure of stretch reflex (Roche et al., 2011). Instead, it could explain why anodal tDCS was effective in previous studies focused on rehabilitation of cortical function. However we cannot completely rule out the efficacy of anodal tDCS in MS spasticity. Limitations of this study are the small simple size and the only one side studied in each patient. In addition, anodal tDCS was specifically applied over the motor cortex connected with more affected leg, the modulatory effects produced by anodal tDCS could occur at distant interconnected site in the brain and in particular in the contralateral non stimulated motor cortex (Lang et al., 2005). Moreover, it remains to be investigated whether other approaches such bihemispheric stimulation (Tecchio et al., 2014), combined or not with spinal DC stimulation (Lamy et al., 2012) and higher intensity of stimulation could be more effective, what is the best stage of disease to treat, since in the earlier stage of disease rather than in chronic stage, LTP is still possible to evoke (Mori et al., 2013). Further studies performed in a larger samples of patients and more selected population of MS patients, are needed to verify the potential clinical impact of other approaches based on non-invasive brain stimulation.

Acknowledgments

Conflict of interest

None of the authors have potentially conflict of interest to be disclosed.

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