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Short communication

Anodal transcranial direct current stimulation over left inferior frontal gyrus enhances sentence comprehension

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A R T I C L E I N F O

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A B S T R A C T

We tested the possibility of enhancing natural language comprehension through the application of anodal tDCS (a-tDCS) over the left inferior frontal gyrus, a key region for verbal short-term memory and language comprehension. We designed a between subjects sham- and task-controlled study. During tDCS stimulation, participants performed a sentence to picture matching task in which targets were sentences with different load on short-term memory. Regardless of load on short-term memory, the Anodal group performed significantly better than the Sham group, thus providing evidence that a-tDCS over LIFG enhances natural language comprehension.

To our knowledge, we apply for the first time tDCS to boost sentence comprehension.

This result is of special interest also from a clinical perspective: applying a-tDCS in patients manifesting problems at the sentence level due to brain damage could enhance the effects of behavioral rehabilitation procedures aimed to improve language comprehension.

1. Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory technique that uses a weak constant direct current to modify the spontaneous firing rate of neurons in a polarity-dependent way: anodal tDCS (a-tDCS) depolarizes membrane potential, while cathodal tDCS yields to opposite effects (Bindman, Lippold, & Redfearn, 1964; Purpura & McMurtry, 1965).

As reviewed in Monti et al. (2013), tDCS has been applied successfully in several works aimed at studying language processing in healthy individuals. Among others, a-tDCS has been shown to improve verbal fluency (Cattaneo, Pisoni, & Papagno, 2011; Iyer et al., 2005), word retrieval (Fiori et al., 2011) picture naming (Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010; Holland et al., 2011; Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008), verbal learning (Flöel, Rösser, Michka, Knecht, & Breitenstein, 2008), and artificial grammar learning (De Vries et al., 2010).

Furthermore, single sessions of a-tDCS have been reported to affect performance of healthy subjects in tasks tapping working memory (Brunoni & Vanderhasselt, 2014). Specifically, a-tDCS stimulation over the dorsolateral prefrontal cortex has been found to enhance working memory performance, as measured by a sequential-letter working memory task (e.g. Fregni et al., 2005).

Still, to our knowledge no study has ever been devoted to exploring tDCS effects at the sentence level. This gap in the existing literature prompted us to investigate whether anodal tDCS may indeed boost sentence comprehension.

Sentence comprehension involves a complex interaction of cognitive abilities (phonological skills, word decoding, morpho-syntactic processing, pragmatic abilities etc.) and, in principle, the effects of tDCS on each of these components might be the topic of a separate study. However, we decided to start our investigation on the enhancing role of tDCS (if any) by focusing on another essential cognitive component for sentence comprehension, namely working memory resources. We did that because their role in language comprehension has been studied fairly extensively with neurostimulation techniques other than tDCS, as we are going to report, so we could build on findings emerging from these previous studies.

It is uncontroversial that language comprehension requires memory resources, either related to the length of the sentence (e.g. "*Yesterday the sun was shining and I went to the park with my cousin Mario*"), or to syntactic complexity, and specifically to the presence of long-distance

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dependencies. For example, in a sentence like "*The dog that the boy is watching is chasing the cat*", the relative clause < that the boy is watching > is embedded within the main sentence. This means that, in order to correctly understand the sentence, the matrix subject < the dog > , uttered before the relative clause, has to be retained in memory until the predicate < is chasing the cat > has been uttered (i.e., after the relative clause).

Memory resources involved in language comprehension might be those identified as the Phonological Loop in Baddeley and Hitch's (1974) model, namely the limited capacity verbal short-term memory system (VSTM) in which verbal information is temporarily held and manipulated during cognitive tasks that require its maintenance. These resources should be the same used in non-syntactic tasks execution, i.e. remembering lists of digits (Baddeley, 2003; See Fedorenko, Gibson, & Rohde, 2006; Just & Carpenter, 1992; and Romero Lauro, Reis, Cohen, Cecchetto, & Papagno, 2010). Alternatively, other authors suggested that memory resources involved in comprehension might be a separate and specialized subset devoted to syntactic and semantic sentence processing (Caplan & Waters, 1999; Makuuchi, Bahlmann, Anwander, & Friederici, 2009). While this debate is still open, the involvement of short-term memory resources if the sentence is sufficiently long or complex is not controversial, so boosting these short-term memory resources by tDCS might be a way to improve sentence comprehension.

Studies exploring the neural correlates of VSTM reported the involvement of the Left Inferior Frontal Gyrus (LIFG). Specifically, neuropsychological reports (for a review see Vallar & Papagno, 2002), neuroimaging (Awh et al., 1996; Henson, Burgess, & Frith, 2000; Hinke et al., 1993; Paulesu, Frith, & Frackowiak, 1993) and brain stimulation (Romero Lauro, Walsh, & Papagno, 2006) studies suggest an involvement of left BA44 (pars opercularis) on articulatory rehearsal. For example, in an fMRI study Paulesu et al. (1993) compared the subjects' performance in a rhyming judgement task, in which English stimuli were visually presented, hence requiring the subvocal rehearsal system, with a control task in which the stimuli consisted of Korean letters that cannot be to transcoded phonologically. The subtraction between this two tasks revealed a significant activation in BA44, indicating this region as the neural correlate of articulatory rehearsal. Analogously, disrupting the activity of the same region by 5-Hz repetitive rTMS resulted in a lower performance in two phonological judgement tasks (an initial sound similarity task and a stress assignment task), both engaging articulatory rehearsal, as compared with a visual pattern span as control task (Romero Lauro et al., 2006).

Furthermore, LIFG has been described as the locus for syntax specific aspects of language (e.g. Makuuchi et al., 2009), suggesting its involvement in complex sentence comprehension (for a review see Friederici, 2011).

In a previous study of Romero Lauro et al. (2010), 1 Hz offline rTMS over BA44 (neural correlate of rehearsal) reduced accuracy only on syntactically complex sentences whereas rTMS over BA40 (neural correlate of short-term storage) reduced accuracy on both complex sentences and long but syntactically simple sentences. Based on this study, we hypothesize that increasing memory resources involved in rehearsal by applying online a-tDCS over LIFG, and specifically over BA 44 might *selectively* enhance comprehension of syntactically complex sentences. Therefore, in addition to addressing our main research question (whether it is possible to improve sentence comprehension by means of tDCS), we aimed at detecting which kind of syntactic structures, if any, can be improved, focusing on sentences involving different degrees of short-term memory load and syntactic complexity.

In addition to online effects occurring during stimulation, tDCS might lead to long-term effects, likely mediated by synaptic plasticity. This fostered the use of the technique in rehabilitative settings (Lefaucheur et al., 2017). Therefore, any result showing that a-tDCS can improve sentence comprehension might be of great interest from the neuro-rehabilitation perspective.

2. Methods

2.1. Participants

Forty-four healthy young participants (12 male and 32 female; mean age = 22, SD = 2) took part in the study. Half of them received tDCS anodal stimulation (Anodal Group) and half of them received sham/placebo stimulation (Sham Group). All participants were naïve to the procedure of the study and they were not informed about the purpose of the experiment until the final debriefing.

Each participant completed an Adult Safety Screening Questionnaire (Keel, Smith, & Wassermann, 2001) and gave informed written consent prior to study procedures. Participants with any contraindication to tDCS procedures were excluded (Rossi, Hallett, Rossini, Pascual-Leone, & Safety of TMS Consensus Group, 2009).

All participants declared to be right-handed, this was confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971) for all participants (mean laterality coefficient = 0.78, SD = 0.15) except one (laterality coefficient = 0.4). This participant was assigned to the Sham Group; the other participants were randomly divided between the Sham and the Anodal groups.

Participants were all Italian native speakers.

The study was approved by the local Ethical Committee.

2.2. tDCS procedure

TDCS was delivered using a BrainSTIM stimulator (EMS) through two electrodes: to stimulate BA44, the anode electrode was placed over F5 according to the 10–20 international system for EEG electrodes placement, while the cathode was placed over the contralateral supraorbital area.

The anode was 9 cm^2 (3 × 3 cm) whereas the cathode was 35 cm^2 (7 × 5 cm), in order to increase the focality of the stimulation (Nitsche et al., 2008). A constant current of 0.75 mA intensity was applied for 30 min. For the sham condition, the stimulator turned off automatically after 30 s; this procedure has been shown to be effective in blinding participants from their assigned condition (sham vs real tDCS) (Ambrus et al., 2012; Gandiga, Hummel, & Cohen, 2006; Woods et al., 2016). Indeed, the sham stimulation included, as the real condition did, a ~10 s fade-in and a fade-out phases at the beginning and at the end of the protocol, in which current ramped on and off. The ramp-in and ramp out phases are the only periods during the stimulation in which itching sensations on the skin are perceived by the subjects, thus making the two conditions undistinguishable for naïve subjects as those enrolled in our experiment (Nitsche et al., 2003; Paulus, 2003).

The experiment started 10 min after stimulation onset and lasted until the end of stimulation (Boggio et al., 2008). In order to standardize the procedure during the first ten minutes of tDCS participants watched two silent cartoon videos of 5 minutes each.

Half of the participants began with the Linguistic Task, and half with the Control task.

2.3. Materials and procedure: linguistic task

Stimuli were 90 pre-recorded sentences in Italian, each one followed by two pictures. One picture correctly displayed the sentence meaning, the second picture showed the same characters playing a different role in the same event. Both sentences and pictures came from the standardized test "COMPRENDO" (Cecchetto, Di Domenico, Garraffa, & Papagno, 2012). Target sentences (N = 54) could be of three types: a) coordinate sentences (Coord, e.g. "*The boy is watching the cat and the woman is caressing the dog*") and two groups of sentences with relative clauses: b) relative clauses in center embedded position (Rel_CE: subject relatives, e.g. "*The dog that is chasing the cat is watching the girl*" and object relatives, e.g. " *The man whom the woman is watching is eating pasta*") and c) relative clauses in the right peripheral position (Rel_RP:

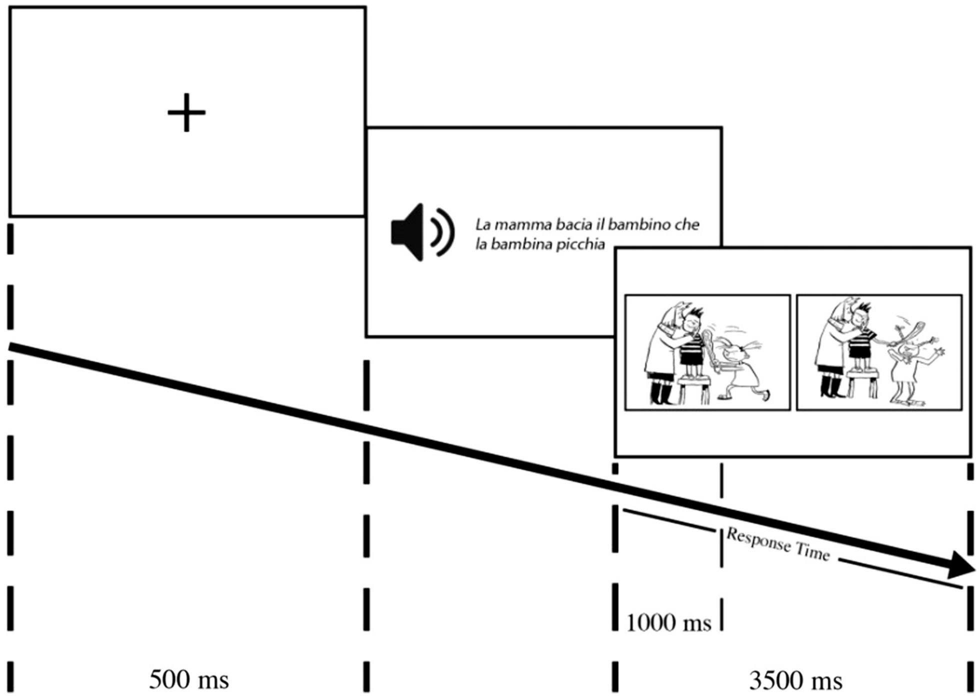

Fig. 1. Experimental procedure for the linguistic task. In this example participants heard the sentence "La mamma bacia il bambino che la bambina picchia" (*The mother is kissing the boy whom the girl is hitting*). In this case the matching picture is the one on the left of the screen.

subject relatives, e.g. "*The man is watching the dog that is chasing the cat*" and object relatives, e.g. "*The man is watching the cat that the dog is chasing*"). Crucially, the memory load required to understand those sentences is different: center embedded relative clauses are more demanding for short-term memory because the relative clause interrupts the main sentence processing. Half of the relative clauses in the center-embedded position were subject relatives ("*the dog that is chasing the cat*") and half were object relatives ("*the dog that the cat is chasing*"). The same for relatives in right peripheral position. The subject/object dimension must be kept under control because, ceteris paribus, objects relatives are more difficult than subject relatives (e.g. Traxler, Morris, & Seely, 2002). Filler sentences (N = 36) were short simple sentences (e.g. "*The dog is chasing the cat*"), in which accuracy is at ceiling (see Cecchetto et al., 2012).

Subjects heard the sentences through headphones and 1000 ms before the end of the auditory trace two pictures were displayed on the computer screen for 3500 ms (see Fig. 1). In this way, the onset of the picture was uniform across trials even though the length of the auditory trace was variable. Subjects were asked to judge which picture represented the meaning of the sentence by pressing "left arrow" if the matching picture was on the left of the screen, "right arrow" if it was on the right. Pictures position was counterbalanced across participants. Each participant performed all 90 trials, with a brief break of 30 s every 30 sentences. Sentences were presented in a random order. The experiment was preceded by a short practice session.

2.4. Material and procedure: control task

A visual pattern task was prepared using checkboards, with half of the squares black and half-white. In each trial a fixation point was presented for 2000 ms, then a first checkboard appeared on a computer screen for 500 ms. This was followed by a 2000 ms interval with a white screen after which two checkboards were presented for 3500 ms: one was identical to the previous and the other was different for the position of one square. Subjects were asked to judge which checkboard was identical to the previous one by pressing "left arrow" when the identical checkboard was on the left of the screen and the "right arrow" when it was on the right. This procedure was chosen to be similar to that of the comprehension task.

The size of the checkboards used in the task was individually established based on the result of a preliminary test performed prior to the experiment. In this test, checkboards of increasing size were used 3×4, 4×4, 5×4, 6×4, 7×4, 6×5. For each of the 6 different sizes, 15 trials were presented. The biggest checkboard dimension in which accuracy was the closest to 80% was then used in the experiment. In this way, we matched the accuracy percentage at baseline of the visual control task with that for the most difficult type of sentence obtained in previous pilot experiments. Checkboards patterns used in the preliminary test were different from those used in the control task.

3. Results

3.1. Linguistic task

Invalid trials due to technical failures were discarded from the analysis (3.7% of all data points). One item (n° 90) was excluded from analyses because of low rate of accuracy (57%). Analysis was therefore conducted on 2288 data points.

Results are depicted in Fig. 2. Accuracy was higher for the Anodal group than for the Sham group, and was higher for coordinate sentences than for sentences with relative clauses. Accuracy was analyzed using general mixed-effects models (Baayen, Davidson, & Bates, 2008), fitted using the glmer function of the lme4 package (Bates, Maechler, Bolker, & Walker, 2015), implemented for the R software (R Core Team, 2016). «Group» (ANODAL vs. SHAM) and «Type of sentence» (Coord, Rel_CE, Rel_RP. Reference level: Coord) were entered into the model as fixed factors. «Participant» and «item» were entered as random factors to account for participant-specific variability and for item-specific idiosyncrasies. We performed a stepwise regression following a backward elimination procedure. The first model we considered was the model with two main effects and the two-way interaction: The type of sentence by group interaction was not significant, so we dropped it from the analysis without decreasing the model goodness of fit ($\chi^2 = 3.44$, $p = .18$). The model without interaction revealed that the effect of both factors was significant: participants performed better in the Anodal condition than in the Sham condition ($\beta = 0.46$, $SE = 0.21$, $z = 2.16$, $p = .03$) and participants performed better in Coordinate Sentences with respect to both type of relative sentences: Type Coord

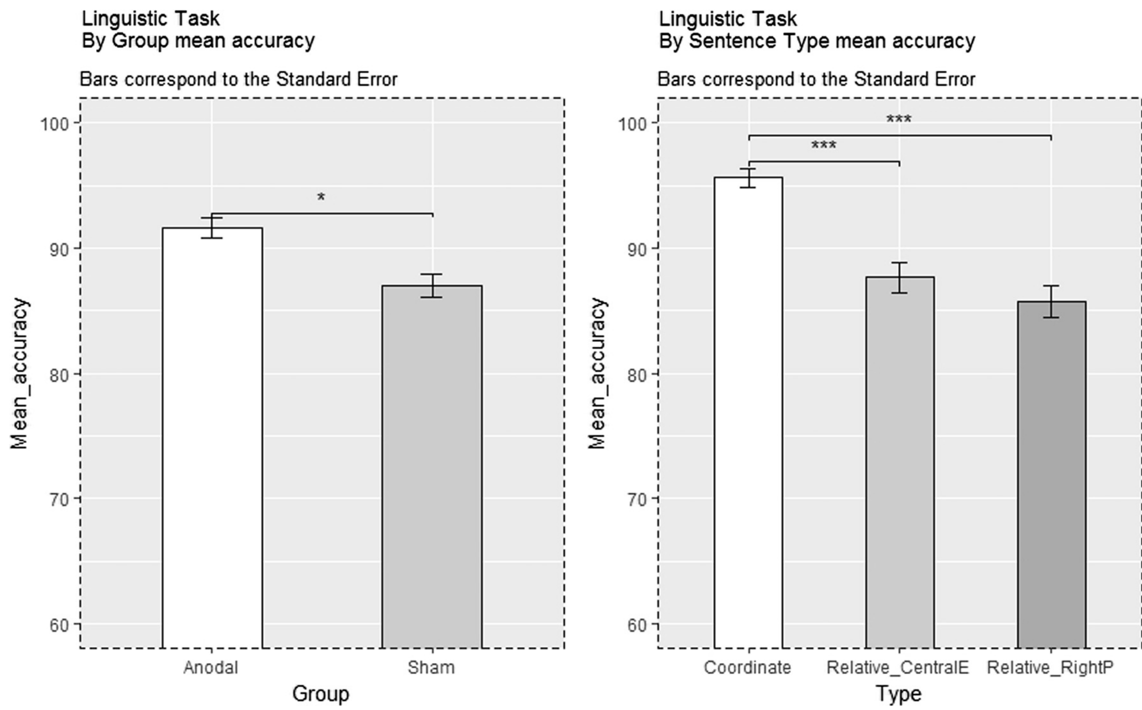

Fig. 2. Linguistic task. The left panel depicts mean accuracy (vertical axis) by group (horizontal axis): Anodal (white bar) and Sham (light gray bar). Accuracy wash higher in the anodal group compared to the sham group. The right panel represents accuracy (vertical axis) by type of sentence (horizontal axis): Accuracy was higher in coordinate sentences (white bar) than in relative sentences (central embedded relative clauses, light gray bar and right peripheral relative clauses, dark gray bar).

vs. Rel_CE ($\beta = 1.17$, SE = 0.33, z = 3.509, $p < .001$); Type Coord vs. Rel_RP ($\beta = 1.33$, SE = 0.33, z = 4.00, $p < .001$).

3.2. Control task

Invalid trials due to technical failures were discarded from the analysis (< 1% of all data points). Analysis was conducted on 792 data points. Mean accuracy was 86% (SD = 34) for the Anodal group and 79% (SD = 41) for the Sham group. «Group» (ANODAL vs. SHAM) was entered into the model as fixed factor, whereas «Participant» and «Item» were entered as random factors. In the control task we observed a tendency with higher accuracy for the Anodal Group compared to the Sham one, however this effect did not reach significance (z = 1.643, p = .1).

4. Discussion

The current study examined the possibility of enhancing natural language comprehension applying a-tDCS over LIFG, placing the anode electrode over BA44. We ran a between subjects task-controlled experiment, in which half of the participants received a-tDCS and the other half sham stimulation during a language comprehension task.

The main goal of our study was to investigate the possibility of improving language comprehension in healthy subjects by means of tDCS. Moreover, we wanted to analyze which kind of syntactic structures, if any, are enhanced by tDCS. Our initial hypothesis was that by increasing memory resources involved in rehearsal we might have been able to selectively increase the comprehension of syntactically complex sentences.

The main result of the present study is that a-tDCS over LIFG significantly improved accuracy in the linguistic task compared to sham stimulation. However, our results did not fit with our first hypothesis, as we found a main effect of Group regardless of sentence complexity. This result might seem in conflict with that of Romero Lauro et al. (2010), who found that 1 Hz offline rTMS over left BA44 reduced accuracy for syntactically complex sentences but not on syntactically simple sentences.

The differences between the present results and those reported in Romero Lauro et al. (2010) might be due to the less focality of tDCS compared to TMS and we can speculate to the current spreading to other regions functionally connected to BA44. In fact, although tDCS was targeting BA44, as shown in the estimated electric field pictured in the graphical abstract, the stimulation spread over LIFG and further left frontal regions, and in an anterior fashion, reaching left prefrontal cortex (PFC). This means that we cannot disentangle whether the improvement in sentence comprehension was a consequence of a boosted rehearsal and/or a more spread effect over LIFG tapping also portions involved in sentence processing. The stimulation targeted indeed the so called Broca's area, involved in different aspects of linguistic processing, e.g. syntactic processing (BA44/45), semantic processing (BA45/47) (Friederici, 2002) or unification of different type of information (Hagoort, 2005).

The spread of stimulation toward PFC might explain also the tendency for the greater mean accuracy in the control task of the Anodal group compared to the Sham one. Even if the direct involvement of PFC in visual working memory tasks has been challenged (see e.g. Postle, Druzgal, & D'Esposito, 2003), PFC should be involved in control processes that are in use while performing working memory tasks (Lara & Wallis, 2015).

Another possible explanation for our data regards the chance that tDCS current spread to brain regions that are functionally connected to the target stimulated region (Pisoni et al., 2017; Romero Lauro et al., 2014, 2016). For example, by means of tDCS combined with TMS-EEG, Pisoni et al. (2017) found that tDCS effects were traceable not only in the stimulated region, but also in other areas involved in task execution. In light of these recent studies, we could therefore speculate that our present results in the linguistic task might be a consequence of a broader tDCS effect on functional areas connected to BA44. TDCS current then might have spread also to parietal regions (in particular left BA40) that are also involved as neural substrate for short-term storage functions, thus explaining the enhancement in the performance also for long but not syntactically complex sentences. Indeed, in the study of Romero Lauro et al. (2010) rTMS over left BA40 led to a better performance in long but syntactically simple sentences. However, we cannot provide any conclusive remarks on the mechanism underlying our behavioral effects. Future studies combining tDCS with fMRI or EEG will be essential to test the validity of our speculation.

Irrespective of that, we want to stress that the low focality of tDCS does not question the main finding of the present study, which is having shown that the stimulation of LIFG could improve sentencecomprehension, suggesting the importance of trying the same protocol with brain-damaged patients. Furthermore, as different authors pointed out (e.g. Vallar & Bolognini, 2011), the low spatial resolution of tDCS could be considered an advantage in neuro-rehabilitation, since behavioral deficits are generally due not only to the primarily damaged brain regions but also to the connected areas.

To sum up, to our knowledge this is the first study applying a-tDCS in a language comprehension task, and the first one highlighting the possibility of enhancing language comprehension at a sentence level by this technique. As mentioned in the introduction, several studies reported tDCS effects in the language domain, from picture naming to artificial grammar learning (see Monti et al., 2013 for a comprehensive review), but investigation on tDCS effects on sentence comprehension were lacking.

Despite substantial literature that provides a large amount of evidence on the effects of tDCS in many different tasks, the efficacy of the technique to modulate cognitive performances in healthy participants has been questioned in recent works (e.g. Horvath, Forte, & Carter, 2015; Westwood, Olson, Miall, Nappo, & Romani, 2016). However, different results might come out from different experimental paradigms. Recent studies employing direct measures of tDCS-induced cortical excitability confirmed the effectiveness of the technique in modulating cortical response at a neurophysiological level (Pellicciari, Brignani, & Miniussi, 2013; Romero Lauro et al., 2014, 2016). Moreover, a recent meta-analysis (Price & Hamilton, 2015) applying a rigorous method in study selection, reported reliable effects of single session a-tDCS over a broad range of language tasks. Within this debate, the present study provides further support to the efficacy of the technique in affecting performance of healthy individuals in language tasks, adding the crucial domain of sentence comprehension.

Regarding the limitations of the present study, the experimenter was not blind to the stimulation type and we acknowledge that this might be an issue. However, the experimenter-participant interaction was minimized: participants wore headphones since the beginning of the stimulation until the end of the experiment, without any interaction with the experimenter, thus limiting any effect of his/her expectations.

In conclusion, our data indicates that a-tDCS stimulation over LIFG in healthy subjects might boost language comprehension of both syntactically simple (but long) sentences and syntactically complex sentences. This result is of special interest also from a clinical perspective: applying tDCS in brain-damaged patients with impaired language comprehension could enhance the effects of behavioral rehabilitation procedures. In order to confirm this, further investigation on appropriate clinical populations is required.

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