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Transcranial Cerebellar Direct Current Stimulation (tDCS) enhances verb generation but not verb naming in post-stroke aphasia.

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Abstract

Although the role of the cerebellum in motor function is well recognized, its involvement in the lexical domain remains to further elucidate. Indeed, it has not yet been clarified if the cerebellum is a language structure *per se* or it contributes to language processing when other cognitive components (e.g. cognitive effort, working memory) are required by the language task. Neuromodulation studies in healthy subjects have suggested that cerebellar tDCS is a valuable tool to modulate cognitive functions. However, so far, only a single case study has investigated whether cerebellar stimulation enhances language recovery in aphasic individuals. In a randomized cross-over double blind design, we explored the effect of cerebellar tDCS coupled with language treatment for verb improvement in twelve aphasic individuals. Each subject received cerebellar tDCS (20 min, 2 mA) in four experimental conditions: 1) right cathodal and 2) sham stimulation during a verb generation task; 3) right cathodal and 4) sham stimulation during a verb naming task. Each experimental condition was run in five consecutive daily sessions over four weeks. At the end of treatment, a significant improvement was found after cathodal stimulation only in the verb generation task. No significant differences were present for verb naming among the two conditions. We hypothesize that cerebellar tDCS is a viable tool for recovery from aphasia but only when the language task, such as verb generation, also demands the activation of non-linguistic strategies.

Keywords: Cerebellar tDCS, language recovery, aphasia, verb generation, brain stimulation

Introduction

During the past two decades, converging neuroscientific evidence has largely documented that the human cerebellum contributes to a much wider range of higher-level cerebral functions than previously accepted. Indeed, while traditionally, there has been unanimous agreement that the cerebellum is primarily involved in autonomic and somatic motor processes (De Smet, Baillieux, De Deyn, Mariën, & Paquier, 2007; Holmes, 1939; Leiner, 2010; Schmahmann, 2010; Strick, Dum, & Fiez, 2009), particularly following aphasia reports, there has been rapidly increasing interest in the cerebellum's role in cognition (Manto & Haines, 2012; Reeber, Otis, & Sillitoe, 2013; Strick et al., 2009). Indeed, several linguistic disorders following acquired cerebellar lesions have been documented (De Smet et al., 2007), such as impaired verbal fluency (Akshoomoff, Courchesne, Press, & Iragui, 1992; Appollonio, Grafman, Schwartz, Massaquoi, & Hallett, 1993; Leggio, Silveri, Petrosini, & Molinari, 2000; Meinzer, Yetim, McMahon, & de Zubicaray, 2016; Molinari, Leggio, & Silveri, 1997; Richter et al., 2007; Schmahmann & Sherman, 1998; Stoodley & Schmahmann, 2009), agrammatism (Mariën et al., 1996; Molinari et al., 1997; Schmahmann & Sherman, 1998) and naming difficulties (Fabbro, Moretti, & Bava, 2000; Gasparini et al., 1999; Schmahmann & Sherman, 1998). Based on these findings, some authors have assumed that the cerebellum represents an "inter-area functional coordinator" subserving precisely timed sequential organization of verbal sentences" (Silveri, Leggio, & Molinari, 1994; Zettin, Cappa, D'amico, Rago, & Perino, 1997). Indeed, this process might be compromised in patients with cerebellar lesions (Molinari et al., 1997). Several other cases of aphasia, predominantly, as a result of right cerebellar lesions, characterized by prevailing verbal fluency disturbances, have been described (Gasparini et al., 1999; Mariën & Beaton, 2014; Mariën, Engelborghs, Pickut, & De Deyn, 2000; Stoodley & Schmahmann, 2009). The frequent co-occurrence of a right cerebellar lesion and aphasia led some authors to hypothesize the existence of a "lateralized linguistic cerebellum" (Mariën et al., 1996, 2000, 2014). According to Mariën et al. (1996, 2000, 2014), the aphasic disorder reflects a "diaschisis" phenomenon whereby the damage of the right cerebellum causes a hypofunction of the left frontal cortical areas, “home” of our language representation (Mariën et al., 1996, 2000, 2014). The cerebellum would thus have a role in linguistic representation but only through its connections with the left frontal cerebral language areas (but see Gasparini et al., 1999).

In line with this hypothesis, several neuroimaging reports in healthy subjects have confirmed the activation of the posterior lateral area of the right cerebellum together with an activation of the left frontal cortex during different linguistic tasks (Chen, Ho, & Desmond, 2014; Gurd et al., 2002; McDermott, Petersen, Watson, & Ojemann, 2003; Ojemann et al., 1998; Schlösser et al., 1998; Stoodley & Schmahmann, 2009) but many conclusions about the role of the cerebellum in language originate from applying word generation tasks (Frings et al., 2006; Petersen, Fox, Posner, Mintun, & Raichle, 1989; Stoodley, Valera, & Schmahmann, 2010, 2012). Petersen and co-workers (1989) reported the first non-motor linguistic PET activation study in which subjects were requested to produce a verb semantically associated to a presented noun. In contrast to the control condition in which the nouns only had to be read or merely repeated, the verb generation condition activated the right lateral cerebellum and a number of left frontal regions. Indeed, this task, which reflects the capacity to generate words according to a given semantic category, requires a large amount of cognitive effort and it is generally considered to depend on a close cooperation between verbal, executive and working memory functions which rely on frontal lobes (Bellebaum & Daum, 2007; Gottwald, Mihajlovic, Wilde, & Mehdorn, 2003; Grafman et al., 1992; Schmahmann & Sherman, 1998; Stoodley & Schmahmann, 2009). Thompson-Schill and colleagues (1998) have suggested that verb generation is a more “difficult” task than naming because it requires selection of a response from among multiple competitors due to the association strength between an object (noun) and its corresponding verbs (e.g. knife → “cut”, “spread”, “sharp”, “stab”, etc.).

Despite variations on the original task design, several other studies have consistently reproduced activation of the right lateral cerebellum during word generation tasks (Grabowski et al., 1996; Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995; Raichle et al., 1994). Leiner et al. (1989) interpreted the simultaneous activation of the right cerebellum and the left Broca’s language area during word generation as "the reflection of accelerated transmission of signals between these two centers during word finding". Consistent with this assumption, some neuroimaging studies in aphasic individuals have provided evidence in favour of a close connection between the right cerebellar activity and the activation of the contralateral left frontal regions. Indeed, aphasic patients showed an abnormal response from the right cerebellum due to the absence of inputs from the damaged left frontal regions (Connor et al., 2006) and a reactivation of the right cerebellar area following language recovery due to a recruitment of the left perilesional frontal cortex (Heath et al., 2013; Marangolo et al., 2016; Szaflarski, Allendorfer, Banks, Vannest, & Holland, 2013).

Parallel to this increasing interest in the role of the cerebellum in cognition, in more recent years, non invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS) have been used to modulate cognitive functions, such as working memory, attention and language (Lefaucheur et al., 2016; Nitsche & Paulus, 2011).

The assumption on which tDCS is based is that a constant, weak and continuous current is able to alter the firing rate of the neurons. It has been proposed that cerebellar tDCS is most likely to produce its effects by polarizing Purkinje cells (see Pope & Miall, 2014; van Dun, Bodranghien, Mariën, & Manto, 2016) and changing the levels/pattern of activity in the deep cerebellar output nuclei, thereby also affecting distant plasticity in human cortical areas (Grimaldi et al., 2016; van Dun et al., 2016). Indeed, it has been shown that, while anodal stimulation, through its excitatory effects, increases the discharge from the Purkinje cells, augmenting the inhibition of the facilitatory pathways from the cerebellar nuclei to the cerebral cortex; cathodal stimulation exerts the opposite effect, through a disinhibition of Purkinje cells, it activates the frontal cerebral cortex (Galea & Celnik, 2009; Pope, 2015; Pope & Miall, 2012).

Pope and Miall (2012) have suggested that one crucial factor for cerebellar tDCS impact is task difficulty. In their study, three groups of twenty-two participants each performed the Paced Auditory Serial Addition Task (PASAT) and a variant of this task called the Paced Auditory Serial Subtraction Task (PASST), together with a verb generation task, before and after anodal, cathodal or sham tDCS over the right cerebellum. The authors reported an effect on the difficult PASST but not on the easier PASAT. Interestingly, an improvement in the PASST and a reduction in verbal response latencies in verb generation were observed after cathodal right cerebellar tDCS while no effect of anodal stimulation was found (Pope & Miall, 2012). According to Pope and Miall (2012), right cerebellum stimulation has influenced working memory and attention abilities differently depending on task difficulty. Thus, the cerebellum is capable of releasing cognitive resources by disinhibition of the left prefrontal regions, enhancing performance only when the task is cognitively demanding (Pope & Miall, 2012).

Contrary to these findings, in a group of healthy subjects, Turkeltaub and collaborators (Turkeltaub, Swears, D'Mello, & Stoodley, 2016) showed that both anodal and cathodal stimulation over the right cerebellum improves word generation but the effects were found using a different task, namely a phonemic fluency task. Following Pope and Miall's suggestion (Pope & Miall, 2014; Pope & Miall, 2012), the authors hypothesized that cerebellar tDCS did not act directly on the language function *per se* but on the executive control and response selection components required by the generation task (Turkeltaub et al., 2016).

To date, only a single case study has investigated whether cerebellar tDCS leads to recovery from aphasia. In a patient with large bilateral fronto-parietal and insular infarct, Sebastian et al. (2016) found that both anodal and sham coupled with language treatment resulted in improved spelling to dictation for trained and untrained word immediately after and two months post-treatment but the improvement was greater with anodal tDCS than with sham especially for untrained items. Although the results are interesting and suggest therapeutic potential of cerebellar tDCS for language recovery, we believe that any final conclusion deserves further investigations. Indeed, as the authors also pointed out, a crucial limitation of their study was that it includes a single case with a large bilateral damage which is not a lesion typically observed in the aphasic population. In addition, in their experimental design, active tDCS followed sham, thus, any extra benefits of tDCS might be due of having a second treatment after already having had the first treatment (Sebastian et al., 2016).

In the present study, we aimed to verify the role of cerebellar tDCS in language processing in a group of twelve left unilateral damaged aphasic subjects by contrasting two different language tasks with different demands in terms of cognitive effort: a verb naming and a verb generation task. Indeed, with respect to verb naming in which the production of the correct answer is facilitated by the presented picture, verb generation, due to some combination of both retrieval and competition demands (Snyder, Banich, & Munakata, 2011), relies on different cognitive strategies (Ackermann, Mathiak, & Riecker, 2007; Justus, Ravizza, Fiez, & Ivry, 2005).

Since cathodal stimulation, reducing the inhibition of the Purkinje cells, favours increased excitability of the left frontal language areas (Connor et al., 2006; Pope & Miall, 2014), in the present work, two experimental conditions were used: right cathodal and sham cerebellar tDCS. Based on previous findings, we expected to find that cathodal stimulation would lead to a greater improvement in verb retrieval with respect to the sham condition only in the verb generation task.

MATERIAL AND METHODS

Participants

Twelve left brain-damaged participants (6 males and 6 females) with chronic aphasia were included in the study (see Figure 1). Inclusion criteria were native Italian speaker, premorbid right handedness (Oldfield, 1971) a single left hemispheric stroke at least 6 months prior to the investigation, mild non fluent aphasia with no articulatory difficulties, preserved basic comprehension skills (so to allow them to be engaged in verbal exchanges with the therapist) and no attentive or memory deficits that might bias their performance. The data analysed in the current study were collected in accordance with the Helsinky Declaration and the Institutional Review

Board of the IRCCS Fondazione Santa Lucia, Rome, Italy. Prior to participation, all patients signed informed consent forms.

- Insert Figure 1 about here -

Clinical Data

The aphasic disorders were assessed using standardized language tests (the Battery for the Analysis of Aphasic Disorders, BADA test, (Miceli, Laudanna, Burani, & Capasso, 1994); De Renzi & Vignolo, 1962). All patients were classified as non fluent aphasics as they had reduced verbal output in spontaneous speech. Their utterances were short and they were mainly characterized by omissions of verbs as well as errors in verb inflection. Their basic comprehension skills were preserved but they still have difficulty in comprehending complex materials (mean= 17/36; 29/36 cut-off score, < 29 impaired performance Token test (De Renzi & Vignolo, 1962). In the noun and verb naming task, moderate-to-severe word finding difficulties were still present. A neuropsychological battery of tests was also administered which excluded the presence of attention (i.e. Alertness, Sustained and Selective attention), working memory (i.e. digit span) and executive functions deficits that might confound the data (Spinnler & Tognoni, 1987; Zimmermann & Fimm, 1994) (see Table 1).

- Insert Table 1 about here -

Materials

Sixty pictures of verbs (i.e. to sing, to write) for the verb naming task and sixty nouns associated to a correspondent verb (i.e. pen → to write) for the verb generation task were selected. For each task, the sixty stimuli were subdivided into two lists of 30 items each matched for frequency (verb naming (VN) list 1: mean= 28, SD=31, list 2: mean=28, SD=31; nouns (N) list 1: mean= 33, SD=32, list 2: mean=32, SD=33, unpaired t test, p>.05 for each comparison) and length (verb naming (VN) list 1: mean= 8, SD=1, list 2: mean=8, SD=2; nouns (N) list 1: mean= 7, SD=2, list 2: mean=7, SD=2, unpaired t test, p>.05 for each comparison; Bertinetto et al., 2005). The lists were also matched for imageability (estimated on the basis of a sample of 30 normal participants along a seven-point scale, from 1 (no imageability) to 7 (clear imageability) (verb naming (VN) list 1: mean= 6, SD=1, list 2: mean=6, SD=1; nouns (N) list 1: mean= 6, SD=1, list 2: mean=6, SD=1, unpaired t test, p>.05 for each comparison).

The correlations between the above variables were not significant among the lists suggesting that each measure represented an independent attribute (frequency vs. length verb naming (VN) list 1: r = -.22, p=.25; frequency vs. imageability verb naming (VN) list 1: r =-.13, p=.50; imageability vs. length verb naming (VN) list 1: r =-.08, p=.66; frequency vs. length verb naming (VN) list 2: r = -.29, p=.12; frequency vs. imageability verb naming (VN) list 2: r =-.23, p=.23; imageability vs. length verb naming (VN) list 2: r = .03,p=.86; frequency vs. length nouns (N) list 1: r = -.28, p=.14; frequency vs. imageability nouns (N) list 1: r = -.23, p=.23; imageability vs. length nouns (N) list 1: r = .29, p=.12; frequency vs. length nouns (N) list 2: r = -.32, p=.09; frequency vs. imageability nouns (N) list 2: r =.13, p=.50; imageability vs. length nouns (N) list 2: r = .18; p=.34).

Procedure

Transcranial cerebellar direct current stimulation

tDCS was applied using a battery-driven EMS (Bologna, Italy) Programmable Direct Current Stimulator with a pair of surface-soaked sponge electrodes (5 cm × 7 cm). A constant current of 2 mA intensity was applied through the cathode on the right cerebellar cortex, 1 cm under and 4 cm lateral to the inion (approximately comparable to the projection of cerebellar lobule VII into the scalp) for 20 min while the reference electrode was positioned over the right shoulder on the deltoid muscle (Pope & Miall, 2012). If applied according to safety guidelines, tDCS is considered to be a safe brain stimulation technique with minor adverse effects (Fregni et al., 2015; Lefaucheur et al., 2016). For each task (verb naming vs. verb generation), two different stimulation conditions were carried out: 1) cathodal and 2) sham. Sham stimulation was performed exactly like the cathodal condition but the stimulator was turned off after 30s (Gandiga, Hummel, & Cohen, 2006). Thus, we had four different experimental conditions: 1) right cathodal cerebellar tDCS for verb naming, 2) sham for verb naming, 3) right cathodal cerebellar tDCS for verb generation, 4) sham for verb generation. For each task, the sixty stimuli were subdivided into two lists of 30 items each matched for frequency, length and imageability. The assignment of each list of stimuli was randomized across the two conditions (cathodal vs. sham). All patients underwent the four experimental conditions whose order was randomized across subjects. To ensure the double-blind procedure, both the experimenter and the patient were blinded regarding the stimulation condition and the stimulator was turned on/off by another person. At the end of each experimental condition, subjects were asked if they were aware of which condition (real or sham) they were in. We inferred that all subjects well tolerated the stimulation by interpreting their spontaneous report as well as the results from a questionnaire completed by the participant at the end of each experimental condition (see Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010 for the questionnaire). Itch was the most commonly reported sensation with light (16% of the subjects) to moderate (83% of the subjects) intensity. Participants reported that the sensation started at the beginning of the stimulation and stopped after few minutes both during the real and/or the sham stimulation. Thus, none of the subjects were able to distinguish between the two conditions. A paired t -test did not show any significant difference in the subjects' perception of sensation between the real and the sham condition ($p>.05$).

Treatment

Once the electrodes were placed, subjects performed the two tasks while they received 20 min of cerebellar tDCS. Each stimulation condition was performed in five consecutive daily sessions over one week with six days of intersession interval. The order of items presentation was randomized across sessions. During the verb naming task, subjects were asked to name aloud each picture that appeared on the PC screen (screen size 15”, viewing distance 1m) for 20 s preceded by a fixation point, which lasted 800 ms (see also (Fiori et al., 2013) for similar procedure). If the subject failed or did not answer within 20s, the corresponding written name was presented below the picture for 5s and the subject was asked to read the word aloud. The pair of stimuli remained on the screen until the subject read the word or 5s elapsed. In all cases, subjects were able to correctly read the word. During the verb generation task, the examiner orally presented a noun (i.e. trampoline) and subjects were required to produce within 20s the most appropriate corresponding verb (i.e. to jump). Since previous studies have reported activation of the right lateral cerebellum during a verb generation task independently of the input modality (Petersen et al., 1989; Richter et al., 2004), we chose to orally present the noun in order to prevent subjects from “task errors” such as reading the noun by presenting a written noun (Thompson-Shill et al., 1998) or naming the object by presenting the object picture (Kurland, Reber & Stokes 2014).

For both tasks, the examiner manually recorded the response on a separate sheet. If the subject did not respond within the 20s-interval, the program automatically presented the subsequent picture or noun. Vocal reaction times were calculated from the presentation of the picture or the noun to the pronunciation of the first phoneme through A*udacity 2.1.2 Software*. Only if the subjects responded within 20s, reaction times were recorded.

Data Analysis

Prior to the experiment, the two lists of stimuli were presented to a group of thirty healthy individuals (15 males and 15 females) matched for age (40 to 75 years) and education level (13 to 17 years) to the aphasic group. Each participant was asked to produce for each presented verb for the verb naming task and noun for the verb generation task the most appropriate corresponding verb, with no interference from the examiner. Only those verbs which elicited at least 80% of agreement among participants in the two lists were considered correct responses and, therefore, used for response accuracy analysis in the aphasic group.

Data were analyzed with STATISTICA 10 (StatSoft, Inc., Tulsa, OK). Statistical analyses were performed with two separate analyses of variances (ANOVAs), respectively, for response accuracies and vocal reaction times with three within-subject factors: TASK (verb generation vs. verb naming), CONDITION (cathodal stimulation vs. sham) and TIME (baseline (T0) vs. end of the treatment (T5) vs. follow up (FU)). If the ANOVA showed significant effects, respective post-hoc Bonferroni tests were conducted.

RESULTS

Accuracy

The analysis showed a significant effect of CONDITION ($F(1,11)=13.88$, $p<.01$) and TIME ($F(2, 22) = 77.94$, $p <.001$). The interaction TASK*CONDITION*TIME was also significant ($F(2,22) = 16.21$, $p <.001$). Indeed, although all experimental conditions led to a significant greater percentage of correct responses at the end of treatment (T5) compared to the baseline (T0) (verb generation: difference between T5 – T0 cathodal = 44% , $p <.001$; sham=15%, $p =.001$; verb naming: difference between T5 – T0 cathodal = 15% , $p =.001$; sham = 12%, $p =.007$), at the end of treatment, only in the verb generation task the percentage of correct responses was greater after cathodal stimulation compared to sham (cathodal vs. sham =28%, $p <.001$) and this difference persisted at FU (cathodal vs. sham =25%, $p <.001$). No differences between the two stimulation conditions were found for the naming task (cathodal vs. sham T5= 4%, $p=1$; cathodal vs. sham FU= 2%, $p=1$) (see Figure 2).

-Insert Figure 2 about here-

In order to further investigate if tDCS had a different impact on the subject's response, we classified the errors made by each subject in all experimental conditions. As shown in Table 2, errors were 1) no responses, 2) semantic paraphasias and 3) unrelated verb responses but, at baseline (T0), both for the verb naming and the verb generation task, errors were predominantly “no responses”. Thus, we conducted an analysis of variance (ANOVA) on the number of “no responses” with three within-subject factors: TASK (verb generation vs. verb naming), CONDITION (cathodal vs. sham) and TIME (baseline (T0) vs. end of the treatment (T5)). The analysis revealed a significant interaction TASK*CONDITION*TIME ($F(1,11) = 8.29$, $p = .01$). Indeed, although all experimental conditions led to a lower number of “no responses” at the end of treatment (T5) compared to the baseline (T0) (verb generation: difference between T5 – T0 cathodal = 12 , $p < .001$; sham=5, $p = .04$; verb naming: difference between T5 – T0 cathodal = 5 , $p = .04$; sham = 6, $p = .03$), at the end of treatment (T5), only in the verb generation task the number of “no responses” was lower after cathodal stimulation compared to sham (cathodal vs. sham = -6, $p = .02$). No differences between the two stimulation conditions were found for the verb naming task (cathodal vs. sham T5= 1 $p = 1$). Thus, these results resembled those previously found for the accuracy data.

- Insert Table 2 about here -

Vocal reaction times

The analysis showed a significant effect of CONDITION ($F(1,11)=6.20$, $p=.03$) and TIME ($F(2, 22) = 40.24$, $p < .001$). The interaction TASK*CONDITION*TIME was also significant ($F(2,22) = 11.12$, $p < .001$). Indeed, although all experimental conditions led to faster vocal reaction times at the end of treatment (T5) compared to baseline (T0) (verb generation: difference between T5 – T0 cathodal = 4334 ms, $p < .001$; sham=1644 ms, $p = .003$; verb naming: difference between T5 – T0 cathodal = 1897 ms , $p = .001$; sham = 1932 ms, $p < .001$), at the end of treatment, only in the verb generation task vocal reaction times were faster after cathodal stimulation compared to sham (cathodal vs. sham =-2350 ms, p <.001) and this difference persisted at FU (cathodal vs. sham =-2250 ms, p <.001). No differences between the two stimulation conditions were found for the verb naming task (cathodal vs. sham T5= 10 ms, p=1; cathodal vs. sham FU= 23 ms, p=1) (see Figure 3).

-Insert Figure 3 about here-

DISCUSSION

The aim of the present study was to investigate whether cerebellar tDCS coupled with language training improves verb retrieval in non fluent chronic aphasic individuals. Our findings showed that cathodal stimulation differently affected verb recovery depending on the language task. Indeed, at the end of treatment, only the verb generation task led to a significant improvement in verb retrieval. Moreover, follow-up testing showed that these effects lasted over one week after the intervention. This specificity argues against an effect simply due to enhanced cognitive arousal which should have influenced both language tasks.

As stated in the Introduction, several studies have already supported the hypothesis that the cerebellum plays a role in language processing but it depends on task demands (Ackermann et al., 2007; Pope & Miall, 2014; Pope & Miall, 2012; Stoodley et al., 2010, 2012). Ackermann et al. (2007) have argued that non-linguistic aspects of task performance, such as the amount of effort or the degree of automaticity, might account for cerebellar involvement during verb generation tasks. Similarly, Stoodley and Schmahmann (Stoodley & Schmahmann, 2009) have claimed that the cerebellum takes part not in the language function *per se* but only when the task is cognitively demanding and, therefore, it engages other cognitive components, such as working memory and/or executive functions (Stoodley & Schmahmann, 2009). Indeed, apart from motor control and higher-order aspects of speech production, a variety of studies point to a contribution of the cerebellum to executive and memory tasks (Ackermann et al., 2007). Since the paradigm of verb generation involves the production and selection of different verbal responses (Thompson-Schill et al., 1998), prearticulatory rehearsal processes are engaged as well which rely to working memory processes (Ackermann et al., 2007; Helmuth, Ivry, & Shimizu, 1997). Indeed, our choice to directly compare cerebellar tDCS effects in two verb production tasks was made taking into account the substantial differences between the two tasks.

Like confrontation naming, verb generation is a semantic association task in which the subject has to produce a verb strictly associated to a given noun. Much of the cognitive demand between the two tasks is shared, including semantic, lexical retrieval processes and the planning, execution, and monitoring of speech production (e.g., Levelt, 1989). However, while verb generation requires the patient to creatively link a noun to a verb choosing among competing response alternatives (Thompson-Schill et al., 1998), in verb naming, the correct answer is univocally determined by the presented picture and the task is one of the earliest linguistic skills developmentally mastered, and, thus, is an overlearned task (Herholz et al., 1997). Interestingly, although verb generation is a task more cognitive demanding than verb naming and, persons with aphasia, generally, experience greatest difficulty with verb generation (Martin & Cheng, 2006; Thompson-Schill et al., 1998), our aphasic patients benefited only for this task after right cerebellar cathodal stimulation.

Although our data are only behavioural, we might speculate that right cathodal cerebellar stimulation, through a disinhibition of the Purkinje cells, has favoured the engagement of the left frontal areas which, in turn, enhanced the activation of executive and memory components required by the verb generation task (Connor et al., 2006; Mariën et al., 1996; Mariën, Engelborghs, Fabbro, & De Deyn, 2001; Pope & Miall, 2014). Indeed, most of our patients had a partial damage to the left frontal areas (see Figure 1), thus, the hypothesis can be advanced that subregions of the left frontal cortex took part in verb recovery. Accordingly, several studies have already shown that the same facilitatory patterns may be observed in verbal fluency task after cathodal cerebellar tDCS or anodal stimulation over the frontal cortex (Pope & Miall, 2012; Iyer et al., 2005). Confirming evidence for a functional relationship between the left frontal cortex and the cerebellum comes also from a recent study combining bilateral tDCS and resting state functional magnetic resonance imaging (rsfMRI) in a group of left brain-damaged population (Marangolo et al., 2016). Indeed, in nine chronic aphasics, Marangolo et al. (2016) found that bilateral anodic stimulation over the left inferior frontal area and cathodal contralesional stimulation over its right homologue coupled with an intensive language treatment led to functional connectivity changes within the left damaged hemisphere, together with the cerebellum (Marangolo et al., 2016). In agreement with our hypothesis that the cerebellum is functionally connected to the language network, very recently, D'Mello et al. (2017) acquired behavioral and rsfMRI data, during a sentence completion task, before and after cerebellar tDCS in a group of healthy adults. Relative to sham, anodal tDCS increased activation in the right cerebellum only when the preceding context in the sentence modulated the predictability of the target word (predictive sentences). In the same study (D'Mello et al., 2017), functional connectivity changes were also found in the left language areas, including the left inferior frontal gyrus. Thus, these data showed that cerebellar neuromodulation specifically alters activation patterns during semantic prediction tasks (D'Mello et al., 2017). Similarly, in our work, cerebellar tDCS improved the generation of highly predictable verbs semantically associated to the presented nouns.

It might be finally argued that the effects found were an artifact of linguistic variables, so that, at the end of treatment, the verbs produced in the generation task had higher frequency and/or were shorter (in terms of number of phonemes) than the verbs produced in the naming task. However, statistical analyses performed to control for those factors did not show any significant difference between the correct responses given in the two tasks (Verb generation: mean frequency= 32, SD=9; mean length=8, SD=1; Verb naming: mean frequency=31, SD=8; mean length=8, SD=0; T tests p= .72 and p=.69, respectively, for frequency and length).

In conclusion, although our data deserve further investigations, they suggest that cerebellar tDCS might be a viable tool for enhancing language recovery in chronic aphasia. Since our results point to potential therapeutic benefits of cerebellar stimulation only for complex language tasks, we believe that these findings have important implications for aphasia. Indeed, they address the possibility that the cerebellum supports cognitive functions which are important for language recovery.

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Table 1. Sociodemographic and Clinical data of the twelve non fluent aphasic patients

P	AGE (Years)	EDUC LEVEL (Years)	TIME POST-ONSET	NN (%)	VN (%)	NC (%)	VC (%)	TT (cut/off 29/36, < 29 impaired)	Attentional Abilities (scores in percentile < 5 impaired)	WM (cut/off 5±2, < 5 impaired)	WEIGL'S (cut/off 4,50, < 4,50 impaired)
1	50	16	2 years	48	20	100	100	14/36	Alertness (tot): 60 Sustained Att (tot): 75 Selective Att (tot): 55	WM: 4	9,75
2	61	13	1 year, 3 months	90	64	100	100	14/36	Alertness (tot): 99 Sustained Att (tot): 76 Selective Att (tot): 94	WM: 5	10
3	46	8	1 year, 10 months	30	20	100	100	14/36	Alertness (tot): 30 Sustained Att (tot): 34 Selective Att (tot): 28	WM: 4	10
4	65	13	1 year, 7 months	45	40	100	100	15/36	Alertness (tot): 65 Sustained Att (tot): 70 Selective Att (tot): 60	WM: 4	9.25
5	68	18	1 year, 9 months	77	67	100	100	21/36	Alertness (tot): 89 Sustained Att (tot): 54 Selective Att (tot): 66	WM: 5	12,5
6	57	13	2 years, 9 months	67	64	100	100	14/36	Alertness (tot): 35 Sustained Att (tot): 30 Selective Att (tot): 35	WM: 5	10,75
7	70	13	1 year, 9 months	70	65	100	100	21/36	Alertness (tot): 95 Sustained Att (tot): 80 Selective Att (tot):	WM: 5	11,5

									70		
8	48	18	1 year, 2 months	33	40	100	100	14/36	Alertness (tot): 94 Sustained Att (tot): 55 Selective Att (tot): 50	WM: 5	9,75
9	51	8	1 year, 6 months	30	30	100	100	23/36	Alertness (tot): 97 Sustained Att (tot): 60 Selective Att (tot): 84	WM: 5	11
10	60	13	1 year, 6 months	55	60	100	100	23/36	Alertness (tot): 90 Sustained Att (tot): 80 Selective Att (tot): 60	WM: 6	10
11	61	10	1year, 5 month	43	25	100	100	14/36	Alertness (tot): 78 Sustained Att (tot): 81 Selective Att (tot): 50	WM: 5	10,5
12	56	13	3 years, 1 month	70	71	100	100	14/36	Alertness (tot): 90 Sustained Att (tot): 62 Selective Att (tot): 85	WM: 6	10,75

Legend: P= Participants; Educ. Level= Educational Level; Percentage of correct responses in NN=Noun Naming; VN=Verb Naming; NC=Noun Comprehension; VC= Verb Comprehension (BADA test, Miceli et al., 1994); TT=Token test, cut off= 29/36 (De Renzi & Vignolo, 1972); Attentional Abilities (Zimmermann & Fimm, 1994; patient's scores are reported in percentile: scores below the 5th percentile are considered impaired; Att= attention; WM=Working Memory (i.e. digit span, Orsini et al., 1987; Spinnler & Tognoni, 1987); Weigl's Sorting test (Italian Version, Spinnler & Tognoni, 1987; for each patient, row scores are reported).

Table 2. Mean number of errors in the verb generation and verb naming task for cathodal and sham tDCS, respectively (±SD, standard deviation).

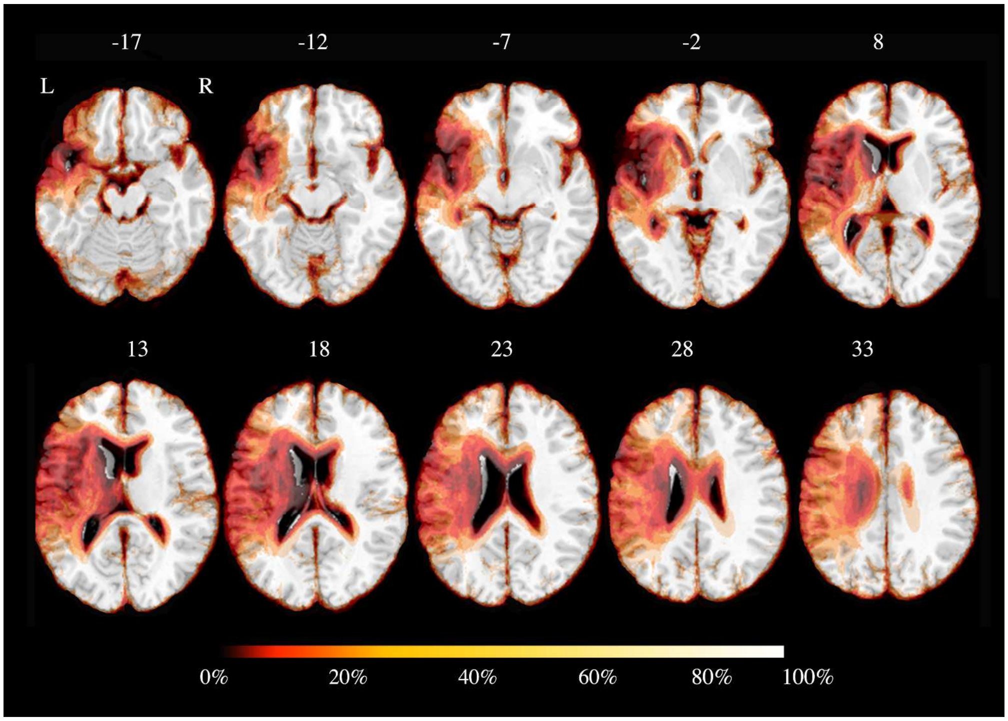
TYPE OF ERRORS	VERB GENERATION CATHODAL		VERB GENERATION SHAM		VERB NAMING CATHODAL		VERB NAMING SHAM	
	T0	T5	T0	T5	T0	T5	T0	T5
NO RESPONSES	19 (±5)	7 (±3)	18 (±6)	13(±7)	17 (±6)	13 (±6)	18 (±7)	12 (±6)
SEMANTIC PARAPHASIAS	3 (±2)	2 (±1)	3(±2)	3(±2)	2 (±1)	2 (±2)	2 (±2)	3 (±2)
UNRELATED VERB RESPONSES	2 (±2)	2 (±2)	2(±2)	3(±3)	1 (±1)	1 (±2)	1 (±1)	1 (±2)

Figure captions

Figure 1. Brain parenchyma overlap across patients. Color bar refers to the amount of saved voxels, implying 0% being related to the total absence of tissue and 100% to the total presence of tissue. As shown, lesions extent included the temporal lobe, the inferior frontal gyrus, the insula and partially the post-central and pre-central gyrus. Axial coordinates refer to the standard space (MNI152).

Figure 2. Mean percentage of response accuracy for verb generation and verb naming task at baseline (T0), at the end of the treatment (T5) and at follow-up (FU) for the cathodal and sham condition, respectively (*≤.001, **<.01). Error bars represent standard error of the mean.

Figure 3. Mean vocal reaction times for verb generation and verb naming at baseline (T0), at the end of the treatment (T5) and at follow-up (FU) for the cathodal and sham condition, respectively (*≤.001, **<.01). Error bars represent standard error of the mean.



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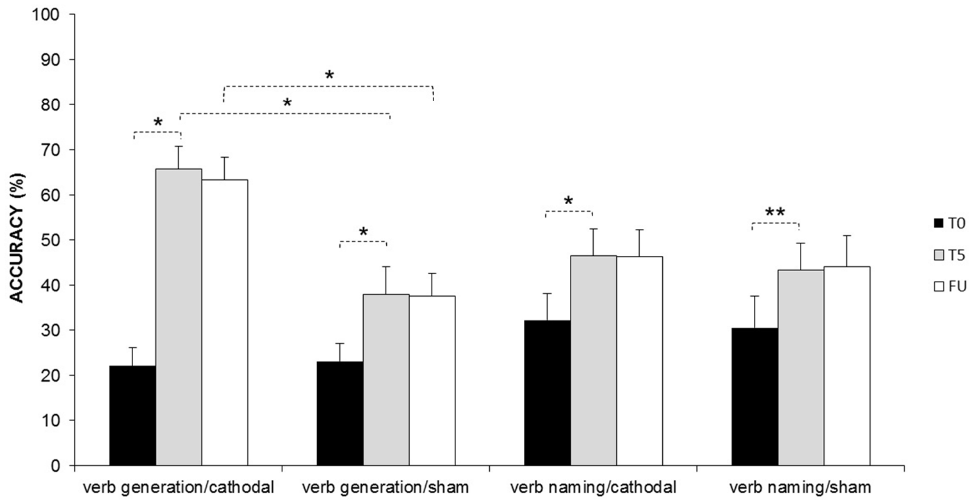
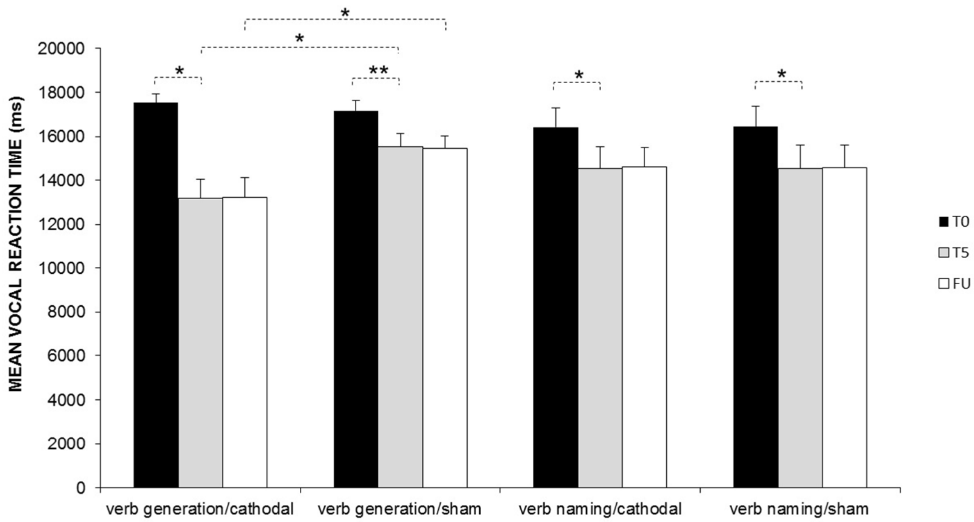


202x104mm (150 x 150 DPI)



206x115mm (150 x 150 DPI)