

1 **A PILOT STUDY ON THE EFFICACY OF TRANSCRANIAL DIRECT CURRENT**  
2 **STIMULATION APPLIED TO THE PHARYNGEAL MOTOR CORTEX FOR DYSPHAGIA**  
3 **ASSOCIATED WITH BRAINSTEM INVOLVEMENT IN MULTIPLE SCLEROSIS**

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6 **Running title: tDCS for dysphagia in MS**

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1 **Highlights:**

- 2 • Dysphagia can complicate Multiple Sclerosis (MS), causing considerable morbidity, due to  
3 respiratory sequelae.
- 4 • Anodal tDCS over the pharyngeal motor cortex may improve swallowing in dysphagic MS  
5 patients.
- 6 • Our findings suggest a potential benefit of pharyngeal motor cortex tDCS in MS-associated  
7 dysphagia.

1 **Abstract**

2 *Objective:* we investigated the effect of anodal transcranial direct current stimulation (tDCS) applied  
3 over the pharyngeal motor area in dysphagia associated with multiple sclerosis (MS). *Methods:*  
4 Eighteen MS patients with dysphagia associated with brainstem involvement were randomized to  
5 receive either “real” or “sham” tDCS. Primary outcome: The Penetration/Aspiration Scale (PAS).  
6 Secondary outcomes: changes in electromyographic (EMG) parameters and pharyngeal cortical  
7 motor evoked potentials (MEPs). Patients were evaluated at baseline (T<sub>0</sub>), at the end of 5-session  
8 cycle of tDCS stimulations (T<sub>1</sub>), after two (T<sub>2</sub>), and four (T<sub>3</sub>) weeks.

9 *Results:* the PAS values were significantly lower in the active group than in “sham” group at T<sub>1</sub>, and  
10 at T<sub>3</sub>. Over the post-stimulation periods, PAS significantly improved only in the “real” group. As  
11 regards the secondary outcomes, we observed a statistically significant difference between the 2  
12 groups only in the MEPs amplitude at T<sub>1</sub>. The comparison between baseline and each of the post-  
13 stimulation times showed significant differences only of the “real” group across all the secondary  
14 parameters.

15 *Conclusions:* Our findings support a beneficial effect of anodal tDCS applied to the pharyngeal motor  
16 cortex in MS-associated dysphagia. *Significance:* Considering its safety and efficacy, tDCS may  
17 represent an important resource in MS-associated dysphagia.

18

19 **Key words:** Multiple Sclerosis-associated dysphagia, transcranial direct current stimulation (tDCS),  
20 cortico-pharyngeal excitability, swallowing motor cortex, cricopharyngeal muscle, pharyngeal  
21 MEPs.

## 1 **Introduction**

2 Swallowing is a stereotyped sequence of movements controlled by a trigger center in the brainstem,  
3 called the central pattern generator (CPG). CPG receives afferents from the cerebral cortex, combines  
4 them with the peripheral inputs originating in the oral, laryngeal and pharyngeal muscles and mucosal  
5 areas, to orchestrate the final, complex sequence of swallowing (Jean A., 2001). The CPG is located  
6 in the medulla oblongata (Jean A., 2001) and it allows the ingestion of fluids and food, preventing  
7 aspiration. Dysphagia can be defined as the disruption of normal swallowing. This dysfunction can  
8 frequently complicate multiple sclerosis (MS), where it may cause considerable morbidity, due to its  
9 nutritional and respiratory sequaelae. Moreover, aspiration pneumonia, the most severe, and life-  
10 threatening complication is the leading cause of death in MS patients (Abraham et al., 1997; Thomas  
11 et al., 1999; Prosiegel et al., 2001; Abraham SS, Yun PT., 2002; Calcagno et al., 2002; Bergamaschi  
12 et al., 2008; Poorjavad et al., 2010). The prevalence of dysphagia in MS has been reported to be as  
13 high as 30-40% (Abraham et al., 1997; Thomas et al., 1999; Prosiegel et al., 2001; Calcagno et al.,  
14 2002; Bergamaschi et al., 2008; Poorjavad et al., 2010). The causes of dysphagia in MS patients are  
15 multiple, as they reflect the involvement of multifocal areas in the central nervous system (CNS). The  
16 evolutive and multifocal nature of MS makes recovery of neurogenic dysphagia in these patients  
17 highly unlikely. The situation is even more serious when considering that no specific pharmacological  
18 treatment is available for improving dysphagia associated with MS.

19 We have previously reported that botulinum toxin type A (BoNT/A) improves swallowing in MS  
20 patients with dysphagia associated to the hyperactivity of the cricopharyngeal (CP) muscle (Restivo  
21 et al., 2011). However, BoNT/A inoculation should be limited to patients with isolated hyperactivity  
22 of the upper esophageal sphincter (UES), as such treatment is ineffective in MS patients in which  
23 also other pathophysiological mechanisms in oral and pharyngeal phases of swallowing contribute to  
24 dysphagia (Alfonsi et al., 2010).

25 A variety of rehabilitative approaches have been proposed over time for improving the swallowing  
26 ability of dysphagic patients, but a protocol fulfilling the need for a safe swallowing has yet to be

1 established. Hence the importance of identifying novel, effective treatments that can be administered  
2 non-invasively and repeatedly at the patient's bedside to prevent or at least reduce penetration and  
3 aspiration.

4 Recently, intraluminal pharyngeal electrical stimulation (PES) proved effective in improving  
5 swallowing physiology in health and after stroke by increasing cortico-bulbar excitability (Fraser et  
6 al., 2002; 2003). The mechanism underlying this effect is likely a stimulus-induced cortical plasticity,  
7 which is thought to accelerate the long-term changes that take place during stroke recovery (Fraser et  
8 al., 2002; 2003). Fraser et al. (2003) have observed that PES-related changes in the cortex correlate  
9 with measurable improvements in swallowing physiology and reduce the occurrence of aspiration  
10 episodes. In a recent study, we demonstrated that PES, delivered at a frequency of 5 Hz with a 75%  
11 maximum tolerated intensity, significantly improves swallowing physiology and reduce aspiration in  
12 MS patients with dysphagia associated to bulbar involvement (Restivo et al., 2013a). The effect of  
13 PES might be ascribed to the capacity of sensory stimulation of pharyngeal afferents to increase motor  
14 excitability (Sweazey, 1988; 1995; Gow et al., 2004; Restivo et al., 2013a).

15 Transcranial direct current stimulation (tDCS) is another non-invasive, safe, and well-tolerated brain  
16 stimulation technique that proved able to directly cause changes in the excitability of the brain that  
17 outlast the duration of the stimulation (Nitsche et al., 2001; Gandiga et al., 2006; Jeffrey et al., 2007;  
18 Poreisz et al., 2007). tDCS acts by delivering a small electric continuous current across the cerebral  
19 cortex (Nitsche et al., 2001; Jeffrey et al., 2007). Anodal tDCS is obtained when the anode is placed  
20 over the motor cortex and the cathode over the supraorbital ridge and it is associated with a facilitatory  
21 effect. When the current flow is reversed (cathodal tDCS) the final effect is inhibitory.

22 The effects of tDCS on cortical swallowing areas have been investigated in healthy subjects by  
23 Jefferson et al. (Jefferson et al., 2009a). The authors showed that anodal stimulation increases the  
24 excitability of the pharyngeal motor cortex in an intensity- and duration-dependent manner, to indicate  
25 that tDCS produces a facilitatory effect quite similar, in terms of magnitude, to the effect elicited by  
26 intraluminal PES (Jefferson et al., 2009a), probably via the modulation of plasticity in the pharyngeal

1 cortical area. Anodal tDCS also induces a facilitation of the sucking activity of liquid bolus in healthy  
2 subjects (Cosentino et al., 2014). Moreover, it has been evidenced that tDCS applied over the  
3 swallowing motor cortex of the unaffected hemisphere was capable of ameliorating stroke-related  
4 dysphagia when compared to sham stimulation (Kumar et al., 2011; Suntrup-Krueger et al., 2018).  
5 Overall, these results suggest that tDCS may be effective in the treatment of dysphagia. We therefore  
6 postulated that anodal tDCS applied to the pharyngeal motor cortex might show a beneficial effect  
7 upon swallowing performance in dysphagic MS subjects. In the present study we thus aimed at  
8 assessing the effects of anodal tDCS, delivered at an intensity of 2mA for 20 minutes, on swallowing  
9 function in a sample of MS subjects with severe dysphagia with aspiration associated to active  
10 brainstem lesions.

11

## 12 **Research design and methods**

13 We enrolled 18 subjects with MS and severe dysphagia: 13 with a relapsing-remitting form, and 5  
14 with a secondary progressive form. The female/male ratio was 11/7; mean age:  $38.4 \pm 5.6$  years; mean  
15 score at the Extended Disability Status Scale (EDSS):  $5.8 \pm 0.7$ ; mean disease duration:  $8.9 \pm 2.7$   
16 years; mean dysphagia duration:  $21.7 \pm 7.2$  months. Four patients were fed by percutaneous  
17 endoscopic gastrostomy (PEG), the remaining 14 patients were on a diet with modified food  
18 consistency.

19 All patients underwent brain MRI studies. In order to rule out any bias or carry over effect, none of  
20 the patients had undergone swallowing therapy in the 3 months preceding the enrolment. No  
21 swallowing therapy was allowed for the entire study period. All subjects had a history of episodic  
22 dysphagia for liquid food that had progressed over time to severe dysphagia for both liquids and  
23 solids with aspiration and penetration. Individual clinical and demographical data of the 18 patients  
24 are illustrated in **Table 1**. All patients signed an informed consent prior to study inclusion. The study  
25 was conducted in accordance with the Declaration of Helsinki and received the approval of the local  
26 Ethics Committee. As swallowing alterations in MS patients could be related to different

1 pathophysiological mechanisms (i.e. brainstem dysfunction, cerebellar involvement and alterations  
2 of either sensory or motor central pathways) (Alfonsi et al., 2013), to avoid possible confounding  
3 factors, only MS patients with dysphagia caused by brainstem lesions were included in the present  
4 study.

5 *Inclusion criteria were:* 1) age > 18 years; 2) EDSS score < 7.6; 3) stable phase of disease, i.e. no  
6 changes > 1 point at the EDSS in the previous three months; 4) severe dysphagia for liquids, solids  
7 or both, present for at least two consecutive months at the time of enrolment; 5) at least one active  
8 (new) lesion within the brainstem at the MRI, without any active lesions in other cerebral regions.

9 *Exclusion criteria were:* 1) any other neurologic disease in addition to MS; 2) age > 60 years, to rule  
10 out non-specific swallowing abnormalities associated to presbiphagia; 3) any concurrent illness or  
11 disease of upper gastrointestinal tract; 4) inability to sign the informed consent due to cognitive  
12 impairment.

13 *Swallowing assessment:* swallowing function was investigated using a dual modality which consisted  
14 in videofluoroscopy (VFS) and electromyography (EMG) of the muscles involved in oropharyngeal  
15 swallowing. The Penetration/Aspiration Scale (PAS) was adopted to assess and grade penetration and  
16 aspiration in our patients (Rosembek et al., 1996). PAS is an 8-point severity scale from 1 = no  
17 material enters the airways to 8 = material enters the airways, passes below the vocal folds in the  
18 absence of any effort to eject it. It is largely used for the semi-quantitative assessment of the degree  
19 of endoscopically and/or radiologically measured penetration/aspiration. VFS was carried out using  
20 a standard radiographic fluoroscopic system with remote monitor and videofluoroscopic capabilities,  
21 using the modified barium protocol. Images were acquired at the frequency of 30 frames/sec and  
22 recorded on a VHS digital videotape for subsequent frame-by-frame revision. All subjects were  
23 instructed to keep the bolus in their mouth until they were asked to swallow. Images were obtained  
24 in the lateral view using the following anatomic markers: the lips anteriorly, the cervical spine  
25 posteriorly, the naso-pharynx superiorly, and the upper margin of the thoracic esophagus inferiorly.  
26 The total exposure time was strictly maintained below 80 sec for each study, with a radiation dose



1 lower than 0.3 millisieverts (mSv). Patients were asked to swallow 3 different types of consistencies  
2 of a standardized volume of bolus: thin liquid (equivalent to milk), semi-solid (equivalent to jelly),  
3 and solid (dry toast coated in barium). Two swallows per consistency were performed and the scores  
4 were averaged. VFS examinations were analyzed by a speech and language pathologist blind to  
5 treatment group and scored according to PAS. Penetration and aspiration were selected as indicators  
6 because of their clinical association with a more severe degree of swallowing impairment than other  
7 traditional signs of dysphagia and because a reduction in the severity of penetration and aspiration is  
8 considered as clinically meaningful in the management of neurogenic dysphagia.

9 Electromyography (EMG) of Swallowing Muscles: the evaluation was performed simultaneously  
10 recording with 3 channels: 1) from the suprahyoid/submental complex, 2) from the cricopharyngeal  
11 muscle (CP) and 3) from the skin above the larynx. The suprahyoid/submental muscles group  
12 (SHEMG) is a muscle complex consisting of the mylohyoid, the genioglossus, and the ventral belly  
13 of the digastric muscle. The EMG activity of this complex was obtained using two surface electrodes  
14 applied to the skin over the suprahyoid region and set 30 mm apart. The activity of the SHEMG marks  
15 the beginning of the propulsive action of the tongue during the oral phase of swallowing and it persists  
16 throughout the pharyngeal phase of swallowing (Alfonsi et al., 2010; 2013; Restivo et al., 2011;  
17 Restivo et al., 2013a; 2013b). SHEMG activity therefore reflects the behaviour of the muscular  
18 components mainly involved in the oral and pharyngeal phases of swallowing. The EMG activity of  
19 the CP muscle was recorded using a concentric needle electrode that was inserted at a distance of 1.5  
20 cm from the lateral border of the cricoid cartilage, following a posteromedial direction (Alfonsi et al.,  
21 2010; 2013; Restivo et al., 2011; 2013a; 2013b). The CP is a major contributor to the functional area  
22 known as the upper esophageal sphincter (UES) and therefore shows a tonic activity at rest. The tonic  
23 activity of the CP disappears completely for a brief time, lasting about 0.4-1 sec, during the  
24 pharyngeal (hypo-pharyngeal) phase of swallowing. The period corresponding to the disappearance  
25 of the tonic activity of the CP muscle is called inhibitory pause, which is instrumental to passage of  
26 the bolus transit into the upper esophageal tract (Alfonsi et al., 2013; Restivo et al., 2013a; 2013b).

1 The inhibitory pause of the CP muscle is used as a marker of the activity of this muscle and is strictly  
2 connected to the pharyngeal phase of swallowing (Alfonsi et al., 2013; Restivo et al., 2013b). Finally,  
3 the third channel was used for recording the laryngeal excursion movements of elevation during  
4 voluntary swallowing via a piezoelectric transducer placed over the crico-thyroid membrane using  
5 adhesive tape wrapped around the neck. The transducer consists of a rectangular strip with a triangular  
6 rubber button in the centre and showed a linear force-to-signal ratio ranging from 0.1 to 300 g. All  
7 EMG signals were band pass-filtered between 100 Hz and 2 KHz, whereas the transducer signals  
8 were band pass-filtered between 0.01 and 30 Hz. The sampling rate of the signal for each channel  
9 was set at 1 KHz. The signals derived from the myoelectric activity were preamplified (CED 1902  
10 Preamplifier, Cambridge Electronic Design, Cambridge, England, United Kingdom) and  
11 subsequently captured via a control and acquisition software (CED 1401). Data were visualized in  
12 real time on a PC screen and subsequently stored for in-depth analysis. Each patient was examined  
13 while seating with the head in a neutral position and was invited to swallow 5 ml of water introduced  
14 into the mouth with a disposable syringe.

15 We analyzed the following neurophysiological parameters: 1) duration of the excursion of the  
16 laryngeal transducer (LTE-D); 2) duration of the activation of the SHEMG (SHEMG-D); 3) the  
17 duration of the inhibitory pause of the CP muscle (CPEMG-PD) during the pharyngeal phase of  
18 swallowing; and 4) the interval between the onset of the EMG activity of SHEMG and the onset of  
19 the laryngeal elevation (SHEMG-LE interval). The recording of EMG traces was triggered when the  
20 activity of the SHEMG reached an amplitude  $\geq 50 \mu\text{V}$ . We obtained the recordings of 10 subsequent  
21 swallowing acts for calculating the average value of each electrophysiological parameter. For each  
22 electrophysiological parameter, we considered as normative values the 5th-95th percentiles computed  
23 in our laboratory from the data on 30 age-matched healthy controls. More specifically, the normative  
24 limits were: LTE-D: 1580-2100ms; SHEMG-D: 975-1274ms; CPEMG-PD: 327-563ms; SHEMG-  
25 LE interval: 165-268ms.

1 Transcranial Magnetic Stimulation (TMS): cortical excitability of the area corresponding to  
2 pharyngeal muscles was evaluated using TMS. The motor cortex was stimulated using a figure-eight  
3 coil connected to the magnetic stimulator (Magstim 200, 2.2 T, Whitland Dyfed, Wiles, UK) placed  
4 over the right or left pharyngeal area of the motor cortex, 2 cm anterior and 4-8 cm lateral to the Cz  
5 point (Fraser et al., 2003; Restivo et al., 2013a). Recordings were obtained using concentric needle  
6 electrodes inserted in the contralateral CP muscle using the above described insertion procedure for  
7 the evaluation of CP activity. CP-EMG signal was band pass-filtered between 20 Hz and 5 KHz.  
8 Motor threshold (MT) was expressed as a percentage of the stimulator output and it was defined as  
9 the lowest intensity of the stimulus capable of producing a 50- $\mu$ V motor evoked potential (MEP) in  
10 at least 5 out of 10 consecutive stimulations (Restivo et al., 2013a). We assessed the active CP MT,  
11 because this muscle is spontaneously active during non-swallowing periods, while it is inhibited  
12 during the swallowing act. Therefore, the MT was recorded in the tonically activated CP muscle.  
13 After achieving the MT, the stimulus intensity was increased step-by-step until the maximal MEP  
14 amplitude, measured peak-to-peak, was obtained. For each subject MEP amplitude was expressed as  
15 the average of 5 traces. In order to define hemispheric dominance for swallowing, during baseline  
16 evaluation we recorded MEPs in each subject from both the right and left CP muscle after stimulating  
17 the contralateral pharyngeal motor cortex. The hemisphere that displayed the higher amplitude of  
18 evoked motor response was considered the dominant hemisphere (Fraser et al., 2013) and it was  
19 chosen for tDCS application and TMS evaluation. In all patients the maximum MEP amplitude was  
20 obtained at stimulation intensities lower than 100% of stimulator output.

21 *Transcranial direct current stimulation (tDCS)*: anodal tDCS was delivered with the tDCS device  
22 (EMS, Bologna, Italy) through two 25-cm<sup>2</sup> rectangular surface electrodes, with the active one placed  
23 over the “pharyngeal” area of the motor cortex that produced the largest MEPs and the reference one  
24 on the contralateral supraorbital ridge. A water-soaked sponge was positioned underneath the  
25 electrodes in order to maximize their contact with the scalp. Furthermore, the electrodes were fixed  
26 in their position using a set of adjustable rubber straps placed around the head. For the active

1 intervention (the “real” stimulation group), current intensity was slowly increased up to 2mA. This  
2 intensity was maintained for 20 min before the stimulation was slowly turned off over a 10-sec period.  
3 For the “sham” intervention, the current was left on only for 30 sec, while the electrodes were left in  
4 place for a further 20-min period. According to previous reports, this modality of sham stimulation  
5 evokes the same initial tingling sensation as the real stimulation, but it does not generate any  
6 significant cortical change (Gandiga et al., 2006).

7 *Experimental Protocol.* During the experimental sessions, patients were seated in a comfortable chair.  
8 Randomization to anodal tDCS (9 patients) or sham tDCS (9 patients) for 5 consecutive days was  
9 performed according to a computer-generated list. Randomization was stratified in order to preserve  
10 treatment group balance. Patients were separately evaluated by two different physicians: one  
11 delivered the stimulation, the other evaluated its effect. The patients and the physician who analyzed  
12 the effect of stimulation were blinded to group allocation.

13 VFS, EMG, PAS scoring and TMS were performed at baseline ( $T_0$ ), immediately after the last session  
14 of tDCS ( $T_1$ ), and then two ( $T_2$ ), and four ( $T_3$ ) weeks after the end of tDCS.

15 Primary Outcome Measure: change in PAS score. Secondary Outcome Measures: changes in LTE-  
16 D, SHEMG-D; SHEMG-LE interval, CPEMG-PD and cortical MEP amplitudes recorded from the  
17 CP muscle of one side following TMS delivered on the contralateral pharyngeal motor area.

18 Statistical Analysis. The data collected during pre- and post-stimulation periods were analyzed using  
19 nonparametric tests, since the test of normality (Shapiro-Wilk test) yielded a  $p$  value below the  
20 threshold value of  $0.05$ . Differences between the two groups for each time period were assessed  
21 applying the Mann-Whitney-test for independent samples. The effect of the tDCS conditions on the  
22 swallowing measures over the periods from  $T_0$  to  $T_3$  was assessed for each group using the Friedman  
23 test, with the Wilcoxon Signed Ranks Test adopted to compare  $T_0$  with each subsequent period ( $T_1$ -  
24  $T_3$ ). Both between- and within-group multiple comparisons were adjusted by Bonferroni correction.  
25 The data are expressed as means and standard errors and the results were considered significant when

1  $p < 0.05$ . Statistical analyses were performed by using SYSTAT version 11 (Systat Inc., Evaston, IL,  
2 USA).

3

#### 4 **Results**

5 As for the specific inclusion criterion, all the subjects enrolled in the study had at least one active  
6 lesion within the brainstem as detected by MRI (Table 1) and no active supratentorial lesion. More  
7 specifically, all the patients had at least one demyelinating lesion localized on the right or left medulla  
8 oblongata and the side of stimulation matched that of the lesion in 10 out of 18 patients (5 out 9 in  
9 each group). Three patients presented an additional lesion in the right (2 patients) or left (1 patient)  
10 mesencephalon and one patient in the left pons. According to the statistical analysis (Mann-Whitney-  
11 test adjusted by Bonferroni correction) no significant differences were observed between the group  
12 of patients who received the tDCS stimulation on the same side of lesion and those who were  
13 stimulated on the contralateral side in either the primary or secondary outcome measures.

14 Anodal tDCS was well tolerated in all patients and no significant adverse events were observed.  
15 Baseline VFS showed a reduction of pharyngeal clearance and incomplete CP opening in all the  
16 patients. EMG alterations at different levels were observed in all patients. LTE-D was abnormal in  
17 16 out of 18 patients (89%), SHEMG-LE interval in 4 (22%), SHEMG-D in 12 (67%) and CPEMG-  
18 PD in 10 (55.5%). Table 2 summarizes the demographic, PAS and electrophysiological data of the  
19 groups of patients at baseline time.

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24 *Primary outcome measure*

1 The mean PAS score did not differ between “real” and “sham” group at baseline (Fig. 1,  $p = 0.25$ ).  
2 PAS scores were instead significantly lower in the “real” stimulation group than the “sham” group at  
3  $T_1$  ( $p = 0.004$ ) and at  $T_3$  ( $p = 0.048$ ), but not at  $T_2$  ( $p = 0.123$ ).

4 Over the post-stimulation periods ( $T_1$ - $T_3$ ) the “sham” stimulation group maintained the mean values  
5 of the primary outcome observed at baseline ( $T_0$ ). Conversely, in the “real” stimulation group we  
6 observed significant changes across the times of measurements (Friedman test:  $p < 0.001$ ). The  
7 comparison between the baseline and each of the post-stimulation periods showed a significant  
8 difference for PAS score recorded at  $T_1$  (Wilcoxon Signed Ranks Test:  $p = 0.019$ ).

9

#### 10 *Secondary outcome measures*

11 The two groups displayed similar electromyographic values at baseline (Fig. 2), while they differed  
12 only for MEP amplitudes at  $T_1$  (Fig. 2E), with the “real” stimulation group exhibiting higher values  
13 than the “sham” stimulation group ( $p = 0.04$ ). The CPEMG-PD showed nearly significant differences  
14 between groups at  $T_1$  ( $p = 0.077$ ) and  $T_2$  ( $p = 0.061$ ).

15 The comparison between baseline and each of the post-stimulation times showed significant  
16 differences only for the “real” stimulation group across all the secondary parameters. The tDCS  
17 induced a significant reduction of LTE-D (Fig. 2A; Friedman test:  $p = 0.012$ ; Wilcoxon Signed Ranks  
18 Test:  $T_0$ - $T_1$ ,  $p = 0.046$ ;  $T_0$ - $T_2$ ,  $p = 0.046$ ;  $T_0$ - $T_3$ ,  $p = 0.038$ ), SHEMG-D (Fig. 2B; Friedman test:  $p <$   
19  $0.001$ ; Wilcoxon Signed Ranks Test:  $T_0$ - $T_1$ ,  $p = 0.023$ ;  $T_0$ - $T_2$ ,  $p = 0.023$ ;  $T_0$ - $T_3$ ,  $p = 0.022$ ), SHEMG-  
20 LE interval (Fig. 2C; Friedman test:  $p < 0.001$ ; Wilcoxon Signed Ranks Test:  $T_0$ - $T_1$ ,  $p = 0.023$ ;  $T_0$ -  
21  $T_2$ ,  $p = 0.023$ ,  $T_0$ - $T_3$ :  $p = 0.032$ ), and a significant increase in CPEMG-PD (Fig. 2D; Friedman test:  
22  $p < 0.001$ ; Wilcoxon Signed Ranks Test:  $T_0$ - $T_1$ ,  $p = 0.023$ ;  $T_0$ - $T_2$ ,  $p = 0.023$ ;  $T_0$ - $T_3$ ,  $p = 0.023$ ), and  
23 in the amplitude of MEPs (Fig. 2E; Friedman test:  $p < 0.001$ ; Wilcoxon Signed Ranks Test:  $T_0$ - $T_1$ ,  $p$   
24  $= 0.023$ ;  $T_0$ - $T_2$ ,  $p = 0.035$ ). Figure 3A and B shows typical CP MEPs responses in 2 subjects  
25 stimulated with the two different tDCS paradigms: *real* anodal (Fig. 3A), and *sham* (Fig. 3B) during  
26 all the experimental sessions.

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**Discussion**

In humans, oro-pharyngeal swallowing undergoes a dual control, voluntary and involuntary. During the oral phase of swallowing, the sequential activation of several striated muscular groups, including suprahyoid/submental muscles, pushes the bolus towards the pharyngeal tract. During the pharyngeal phase, the activation of both suprahyoid/submental and the pharyngeal constrictor muscles, together with the reflex relaxation of the CP muscle permits the passage of the bolus through the UES (Alfonsi et al., 2013; Restivo et al., 2013a; 2013b). In patients with MS and associated oro-pharyngeal dysphagia, this coordinated activity can be deranged due to the damage of the cortico-bulbar projections to oral and/or pharyngeal muscles, with the consequent reduction of the central drive to these muscles. This may cause loss of the physiological balance of force and activation timing among the different muscles with consequent dysphagia (Alfonsi et al., 2013; Restivo et al., 2013a).

The main finding of this study was the demonstration that anodal tDCS was safe and effective on both the primary and secondary outcome measures. In particular, in comparison with sham stimulation, anodal tDCS induced a reduction of PAS scores which was statistically significant at the end of treatment and after 4 weeks. In addition, an increase of cortico-pharyngeal excitability was evidenced after 5 days of anodal tDCS and persisted after 2 weeks.

It has been previously demonstrated (Jefferson et al., 2009a) that anodal tDCS delivered over swallowing motor cortex both as a 10-min stimulation using an intensity of 1.5 mA and as a 20-min stimulation using an intensity of 1 mA significantly increased the excitability of the pharyngeal cortico-bulbar projections in healthy subjects as compared to sham stimulation (Jefferson et al., 2009a). The facilitation promoted by anodal tDCS appears immediately after the end of stimulus application, and the effect persists for 60 minutes after stimulation has been interrupted (Jefferson et al., 2009a). In particular, anodal tDCS may act mainly by prolonging the suprahyoid/submental muscle activity during suction with an improvement of the endurance of these muscles. This is likely due to a potentiation of central activation via the increased recruitment of cortical areas belonging to

1 the swallowing network (Cosentino et al., 2014). It has been observed that anodal tDCS applied daily  
2 (2 mA, for 30 minutes) for 5 consecutive days over the swallowing motor cortex of the unaffected  
3 hemisphere, in conjunction with standardized swallowing maneuvers, induced a modest, though  
4 significant improvement in swallowing in patients with stroke-related dysphagia (Kumar et al., 2011).  
5 The observed improvement is possible related to the combined effect of sensorimotor stimulation  
6 associated to the swallowing maneuvers and the simultaneous brain stimulation of the unaffected  
7 hemisphere, since it is known that sensory inputs from the pharynx can increase the excitability of  
8 the swallowing sensorimotor cortex through convergent afferent activities (Jefferson et al., 2009b).  
9 However, an evaluation arm including patients treated with anodal tDCS not combined with  
10 swallowing maneuvers was not included in this study. For this reason, it is not clear whether tDCS  
11 alone could be able to increase both swallowing sensorimotor cortex excitability and swallowing  
12 behaviour in these patients. In the present study, anodal tDCS applied over the swallowing motor  
13 cortex for 20 min with an intensity of 2mA was associated to a significant improvement in the  
14 swallowing performances in MS patients with severe oro-pharyngeal dysphagia associated with  
15 active brainstem lesions. In particular, the “real” stimulation group showed a significant improvement  
16 for all of the primary and secondary outcome measures as compared to baseline. When comparing  
17 the 2 groups, we detected significant difference at the post-stimulation periods only for two of the  
18 secondary outcome measures: CPEMG-PD duration and cortical MEP amplitude. This discrepancy  
19 may be explained with a variability of measures due to the small samples of MS patients examined.  
20 What is most noteworthy in the present findings is that anodal tDCS stimulation induced a significant  
21 reduction of the aspiration, as demonstrated by the changes of PAS with videofluoroscopy. This is  
22 even more important when considering that the results of our study clearly underscore the tolerability  
23 and the feasibility of tDCS over the pharyngeal motor cortex in MS-associated dysphagia.  
24 In this study we confirm the electrophysiological abnormalities in MS-associated dysphagia observed  
25 in a previous study (Alfonsi et al., 2013). The main abnormalities were a prolongation of both LTE-  
26 D and SHEMG-D, probably dependent on the incoordination between the propulsive oral phase and



1 the rising of the larynx during the pharyngeal phase of deglutition, in analogy to the dysfunction  
2 observed following brainstem and cerebellar lesions (Abraham and Yun, 2002; Alfonsi et al., 2013).  
3 The lack or reduction of the CPEMG-PD, which leads to UES hyperactivity, and the prolongation of  
4 the SHEMG-LE interval may represent a consequence of this incoordination occurring in patients  
5 with more severe dysphagia. These results are in keeping with the idea that laryngo-pharyngeal  
6 dysmotility associated to a prolonged interval between the oral and pharyngeal phases of swallowing  
7 represents one of the primary causes of dysphagia in MS (Abraham and Yun, 2002). The apparent  
8 discordance between the percent reduction in CPEMG-PD and SHEMG-LE (55.5% and 22%,  
9 respectively) observed in our patients and the reduction (30.8% and 57.7%, respectively) reported in  
10 our previous study (Alfonsi et al., 2013) may be due to different clinical phenotypes in the population  
11 under investigation. In the present study, indeed, patients were more severely affected: they had at  
12 least one active brainstem lesion and showed higher EDSS scores. This may explain a more marked  
13 impairment of the pharyngeal phase of swallowing control (detected as a more remarkable CPEMG-  
14 PD reduction) when compared to a less relevant impairment in the oral phase of swallowing (detected  
15 as a less marked reduction in SHEMG-LE reduction).

16 It has been recently demonstrated that in MS patients 5 sessions of anodal tDCS over the right  
17 swallowing motor cortex produced a small but significant reduction of dysphagia as evaluated by  
18 clinical scales (DOSS), lasting up to one month after stimulation (Cosentino et al., 2017). In the  
19 present study we expand these observations confirming that anodal tDCS is effective in reducing  
20 swallowing alterations in a group of MS patients with severe dysphagia caused by brainstem  
21 involvement.

22 In addition, our study seems to indicate that tDCS is able to electrophysiologically interfere with the  
23 different phases of swallowing, as demonstrated by the changes also induced by anodal tDCS in all  
24 electrophysiological measures related to the oral or pharyngeal phase of swallowing. In particular,  
25 the reduction of SHEMG-LE interval and SHEMG-D following anodal tDCS indicates that this  
26 stimulation could modulate the timing of oropharyngeal phases of swallowing. Furthermore, the

1 increase of the CPiEMG-P by anodal tDCS suggests that this type of stimulation can modify the  
2 activity of UES during the pharyngeal phase of swallowing. The increase in the amplitude of MEPs  
3 recorded in the pharyngeal motor cortex following anodal tDCS suggests that an increase of cortico-  
4 pharyngeal pathway excitability is involved in swallowing improvement. This is in keeping with the  
5 fact that the increase in MEP amplitude occurred immediately after the last session of stimulation, it  
6 continued for two weeks after the end of tDCS, but the maximal change occurred immediately after  
7 the end of the last stimulation session. The changes in neuronal excitability and the associated  
8 reorganization of neuronal connections represent indeed one of the main mechanisms of “cortical  
9 plasticity” (Hess and Donoghue, 1996). tDCS interferes with ‘any enduring change in cortical  
10 properties, such as strength of internal connections, altered representational patterns, or neuronal  
11 territories, either morphological or functional (Hess and Donoghue, 1996). In particular, anodal tDCS  
12 might increase the recruitment of cortical neurons of the cortico-pharyngeal motor area inducing  
13 either an increase of the residual neural activity of the affected CPG or a facilitation of the  
14 contralateral unaffected one. Since CPG is bilaterally innervated with evidence of minimal  
15 transcallosal inhibition (Hamdy et al., 1998), it is tempting to hypothesize that stimulation of either  
16 hemisphere would produce an increase in oro-pharyngeal excitability.

17 Overall, these electrophysiological changes indicate that anodal tDCS may restore swallowing  
18 functions probably by interfering at different levels with some of the pathophysiological mechanisms  
19 involved in neurogenic dysphagia.

20 We decided to perform 5 stimulation sessions based on previous reports showing an additive effect  
21 of repeated tDCS sessions (Boggio et al., 2007). With regard to the optimal dose for stimulating the  
22 pharyngeal motor cortex, this has not yet been established. In healthy subjects, Jefferson et al.  
23 (Jefferson et al., 2009), suggested that doses higher than those effective for excitability changes of  
24 (hand) primary motor cortex are necessary to produce remarkable responses from the swallowing  
25 motor cortex with an increase of cortical excitability in an intensity-and duration-dependent manner.

26 We chose our dose based on previous studies (Iyer et al., 2005; Kumar et al., 2011). It has been

1 demonstrated that tDCS with an intensity of 2mA in the dorsolateral frontal lobes is effective and  
2 well tolerated (Iyer et al., 2005). Moreover, Kumar et al. (Kumar et al., 2011) showed that doses of  
3 2mA for 30 minutes of anodal tDCS were effective and safe in both increasing cortico-bulbar pathway  
4 excitability and improving swallowing ability in stroke patients with dysphagia.

5 In conclusion, anodal tDCS over swallowing motor cortex seems to be able to improve the oro-  
6 pharyngeal components of swallowing in MS patients with dysphagia. tDCS can be safely delivered  
7 in the outpatient setting, needing neither hospitalization nor any type of anesthesia. Furthermore,  
8 tDCS is relatively passive and it requires a limited compliance from the patient's side, hence it  
9 qualifies for the use also in severely dysphagic patients, who may face difficulty in performing other  
10 volitional swallowing rehabilitation techniques. Moreover, this treatment proved safe and devoid of  
11 potential risk. Further studies are needed to refine this promising intervention by exploring effects of  
12 timing of the intervention, frequency of stimulation, and stimulation parameters in MS patients with  
13 dysphagia.

1 **Figure legends**

2 **Figure 1.** Mean values and standard errors for the changes in the penetration/aspiration scale (PAS)  
3 observed before the stimulation protocol (T<sub>0</sub>), immediately after the last session of 5 consecutive days  
4 of transcranial direct current stimulation (tDCS) (T<sub>1</sub>), after two (T<sub>2</sub>) and four (T<sub>3</sub>) weeks from the last  
5 stimulation session. “Real”: subjects who received anodal tDCS, 2mA, for 20 min, for 5 consecutive  
6 days; “sham”: subjects who experienced the same protocol of “real” group, but with the current left  
7 on only for 30 sec, and then switched off, with the electrodes being left in place for a further 20 min.  
8 §§  $p < 0.01$  and §  $p < 0.05$  indicate the statistically significant differences between the groups at each  
9 post-stimulation period. \*  $p < 0.05$  indicate the statistically significant differences between T<sub>0</sub> and  
10 each of the post-stimulation periods.

11

12 **Figure 2.** Mean values and standard errors for the changes in the secondary outcomes: 2.A) LTE-D  
13 – duration of laryngeal transducer excursion; 2.B) SHEMG-D – duration of the EMG activity of  
14 suprahyoid/submental muscles; 2.C) SHEMG-LE interval – interval between onset of EMG activity  
15 of suprahyoid/submental muscles and the onset of the laryngeal elevation; 2.D) CPEMG-PD –  
16 duration of the inhibition (pause) of the cricopharyngeal muscle; 2.E) Motor evoked potential (MEP)  
17 amplitudes of cricopharyngeal muscle. Symbols and labels as in Fig. 1.

18

19 **Figure 3.** Typical cricopharyngeal muscle (CP) motor evoked potentials (MEPs) responses recorded  
20 in 2 subjects with different transcranial direct current stimulation (tDCS) paradigms [*real* anodal (A),  
21 and *sham* (B)]. Each trace derives from average of 5 traces of CP MEPs associated with the  
22 stimulation of contralateral pharyngeal motor cortex of the hemisphere displaying swallowing  
23 dominance. Note the changes in amplitude at T<sub>1</sub> and T<sub>2</sub> following *real* anodal stimulation, which are  
24 not observed with *sham* stimulation.

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