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Transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex modulates declarative memory

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Background
Previous studies have claimed that weak transcranial direct current stimulation (tDCS) induces persisting activity changes in the human motor cortex and working memory, but to date no studies have evaluated the effects of tDCS on declarative memory.

Objective
Our aim was to determine whether anodal and cathodal transcranial direct current stimulation would differentially modify performance in a word memorization task during encoding or recognition when administered over the left dorsolateral prefrontal cortex (DLPFC).

Methods
In two experiments, 32 participants underwent a series of word memorization tasks. This task was performed during sham, anodal, and cathodal stimulation applied over the left DLPFC. Moreover, participants in the first experiment performed the same task with anodal tDCS of the primary motor cortex (M1).

Results
During encoding, anodal stimulation of the left DLPFC improved memory, whereas cathodal stimulation of the same area impaired memory performance in later recognition. Anodal stimulation of M1 had no effect on later recognition. During recognition cathodal stimulation of the left DLPFC impaired recognition compared with sham stimulation of the same area and anodal stimulation had a trend toward improving the recognition.

Conclusions
The results indicated that active stimulation of the left DLPFC leads to an enhancement or impairment of verbal memorization depending on the polarity of the stimulation. Furthermore, this effect was specific to the site of stimulation.

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Recent studies have highlighted the importance of noninvasive brain stimulation as a means of modulating cortical excitability. Transcranial direct current stimulation (tDCS) is a noninvasive technique for brain stimulation that induces prolonged functional changes in the cerebral cortex through the application of a weak direct current on the scalp.[1-5] Safety aspects of this kind of stimulation have been addressed in several studies, which demonstrate that this technique can be safely used in human subjects.[6-8] The effect of tDCS varies depending on the polarity of the electrode-anodal polarization increases cortical excitability; whereas cathodal polarization decreases it.[9-12] tDCS performed on humans induces sustained changes beyond the period of stimulation.[13-16] A number of studies using tDCS in humans have been published[17-26] (for reviews see references[27-30]). Several studies have shown that this technique might modulate cortical excitability in the human motor cortex[31-33] and visual cortex,[34-36] can have beneficial effects on motor learning[37-39] and visuomotor coordination tasks,[40,41] and can have clinical applications[42-45] (for review see references[46-49]).

In addition to motor and visual learning tasks, tDCS has been recently used as an investigative tool in working memory studies in both healthy participants[50-55] and patients[56-58] as well as language and verbal memory.[21,22,59-63] In all of these experiments the left DLPFC was targeted for stimulation, except for Ferrucci et al.[50] in which two sites were used, one over the cerebellum and the other over the prefrontal cortex and Marshall et al.,[53] in which stimulation was bilateral on the left and right DLPFC. Fregni et al.[51] showed that anodal tDCS over DLPFC significantly enhances performance in three back letter working memory compared with sham and anodal stimulation of the primary motor cortex (M1). Marshall et al.[53] studied the effect of bilateral stimulation over two frontolateral locations (F3 and F4) on a modified visual Sternberg task.[64] They did not improve participants' behavior using active stimulation and observed slower reaction times both for anodal and cathodal stimulation. Ohn et al.[52] used the paradigm used by Fregni et al.[51] to study the time dependency effect of tDCS and showed that working memory performance is enhanced with longer stimulation.

Flöel et al.[59] enhanced associative verbal learning by application of anodal tDCS posterior part of the left perisylvian area. Fiori et al.[60] studied the effects of anodal tDCS of left Wernicke's (healthy and nonfluent aphasic subjects) and right occipitoparietal areas (healthy subjects). Healthy subjects participated in one session of 20-minute tDCS and nonfluent aphasic subjects participated in 20 minutes of tDCS over 5 consecutive days. They showed that both normal subjects and aphasic patients had shorter naming latencies during anodal tDCS than during sham condition. Fertonani et al.[61] investigated the effects of anodal and cathodal tDCS over the left DLPFC in a language task. They showed that anodal tDCS increased the naming of pictures, whereas cathodal tDCS had no effect. In a recent study Cattaneo, Pisoni and Papagno[63] showed that anodal tDCS over Broca's region can enhance subjects' performance in phonemic and semantic fluency task.

Anodal transcranial direct current stimulation (tDCS) is a reliable technique to improve motor learning. We here wanted to test its potential to enhance associative verbal learning, a skill crucial for both acquiring new languages in healthy individuals and for language reacquisition after stroke-induced aphasia. We applied tDCS (20 minutes, 1 mA) over the posterior part of the left perisylvian area of 19 young right-handed individuals, while subjects acquired a miniature lexicon of 30 novel object names. Every subject participated in one session of anodal tDCS, one session of cathodal tDCS, and one sham session in a randomized and double-blinded design with three parallel versions of the miniature lexicon. Outcome measures were learning speed and learning success at the end of each session, and the transfer to the subjects' native language after the respective stimulation. With anodal stimulation, subjects showed faster and better associative learning as compared with sham stimulation. Mood ratings, reaction times, and response styles were comparable between stimulation conditions. Our results demonstrate that anodal tDCS is a promising technique to enhance language learning in healthy adults and may also have the potential to improve language reacquisition after stroke.

The aim of this study was to investigate the effects of tDCS on verbal memory. Based on previous neuroimaging studies on declarative memory[65-67] and previous studies on working memory,[51,52,56,57] left DLPFC was selected as the main site of stimulation. The location of the other electrode was selected as the contralateral right supraorbital area as suggested by Nitsche et al.[27] and Im et al.[68] We administered anodal, cathodal, and sham stimulation types both during encoding and recognition phases, in two separate experiments, to study effects of stimulation on different stages of memorization and recognition. To investigate the location specificity of the effects, we stimulated primary motor area (M1) as a control site. We postulated that anodal stimulation of the left DLPFC during encoding and recognition would improve verbal memory and cathodal stimulation of the same site during encoding and recognition would impair verbal memory.

Materials and methods

Participants

In total 32 participants (mean age 22.46, standard deviation [SD] 2.31, 19 females) took part in the study comprising of two separates experiments: stimulation during encoding (n = 16) and stimulation during recognition (n = 16). All participants were university students enrolled at the University of London. All participants were naïve to the study, fluent English speakers, and right-handed yielding a laterality quotient of at least +50 on the Edinburgh Handedness Inventor.[69] All participants had normal or corrected-to-normal vision, and all were screened to exclude those with a history of neurologic trauma or psychiatric disorder. No participant was taking any centrally acting medications. All participants gave their written informed consent in accordance with the Declaration of Helsinki and the guidelines approved by the Ethical Committee of University College London.

Experimental design

This study was designed as a single-blind, sham, and cortical-site controlled experiment. Participants were recruited separately for the first and second experiment. In the first experiment, participants were stimulated during the second half of the encoding phase, four sessions, and in the second experiment, participants were stimulated during the second half of the recognition phase, three sessions. The experiment for the former group was conducted first. Each session contained a different type of stimulation; left DLPFC anodal; left DLPFC cathodal; M1; sham. Order of conditions was randomized. To minimize carryover effects, the interval between sessions was at least 48 hours.[57]

Each session was composed of two phases, an encoding phase and a recognition phase. Figure 1 shows the procedure of each session. At the beginning of each phase participants were asked to complete a Stanford Sleepiness Scale (SSS),[70] a standard measure of subjective alertness. In the encoding phase participants were shown words, one at a time, and they were asked to first judge the number of syllables of the word as quickly and as accurately as possible using their left hand and then to memorize it. Participants were instructed to imagine the words to memorize them.

The encoding phase was composed of four blocks. The first block contained 35 words; the remaining three blocks contained 30 words. The first five words of the first block were considered as practice trials to ensure that participants were familiar with the procedure of each trial. These words were later discarded and were not used in the recognition phase. The timeline of a trial in the encoding phase is shown in Figure 2. At the end of each block the percentage of each participant's correct response to the number of syllables of the words was fed back to the subject for 3 seconds. There was a 15-second rest interval in between the blocks.

The retention interval was 60 minutes. In between the two encoding and recognition phases and during the 15 minutes within encoding phase period sketches of a television series were shown.

The recognition phase was also composed of four blocks. Each block consisted of 30 pairs of words. In each trial two words were shown in which one was an old word, i.e., previously presented in the encoding phase, and

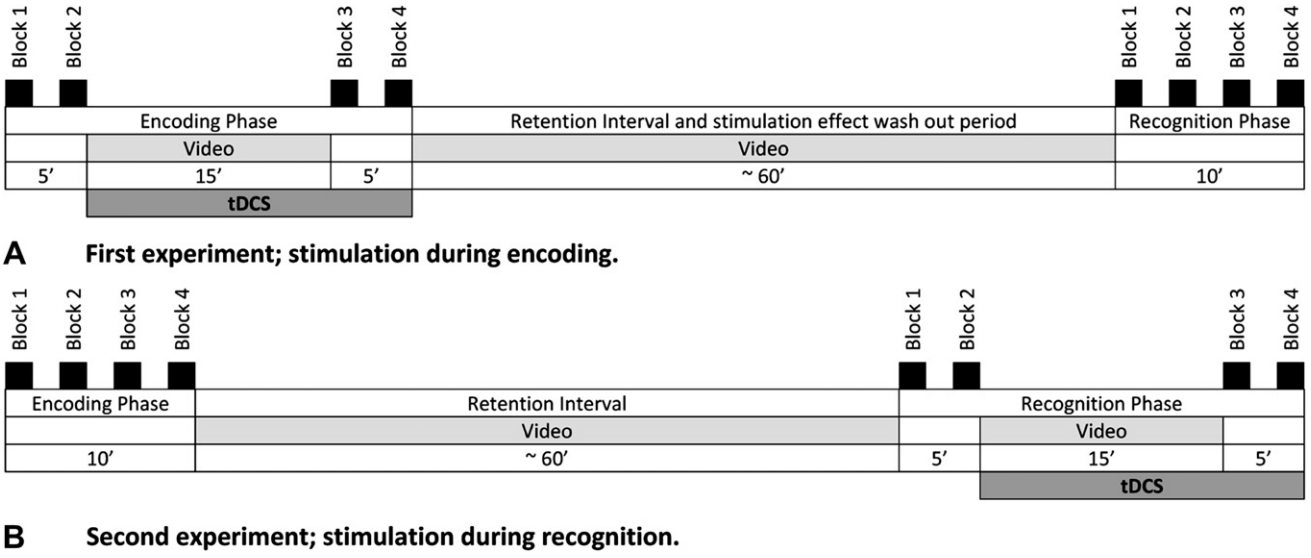

Figure 1 Procedure of each session: **A**, first experiment with stimulation during encoding, **B**, second experiment with stimulation during recognition. Participants were assigned to one of two experiments that differed in the period during which tDCS was applied. Stimulation was either active or sham. In sham stimulation, stimulation was stopped after 30 seconds of stimulation. In the active stimulation type, stimulation was initiated after the second block, either during the encoding phase or recognition phase, and continued for 15 minutes until the beginning the third block and continued for 5 more minutes to the end of the fourth block.

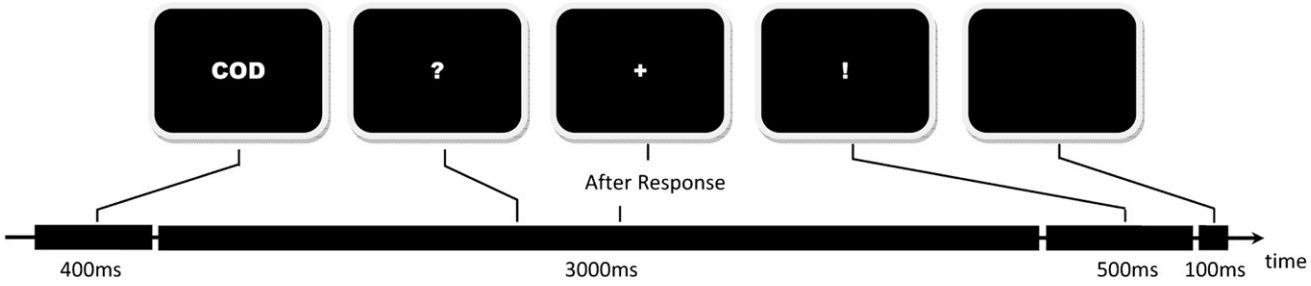

Figure 2 Procedure during the encoding phase: Participants were asked to quickly respond to the number of syllables of the words and then try to imagine the words to memorize them. A question mark appeared on the screen after the word presentation. The question mark changed into a cross after participants responded to the number of syllables. Participants were told that although the cross is on the screen they have time to memorize the word. An exclamation mark was shown to inform the participant that the next word is about to be presented. They were asked to use the mouse with their left hand using the left button for words with one syllable and the right button for words with two syllables.

one was a new word. Participants were asked to select old words as accurately and as quickly as possible. The order of the words in the recognition phase was randomized and was not the same as the order of words in the encoding phase. The procedure of each trial of the recognition phase is shown in Figure 3. Participants were not given any feedback of their performance. There was a 15-second rest interval in between the blocks.

The experiment was performed using a PC computer. Stimuli were presented on a 17-inch monitor, 75 Hz refresh rate, subtending approximately 3-6 degrees of horizontal visual angle. Stimuli were presented on a black background and white Arial font, in capital letters and 53 cm from participants' eyes. Stimulus presentation and timing of all stimuli and response events were achieved using MATLAB (MathWorks Company, Natick, MA) and the Psychtoolbox v3.[71,72]

tDCS

Direct current was transferred by a saline-soaked pair of surface sponge electrodes (35 × 35 mm over the target site and 55 × 55 mm over reference site) and delivered by a DC Brain Stimulator Plus (NeuroConn, Ilmenau, Germany). To test if the effects of the left DLPFC stimulation were location specific, in the first experiment, we applied tDCS over primary motor cortex (M1) in a separate session.[51,57] Sham stimulation was also delivered to control for somatosensory effects. The montage of the electrodes for different conditions was as follows:

1. For anodal stimulation of the left DLPFC, the anode electrode was placed over F3 (according to the 10-20 international system for electroencephalogram electrode placement[73,74]), and the cathode electrode was placed over the contralateral right supraorbital area.
2. For cathodal stimulation the cathode electrode was place over F3 and the anode electrode was placed over the contralateral right supraorbital area.
3. For sham stimulation, the placement of electrodes was the same as anodal stimulation (1) above.
4. For primary motor cortex stimulation the anode electrode was placed over M1 (C3) and the cathode electrode was maintained on the contralateral right supraorbital area.

Table 1 summarizes the stimulation types in the two experiments and Figure 4 shows the schematic presentation of the electrode positions in different stimulation conditions.

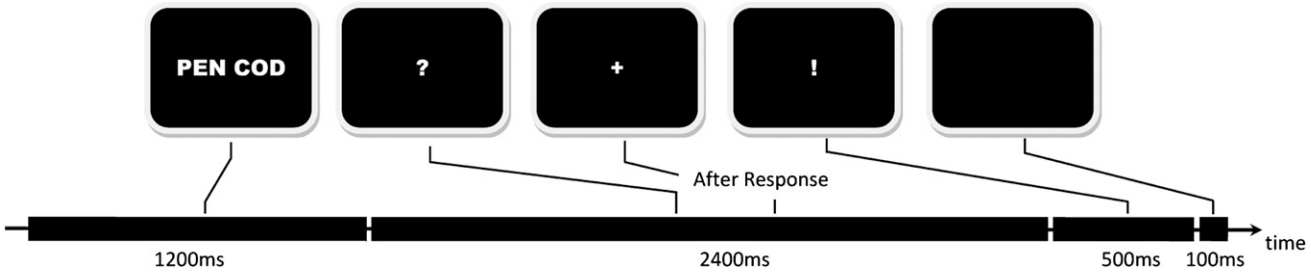

Figure 3 Procedure of the recognition phase: Participants were instructed to select the word that they saw during the encoding phase, as quickly and as accurate as possible. Accuracy was stressed in the instruction. A question mark appeared on the screen after the word presentation. It changed into a cross after participants responded. An exclamation mark was shown to inform the participant that the next pair of words is about to be presented. They were asked to use the mouse with their left hand using the left button to select the left hand side word and the right button to select the right hand side word.

Table 1 Full list of conditions used in this experiment

	Stimulation			Electrode placement	
Experiment	Phase	Name	Site	Anode	Cathode
Experiment 1	Encoding	Anodal	Left DLPFC	Left DLPFC	Supraorbital area
		Cathodal	Left DLPFC	Supraorbital area	Left DLPFC
		Sham	Left DLPFC	Left DLPFC	Supraorbital area
		Control	Primary motor cortex	Primary motor cortex (M1)	Supraorbital area
Experiment 2	Retrieval	Anodal	Left DLPFC	Left DLPFC	Supraorbital area
		Cathodal	Left DLPFC	Supraorbital area	Left DLPFC
		Sham	Left DLPFC	Left DLPFC	Supraorbital area

Encoding phase (for the first experiment) and recognition phase (for the second experiment) were split into two phases: prestimulation and poststimulation. Each phase contained two blocks. Stimulation began after the complication of the first phase. A constant current of 1mA with 15-second fade in/fade out was applied for either 20 seconds for anodal, cathodal and control conditions or 30 second for the sham condition, as shown in Figure 1. For sham stimulation, the stimulator was turned off after 30 seconds of stimulation as previously described (2) above. It has been shown that 1 mA tDCS for 20' is safe for human subjects.[6]

Stimuli

A bank of 1200 words was extracted from The MRC psycholinguistic database.[75] The words were verbs, nouns or adjectives. Words were controlled for number of letters (minimum 3, maximum 8, mean 4.89, SD 1.24), number of syllables (minimum 1, maximum 2, mean 1.49, SD 0.50), printed familiarity (mean 558.48, SD 31.41), concreteness (mean 542.51, SD 67.73), and imagability (mean 555.60, SD 55.21).

The words which were used in the instructions, i.e., "apple," "table," "word," "old," and "new" were excluded from the list. At the beginning of the first session a set of words was randomly assigned to each participant (four sessions of four blocks of 30 words plus five additional practice words for the training phase and 120 new words for the testing phase). Participants in each session were presented with new to prevent any interference with previous sessions.

Statistical analysis

The effect of tDCS was assessed with a two-way repeated measure analysis of variance (ANOVA) with stimulation condition (prestimulation/poststimulation) and stimulation type (anodal/cathodal/sham/control) as within-subject factors. Performance percentage and reaction time were measured as dependent variables. A significance level of $P < 0.05$ was used. Bonferroni-corrected post hoc paired-samples t tests were used to study the difference between conditions. The dependent variables were checked for normal distribution.

Results

All participants tolerated the stimulation well and there was no complaint of pain or discomfort during the stimulation. Explicit questioning at the end of the last session showed that they did not realize that in one session they were stimulated only for the first 30 seconds.

Experiment 1: Stimulation during the encoding phase

Participants took part in this experiment over four sessions with different stimulation types (anodal/cathodal/sham/control).

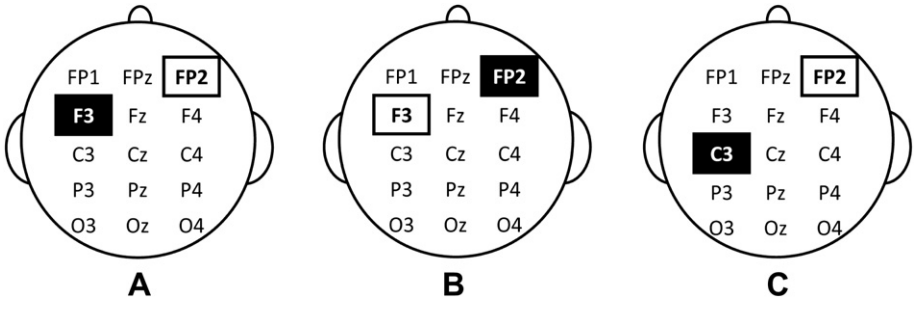

Figure 4 Schematic drawing of electrode positions in the study. **A**, Anodal and Sham stimulation of the left dorsolateral prefrontal cortex (DLPFC), (**B**) cathodal stimulation of the left DLPFC, (**C**) stimulation of primary motor cortex. Darker rectangles show anode electrode and lighter rectangles show cathode electrode.

To analyze the response accuracy in the recognition phase, we conducted a repeated measures 2 × 4 ANOVA with stimulation condition (prestimulation/poststimulation) and stimulation type (anodal/cathodal/sham/control) as within subject factors for performance. This repeated measure ANOVA indicated a nonsignificant effect of stimulation condition ($F[1, 15] = 0.52$, $P = 0.48$), significant effect of stimulation type ($F[3, 45] = 3.62$, $P = 0.02$), and significant interaction between the two factors stimulation condition and stimulation type ($F[3, 45] = 5.37$, $P = 0.003$). Post hoc comparison with Bonferroni correction showed that there was significant difference between pre- and poststimulation for the left DLPFC anodal and cathodal stimulation types but no significant difference between pre- and poststimulation for sham or control stimulation types, Figure 5. These comparisons showed that anodal stimulation of the left DLPFC significantly improved memory performance of the words that were encoded during the second phase ($P < 0.05$) and cathodal stimulation of the same brain area significantly impaired memory performance of the words which were encoded during the second phase ($P < 0.05$).

We analyzed the recognition response time (RT) in the recognition phase with a repeated measure 2 × 4 ANOVA with stimulation condition (prestimulation/poststimulation) and stimulation type (anodal/cathodal/sham/control) as within subject factors for mean RT. This repeated measure ANOVA indicated no significant effect of stimulation condition ($F[1, 15] = 0.33$, $P = 0.57$), no significant effect of stimulation type ($F[3, 45] = 0.61$, $P = 0.61$) and no significant interaction between the two factors stimulation condition × stimulation type ($F[3, 45] = 1.54$, $P = 0.22$). This shows that higher performance with anodal stimulation or lower performance with cathodal stimulation is not due to changes of reaction time.

The effect of stimulation on participants' accuracy and RT in the syllable judgment task was also investigated. A repeated measure 2 × 4 ANOVA with stimulation condition (prestimulation/poststimulation) and stimulation type (anodal/cathodal/sham/control) as within subject factors for mean syllable judgment accuracy and mean RT was conducted. This indicated no significant effect of stimulation condition ($F[1, 15] = 0.45$, $P = 0.51$ for accuracy; $F[1, 15] = 0.28$, $P = 0.60$ for RT), no significant effect of stimulation type ($F[3, 45] = 0.30$, $P = 0.82$ for accuracy; $F[3, 45] = 0.35$, $P = 0.79$ for RT) and no significant interaction between the two factors stimulation condition × stimulation type ($F[3, 45] = 0.58$, $P = 0.63$ for accuracy; $F[3, 45] = 0.37$, $P = 0.77$ for RT).

To analyze the alertness of the participants at the beginning of each phase, we conducted a repeated measures 2 × 4 ANOVA with phase (training/testing) and stimulation type (anodal/cathodal/sham/control) as within subject factors for the SSS rating. This ANOVA indicated no significant effect of phase ($F[1, 15] = 0.04$, $P = 0.84$), no significant effect of stimulation type ($F[3, 45] = 0.35$, $P = 0.79$), and no significant interaction between the two factors phase × stimulation type ($F[3, 45] = 0.64$, $P = 0.59$).

Experiment 2: Stimulation during the recognition phase

Participants in this group attended three sessions with different stimulation types (anodal/cathodal/sham). As there were no effects on memory performance in the control stimulation type in the first experiment, there was no M1 stimulation in this experiment. To analyze the response accuracy in the recognition phase, we conducted a repeated measures 2 × 3 ANOVA with stimulation condition (prestimulation/poststimulation) and stimulation type (anodal/cathodal/sham) as within subject factors for performance. This indicated no significant effect of stimulation condition ($F[1, 15] = 0.15$, $P = 0.70$), no

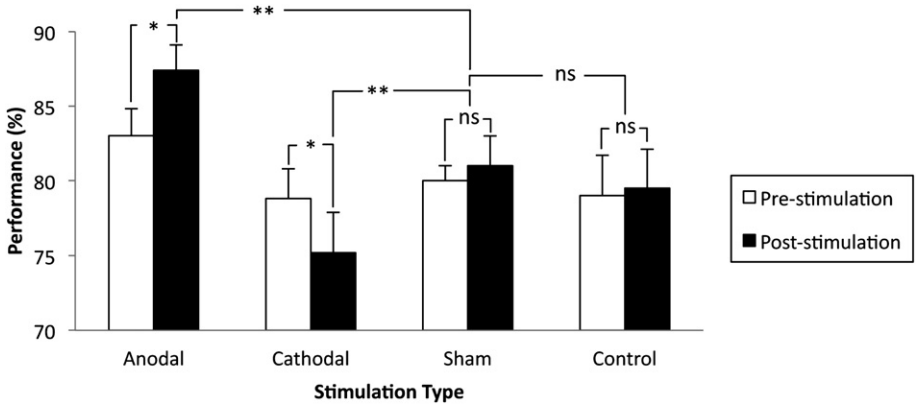

Figure 5 Comparison of pre- and poststimulation conditions of percentage of recognition accuracy when stimulation was administered during the encoding phase; * $P < 0.05$, ** $P < 0.01$, ns not significant. Prestimulation indicates the first half of the encoding phase. Poststimulation indicates the second half of the encoding phase while stimulation was administered. Control stands for anodal tDCS over primary motor area (M1). Error bars represent 1 standard deviation (SD).

significant effect of stimulation type ($F[2, 30] = 1.126$, $P = 0.33$), but a significant interaction between the two factors stimulation condition × stimulation type ($F[2, 30] = 3.89$, $P = 0.03$). Post hoc comparisons with Bonferroni correction showed a significant difference between the two conditions of cathodal stimulation type, see Figure 6.These comparisons showed that cathodal stimulation of the left DLPFC significantly impaired memory performance for the second phase ($P < 0.05$) and anodal stimulation of the same brain area has a trend towards improving memory performance ($P < 0.2$).

To investigate possible effect of stimulation on the recognition RT in the recognition phase we conducted a repeated measures 2 × 3 ANOVA with stimulation condition (prestimulation/poststimulation) and stimulation type (anodal/cathodal/sham) as within subject factors for mean RT. This repeated measure ANOVA indicated no significant effect of stimulation condition ($F[1, 15] = 1.2$, $P = 0.29$), no significant effect of stimulation type ($F[2, 30] = 0.87$, $P = 0.42$) and no significant interaction between the two factors stimulation condition × stimulation type ($F[2, 30] = 0.64$, $P = 0.53$). This shows that different types of stimulation did not change participants' response speed, which means lower performance in cathodal stimulation type is not due to speed accuracy trade off.

To analyze the alertness of the participants at the beginning of each phase, we conducted a 2 × 3 repeated measure ANOVA with phase (training/testing) and stimulation type (anodal/cathodal/sham) as within subject factors for the SSS rating. This indicated no significant effect of phase ($F[1, 15] = 0.17$, $P = 0.68$), no significant effect of stimulation type ($F[2, 30] = 0.19$, $P = 0.83$) and no significant interaction between the two factors phase × stimulation type ($F[2, 30] = 0.22$, $P = 0.80$).

Discussion

The results showed that tDCS of the left DLPFC can significantly modulate verbal memory performance while administered during encoding (first experiment) or recognition (second experiment) and its effects were location specific and polarity dependent. The results of the first experiment showed that anodal stimulation of the left DLPFC during the encoding phase enhanced the memory performance in a later recognition task. Cathodal stimulation, however, impaired the later recognition of stimuli. Sham stimulation and stimulation of primary motor cortex did not affect the memory performance. The results of the second experiment showed that cathodal stimulation of the left DLPFC during recognition impaired the recognition performance and anodal stimulation had a trend toward improving the recognition of studied words. RT did not change in any of the stimulation conditions. The results are considerable in three aspects: improving effect of anodal and impairing effect of cathodal stimulations during encoding and impairing effect of cathodal stimulation during recognition.

Numerous studies showed that anodal tDCS over the left DLPFC has beneficial effects on working memory.[50-52,56,57] We showed that application of anodal tDCS over the left DLPFC can enhance memory performance for verbal memorization as well. However, the exact functional role that tDCS plays in improving memory accuracy remains unclear. Memory enhancement could have resulted from the stronger encoding of target words, or alternatively better retention of encoded words. Furthermore, other systems could have been engaged by the left DLPFC stimulation. Cerruti and Schlaug[21] showed that anodal stimulation of the left DLPFC improves participants performance

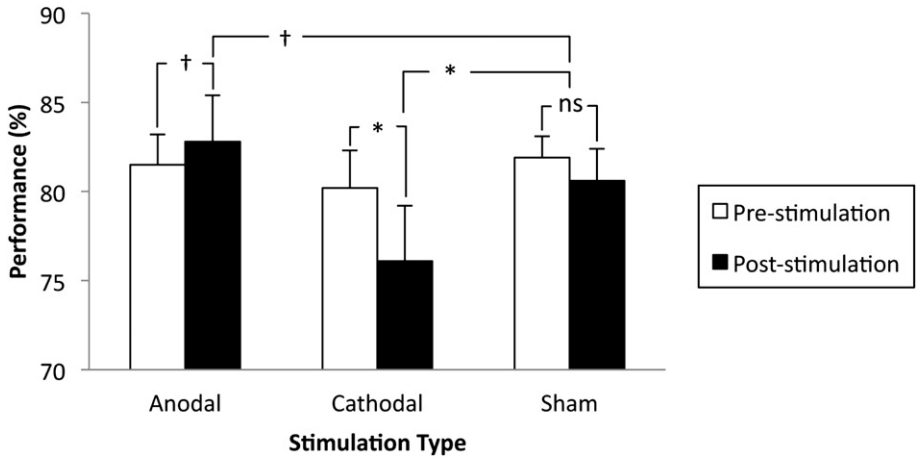

Figure 6 Comparison of pre- and poststimulation conditions of percentage of recognition accuracy when stimulation was administered during the recognition phase; * $P < 0.05$, †$P < 0.2$, ns, not significant. Prestimulation stands for the recognition percentage of the words that were presented in the first half of the recognition phase. Poststimulation stands for the recognition percentage of the words that were shown in the second half of the recognition phase while stimulation was administered. All other comparisons were nonsignificant. Error bars represent 1 standard deviation (SD).

on remote associates test (RAT) that is a complex verbal task compared with sham and cathodal stimulation. There is also evidence that the stimulation of left DLPFC modulates planning abilities[17] as well as probabilistic decision-making tasks[24,76] in which they showed anodal stimulation of the left DLPFC enhances participants performance. These factors may have contributed to the modulatory effect of tDCS over the DLPFC, e.g., participants are more cable of monitoring information.

The results of the second experiment showed that cathodal stimulation of the left DLPFC has impairing effect on a recognition task, whereas anodal stimulation has no effect. Tulving et al.[77] showed that left DLPFC is more involved with encoding and right DLPFC is more involved in retrieval of episodic memory. There are also transcranial magnetic stimulation (TMS) studies confirming their finding.[78,79] Thus, anodal stimulation during a recognition task might become effective if it is delivered over the right DLPFC. Further studies should be conducted to study the functional difference between left and right DLPFC.

One might argue that the higher accuracy performance on later recognition of the words presented during the second half of the encoding phase is due to 15 minutes shorter retention interval. Shorter retention interval cannot be the cause of higher accuracy performance, because the same timing is used for sham or control stimulations in which no significant enhancement has been observed.

tDCS in the human is able to induce sustained changes beyond the period of stimulation.[13-15] Using TMS, Nitsche and Paulus[13] showed that the effect of tDCS over motor cortical area last up to 90 minutes after the end of stimulation. The lasting effects of tDCS over DLPFC, however, is not systematically studied yet. The better or worse recognition of the words in the recognition phase for anodal and cathodal stimulation conditions, respectively, can partly be explained by the possible lasting effects of tDCS over DLPFC as there is a general trend toward improvement for anodal and impairment for cathodal stimulation. The effects are, however, highly selective for the second phase: significant improvement for anodal stimulation and significant impairment for cathodal stimulation.

Although it has been shown that the effects of tDCS can be highly selective to a certain brain area,[80] the application of relatively large electrodes (35 × 35 mm) might diffuse the effects of tDCS and involve larger area of the left hemisphere. This possibility is ruled out by the stimulation of the motor cortex. The result showed that anodal stimulation of the motor cortex has no significant effect on the later recognition that shows that the effects of the tDCS were relatively focal.

In this study, we used a smaller electrode size for the DLPFC compared with some other studies[17,21,43,52,56] to make the stimulation more focused. Furthermore, we used a smaller electrode for the target area compared with the reference electrode (35 × 35 mm and 55 × 55 mm, respectively) to increase the ratio of the stimulation intensity at the main electrode against that at the reference electrode (approximately 2.5:1).

There are many studies showing that the left prefrontal cortex is highly active in so many cognitive tasks specifically attention (for review see references[81-85]). By introducing a secondary task (syllable judgement) we aimed to investigate the effect of tDCS on attention. Two evidences in our study partly reject the possibility of functional change of other systems because of the stimulation, accuracy, and reaction time in syllable judgment in the encoding phase and response time in the recognition phase. As showed in the results, all these measurements are comparable in between different conditions and stimulation types, which can suggest tDCS has not modulated attention or single word processing systems under the influence of stimulation. This is still, however, unclear. None of previous studies that studied effect of stimulation on frontal cortex has mentioned or completely rejected the possibility of more or less modulation of other systems (such as attention) because of stimulation either.[20-22,50,51,56,57]

In an experiment Elmer et al.[22] studied the effect of tDCS over the left DLPFC on learning auditory presented nouns. In line with our study, they showed that cathodal tDCS during recognition impaired verbal learning compared with the baseline. Contrary to our results, their study showed that anodal stimulation has no significant effect on the verbal learning. Our study, however, differs with theirs in a several ways: modality of stimuli, electrode montage, electrical current strength, and duration of stimulation. They used auditory stimuli and we used visual stimuli. We placed the reference electrode over the contralateral supraorbital area, whereas they put the reference electrode over mastoid. It has been shown that the electrode montage vastly effects the flow of the current and so likely the stimulated brain area.[68,86] The duration of stimulation in their study was 5 seconds and in our study it was 15 seconds prior and 5 seconds during the presentation of the stimuli. Possibly in their case the targeted brain area did not undergo enough stimulation to see pronounce behavioral effects as has Although they applied higher electrical current amplitude (1.5 mA) compared with our study (1 mA), the larger size of their electrode over target area (70 × 40 mm in their study versus 35 × 35 mm over the target area in our study) induced the overall current density of 53 $\mu A/cm^2$ in their study versus 81 $\mu A/cm^2$ (over the target area) in our study. It has been shown that the intensity of the stimulation is a critical parameter. Boggio et al.[57] showed that 2 mA anodal tDCS over the left DLPFC significantly improved working memory accuracy in patients with Parkinson's disease, whereas stimulation with half of the intensity, 1 mA, did not show any significant behavioral effect. This can also be the case with our finding on anodal stimulation of the left DLPFC during recognition phase in which we observed a trend toward better recognition but not significant. Possibly higher electrical current intensity can significantly improve the recognition accuracy.

In conclusion, our study demonstrates that active stimulation of the left DLPFC affected later recognition of words in verbal memorization paradigm. It is shown that anodal tDCS over the left DLPFC improved later recognition and cathodal tDCS over the same area impaired the recognition of the words. Moreover, the results showed that cathodal stimulation of the left DLPFC during recognition impaired the accuracy percentage of the recognition task. This study failed to show any significant effect of anodal tDCS over the left DLPFC during recognition, although it tended to improve recognition task.

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References

1. Paulus W. Transcranial direct current stimulation (tDCS). Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation (Suppl Clin Neurophysiol) 2003;249.
2. Gandiga P, Hummel F, Cohen L. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol 2006;117(4):845-850.
3. Kesner R, Wilburn M. A review of electrical stimulation of the brain in context of learning and retention. Behav Biol 1974;10(3):259.
4. McGaugh JL, Gold PE. Modulation of memory by electrical stimulation of the brain. Neural Mechan Learning Memory 1976;549-560.
5. Wassermann E. Direct current brain polarization. Oxford Handbook of Transcranial Stimulation 2008:57.
6. Iyer M, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann E. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology 2005;64(5):872-875.
7. Nitsche M, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. Modulation of cortical excitability by weak direct current stimulation—technical, safety and functional aspects. Suppl Clin Neurophysiol 2003;56:255.
8. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull 2007;72(4-6):208-214.
9. Nitsche M, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527(3):633-639.
10. Galea JM, Jayaram G, Ajagbe L, Celnik P. Modulation of cerebellar excitability by polarity-specific noninvasive direct current stimulation. J Neurosci 2009;29(28):9115.
11. Terney D, Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci 2008;28(52):14147.
12. Miranda P, Lomarev M, Hallett M. Modeling the current distribution during transcranial direct current stimulation. Clin Neurophysiol 2006;117(7):1623-1629.
13. Nitsche M, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. St Paul (MN): AAN Enterprises 2001;1899-1901.
14. Ardolino G, Bossi B, Barbieri S, Priori A. Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. J Physiol 2005;568(2):653.
15. Priori A. Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. Clin Neurophysiol 2003;114(4):589-595.
16. Quartarone A, Morgante F, Bagnato S, et al. Long lasting effects of transcranial direct current stimulation on motor imagery. Neuroreport 2004;15(8):1287.
17. Dockery C, Hueckel-Weng R, Birbaumer N, Plewnia C. Enhancement of planning ability by transcranial direct current stimulation. J Neurosci 2009;29(22):7271.
18. Sparing R, Mottaghy F. Noninvasive brain stimulation with transcranial magnetic or direct current stimulation (TMS/tDCS)—from insights into human memory to therapy of its dysfunction. Methods 2008;44(4):329-337.
19. Boggio P, Khoury L, Martins D, Martins O, de Macedo E, Fregni F. Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. BMJ 2009; 80(4):444.
20. Wassermann E, Grafman J. Recharging cognition with DC brain polarization. Trend Cogn Sci 2005;9(11):503-505.
21. Cerruti C, Schlaug G. Anodal transcranial direct current stimulation of the prefrontal cortex enhances complex verbal associative thought. J Cogn Neurosci 2008;21(10):1980-1987.
22. Elmer S, Burkard M, Renz B, Meyer M, Jancke L. Direct current induced short-term modulation of the left dorsolateral prefrontal cortex while learning auditory presented nouns. Behav Brain Funct 2009;5:29.
23. Rosenkranz K, Nitsche M, Tergau F, Paulus W. Diminution of training-induced transient motor cortex plasticity by weak transcranial direct current stimulation in the human. Neurosci Lett 2000;296(1): 61-63.
24. Kincses T, Antal A, Nitsche M, Bártfai O, Paulus W. Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. Neuropsychologia 2004; 42(1):113-117.
25. Stone D, Tesche C. Transcranial direct current stimulation modulates shifts in global/local attention. Neuroreport 2009;20(12):1115.
26. Tanaka S, Hanakawa T, Honda M, Watanabe K. Enhancement of pinch force in the lower leg by anodal transcranial direct current stimulation. Exp Brain Res 2009;1-7.
27. Nitsche M, Cohen L, Wassermann E, et al. Transcranial direct current stimulation: State of the art 2008. Brain Stimulation 2008;1(3): 206-223.
28. Been G, Ngo T, Miller S, Fitzgerald P. The use of tDCS and CVS as methods of non-invasive brain stimulation. Brain Res Rev 2007;56(2): 346-361.
29. Flöel A, Cohen L. Contribution of noninvasive cortical stimulation to the study of memory functions. Brain Res Rev 2007;53(2):250-259.
30. Hummel FC, Cohen LG. Drivers of brain plasticity. Curr Opin Neurol 2005;18:667-674.
31. Nitsche M, Nitsche M, Klein C, Tergau F, Rothwell J, Paulus W. Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. Clin Neurophysiol 2003;114(4):600-604.
32. Kwon Y, Ko M, Ahn S, et al. Primary motor cortex activation by transcranial direct current stimulation in the human brain. Neurosci Lett 2008;435(1):56-59.
33. Di Lazzaro V, Oliviero A, Pilato F, et al. The physiological basis of transcranial motor cortex stimulation in conscious humans. Clin Neurophysiol 2004;115(2):255-266.
34. Antal A, Kincses T, Nitsche M, Bartfai O, Paulus W. Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence. Invest Ophthalmol Visual Sci 2004;45(2):702.
35. Antal A, Nitsche M, Paulus W. External modulation of visual perception in humans. Neuroreport 2001;12(16):3553.
36. Sparing R, Thimm M, Hesse M, Kust J, Karbe H, Fink G. Bidirectional alterations of interhemispheric parietal balance by non-invasive cortical stimulation. Brain 2009;1-10.
37. Bolognini N, Pascual-Leone A, Fregni F. Using non-invasive brain stimulation to augment motor training-induced plasticity. J Neuroeng Rehabil 2009;6(1):8.

38. Nitsche M, Schauenburg A, Lang N, et al. Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. J Cogn Neurosci 2003;15(4): 619-626.
39. Hunter T, Sacco P, Nitsche M, Turner D. Modulation of internal model formation during force field-induced motor learning by anodal transcranial direct current stimulation of primary motor cortex. Exp Physiol 2009;587(12):2949-2961.
40. Antal A, Nitsche M, Kruse W, Kincses T, Hoffmann K, Paulus W. Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. J Cogn Neurosci 2004; 16(4):521-527.
41. Antal A, Nitsche M, Kincses T, Kruse W, Hoffmann K, Paulus W. Facilitation of visuo-motor learning by transcranial direct current stimulation of the motor and extrastriate visual areas in humans. Eur J Neurosci 2004;19(10):2888.
42. Ferrucci R, Mameli F, Guidi I, et al. Transcranial direct current stimulation improves recognition memory in Alzheimer disease. Neurology 2008;71(7):493.
43. Arul-Anandam A, Loo C. Transcranial direct current stimulation: a new tool for the treatment of depression? J Affect Disord 2009; 117(3):137-145.
44. Ferrucci R, Bortolomasi M, Vergari M, et al. Transcranial direct current stimulation improves patients with severe major depression. Brain Stimulation 2008;1(3):259.
45. Ferrucci R, Bortolomasi M, Vergari M, et al. Transcranial direct current stimulation in severe, drug-resistant major depression. J Affect Disord 2009;118(1-3):215-219.
46. Nitsche M, Boggio P, Fregni F, Pascual-Leone A. Treatment of depression with transcranial direct current stimulation (tDCS): a review. Exp Neurol 2009;219(1):14-19.
47. Murphy D, Boggio P, Fregni F. Transcranial direct current stimulation as a therapeutic tool for the treatment of major depression: insights from past and recent clinical studies. Curr Opin Psychiatry 2009; 22(3):306.
48. Rosen A, Ramkumar M, Nguyen T, Hoeft F. Noninvasive transcranial brain stimulation and pain. Curr Pain Headache Rep 2009;13(1): 12-17.
49. Schlaug G, Renga V. Transcranial direct current stimulation: a noninvasive tool to facilitate stroke recovery. Expert Rev Med Devices 2008;5(6):759-768.
50. Ferrucci R, Marceglia S, Vergari M, et al. Cerebellar transcranial direct current stimulation impairs the practice-dependent proficiency increase in working memory. J Cogn Neurosci 2008;20(9):1687-1697.
51. Fregni F, Boggio P, Nitsche M, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 2005;166(1):23-30.
52. Ohn S, Park C, Yoo W, et al. Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. Neuroreport 2008;19(1):43.
53. Marshall L, Molle M, Siebner H, Born J. Bifrontal transcranial direct current stimulation slows reaction time in a working memory task. BMC Neurosci 2005;6(1):23.
54. Zaehle T, Sandmann P, Thorne JD, Jancke L, Herrmann CS. Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. BMC Neurosci 2011;12(1):2.
55. Andrews SC, Hoy KE, Enticott PG, Daskalakis ZJ, Fitzgerald PB. Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain Stimulation 2011.
56. Jo J, Kim Y, Ko M, Ohn S, Joen B, Lee K. Enhancing the working memory of stroke patients using tDCS. Am J Phys Med Rehabil 2009;88(5):404.
57. Boggio P, Ferrucci R, Rigonatti S, et al. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J Neurol Sci 2006;249(1):31-38.
58. Fregni F, Boggio P, Nitsche M, Rigonatti S, Pascual-Leone A. Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. Depression and Anxiety 2006;23(8):482.
59. Flöel A, Rösser N, Michka O, Knecht S, Breitenstein C. Noninvasive brain stimulation improves language learning. J Cogn Neurosci 2008; 20(8):1415-1422.
60. Fiori V, Coccia M, Marinelli CV, et al. Transcranial direct current stimulation improves word retrieval in healthy and nonfluent aphasic subjects. J Cogn Neurosci 2011;23:2309-2323.
61. Fertonani A, Rosini S, Cotelli M, Rossini PM, Miniussi C. Naming facilitation induced by transcranial direct current stimulation. Behav Brain Res 2010;208(2):311-318.
62. Sparing R, Dafotakis M, Meister I, Thirugnanasambandam N, Fink G. Enhancing language performance with non-invasive brain stimulation—a transcranial direct current stimulation study in healthy humans. Neuropsychologia 2008;46(1):261-268.
63. Cattaneo Z, Pisoni A, Papagno C. Transcranial direct current stimulation over Broca's region improves phonemic and semantic fluency in healthy individuals. Neuroscience 2011;183:64-70.
64. Sternberg S. High-speed scanning in human memory. Washington (DC): American Association for the Advancement of Science 1966; 652-654.
65. Cabeza R, Nyberg L. Imaging cognition II: an empirical review of 275 PET and fMRI studies. J Cogn Neurosci 2000;12(1):1-47.
66. Martin A. Functional neuroimaging of semantic memory. In: Handbook of functional neuroimaging of cognition. Cambridge (MA): MIT; 2001. 153–186.
67. Cabeza R, Nyberg L. Neural bases of learning and memory: functional neuroimaging evidence. Curr Opin Neurol 2000;13(4):415.
68. Im C, Jung H, Choi J, Lee S, Jung K. Determination of optimal electrode positions for transcranial direct current stimulation (tDCS). Phys Med Biol 2008;53(11):219.
69. Oldfield R. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9(1):97-113.
70. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement W. Quantification of sleepiness: a new approach. Psychophysiology 1973; 10(4):431-436.
71. Brainard D. The psychophysics toolbox. Spatial Vision 1997;10(4): 433-436.
72. Pelli D. The VideoToolbox software for visual psychophysics: transforming numbers into movies. Spatial Vision 1997;10(4): 437-442.
73. Homan R, Herman J, Purdy P. Cerebral location of international 10-20 system electrode placement. Electroencephalogr Clin Neurophysiol 1987;66(4):376.
74. Herwig U, Satrapi P, Schönfeldt-Lecuona C. Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr 2003;16(2):95-99.
75. Coltheart M. The MRC psycholinguistic database. Q J Exp Psychol A 1981;33(4):497-505.
76. Hecht D, Walsh V, Lavidor M. Transcranial direct current stimulation facilitates decision making in a probabilistic guessing task. J Neurosci 2010;30(12):4241.
77. Tulving E, Kapur S, Craik F, Moscovitch M, Houle S. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. Proc Natl Acad Sci 1994;91(6): 2016-2020.
78. Rossi S, Cappa S, Babiloni C, et al. Prefontal cortex in long-term memory: an "interference" approach using magnetic stimulation. Nat Neurosci 2001;4:948-952.
79. Sandrini M, Cappa SF, Rossi S, Rossini PM, Miniussi C. The role of prefrontal cortex in verbal episodic memory: rTMS evidence. J Cogn Neurosci 2003;15(6):855-861.
80. Jantzen K, Steinberg F, Kelso J. Functional MRI reveals the existence of modality and coordination-dependent timing networks. Neuroimage 2005;25(4):1031-1042.

81. Fletcher P, Henson R. Frontal lobes and human memory: insights from functional neuroimaging. Brain 2001;124(5):849.
82. Desgranges B, Baron J, Eustache F. The functional neuroanatomy of episodic memory: the role of the frontal lobes, the hippocampal formation, and other areas. Neuroimage 1998;8(2):198-213.
83. Fletcher P, Frith C, Rugg M. The functional neuroanatomy of episodic memory. Trend Neurosci 1997;20(5):213-218.
84. Fletcher P, Shallice T, Dolan R. The functional roles of prefrontal cortex in episodic memory, I: encoding. Brain 1998;121(7):1239.
85. Fletcher P, Shallice T, Frith C, Frackowiak R, Dolan R. The functional roles of prefrontal cortex in episodic memory, II: retrieval. Brain 1998;121(7):1249.
86. Nitsche M, Doemkes S, Karakose T, et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. J Neurophysiol 2007;97(4):3109.