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Transcranial Direct Current Stimulation Enhances Sucking of a Liquid Bolus in Healthy Humans

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a non-invasive technique used for modulating cortical excitability in vivo in humans. Here we evaluated the effect of tDCS on behavioral and electrophysiological aspects of physiological sucking and swallowing.

Methods: Twelve healthy subjects underwent three tDCS sessions (anodal, cathodal and sham stimulation) on separate days in a double-blind randomized order. The active electrode was placed over the right swallowing motor cortex. Repeated sucking and swallowing acts were performed at baseline and at 15 and 60 min after each tDCS session and the mean liquid bolus volume ingested at each time point was measured. We also calculated average values of the following electrophysiological parameters: 1) area and 2) duration of the rectified EMG signal from the suprahyoid/submental muscles related to the sucking and swallowing phases; 3) EMG peak amplitude for the sucking and swallowing phases; 4) area and peak amplitude of the laryngeal-pharyngeal mechanogram; 5) oropharyngeal delay.

Results: The volume of the ingested bolus significantly increased (by an average of about 30% compared with the baseline value) both at 15 and at 60 min after the end of anodal tDCS. The electrophysiological evaluation after anodal tDCS showed a significant increase in area and duration of the sucking phase-related EMG signal.

Conclusions: Anodal tDCS leads to stronger sucking of a liquid bolus in healthy subjects, likely by increasing recruitment of cortical areas of the swallowing network. This finding might open up interesting perspectives for the treatment of patients suffering from dysphagia due to various pathological conditions.

Introduction

In recent years, there has been considerable interest in the use of non-invasive brain stimulation techniques as a means of studying brain functions, thanks to the ability of these techniques to modulate the activity of different cortical regions in both physiological and pathological conditions [1]. In the space of just a few years, transcranial direct current stimulation (tDCS), being easy to use and useful for sham-controlled double-blind experiments, has become one of the most widely used brain stimulation methods [2–5]. tDCS uses constant, low currents delivered to the brain area of interest via electrodes placed over the scalp. It induces polarity-dependent changes in the spontaneous neuronal firing rate that outlast the end of the stimulation. These long-lasting effects, observed with both anodal and cathodal tDCS, are likely mediated, respectively, by induction of long-term potentiation- and long-term depression-like mechanisms [6,7].

Two recent studies, both conducted in healthy human subjects, have evaluated the possibility of using tDCS to modulate the activity of the swallowing motor cortex. In the first, by Jefferson et al. [8], anodal tDCS was shown to be capable of increasing pharyngeal motor cortex excitability as assessed by transcranial magnetic stimulation (TMS). In the second, performed using the magnetoencephalographic technique, Suntrup et al. [9] provided evidence

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Conflict of interest: None of the authors of the above manuscript declare any conflict of interest.

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that anodal tDCS, when applied over the swallowing motor cortex of either hemisphere, may bilaterally increase the activity of the swallowing cortical network. These findings have opened up interesting perspectives for the treatment of dysphagia; indeed, anodal tDCS has already been used to treat dysphagic stroke patients and given encouraging results [10,11].

Normal swallowing is a complex act involving a sequence of finely integrated neuromuscular events. Both conscious and subconscious areas of the brain, such as the swallowing centers in the motor cortex and brainstem, the cranial nerves and specific musculo-cartilaginous structures of the pharynx and larynx, contribute to normal, safe swallowing [12,13]. The aim of the present study was to evaluate whether tDCS applied over the swallowing motor cortex could affect the sucking and swallowing of a liquid bolus in healthy subjects. We were particularly interested in investigating, along with the electrophysiological aspects of oropharyngeal deglutition, the effective impact of tDCS on the normal motor behavior of sucking and swallowing. We therefore used a non-invasive method to evaluate changes in sucking and swallowing capacity, i.e. we measured the volume of the water boluses ingested during repeated sucking and swallowing actions. The electrophysiological aspects were monitored by recording various parameters related to activation of different structures involved in sucking and oropharyngeal swallowing. It was hypothesized that the present study might provide results that would be useful for assessing the therapeutic potential of tDCS in pathological conditions in which the ability to suck and swallow effectively can be impaired.

Materials and methods

Subjects

Twelve right-handed healthy subjects, 7 males and 5 females, mean age 30.1 ± 9.5 SD years, participated as volunteers in this study. Informed consent was obtained from all the participants, none of whom had a history of swallowing difficulties, neurological disease, speech disorders, voice problems or pulmonary disease. The research protocol was approved by our institute's ethics committee, and the study complied with the Declaration of Helsinki.

Experimental paradigm and study design

Each subject was evaluated while seated in a chair equipped with its own flat table on which was placed a graduated transparent glass beaker containing 500 ml room-temperature water. The study was carried out after the participants had received an exhaustive explanation about the swallowing test they were about to perform. All volunteers were instructed to drink the water through a bent straw (diameter 6 mm), while keeping their head and trunk in a natural position, avoiding excessive flexion or extension postures. To evaluate maximum oropharyngeal swallowing capacity all the subjects were instructed to suck hard on the straw and ingest, in a single deglutition, the largest volume of water they could. We recorded eight consecutive swallows separated by intervals of 5 s; each one was performed on the examiner's command and, each time, the examiner carefully recorded the change in the volume of water in the beaker, by making a mark with a pencil on a strip of white tape applied longitudinally to the outer surface of the graduated beaker. The study had a randomized, double-blind, sham-controlled design. To ensure their ability to perform the test correctly, all the participants underwent a training session prior to the study. Each subject was tested on three different days separated by intervals of at least a week. The order of the interventions was pseudo-randomized and balanced across the participants. Each experimental session consisted of three trials (i.e. three series of eight sucking and swallowing acts), the first performed in the baseline condition and the second and third at 15 and 60 min after the end of tDCS. The three experimental sessions differed from each other only in the type of stimulation used: anodal, cathodal or sham (placebo). To ensure maintenance of the correct positioning of the electrodes and the piezoelectric transducer, the subjects were asked to remain seated throughout the duration of each experimental session and to speak only if strictly necessary. Both the healthy volunteers and the examiner were always unaware of the type of tDCS delivered.

tDCS intervention

In each session, continuous tDCS was delivered starting from 5 min after the end of the baseline evaluation, through a pair of electrodes in 5 × 5 cm water-soaked synthetic sponges, by means of a battery-driven constant current stimulator (Newronika HDCstim, Newronika s.r.l., Milan, Italy). For the anodal condition, the anode electrode was placed over the right swallowing motor cortex, according to the cortical topography of the human swallowing musculature in healthy subjects, as established by previous TMS studies [14,15], while the cathode was positioned over the contralateral orbitofrontal cortex. For cathodal tDCS the montage was reversed. In each patient, the optimal position for placing the active electrode was taken as the site where three out of five consecutive magnetic stimuli delivered at the lower stimulus intensity elicited motor evoked potentials (MEPs) of at least 50 μV in amplitude. MEPs were recorded from the resting contralateral submental muscle complex.

The tDCS montage used was expected to generate the maximum current density over the precentral and perisylvian cortices. These include the motor and premotor areas for the human swallowing musculature, which, as shown by previous brain-imaging studies [16,31] as well as physiological studies in humans [14] and primates [13], play a prominent role in swallowing function.

The decision to place the active electrode over the right swallowing motor cortex was based on evidence that swallowing functions may be more consistently represented in the right hemisphere [14,16]. Currents were applied for 20 min at an intensity of 1.5 mA (current density 0.06 mA/cm^2), and they were ramped up or down over the first and last 8 s of stimulation. For the sham condition, the intensity was set to 1.5 mA (as for anodal and cathodal tDCS) and the site for anode placement was randomly chosen. The DC stimulator was turned off after 30 s of stimulation, so that subjects felt the initial itching sensation, as in the anodal and cathodal condition, but received no current for the rest of the stimulation period. At the end of the sham condition, the DC stimulator was switched on for 30 s to mimic the sensation, due to current ramp down, which is perceived at the end of real tDCS. This technique has been reported to be a reliable method of sham stimulation [3,5].

Electrophysiological assessment

We used a previously described combined electrophysiological-mechanical method for measuring submental electromyographic (EMG) activity and laryngeal movements during swallowing [17]. The electrophysiological parameters were recorded using a Medelec Synergy SINC5−C (©Viasys Healthcare, Manor Way, Old Woking, Surrey, UK) electromyograph with two recording channels operating simultaneously. The first channel recorded the EMG activity of the suprahyoid/submental muscles (a muscle complex consisting of the mylohyoid, the genioglossus, and the ventral belly of the digastric) using two surface electrodes applied to the skin over the suprahyoid region at an interelectrode distance of 30 mm. This activity reflects both the sucking and the propulsive action of the tongue in the oral and pharyngeal phases of swallowing [18,19]. The EMG signal from the first channel was bandpass filtered between 100 Hz and 2 kHz and then full-wave rectified. The second channel recorded the mechanogram obtained from a piezoelectric transducer that detects the deformations produced by the pharyngeal-laryngeal structures during swallowing. In particular, the transducer detects the movement of the hyo–laryngeal complex and the time of elevation-retroflection, and return to rest position, of the epiglottis. This transducer consisted of a rectangular strip with a triangular rubber button in the center, which was applied to the skin over the cricothyroid membrane and kept in place by adhesive tape wrapped around the neck. It showed a linear force-to-signal ratio for forces ranging from 0.1 to 300 g; its signals were bandpass filtered between 0.01 and 30 Hz. In both recording channels sweep was 500 ms/div with a sampling rate of 200 Hz.

Measurements

In each experimental session, we calculated the mean ingested water bolus volume for each of the three swallowing trials, performed respectively at baseline and 15 and 60 min after the end of tDCS. We also calculated the average values of the following electrophysiological parameters obtained from the eight deglutitions comprising each trial: 1) area of the rectified EMG signal from the suprahyoid/submental muscles (SHEMG-A) related to the sucking and swallowing phases; 2) duration of the rectified EMG signal from the suprahyoid/submental muscles (SHEMG-D) related to the sucking and swallowing phases; 3) EMG peak amplitude for the sucking and swallowing phases; 4) area and peak amplitude of the laryngeal-pharyngeal mechanogram (LPM); 5) oropharyngeal delay measured as the interval between the onset of swallowing-related SHEMG activity and the onset of the laryngeal-pharyngeal mechanogram (I-SHEMG-LPM). As regards SHEMG we calculated the area and duration of the EMG activity related to the sucking and swallowing phases, which are characterized by distinct patterns of EMG activity (see Fig. 1). The EMG activity corresponding to the sucking phase reflects a continuous, intermediate activation of the suprahyoid/submental muscle group, whilst the EMG signal related to the swallowing phase is characterized by a rapid increase and decrease of amplitude giving an overall triangular shape. The minimum mechanical deformations produced at the level of the laryngeal and pharyngeal structures by sucking were excluded from the LPM analyses (see Fig. 1). The electrophysiological parameters were rated offline by two different experts who were blinded to the stimulation performed in each subject.

Statistical analyses

The mean parameter values for each trial (each set of eight traces) were determined for each subject and used for statistical analyses. Two-way repeated-measures analyses of variance (ANOVAs) with within-subjects factors “Condition” (3 levels: anodal, cathodal, sham condition) and “Time” (3 levels: baseline, 15 and 60 min after tDCS) were performed to evaluate changes in the bolus volume and in each electrophysiological parameter. Mauchly’s test was used to check the sphericity assumption, and, if necessary, the Huynh-Feldt correction for degrees of freedom was adopted. Tukey’s test was used for post-hoc analysis. Pearson’s test was used to check for correlation of the volume of the ingested bolus with the electrophysiological measures recorded before tDCS was applied (average values of the three baseline recordings were used in the analysis). Statistical analyses were performed using Statistica 7.0 software (StatSoft, Tulsa, OK). For all analyses the level of statistical significance was set at $P < 0.05$.

Results

All the participants enrolled in the study were able to carry out the experimental task effectively and completed the entire experimental protocol. No drop outs occurred during the study. The

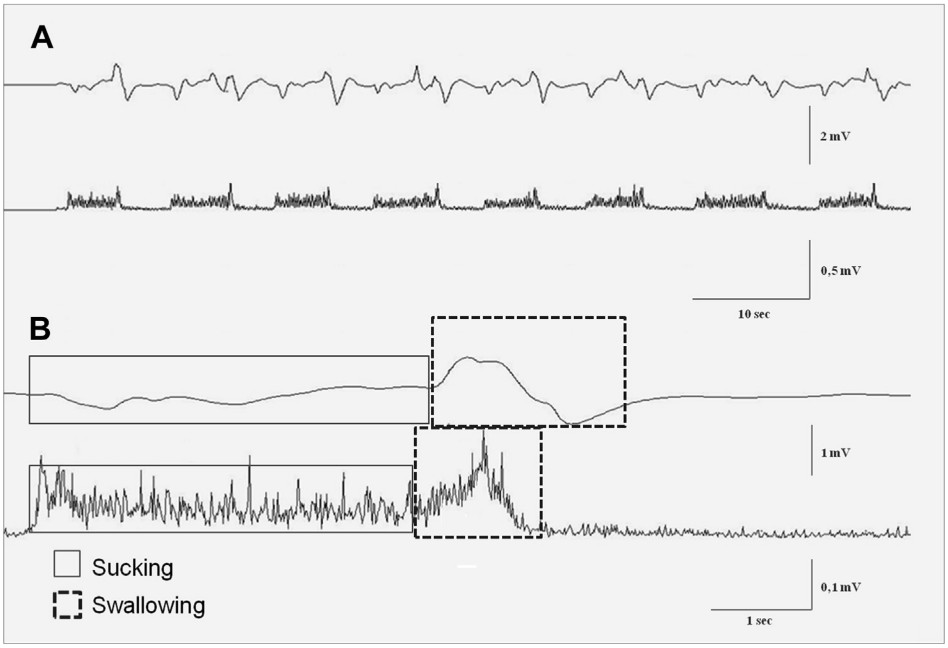

Figure 1. Representative examples of the mechanical and electromyographic signals recorded in a subject performing the sucking and swallowing task. In A: Pharyngeal-laryngeal mechanogram (upper trace) and EMG activity of the suprahyoid/submental muscles (lower trace) during eight successive sucking and swallowing acts. In B: Pharyngeal-laryngeal mechanogram (upper trace) and EMG activity of the suprahyoid/submental muscles (lower trace) recorded during a single sucking and swallowing act. Notice the different features of the mechanogram and EMG activity related to the sucking and swallowing phases (see text for more details).

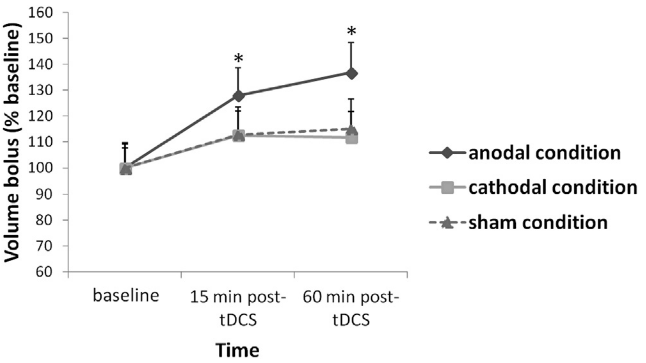

Figure 2. Changes in the volume of the ingested volume (mean value calculated from eight sucking and swallowing acts) before and 15 and 60 min after anodal, cathodal or sham tDCS. Error bars indicate standard error of means (SE). Asterisks (*) indicate significant variations from baseline.

experimental procedures were well tolerated and no adverse effects were observed. The site of maximum right hemisphere responses for the contralateral suprahyoid/submental muscles was 9.2 ± 1.0 SD cm lateral, and 5.8 ± 1.6 SD cm anterior to the vertex as assessed by TMS.

Changes in the volume of the ingested bolus

On evaluation of the changes in bolus volume between baseline and post-tDCS (15 and 60 min after the end of stimulation) (Fig. 2), ANOVA showed a significant effect of the factor "Time" ($F_{(1,1;\ 12,6)} = 5.10$, $P < 0.05$) and a significant interaction between "Condition" and "Time" ($F_{(4;\ 114)} = 3.95$, $P < 0.01$). Post-hoc analysis showed that bolus volume at 15 and 60 min post-tDCS increased significantly with respect to the baseline value ($P < 0.001$) only in the anodal condition. No significant changes were found between the three mean baseline values or between pre- and post-cathodal or sham stimulation sessions.

The correlation analysis tests showed that, at baseline, the ingested bolus volumes were correlated with the duration of the sucking-related SHEMG ($r = 0.61$, $P < 0.05$), but not with other electrophysiological measures.

Changes in the electrophysiological parameters

ANOVA, used to evaluate the sucking-related SHEMG-A (Fig. 3A), showed a significant effect of the factor "Time" ($F_{(2,\ 22)} = 12.4$, $P < 0.0005$) and a significant interaction between "Condition" and "Time" ($F_{(3,5;\ 38,4)} = 3.1$; $P < 0.05$). No significant effects or interactions were found for the swallowing-related SHEMG-A (Fig. 3B). Post-hoc analysis of the sucking-related SHEMG-A showed significantly increased mean values at 15 and 60 min after tDCS with respect to baseline ($P < 0.05$) only in the anodal condition.

As regards the sucking-related SHEMG-D (Fig. 4A), ANOVA revealed a significant effect of the factor "Time" ($F_{(1,9;\ 21)} = 9.3$, $P < 0.01$) and a significant interaction between "Condition" and "Time" ($F_{(3,3;\ 36,8)} = 3.6$, $P < 0.002$). No significant effects or interactions were found for the swallowing-related SHEMG-D (Fig. 4B). Post-hoc analysis of the sucking-related SHEMG-D revealed significantly increased mean values both at 15 and 60 min post-tDCS as compared to the baseline ($P < 0.02$), but only after anodal tDCS. No significant changes were observed between the baseline values of the three different conditions, or between pre- and post-cathodal or sham stimulation sessions.

ANOVA showed no significant effects of EMG peak amplitude (either in the sucking or in the swallowing phase), LPM area and peak amplitude, or I-SHEMG-LPM.

Discussion

The main finding of the present study is that tDCS, when applied to the right swallowing motor cortex of healthy humans, increases the volumes of liquid boluses ingested during a sucking and swallowing task. This effect is polarity dependent, being observed only after anodal, and not cathodal or sham tDCS, and it persists for up to an hour from the end of stimulation. Our analysis of changes in the electrophysiological parameters related to activation of the suprahyoid/submental muscles during the repeated sucking and swallowing acts suggests that the larger volumes ingested are due mainly to the development of stronger sucking. Indeed we recorded a significant increase in both area and duration of the sucking-related SHEMG activity after "facilitatory" anodal stimulation. This finding is consistent with the positive correlation observed at baseline between the ingested bolus volume and the duration of sucking-related SHEMG, which suggests that this latter parameter may play a major role in determining the volume of the ingested water bolus.

The suprahyoid/submental muscles play a key role in both sucking and swallowing. During sucking, the lips and cheeks seal the oral cavity thereby allowing fluids to move into the mouth due to the negative intraoral pressure created by the dropping down of the tongue and contraction of the suprahyoid/submental muscles [20]. In swallowing, these muscles form a platform and provide support for the tongue, which rises toward the palate and generates forces that push the liquid bolus into the pharynx [21,22]. In addition, contraction of the suprahyoid/submental musculature serves to lift the hyolaryngeal complex in order to position the entrance to the airway out of the path of the bolus and prevent aspiration into the respiratory tract [23]. The suprahyoid/submental muscles thus play a role in a series of relatively simple reflex behaviors (principally mediated by brainstem mechanisms) fundamental for mammalian feeding [12]. Converging evidence from electrophysiological, neuroimaging and clinical studies also indicates that multiple cortical regions play a pivotal role in the regulation of swallowing [24,25]. In the present study, anodal tDCS applied over the swallowing motor cortex was found to be capable of specifically modulating sucking-related, but not swallowing-related, suprahyoid/submental muscle activity. This selective capacity may be due to the functional compartmentalization that exists within the suprahyoid/submental musculature; indeed, there is evidence that separate subgroups of fibers, under the control of different peripheral and central neural mechanisms, may be selectively activated during different stages of sucking and swallowing [26–30]. It has been shown that, at the cortical level, a number of spatially and functionally distinct loci may participate differentially in the regulation of various aspects of swallowing, also in relation to the degree to which it is performed under volitional control [14,16,25,31]. It is worth noting that in the present study the sucking and swallowing acts were performed on command rather than spontaneously. In particular, the sucking phase was executed under conscious control following the verbal instruction to expend maximum effort. This likely resulted in greater activation of the cortical areas responsible for the voluntary regulation of the bolus size (i.e. premotor and motor cortices), whose activity could also have been modulated by the tDCS. This interpretation agrees with evidence that sensorimotor cortex and supplementary motor area activation significantly increases with greater force of muscle contraction [32].

A possible explanation for the absence of significant tDCS-induced changes in the swallowing-related SHEMG, as well as in the LPM parameters and oropharyngeal delay, is that tDCS probably

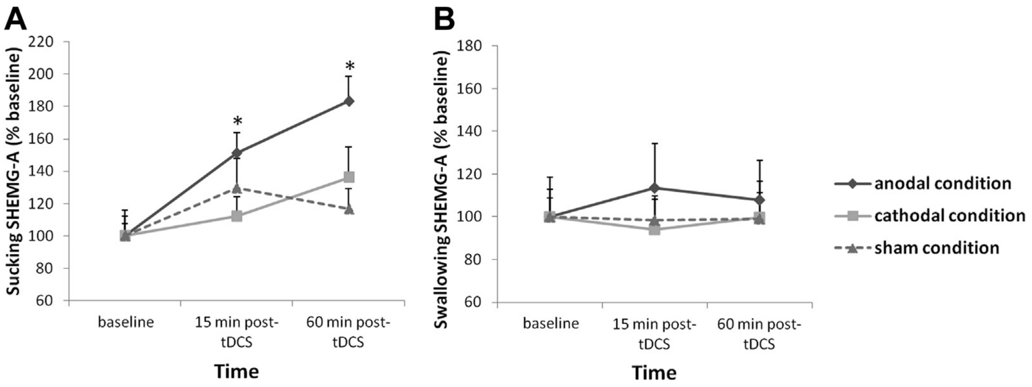

Figure 3. Changes in the area of the EMG signal from the suprahyoid/submental muscles related to sucking (A) and swallowing (B) (mean value calculated from eight sucking and swallowing acts) before and 15 and 60 min after anodal, cathodal or sham tDCS. Error bars indicate standard error of means (SE). Asterisks (*) indicate significant variations from baseline.

has less influence on the swallowing automatisms mediated by the brainstem neural circuits. Indeed, even though the initiation of swallowing may be triggered at cortical level, it is known that deglutition is largely mediated by automatic reflex mechanisms activated by peripheral afferent inputs from the oral region [12]. Moreover, it is noteworthy that the large liquid boluses ingested in the sucking and swallowing test performed in this study could facilitate deglutition per se, due to better sensorimotor integration, and to the facilitating effect of gravity, which helps the tongue and pharyngeal musculature to transport the bolus to the hypopharynx [33]. As regards the mechanisms of action of tDCS, it has been shown that in healthy volunteers tDCS induces a long-term effect on the excitability of the corticobulbar projections [6,7]. Thus we suppose that, in the present study, anodal tDCS provided an additional excitatory input to the swallowing motor cortex thereby boosting the volitional neural drive (central activation) needed to perform the sucking and swallowing task. We cannot infer, on the basis of our results, whether this facilitatory effect was due mainly to the enhancing of motivation and/or descending drive to the motorneuron pool. The finding that anodal tDCS prolonged the contraction time of the suprahyoid/submental muscles agrees with evidence that anodal tDCS may prolong the duration of muscle contraction during a high degree of effort [34,35]. Moreover, it could indicate the involvement of cortical areas responsible for motor planning. Indeed, given the size of the active electrode used, it can be assumed that maximal current density was generated not only over the inferior sensorimotor cortex but also over the neighboring premotor brain regions, which are critical for motor planning.

Finally, considerations and limitations of the current study need mentioning. First, although swallowing behavior involves both cerebral hemispheres, there is clear evidence that in some individuals one hemisphere, i.e. the right or the left one, tends to be more important than the other in mediating swallowing [14,16,25,36,37]. In this study, we placed the active electrode on the right hemisphere in all the subjects and did not assess swallowing laterality, e.g. by means of TMS or functional MRI. Therefore, it is reasonable to assume that in a rather large proportion of subjects we stimulated the swallowing-non-dominant hemisphere. It is also to be noted that each hemisphere has functional specializations; indeed, evidence has been provided that specific components of swallowing may be differentially lateralized or dissociated at the cortical level [36]. On the basis of these considerations, it is conceivable that a different modulation of sucking, or even an effect on swallowing, might have been observed had we targeted, in all the subjects, the swallowing-dominant hemisphere or the left one. Future studies will be needed to address this issue.

In addition, it should be noted that we did not assess tDCS-induced changes in motor cortical excitability, e.g. by evaluating changes in MEP amplitude or in other TMS measures of intracortical activity. Therefore we can only hypothesize that the observed effects on sucking behavior were due to long-lasting modifications of cortical excitability induced by tDCS.

Another aspect to be taken into account is that our results cannot be directly generalized to drinking from a cup, or eating solid foods or two-phase foods (i.e. with both solid and liquid phases). Indeed, significant variations in the oropharyngeal phase of swallowing may occur in relation to differences in the texture

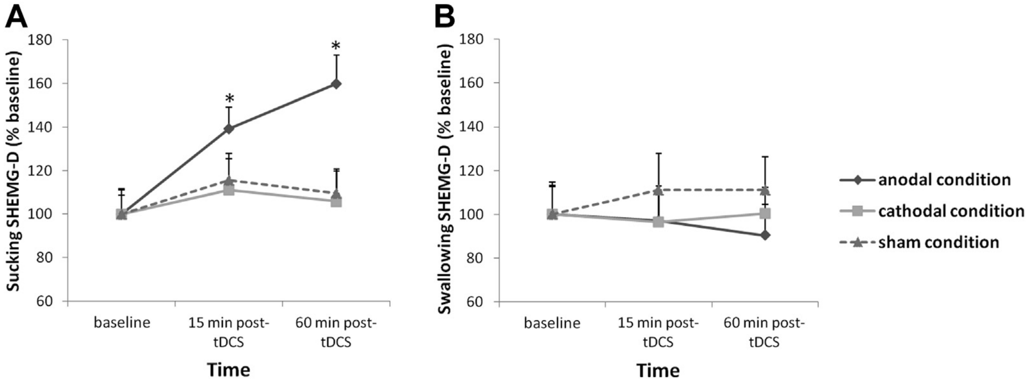

Figure 4. Changes in the duration of the EMG signal from the suprahyoid/submental muscles related to sucking (A) and swallowing (B) (mean value calculated from eight sucking and swallowing acts) before and 15 and 60 min after anodal, cathodal or sham tDCS. Error bars indicate standard error of means (SE). Asterisks (*) indicate significant variations from baseline.

and viscosity of food, which can require different swallowing behaviors [38,39]. Thus, in the future, more specific studies are needed to assess the possible impact of tDCS in all these cases.

In conclusion, our results may open up interesting therapeutic perspectives for patients suffering from dysphagia due to various pathological conditions, especially ones that can be associated with impaired sucking, e.g. neuromuscular diseases, stroke, and Parkinson's disease. First, anodal tDCS could be employed to enhance the effectiveness of exercises targeting the sucking musculature, in accordance with the neurorehabilitation principle that increasing the level of activation of a group of muscles would not only help prevent degradation of function mediated by those muscles, but would also help to actively improve it [40,41]. Furthermore, it is noteworthy that swallowing strategies adopted in patients with dysphagia due to neurological causes often include postural changes and drinking through a straw [42,43]. These strategies are designed to prevent the backward head tilt that occurs when drinking from a cup, as this would result in neck extension, and thus raise the risk of the bolus being misdirected into the airway. Drinking straws that can assist in placing, directing and controlling the liquid bolus may also be very useful in the management of sucking and swallowing difficulties in healthy older people (presbyphagia), even though this approach may be less effective in the presence of weak sucking due to sarcopenia [44]. Thus, in all these conditions tDCS could be a useful tool for promoting stronger sucking and thus for facilitating rehabilitation approaches based on the use of drinking aids. Nevertheless, it must be clearly stated that in dysphagic patients with predominant incoordination of the oropharyngeal musculature, the safety of anodal tDCS should be carefully assessed. Indeed, though it is likely that the increase in sucking volume could have a positive effect on deglutition by allowing better sensory-motor integration, it is also conceivable that it could increase the risk of aspiration.

In conclusion, our results in healthy humans suggest that there is a need to evaluate, in future studies, the safety and the potential role of tDCS in the treatment of dysphagia in the wider clinical setting, also in conjunction with targeted rehabilitation strategies.

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