Anodal tDCS over Wernicke's area improves verbal memory and prevents the interference effect during words learning

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Abstract

Background: Wernicke's area is a key component of the cortical language network, and it is functionally related to the comprehension of oral and written language. In addition to its main role in the perception of language, some other functions related to verbal learning also seem to involve the activity of this cortical region. It is unknown whether different degrees of neuromodulation on this area determine its effect on word learning. ***Objective:*** We aimed to analyze the influence of the application of anodal transcranial direct current stimulation (tDCS) over Wernicke's area at two different intensities on word learning. ***Material and Method:*** We compared the effect of anodal tDCS at an intensity of 0.5 mA and 1.5 mA with sham tDCS, separately in different groups, on performance in a word learning and recall task. ***Results:*** The results show that 1.5 mA anodal tDCS improved performance. The number of words learned in this condition was higher compared with stimulation at 0.5 mA current strength and sham stimulation. Furthermore, stimulation with 1.5 mA specifically prevented the interference effect over word learning, compared to the other two tDCS conditions. ***Conclusions:*** These results show an intensity-dependent effect of anodal tDCS on verbal memory formation. These findings are discussed in the context of the various functions of Wernicke's area and the ability of tDCS to modulate the activity and functionality of this cortical area at different intensities.

Keywords: anodal tDCS, stimulation intensities, verbal learning, verbal memory, Wernicke's area

Significance statements:

Performance in a verbal memory task is improved by anodal transcranial direct current stimulation (tDCS) applied over Wernicke's area. This effect seems to be intensity-dependent as 0.5 mA tDCS did not affect verbal memory, compared with an improvement effect induced by 1.5 mA tDCS. In addition to the sensory function classically attributed to Wernicke's area, this cortical region may also be involved in verbal memory processes.

Introduction

Recent models of language networks have emerged from neuroimaging studies showing multiple brain regions involved in language-related cognitive processes (Fedorenko et al., 2010; Mahowald & Fedorenko, 2016). These models include a set of brain regions located in the frontal and temporal lobes. Complex functional connections between these language areas seem to be necessary for high-level linguistic processing (Binder, 1997; Binder et al., 1997; Price, 2010). In language processing, word production and perception involve two well defined cortical areas (Broca's and Wernicke's area), whose involvement in a multitude of linguistic functions is suggested by these new models of language networks. Broca's area is mainly involved in the motor component of language, and Wernicke's area is related to speech comprehension and sensory processing of oral and written language (Black et al., 1986; Graves, 1997; DeWitt & Rauschecker, 2013; Chang et al., 2015; Ardila et al., 2016). However, increasing evidence in recent years suggests a variety of other linguistic functions related to Wernicke's area, which are not specifically sensory (for a review, see Binder, 2017). Word recall and learning is one candidate verbal function, which is proposed to depend on a complex cortical network including Wernicke's area. In accordance with this possibility, an increased activation of Wernicke's area has been found during performance of a verbal memory task by magnetoencephalography (Pimoradi et al., 2016).

In studies exploring the physiological foundation of language processing, non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), are applied to analyze the effect of temporary activation or inactivation of respective target areas. tDCS modulates cortical excitability in humans in a polarity-specific way (Nitsche & Paulus, 2000, 2011; Stagg &

Nitsche, 2011). In standard tDCS protocols, motor cortex excitability is increased under the anodal electrode and reduced under the cathodal electrode (Nitsche & Paulus, 2000, 2011; Nitsche et al., 2003, 2005). Polarity-specific effects of tDCS on cortical and cortico-spinal excitability have been demonstrated mainly for the motor cortex and are evidenced by motor evoked potential recordings (Nitsche & Paulus, 2000, 2011). Polarity-dependent effects have also been demonstrated for the visual cortex and other areas (Antal et al., 2004a). These, however, depend critically on specific protocol aspects, such as stimulation duration and intensity (Batsikadze et al., 2013; Monte-Silva et al., 2013). Regarding behavioral measures, polarity-specific effects on performance are even less deterministic, which might be caused by different effects of stimulation protocols over different areas, dependent on predominant type and directionality of neurons, as well as receptor compositions, but also task characteristics. Thus, stimulation with the anode positioned over respective target areas improved initial learning of a visuo-motor coordination task, presumably via enhancement of task-related long-term potentiation, whereas in the over-learned state, cathodal tDCS improved performance presumably via noise reduction (Antal et al., 2004b,c). Therefore, the general notion that anodal tDCS improves while cathodal tDCS reduces performance is an oversimplification.

Due to its potential to modulate cortical excitability and activity, tDCS is used to explore the physiological foundation of cognitive processes, including the language domain (Flöel et al., 2008; Hartwisgsen, 2015). In healthy participants, repeated sessions of anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC) enhanced verbal working memory (Richmond et al., 2014), and a single session of anodal tDCS over the DLPFC also improved verbal learning (Nikolin et al., 2015). Moreover, a single session of anodal tDCS over the posterior parietal cortex (P3) enhanced verbal long-term memory when applied during encoding in healthy humans (Jones et al., 2014). Effects of tDCS on verbal memory in healthy humans have been shown in both, young and older adults (Martin et al., 2017). Regarding specific subgroups of verbal material, studies have furthermore found an improvement in the retrieval of proper names after anodal tDCS applied over the right anterior temporal lobe (Ross et al., 2010), and an improved acquisition of action-related words using an associative word learning task in older participants after left motor cortex cathodal tDCS (Branscheidt et al., 2017).

tDCS has helped to identify specific functions of relevant parts of the language network, showing an involvement of Wernicke's area in semantic and categorization task performance. For example, significant effects of anodal and cathodal tDCS over Wernicke's area on language functions include an improvement of semantic processing (Brückner & Kammer, 2017). Cathodal stimulation over Wernicke's area also improved verbal categorization performance in category learning tasks (Perry & Lupyan, 2014). The application of cathodal tDCS over Wernicke's area (with the anodal electrode over the homologous area of the right hemisphere) has furthermore been shown to impair lexical processing, compared to a left anodal/right cathodal electrode montage (Weltman & Lavidor, 2013). Partially heterogeneous effects of stimulation over Wernicke's area in healthy participants may be due to differences in the specific verbal function evaluated (memory, production, comprehension, naming, etc.), tDCS procedure, interindividual variability of samples, among other factors. Overall, improvements in different language tasks after application of tDCS have been reported in both, healthy participants (Perry & Lupyan, 2014; Brückner & Kammer, 2017) and aphasic patients (Monti et al., 2008).

In addition to the effects of tDCS on language functions in healthy humans, its potential usefulness for clinical application has also been demonstrated, particularly in chronic aphasia (Fiori et al., 2011; Flöel et al., 2011; Monti et al., 2013; Galletta et al., 2016; Kazuta et al., 2017; Wortman-Jutt & Edwards, 2017). In aphasic patients, repeated sessions of anodal tDCS applied over Wernicke's area resulted however in heterogeneous outcomes in different studies on verbal production (Fiori et al., 2013; Marangolo et al., 2013). Improved speech functions have also been reported in aphasic patients after stimulation over other cortical areas, such as the left motor cortex (Meinzer et al., 2016), left frontal cortex (Baker et al., 2010), left frontotemporal (Monti et al., 2008) or perilesional brain areas (Fridriksson et al., 2011). These effects of tDCS may be related to an influence on language-related networks, although specific patient and lesion features might determine the efficacy of tDCS and explain heterogeneity of results (Jung et al., 2011; Shah-Basak et al., 2015). In support for these clinical effects, changes in the activity of the language network have been revealed by neuroimaging in stroke patients during application of tDCS (Darkow et al., 2017), in a similar way as those reported in young and older adults (Martin et al., 2017).

To the best of our knowledge, however the relevance of Wernicke's area, or other nearby verbal areas of the left posterior temporal lobe, for word learning and recall has not been explored via tDCS-induced neuromodulation. Based on the latest evidence about the involvement of this area in language processes other than verbal comprehension (Binder, 2017), the objective of this study was to reveal the relevance of this cortical region (specifically the left superior posterior temporal gyrus) for respective processes via application of anodal tDCS during a word learning task. For the investigation of possible cognitive functions of Wernicke's area via non-invasive brain stimulation, appropriate dosing of these interventions is important, as shown also for other areas and functions (Cuypers et al., 2013), to avoid shortcomings of the interpretation of results, including negative findings due to insufficient or suboptimal intervention protocols. Currently, no studies are available which systematically probe the impact of dosing of tDCS intensities on the effect of stimulation over Wernicke's area on verbal learning and memory. Thus, to close this gap, tDCS was applied at low and medium intensities. As mentioned above, this tool has shown promising clinical effects, and therefore we used it in this study despite its relatively low physical specificity. If verbal memory formation is sensitive to the excitability state of the left posterior temporal lobe, including Wernicke's area, during task performance, then anodal tDCS applied over this area could affect the results. In particular, increased performance after anodal tDCS would indicate an involvement of Wernicke's area or, more generally, the left posterior temporal lobe in word learning processes.

Methods and materials

Subjects

Forty-five right-handed healthy volunteers, 18 men (mean age = 22.7 ± 2.7 years) and 27 women (mean age = 21.9 ± 4.2 years), participated in this experiment. Potential participants underwent an individual interview to verify compliance with the inclusion criteria (native Spanish speakers, right-handed, university students or students in the last year of high school education, no pathologies of verbal production or perception abilities) and absence of exclusion criteria. The exclusion criteria included hormonal treatment (including contraceptive medication in females), consumption of psychoactive substances before or during the study, and neurological or psychiatric diseases. All participants provided written informed consent before the start of the study and received economic compensation for participation. The study was approved by the Ethics Committee of the Autonomous University of Baja California and conformed to the World Medical Association Declaration of Helsinki.

Procedure

tDCS

tDCS was applied by battery-driven constant-current stimulators (TCT Research tDCS Stimulator, TST Kowloon, Hong Kong) with conductive rubber electrodes, placed between two saline-soaked sponges. The anode electrode was placed in a slightly anterior position between CP5 and TP7, according to the international 10-20 EEG system for electrode placement (Herwig et al., 2003; Klem et al., 1999), corresponding with the left superior posterior temporal gyrus (Wernicke's area). Stimulation was applied for 15 minutes by a 5 × 5 cm electrode (25 cm^2) covered with a saline soaked sponge, at an intensity of 0.5 mA (first group) or 1.5 mA (second group). Stimulation was gradually ramped up and down for 8 sec at the beginning and the end of stimulation, respectively. The cathode electrode (5 × 7 cm; 35 cm^2) was positioned over the right supraorbital ridge (Fp2 according to the international 10-20 EEG system). This electrode montage has been previously described to affect Wernicke's area during verbal performance (Sparing et al., 2008; Marangolo et al., 2013). Furthermore, the right frontopolar cortex is not relevantly involved in the cognitive processes explored in the present study. The return electrode was larger to ensure that current density under the anodal electrode (positioned over Wernicke's area) was higher.

Figure 1 shows the positions of the anodal and cathodal electrodes with respect to the 10-20 EEG international system. The electrodes were fixed onto the head by a tDCS headstrap (CMUS1209, Caputron Universal Strap, USA). For sham tDCS (third group), current was increased and then decreased over 8 sec at the beginning and end of the session, respectively, to ensure some tingling sensation typical for real tDCS, but avoid after-effects of stimulation. All subjects felt an initial mild tingling sensation under the area of the electrodes, which subsided during the first minutes. Subjects were blinded for tDCS conditions.

Insert Figure 1 approximately here

Word learning task

To evaluate verbal memory, we used the Spain-Complutense Verbal Learning Test (TAVEC), a standardized test in Spanish language (Luna-Lario et al., 2017). This test is used to obtain a typical word-learning curve and measure of verbal memory. A list of 16 Spanish words, which included 4 semantic categories (tools, fruits, clothes and spices), was read aloud to each participant. This procedure was repeated 5 times. After each reading, the participants were asked to recall and name as many words of the list as possible. Scores analyzed were the number of recalled words. At the end of the fifth reading, a second list of 16 different words (introduced as word list which interferes with memory formation of the previous one) was read, and participants were required to recall and name as many words as possible of this second list. The interference aim of this second word list was unknown to participants. Immediately afterwards, the participants were asked to recall and name as many words as possible from the first word list, to evaluate short-term free verbal memory.

After that, each participant was required to recall and name as many words as possible of the first list, but to separate the words in semantic categories, to evaluate short-term verbal memory regarding semantic strategies. Twenty minutes later the participants were asked to recall and name as many words as possible of the first word list to evaluate long-term verbal free memory, and then to recall and name the words according to the respective semantic categories (long-term verbal memory regarding semantic strategies). During this interval of 20 minutes the participants performed a visual-spatial non-verbal task (the WAIS-Block Design task, Wechsler, 1981) to control for the level of cognitive activities between participants. Beyond number of recalled words, verbal perseverations and intrusions were also recorded in each trial of the verbal task. Perseveration was defined as the repetition of words included in the list, and naming a word not included in the list was considered an intrusion. The recall of words using semantic categories (for example, group of words about “tools”) or a serial order (words recalled in the same order as they appeared in the learning trials) without an explicit request for that was considered as a semantic or serial self-strategy. Semantic and serial self-strategies were recorded in all trials except in those to explicitly evaluate the short-term and long-term verbal memory through semantic strategies.

WAIS-Block Design task

The objective of this task is to replicate geometric models using blocks with two red color surfaces, two white color surfaces, and two surfaces with half red and half white. In succeeding trials, the geometric pattern to be reproduced becomes more difficult, and involves more blocks. The number of correct reproductions was recorded.

Experimental procedure

A sham-controlled double-blinded randomized design was used. Participants were randomly assigned to one of three groups with Wernicke's area stimulation: Anodal stimulation at 0.5 mA (n = 15), anodal stimulation at 1.5 mA (n = 15), and sham stimulation (n = 15). All subjects were seated in a comfortable chair and received anodal or sham stimulation over Wernicke's area for 15 minutes in a single session. Neither the subjects nor the researchers were aware of the tDCS condition. After the first 3 minutes of tDCS, subjects started the TAVEC task as described above, which was completed in about 12 minutes (total time of stimulation around 15 minutes). After completion of the last short-term verbal memory test (see above), subjects performed the WAIS-Block Design task. Twenty minutes later, the long-term verbal memory test from the TAVEC task (with and without semantic strategy) was recorded. Figure 2 depicts the time sequence of the procedure.

Insert Figure 2 approximately here

Data analysis

All words which were produced by the participants were recorded for each trial, and were rated as correct words, perseverations, and intrusions. The number of words retrieved via semantic and serial order strategies was also analyzed. A 3 × 10 repeated-measures ANOVA, with one between-subject factor (the three tDCS conditions) and one within-subjects factor (the ten trials of word recall: first list of words × 5, interference list, short-term free memory, short-term memory with semantic strategy, long-term free memory, and long-term memory with semantic strategy), was conducted to analyze differences between the groups in the number of memorized words for each trial of the TAVEC, and in perseverations and intrusions. Two independent 3 × 8 repeated-measures ANOVAs, with one between-subject factor (the three tDCS conditions) and a within-subjects factor (eight trials of words, including all trials except those in which a semantic strategy was explicitly requested), was conducted to analyze differences between the groups in the number of words using semantic or serial order self-strategies, respectively. Post-hoc Bonferroni-corrected Student's *t*-tests were applied for comparisons. With respect to the effect of the interference word list in the short-term free memory, *t*-tests were conducted to analyze performance differences between the fifth learning trial and the short-term free memory trial in each stimulation group. A one-way ANOVA was conducted to analyze differences in the WAIS-Block Design task. A one-way ANOVA of the first memory trial (the short-term free memory trial) for each group and an ANCOVA including all trials and groups, with sex as covariate, were conducted to analyze possible gender differences. The critical level of significance in all tests was set to $p<0.05$. The analyses were carried out using SPSS software.

Results

Apart from tingling sensations, none of the subjects reported any relevant adverse effect during or after the application of real/sham tDCS. Table 1 summarizes the results of the ANOVAs conducted to analyze differences between groups in the number of words recorded in each trial.

The repeated-measures ANOVA conducted for the correct words over all 10 trials showed significant main effects for the factors stimulation ($F_{2,42} = 4.104$, $p = 0.024$, $\eta_p2 =$

.163) and trial ($F_{9,34} = 71.932$, $p < 0.001$, $\eta_p2 = .943$). The interaction between these factors was also significant ($F_{18,70} = 2.491$, $p = 0.004$, $\eta_p2 = .356$). Post-hoc Bonferroni-corrected *t*-tests revealed a higher number of correct words for the group exposed to anodal tDCS with 1.5 mA current strength, compared to the 0.5 mA and sham groups, in all memory trials: the short-term free memory ($p = 0.003$, $d = 1.08$ and $p = 0.004$, $d = 0.85$, respectively), short-term semantic strategy ($p < 0.001$, $d = 1.57$ and $p < 0.05$, $d = 0.\ 97$), long-term free memory ($p < 0.001$, $d = 1.73$ and $p = 0.001$, $d = 1.05$), and long-term semantic strategy ($p < 0.001$, $d = 1.81$ and $p = 0.005$, $d = 1.34$) conditions, respectively. *t*-tests conducted to evaluate differences between the fifth learning trial and the short-term free memory trial for each group revealed significant differences for the anodal 0.5mA ($p = 0.002$, $d = 1.27$) and sham ($p < 0.001$, $d = 0.81$) groups, but not for the anodal 1.5 mA group ($p = 0.103$, $d = 0.54$), indicating that the verbal memory interference effect induced by the second list of words was prevented by anodal tDCS of 1.5 mA. Figure 3 shows the mean number of words recorded in each group throughout the 10 trials of the TAVEC. To explore possible gender effects, we conducted a one-way ANOVA to compare performance between male and female in each stimulation group in the short-term free memory trial. No significant between gender-group differences were found in the 0.5 mA *(*$F_{1,14} = 0.241$, $p = 0.631$, $\eta_p2 = .018$*)*, 1.5 mA *(*$F_{1,14} = 0.049$, $p = 0.829$, $\eta_p2 = .004$*)*, and sham *(*$F_{1,14} = 0.672$, $p = 0.427$, $\eta_p2 = .049$*)* groups. In addition, when all trials and groups were analyzed by an ANCOVA, with sex as covariate, a significant effect was found for the factor stimulation ($F_{2,42} = 4.221$, $p = 0.022$, $\eta_p2 = .171$), trial ($F_{9,34} = 5.179$, $p < 0.001$, $\eta_p2 = .112$), and the interaction between stimulation and trial ($F_{18,70} = 2.704$, $p < 0.001$, $\eta_p2 = .117$). No significant differences were found for the covariate sex ($F_{1,42} = 1.370$, $p = 0.249$, $\eta_p2 = .032$). Table 2 shows demographic information from participants (mean age and standard deviation, number of women and men, educational level, and years of University education).

Insert Table 1 approximately here

Insert Figure 3 approximately here

Insert Table 2 approximately here

The ANOVAs conducted for the perseverations and intrusions throughout the 10 trials showed a significant effect only of the factor trial ($F_{9,34} = 9.237$, $p < 0.001$, $\eta_p 2 = .710$ and $F_{9,34} = 2.473$, $p = 0.027$, $\eta_p 2 = .396$, respectively), indicating no between stimulation group differences regarding these errors. The independent 3 × 8 ANOVAs conducted for the semantic and serial order self-strategies throughout the trials (all trials except those of short-term and long-term memory tests via the explicit semantic strategy) also showed a significant effect only for the main factor trial ($F_{7,36} = 26.260$, $p < 0.001$, $\eta_p 2 = .836$ and $F_{7,36} = 26.245$, $p < 0.001$, $\eta_p 2 = .836$, respectively), which indicates that semantic and serial self-strategies did not lead to different outcomes between tDCS groups. Figure 4 indicates the number of words of each group using semantic and serial order self-strategies, and Figure 5 shows the perseverations and intrusions of each group throughout the 10 trials of the TAVEC. Finally, as shown by the results of the respective one-way ANOVA conducted to analyze differences in the WAIS-Block Design task ($F_{2,42} = 0.327$, $p = 0.723$, $\eta_p 2 = .015$), tDCS did not affect performance of this task. Figure 6 represents the scores of each group obtained in the WAIS-Block Design task.

Insert Figures 4, 5 and 6 approximately here

Discussion

The aim of this research was to explore if Wernicke's area is involved in complex cognitive processes related to verbal learning and memory, as it is a critical area for perception of language. Thus, the relevance of Wernicke's area for performance in a word learning and recall task was evaluated in this study by the application of anodal tDCS at different intensities. The results show that only tDCS at an intensity of 1.5 mA altered verbal memory performance. In the short-term and long-term free and semantic strategy verbal memory trials, more words were retrieved by this group, as compared to the sham and 0.5 mA stimulation groups. These effects on both, short-term and long-term verbal memory, indicate that 1.5 mA tDCS improved memory during application of stimulation (online effect), but also at least for 20 min after the end of stimulation (offline effect). In contrast, in the first five trials, in which the same list of words was repeated, the expected slope of the learning curve was similar in all groups. This might have been due to a ceiling effect, or might hint to a larger effect of tDCS on memory formation and consolidation as compared to the actual learning process. In addition to the effect of anodal tDCS at 1.5 mA on short and long-term verbal memory, there was a remarkable effect of the intervention on verbal memory after the interference trial. When a second list of words followed the last trial of the learning curve (fifth trial), the expected impairment in the recall of the first list of words was evident in the 0.5mA and sham tDCS groups when tested in the short-term free verbal memory trial. However, this impairment was absent in the group exposed to 1.5 mA anodal tDCS. Thus, the interference list did not affect word recall in this group. A blocking of interference effects via tDCS may explain the superior performance in the short-term verbal memory trial of this group. However, the superior performance of the 1.5 mA tDCS group, as compared to the other groups, in the following short and long-term verbal memory trials, may suggest that the application of anodal tDCS over Wernicke's area (which, according to the electrode montage used, does not necessarily imply a specific effect on this area) improved word recall through different mechanisms. A stronger encoding being able to make the newly formed connections more resistant against distractors may be one of such mechanisms. The effects of anodal tDCS applied over the region of Wernicke's area at an intensity of 1.5 mA on verbal memory found in this study may, therefore, be due to a direct influence of stimulation on encoding processes of the first word list (effects on verbal memory), and/or they may be a consequence of an effect of stimulation on the second word list (effects on interference processes). Indeed, tDCS could have induced a stronger encoding of the first word list, but it also could have reduced verbal encoding of the second word list. Both scenarios would reduce interference effects, and thus improve performance regarding the first word list. These potential mechanisms should be explored in larger detail in future studies.

With respect to perseverations, intrusions and memory strategies, no differences were found between groups. Stimulation at 1.5mA was associated only trendwise with a lower number of perseverations and more words recorded via serial order strategies during the learning curve, which might indicate a trend to improved verbal learning by verbal memory strategies. This is consistent with the possibility that different processes contribute to these results, apart from the fact of a reduced interference effect, as perseveration errors and memory strategies affect verbal learning task performance. No differences between the 3 groups were found in the WAIS-Block Design task performance. This task was introduced to keep cognitive activity of the participants at similar levels during the interval between short-term and long-term memory performance. Considering that all participants, except one, were Psychology students and the stage of their studies (years at University) was similar, this result was expected and suggests that, at least for this function not related to verbal memory, cognitive abilities of the participants were homogeneous.

These findings suggest an apparent involvement of Wernicke's area in verbal memory performance and may extend our knowledge about the role of this cortical area in different language processes. With respect to the focality of this effect, the electrode montage used in this study may however have resulted in a diffuse current flow, involving areas of the left peri-sylvian cortex related to verbal functions or even the contralateral prefrontal cortex. Regardless of this possibility, the results of this study mainly show current intensity-dependent effects, which is congruent with previous findings regarding the effects of different stimulation intensities on physiological (Nitsche & Paulus, 2000; Jamil et al., 2017) and cognitive (Cuypers et al., 2013; Pirulli et al., 2014) functions. Both stimulation intensities applied in the present study have been shown before to alter cortical excitability (Rivera-Urbina et al., 2015; Jamil et al., 2017). Different current intensities have been shown to modulate cognitive processes (Faehling & Plewnia, 2016), however, cognitive studies exploring intensity-effect curves are rare. In a study, Cuypers et al. (2013) found a significant increase in the slope of the learning curve in a unimanual motor sequence task with anodal tDCS at a specific intensity of 1.5 mA. In the verbal task used in the present study, only tDCS at 1.5mA of intensity improved verbal memory, compared with an intensity of 0.5 mA and sham stimulation. Thus, anodal tDCS had an intensity-dependent effect on verbal memory and verbal memory interference processes when applied over Wernicke's area. An intensity of 1.5 mA is in the range of stimulation protocols described in previous studies in which language processing was also affected by application of tDCS in other brain areas (Fertonani et al., 2010; Fridriksson et al., 2011). Moreover, it has been shown that anodal and cathodal tDCS applied over Wernicke's area at 1mA improved semantic processing (Brückner & Kammer, 2017), and anodal tDCS over the posterior part of the left peri-sylvian area at 1 mA improved associative verbal learning (Flöel et al., 2008). Since anodal stimulation increases cortical excitability (Nitsche & Paulus, 2000, 2011), and induces long-term potentiation (LTP)-like plasticity critical for learning and memory formation, it is suggested to boost task-related LTP and, consequently, improve performance. Therefore, the enhanced excitability induced by anodal tDCS over Wernicke's area could trigger this plasticity mechanism and induce verbal memory performance improvements. The relationships between tDCS intensity, cortical excitability and plasticity, and Wernicke's area activity need to be clarified in the context of verbal memory. Another factor to be considered in tDCS studies is inter-individual variability of the results (Chew et al., 2015; López-Alonso et al., 2015). In this study, a significant effect of stimulation on verbal memory was found only in the group exposed to 1.5 mA anodal tDCS. In the 4 verbal memory trials of the task, the standard deviation of this group was in all cases smaller than 2, and standard error of the mean was not larger than 0.5. This suggests a relatively low variability of results (see supplemental material regarding dispersion data and Figures).

Some limitations of this study should be mentioned. We did not conduct extensive pre-tests of cognitive and language abilities of the groups at baseline. Taking into account similar age, gender distribution, and educational stage of the groups, and similar WAIS-Block Design task performance, we assume that the cognitive abilities of the participants in the experimental groups were fairly homogeneous. Besides, in this study, only anodal stimulation over Wernicke's area, corresponding with the left superior posterior temporal gyrus, was compared to sham stimulation. The inclusion of cathodal tDCS and other targeted brain areas in future studies will help to identify specific tDCS protocols optimally suited to improve verbal learning and memory performance. tDCS polarity may be another relevant factor to be considered in the exploration of tDCS applications. Although cognitive effects in general seem to be less sensitive to the cortical excitability changes induced by cathodal tDCS (Brückner and Kammer, 2017), it is worth to elucidate if an intensity-dependent effect of tDCS on verbal memory emerges when cathodal stimulation is applied over Wernicke's area. This is especially relevant, since in language-related studies, a complex picture emerged regarding the effects of tDCS, showing performance-improving effects of diverse tDCS protocols with anodal and cathodal electrodes positioned over respective target areas. However, assuming that the improved performance in verbal memory induced by tDCS in this study is linked to an increased activity of Wernicke's area, such improvement might not be expected if activity of this area is reduced by cathodal stimulation. On the other hand, in the present study, the stimulation of one area with a relatively diffuse intervention tool, and the fact that network functions were not explored by physiological measures, limit the possibility of drawing conclusions regarding complex language network alterations caused by the intervention. Nevertheless, the main value of the study is to gain knowledge about functional aspects of the involvement of Wernicke's area in verbal learning and memory, as well as the establishment of efficient stimulation protocols which could have a translational impact. Another aspect to be considered is the implementation of a follow-up to evaluate possible long-term effects of stimulation in future studies. The current flow and spatial focality of stimulation are also important determinants of tDCS effects (Datta et al., 2009). Here we used a relatively large electrode for anodal stimulation over Wernicke's area, although it was smaller compared to the return cathodal electrode. This electrode montage was aimed to induce a larger (anodal) current density underneath the target area. However, the induced current flow could have been somehow diffuse, resulting in a limited focality of stimulation over Wernicke's area, as suggested by computational modeling (Datta et al., 2009). Moreover, despite the fact that the right frontopolar cortex is not apparently related to linguistic functions, possible functional effects due to the cathodal current flow over the supraorbital ridge cannot be ruled out completely. Future studies with more specific stimulation protocols would be helpful to clarify this issue. Finally, the investigation of titration curves for different tDCS intensities and implementation of designs resulting in better targeted brain stimulation through smaller electrodes are also relevant issues to be evaluated in further research.

Conclusions

Intensity-dependent functional effects on verbal memory performance and verbal memory interference processes were observed when Wernicke's area excitability was apparently modulated by anodal tDCS. Increased verbal memory performance and absence of verbal interference on memory performance were found when tDCS was applied at 1.5 mA, but not at 0.5 mA or in a sham stimulation control condition. Knowledge about the functional effects of different tDCS intensities is critical for basic research and for the design of clinical applications. Further studies including other cortical target areas, such as Broca's area, different tDCS polarities, and systematic tDCS titration curves may shed light on the effectiveness of non-invasive brain electric stimulation for the improvement of verbal memory task performance. The implications of the findings of this study are limited regarding the functional details of the complex language network model, but the results show for the first time that a specific intensity of stimulation over Wernicke's area is able to modify verbal memory performance.

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Figure legends

Figure 1. Position of the anodal (red color -most posterior electrode-) and cathodal (blue color -more anterior electrode-) electrodes with respect to a lateral (left image) and dorsal (right image) representation of the 10-20 EEG international system.

Figure 2. Time course of the experiment. After 3 minutes of anodal tDCS applied over Wernicke's area subjects performed the verbal learning task during stimulation. Total time required for task performance was about 12 minutes (total time of stimulation, 15 minutes). When this task was performed, a WAIS-Block Design task was completed in approximately 20 minutes without tDCS. After that (around 35 minutes after the beginning of tDCS), long-term free memory and long-term memory with semantic strategy were evaluated using the same list of words of the verbal learning task.

Figure 3. Mean number of words recorded in each group throughout the 10 trials (5 learning trials, one interference trial, and 4 memory trials) of the TAVEC task. (ST-FM) short term free memory, (ST-SS) short term memory with semantic strategy; (LT-FM) long term free memory, (LT-SS) long-term memory with semantic strategy. After the interference trial (IT), the recall of words was significantly higher in the group with anodal tDCS at 1.5 mA in all trials (*$p<0.05$) compared to sham and 0.5 mA anodal stimulation. An interference effect on memory was found in the 0.5 mA anodal tDCS and sham stimulation conditions after IT (#$p<0.05$, significant differences between the last learning trial -the fifth trial- and the ST-FM trial), but not in the 1.5 mA anodal tDCS group. Error bars represent SEM.

Figure 4. Mean number of words recorded in each group using semantic (A) and serial (B) self-strategies (8 trials, no explicit request to use strategies). (IT) interference trial, (ST-FM) short term free memory, (LT-FM) long term free memory. In both cases (semantic or serial self-strategies), no significant differences were found between the tDCS groups. Error bars represent SEM.

Figure 5. Mean number of perseverations -persistent repetition of words from the list- (A) and intrusions -production of words not included in the list- (B) in each group throughout the 10 trials of the TAVEC task. (ST-FM) short term free memory, (ST-SS) short term memory with semantic strategy; (LT-FM) long term free memory, (LT-SS) long-term memory with semantic strategy. For both types of error (perseverations and intrusions), no significant differences were found between the different groups. Error bars represent SEM.

Figure 6. Number of correct reproductions of geometric models in each group obtained in the WAIS-Block Design task. No significant between group differences were found. Error bars represent SEM.