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# Anodal transcranial direct current stimulation of the right dorsolateral prefrontal cortex impairs long-term retention of reencountered memories

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**Declaration of interests:** None.

## Abstract

Repeated encounter with encoded memories is often a fundamental component of long-term learning processes, however, the role of repeated access to encoded memories in long-term consolidation is yet to be clarified. Here we investigated whether the long-term retention of newly acquired associative memories is affected if one of the central areas of the attentional control network is stimulated before or after repeated access to acquired information. Non-clinical participants (undergraduate students, $N = 118$) were exposed to an associative verbal learning task. Following the initial learning of word pairs, memories for the word pairs were reencountered either by re-presenting the stimuli to the participants for restudying or by cued recall. The reencounter phase was either preceded by (Experiment 1) or followed by (Experiment 2) anodal transcranial Direct Current Stimulation of the right dorsolateral prefrontal cortex. Memory retention was assessed seven days after the reencounter phase. When we measured successful access to learned paired-associates in the reencounter phase, there was no difference between the anodal and sham stimulation condition in either Experiment 1 or 2. However, and importantly, anodal stimulation had a detrimental impact on long-term memory but only when stimulation preceded the reencountering of memories (in Experiment 1). Our results suggest that stimulation of the so-called control network during repeated access to acquired information disrupts the long-term retention of these memories. These findings are in line with earlier results showing that repeated access to learned information systematically decreases the involvement of control processes in retrieval and presumably promotes learning through the automatization of cue-target association. At a neural level, a possible substrate of repeated memory reencountering is a shift in frontohippocampal connectivity.

*Keywords*: dorsolateral prefrontal cortex; transcranial Direct Current Stimulation; long-term memory; memory reencountering; attentional control

## 1. Introduction

The processes that make it possible for recently acquired memories to be stored in long-term memory are key aspects of memory functioning. One of the factors that are known to affect the stability of memories is repeatedly encountering them (Gisquet-Verrier & Riccio, 2012). For the purposes of our study, reencountering a memory might involve retrieving an acquired memory upon a partial cue (retrieval) or being re-exposed to the memory content itself (re-presentation). Re-presentation involves repeated encounter with both the cue and the target, while in the form of retrieval, one reencounters memories by retrieving the targets upon a cue. Reencountering of information is known to play a key role in long-term memory retention (Paller & Voss, 2004; Rasch & Born, 2008), and the number of reencounters predicts later memory performance (Dupret, O'Neill, Pleydell-Bouverie, & Csicsvári, 2010). Although memories are usually replayed spontaneously during sleep (Paller & Voss, 2004; Rasch & Born, 2008) and this replay can be achieved by the presentation of associated memory cues during sleep (Bendor & Wilson, 2012), reencountering naturally tends to occur during wakefulness as well, in the form of repeated encounters with information acquired earlier. The repeated reencounters with memories during wakefulness is associated with lower forgetting (Foster & Wilson, 2006; Jadhav, Kemere, German, & Frank, 2012; Karlsson & Frank, 2009; Oudiette, Antony, Creery, & Paller, 2013) and is assumed to support the strengthening of individual memories (Oudiette et al., 2013).

Besides its behavioural consequences, the neural background of reencountering memories has also been investigated by a wide range of studies. To examine the neural substrates of repeated encountering, first we need to consider the key areas involved in the initial encoding and retrieval of associative memories. There is substantial overlap between the areas involved in these processes: regions of the PFC (including dorsolateral and ventrolateral prefrontal cortices, DLPFC and VLPFC, respectively) and the hippocampus and

surrounding regions are activated both at encoding and at the initial retrieval of associative memories (Ranganath, 2010). At encoding, DLPFC is assumed to be involved in the organization of material and the encoding of relational information (Blumenfeld, Parks, Yonelinas, & Ranganath, 2011; Fletcher, Shallice, & Dolan, 1998; Ranganath, 2010), while the VLPFC has a role in both item-specific and relational encoding (Addis & McAndrews, 2006; Blumenfeld et al., 2011). The main assumed role of the hippocampus at encoding is to bind item representations with their contexts and with other items, and to form individual representations of events (Kirwan & Stark, 2007; Preston & Eichenbaum, 2013).

The initial retrieval of associative memories is also accompanied by increased activity in different prefrontal cortical regions such as the DLPFC (Achim & Lepage, 2005; Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998; Habib, Nyberg, & Tulving, 2003; Kitamura et al., 2017; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994), which is involved in effortful attentional control, monitoring and evaluation processes (Barbey, Koenigs, & Grafman, 2013; Curtis & D'Esposito, 2003, Simons & Spiers, 2003), and the VLPFC which is involved in cue specification and maintenance of retrieved information (Fletcher et al., 1998; Simons and Spiers, 2003). Initial retrieval is also associated with activity in the hippocampus, whose main role at retrieval is assumed to be pattern completion based on a partial or degraded cue, thus making the recall of associative memories possible (Kirwan & Stark, 2007; Neunuebel & Knierim, 2014). There is also evidence that the initial retrieval of a memory is accompanied by synchronized neural activity between the PFC and the hippocampus (Anderson, Rajagovindan, Ghacibeh, Meador, & Ding, 2010). Importantly, although the initial retrieval of associative memories is related to an increased prefrontal activity, recent research has shown that following initial retrieval, repeated retrieval is associated with decreasing activity in the prefrontal cortex (PFC), including the DLPFC, and that this decrease in prefrontal activity predicts later retrieval success of associative memories (Karlsson Wirebring, Wiklund-

Hörnqvist, Eriksson, Andersson, Jonsson, & Nyberg, 2015; Keresztes, Kaiser, Kovács, & Racsmány, 2014; Kuhl, Dudukovic, Kahn, & Wagner, 2007; van den Broek, Takashima, Segers, Fernández, & Verhoeven, 2013).

It has been well established by several human and rodent studies that the PFC and the hippocampus have bidirectional connections (Cohen, 2011; Jin & Maren, 2015; Jones & Wilson, 2005; Preston & Eichenbaum, 2013; Vertes, 2004; Xu & Südhof, 2013) and that these connections are implicated in memory functions such as episodic retrieval (Preston & Eichenbaum, 2013; Simons & Spiers, 2003). Projections from the VLPFC through the perirhinal, parahippocampal and entorhinal cortices, and from DLPFC through parahippocampal and entorhinal cortex to the hippocampus (Ranganath, 2010; Jin & Maren, 2015) are considered to underlie search and monitoring processes (in accordance with the proposed role of PFC in attentional control). In this manner prefrontal areas interact with, and send input to the hippocampus to execute the highly control-demanding processes of cue specification, strategic search and monitoring that are essential for initial memory retrieval (Simons & Spiers, 2003).

Studies showing a deactivation of frontal regions during both rapid-eye movement (REM) and slow-wave (SWS) sleep (Braun et al., 1998; Maquet et al., 1996) – both of which are known to play a role in memory stabilization (Diekelmann & Born, 2010) – further corroborate the importance of decreased prefrontal activity for memory stabilisation. In contrast, increased activation in the hippocampus during REM sleep compared to wake state has been observed (Braun et al., 1997; Maquet et al., 2005). Furthermore, reactivation of memories by odour cues in rats during SWS – a sleep phase assumed to preferentially aid episodic memory consolidation (Diekelmann & Born, 2010; Plihal & Born, 1997, 1999) – was shown to induce increased hippocampal activity (Rasch, Büchel, Gais, & Born, 2007), and results in better memory performance following sleep. Taken together, these results

suggest that neural features of sleep (including an overall decrease in prefrontal activity and increased hippocampal activity during REM) and of repeatedly encountering memories provide ideal circumstances for memory consolidation.

In sum, previous results indicate increased level of activity in the PFC (e.g. Lee, Robbins, & Owen, 2000; Levine et al., 2004), and synchronization between the PFC and the hippocampus at initial memory retrieval (Anderson et al., 2010), and a gradual decrease in the activity in PFC at repeated reencountering by retrieval (e.g. Karlsson Wirebring et al., 2015; Keresztes et al., 2014; Kuhl et al., 2007). Also, decreased frontal and increased hippocampal activity during sleep seem to be fundamental for memory stabilization (Braun et al., 1997; Maquet et al., 2005, Diekelmann & Born, 2010). Combined with findings demonstrating the connectivity of frontal and hippocampal regions (e.g. Cohen, 2011; Jin & Maren, 2015; Jones & Wilson, 2005), the above mentioned studies suggest that repeated encounters with memories is normally accompanied by a change in neural activation patterns in the frontohippocampal path. That is, we assume that prefrontal (e.g. DLPFC) input to the hippocampus may gradually decrease with repeated memory encounters, and this might play a key role in the stabilization of memories. This assumption relies on the decreasing DLPFC activity observed at repeated encounters with memories (e.g. Kuhl et al., 2007) and the highly interconnected nature of frontal cortices (including the DLPFC) and the hippocampus (e.g. Jin & Maren, 2015; for a review of how attentional process traditionally linked to prefrontal regions modulate hippocampal activity, see Aly and Turk-Browne, 2017; and also Bilek et al., 2013). Thus, it is assumable that the maintenance of activity in the DLPFC during repeated encounters with memories (in the form of either re-presentation or retrieval) disrupts the long-term retention of memories, possibly by way of altering normally occurring changes in frontohippocampal communication. One possibility to keep the DLPFC in an active state is the stimulation of this area.

One of the most prominent techniques for brain stimulation in current research is transcranial Direct Current Stimulation (tDCS), which involves application of weak electric current on the scalp via electrodes (Bikson & Rahman, 2013; Dayan, Censor, Buch, Sandrini, & Cohen, 2013; Fregni & Pascual-Leone, 2007; Nitsche et al., 2003; Nitsche & Paulus, 2000). Albeit the exact mechanism of action of this method is not entirely understood (Fertonani & Miniussi, 2016), it has been shown that the threshold for neural activity can be shifted by tDCS (Creutzfeldt, From, & Kapp, 1962; Nitsche & Paulus, 2000), without actually evoking action potentials (Ruhnau, Rufener, Heinze, & Zaehle, 2018). According to the most widely accepted view, anodal stimulation achieves an excitatory effect by depolarizing neurons within the stimulated area, increasing the chance of action potentials (Fertonani & Miniussi, 2016). There is also evidence that anodal stimulation locally reduces the concentration of inhibitory neurotransmitter GABA in the neocortex (Barron et al., 2016; Kim, Stephenson, Morris, & Jackson, 2014; Stagg et al., 2009), further corroborating the excitatory nature of anodal stimulation. On-line application of this technique has been used to shed light on the role of different prefrontal cortical areas in certain cognitive processes. For example, it has been demonstrated that the anodal (excitatory) stimulation of the PFC improves performance in working memory tasks that require the contribution of attentional control processes (Fregni et al., 2005; Giglia et al., 2014; Oliveira et al., 2013; Ruf, Fallgatter, & Plewnia, 2017). Findings also indicate that transcranial stimulation of a cortical area might not only affect that particular area but connected regions as well (Ruhnau et al., 2018; Weber, Messing, Rao, Detre, Thompson-Schill, 2014). Importantly, off-line effects of tDCS have been established - that is, the effect of stimulation has been shown to last up to several hours after the end of stimulation (Brunoni & Vanderhasselt, 2014; Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016; Kang, Baek, Kim, & Paik, 2009; Nitsche & Paulus, 2001).

In the present study, we examined the role of the DLPFC in the long-term retention of repeatedly encountered memories by using tDCS. To investigate the effects of stimulation on two different types of memory reencountering, cued recall and re-exposure to the memory, we adopted the experimental paradigm from studies investigating long-term retrieval-based learning (Karpicke & Roediger, 2008; Roediger & Butler, 2011; Roediger & Karpicke, 2006). In our experiments, following the initial learning of paired associates, memories were reencountered either by re-presentation of the stimuli or by cued recall. Memory retention was assessed following a seven-day retention interval. Since tDCS exerts its effect not only during the stimulation period but also after that (Nitsche & Paulus, 2001; Priori, 2003), the anodal stimulation of the right DLPFC occurred before the reencounter phase of the memory task. In a control experiment, stimulation occurred immediately after the reencounter phase in order to investigate whether stimulation exerted its effect during the reencounter phase or during the period of subsequent memory consolidation. We hypothesized that when the DLPFC is kept in an activated state during encounters with earlier encoded memories (following the anodal stimulation of the right DLPFC in Experiment 1), it disrupts long-term memory retention. However, when stimulation follows the reencounters with memories (Experiment 2), no such effect is observable.

## 2. Experiment 1

### 2.1. Materials and Methods

#### 2.1.1. Participants

Sixty-seven Hungarian undergraduate students participated in Experiment 1. Participants had normal or corrected-to-normal vision, and by their own admission, they fit the criteria for electrical brain stimulation. Excluding criteria were as follows: psychiatric and chronic neurological illnesses, stroke or brain injury, epilepsy, epilepsy in ancestors, migraine,

language disorders, diabetes, vascular disorders, drug addiction, pacemaker, metal implants in body, pregnancy, and undergoing treatment with drugs acting on the central nervous system.

Due to an extremely low level of performance on the final test of the memory task (overall recall rate of 5%), one participant was excluded from the sample. Therefore, we analyzed the data of 66 participants (24 men; age: 19-31 years, $M$ = 23.2, $SD$ = 2.5) who had been randomly assigned to either an anodal ($N$ = 33; 10 men) or a sham ($N$ = 33; 14 men) stimulation condition.

Subjects (in both experiments) received money (cca. 10 Euro) for their participation and gave written informed consent. The study was approved by the United Ethical Review Committee for Research in Psychology, Hungary. The work described has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

**2.1.2. Memory Task**

Stimuli were 40 Swahili-Hungarian word pairs selected and translated from Nelson and Dunlosky (1994). The Swahili and the Hungarian words were randomly paired for each participant. The experimental procedure is illustrated in Figure 1.

In the initial learning phase, participants were presented with the 40 word pairs (for 5000 ms each; inter-stimulus interval [ISI]: 500 ms) in random order in five consecutive cycles (i.e., each word pair was presented five times in total). After all 40 word pairs were presented in one cycle, participants could proceed to the next learning cycle by pressing the Space bar, and then, all word pairs were presented again in a different random order. Before each learning cycle, subjects were instructed to memorize the word pairs.

The initial learning phase was followed by a 30-min delay, during which a list of paper-and-pencil arithmetic distractor tasks was administered. Subjects were given a sheet of paper with exercises (additions, subtractions, multiplications and divisions) printed on it and

were instructed to solve these tasks without a calculator, in any order they felt comfortable with. The aim of this task was to eliminate the possible effect of rote rehearsal on memory retention. Following the delay, subjects participated in the reencounter phase of the experiment, which consisted of five consecutive cycles. Each cycle consisted of a re-presentation and a retrieval block, and the order of these blocks varied randomly across the cycles.

In the *re-presentation blocks*, half of the word pairs were presented to the participants in a random order (8000 ms each; ISI: 500 ms). In the *retrieval blocks*, subjects were presented with the remaining 20 Swahili words as cues in a random order. Participants' task was to press the Space bar as soon as they had the Hungarian equivalent in mind, enabling us to record response speed. After pressing the Space button, participants were allowed to type the Hungarian meaning of the Swahili word. They had a maximum of 8000 ms to complete one word pair; 8000 ms after the onset of a stimulus, the next stimulus was presented automatically (preceded by an ISI of 500 ms).

Seven days after the reencounter phase, participants' memory for all word pairs was tested in one round. The circumstances of the final test were identical to those in the retrieval blocks of the reencounter phase with the exception that in the final test phase, all 40 word pairs were tested and each word pair was tested only once. At the end of the experiment, participants were debriefed.

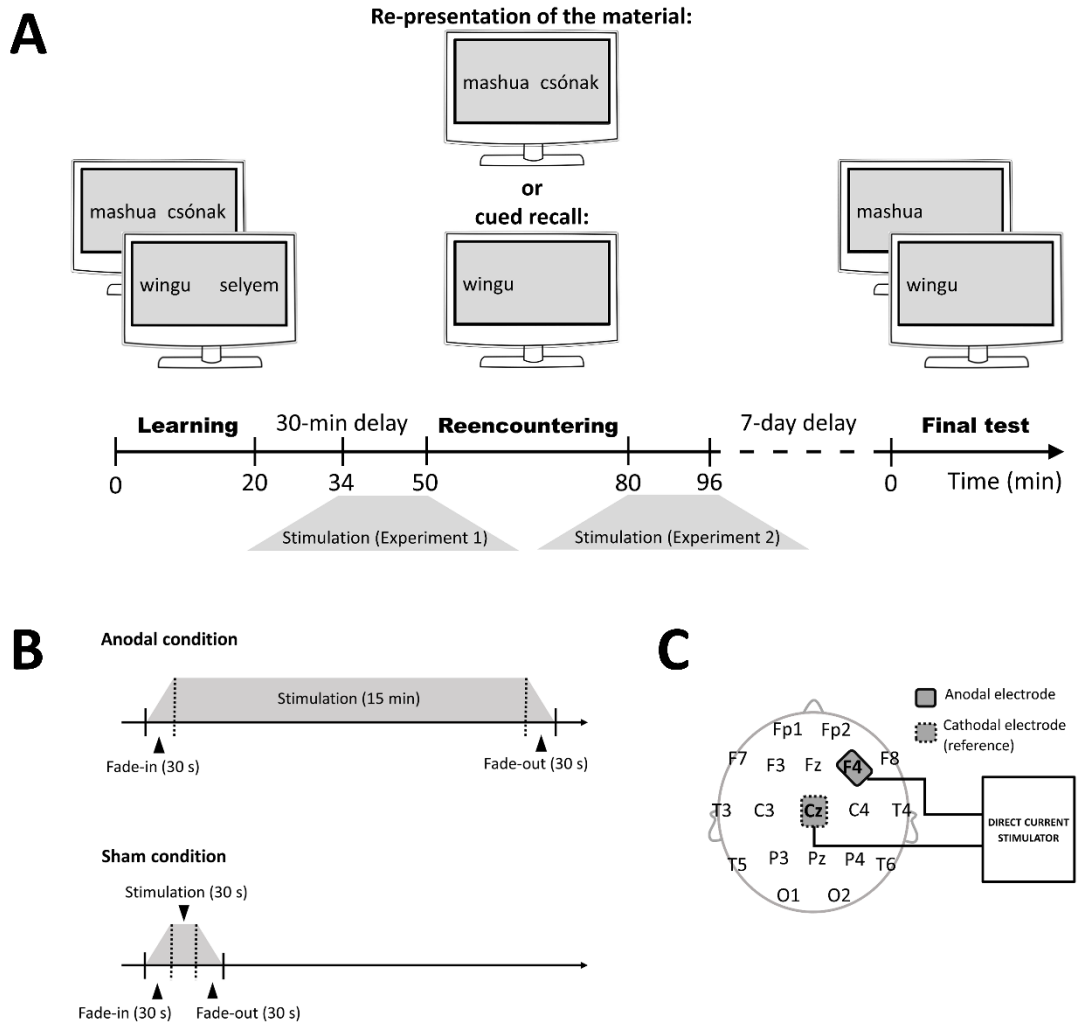


**Figure 1.** A) The procedure of Experiment 1 and 2. The stimulation was executed over the right DLPFC with 2 mA for 15 min in the anodal group and with 2 mA for 30 s in the sham group. Stimulation occurred either before (Experiment 1) or after (Experiment 2) the reencounter phase. B) Stimulation protocols in the anodal and sham conditions. C) Electrode configuration. Electrodes were placed according to the international 10/20 EEG coordinate system.

### 2.1.3. Transcranial Direct Current Stimulation

Stimulation by direct current took place during the 30-min delay between the initial learning and the reencounter phase of the memory task. At the beginning of the delay, the electrodes

were applied, and then participants were presented with arithmetic distractor tasks. In the last 16 min of the delay, the 15-min stimulation was executed together with the short fade-in (30 s) and fade-out phases (30 s). Fade-in and fade-out phases ensured that participants could gradually accommodate to the itching sensation caused by the stimulation and the cessation of such sensation at the end of the stimulation, respectively.

Participants received either anodal or sham stimulation. Electrical current was delivered using an Eldith (Electro-Diagnostic & Therapeutic Systems GmbH, Germany) direct current stimulator. The international 10/20 EEG coordinate system served as the basis for electrode placement. The anodal electrode was placed over the F4 mark, corresponding to the right DLPFC. The cathodal (reference) electrode was placed over the Cz mark. Both electrodes were placed in saline soaked 4 x 6 cm sized sponges, and were fixed on the head using rubber bands.

In both groups, current intensity was set to 2 mA, thus the density of current was 0.08 $mA/cm^2$. The stimulation started with a fade-in phase of 30 s, followed by the actual stimulation of 15 min in the anodal group and of 30 s in the sham group, and ended with a fade-out phase of 30 s. The short stimulation period of 30 s in the Sham condition was necessary to ensure that participants in both groups experienced the slightly unpleasant sensation, creating very similar experimental circumstances.

We assigned every second participant to the sham stimulation condition, assuring randomization. Participants were unaware of this experimental manipulation: all subjects were given the information that they would receive stimulation, and thus were not aware whether they belonged to the anodal or the sham group. Debriefing reports collected at the end of each experiment indicated highly similar sensations on behalf of the participants (initial tingling sensation that gradually faded away in a few minutes) in the two stimulation conditions. In

other words, the stimulation groups did not differ in their ability to judge whether they received anodal or sham stimulation.

### 2.1.4. Statistical analysis

We used an alpha level of 0.05 for all statistical tests. To investigate whether stimulation influenced memory performance shortly after the stimulation (i.e., in the retrieval blocks of the reencounter phase), recall success (proportion of correctly recalled items) and reaction times (RTs; i.e., time interval between the onset of the Swahili word and press of the Space button) of correct responses were analyzed by conducting mixed-design ANOVAs with BLOCK (1-5) as a within-subjects variable and STIMULATION (anodal/sham) as a between-subjects factor. During post hoc tests, we conducted simple contrasts with the last (fifth) block as a reference point. Finally, we analyzed whether stimulation had a long-term effect on memory (i.e., at final test) by conducting mixed-design ANOVAs for recall success and also for RTs with REENCOUNTER TYPE (re-presentation/retrieval) as a within-subjects variable and STIMULATION (anodal/sham) as a between-subjects variable. During post hoc tests, we used paired-samples *t*-tests to compare the effectiveness of the two reencounter types, and independent *t*-tests to compare the impact of stimulation.

Additionally, to exclude the possibility that in the case of items reencountered by retrieval, recall success in the reencounter phase alone could account for the recall success rate on the final test, we conducted a multiple linear regression analysis with performance in the reencounter phase (REENCOUNTER SUCCESS, as indicated by the recall success on the fifth [last] reencounter cycle in the repeated retrieval condition) and STIMULATION as independent variables and recall success on the final test (for items previously reencountered by retrieval) as a dependent variable. The aim of this analysis was to ascertain whether the effect of stimulation had a unique contribution to recall success on the final test, independently of recall success in the reencounter phase.

## 2.2. Results

### 2.2.1. Reencounter Phase: Short-Term Recall

For recall success (Table 1), the ANOVA indicated a significant main effect of BLOCK, $F(4, 260) = 18.026$, $p < .001$, $\eta^2_p = .220$. The main effect of STIMULATION, $F(1, 64) = 1.112$, $p = .296$, $\eta^2_p = .017$, and the BLOCK x STIMULATION interaction $F(4, 256) = 0.708$, $p = .587$, $\eta^2_p = .011$, were not significant. For RTs (see Table 1), a similar pattern of results was found as for recall success: the ANOVA revealed a significant main effect of BLOCK, $F(4, 256) = 71.671$, $p < .001$, $\eta^2_p = .528$, whereas the main effect of STIMULATION, $F(1, 64) = 0.390$, $p = .534$, $\eta^2_p = .006$, and the BLOCK x STIMULATION interaction, $F(4, 256) = 0.870$, $p = .482$, $\eta^2_p = .013$, were not significant.

Since STIMULATION had no effect either on recall success or on RTs, post hoc analyses were conducted for data of the entire sample[1]. Recall success was better in the last than it was in the first retrieval block, $F(1, 65) = 32.442$, $p < .001$, $\eta^2_p = .333$. The RT in the last block was lower than it was in each previous block (all $F$s $\geq 4.571$, all $p$s $< .05$).

In brief, whereas recall success improved, RT decreased during the retrieval blocks. More importantly, the anodal stimulation of the right DLPFC had no effect either on recall success or on RTs.

[1] When post hoc analyses were conducted for the two groups (anodal, sham) separately, a similar pattern of results was found, i.e., increasing recall success and decreasing reaction times during the retrieval blocks of the reencounter phase.

| Measures | Experiment | Block 1 | Block 2 | Block 3 | Block 4 | Block 5 |
|---|---|---|---|---|---|---|
| Recall success | Experiment 1 | 55.5 | 60.5 | 60.6 | 61.1 | 61.7 |
| | | (2.9) | (3.0) | (3.1) | (3.1) | (3.1) |
| Recall success | Experiment 2 | 54.1 | 55.9 | 57.9 | 58.7 | 58.8 |
| | | (3.1) | (3.2) | (3.3) | (3.3) | (3.2) |
| Reaction time | Experiment 1 | 2163.4 | 1725.4 | 1526.1 | 1342.0 | 1264.3 |
| | | (77.5) | (63.9) | (66.0) | (47.1) | (48.3) |
| Reaction time | Experiment 2 | 2128.8 | 1697.0 | 1461.2 | 1422.8 | 1321.3 |
| | | (60.2) | (65.5) | (59.6) | (64.8) | (52.8) |

**Table 1.** Recall success (%) and reaction times (ms) during the retrieval blocks in the reencounter phase of Experiments 1 and 2. (Standard errors of the mean are shown in parentheses.)

### 2.2.2. Final Test Phase: Long-Term Recall

Recall success at the final test is illustrated in Figure 2. Whereas both REENCOUNTER TYPE, $F(1, 64) = 54.684$, $p < .001$, $\eta^2_p = .461$, and STIMULATION, $F(1, 64) = 6.422$, $p < .05$, $\eta^2_p = .091$, had main effects on recall rate, the interaction between the two factors was not significant, $F(1, 64) = 0.000$, $p > .999$, $\eta^2_p < 10^{-30}$.

According to the post hoc analysis, long-term recall success was better for word pairs reencountered by retrieval than it was for those items that were reencountered by re-presentation – a typical finding in testing effect experiments showing a long-term retention benefit of retrieval compared to the re-presentation of a material (Roediger & Butler, 2011; Roediger & Karpicke, 2006). Here this difference was present both in the anodal, $t(32) = 5.766$, $p < .001$, $d = 1.004$, and sham conditions, $t(32) = 4.819$, $p < .001$, $d = 0.839$. Most

importantly, recall rate was lower in the anodal than it was in the sham group for word pairs of the re-presentation condition, $t(64) = 2.558$, $p < .05$, $d = 0.640$, and also for word pairs of the retrieval condition, $t(64) = 2.059$, $p < .05$, $d = 0.515$.

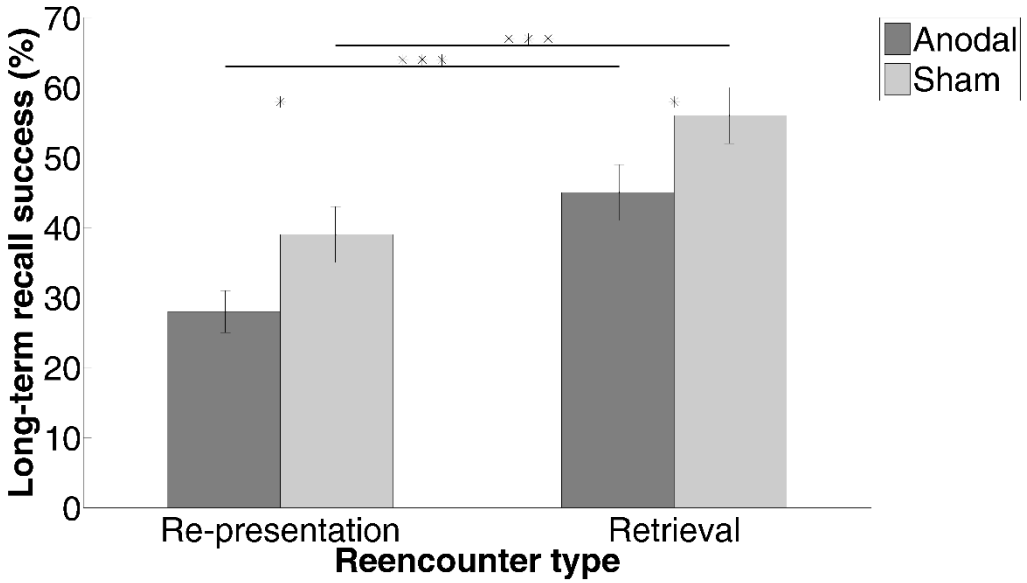


**Figure 2.** Recall success in the final test phase of Experiment 1.

*Notes.* When memory reencounter (re-presentation and retrieval) was preceded by the anodal tDCS of the right DLPFC, it disrupted long-term recall success (seven days after the reencounter phase). * Significant between-subjects difference at the level of $p < .05$. *** Significant within-subjects difference at the level of $p < .001$. Error bars represent the standard error of the mean.

Similarly to recall success, REENCOUNTER TYPE had a main effect on RT, $F(1, 63) = 16.414$, $p < .001$, $\eta^2_p = .207$. However, the main effect of STIMULATION, $F(1, 63) = 0.533$, $p = .468$, $\eta^2_p = .008$, and the REENCOUNTER TYPE x STIMULATION interaction, $F(1, 63) = 0.760$, $p = .387$, $\eta^2_p = .012$, were not significant. The RT for word pairs reencountered by retrieval was lower than it was for word pairs reencountered by re-presentation in the anodal group (retrieval: $M = 2213.6$, $SEM = 66.2$; re-presentation: $M = 2508.9$ ms, $SEM = 113.6$), $t(31) = 2.391$, $p < .05$, $d = 0.423$, and also in the sham condition

(retrieval: $M$ = 2043.1, $SEM$ = 118.3; re-presentation: $M$ = 2484.5 ms, $SEM$ = 151.8), $t(32)$ = 3.308, $p < .01$, $d$ = 0.575.

As a result of the multiple regression analysis, a significant regression equation was found, $F(2, 63) = 148.31$, $p < .001$, $R^2 = .825$. REENCOUNTER SUCCESS significantly predicted recall success on the final test, $F(1, 64) = 268.47$, $p < .001$, $R^2 = .808$, and STIMULATION had a significant unique contribution to recall success on the final test: inclusion of stimulation condition as a predictor variable in the model resulted in a significantly better prediction of recall success on the final test, $\Delta R^2 = .02$ $p < .05$. Coefficient values of this regression analysis are included in Table 2.

Summarizing the most important results of the final test phase in Experiment 1, anodal stimulation of the right DLPFC before memory reencounter had a detrimental impact on the long-term retention of the reencountered memories irrespective of the type of reencounter (re-presentation and retrieval).

In a control experiment, we investigated whether stimulation exerted its effect during the period of memory consolidation (and not during memory reencounters), therefore, in Experiment 2, stimulation occurred after the reencounter phase of the memory task.

| Experiment | Steps | Variables | B | SE | β |
|---|---|---|---|---|---|
| Experiment 1 | Step 1 | Constant | -0.01 | 0.03 | |
| | | Reencounter success | 0.83 | 0.05 | 0.90*** |
| | Step 2 | Constant | -0.09 | 0.05 | |
| | | Reencounter success | 0.82 | 0.05 | 0.88*** |
| | | Stimulation | 0.06 | 0.02 | 0.13* |
| Experiment 2 | Step 1 | Constant | -0.04 | 0.04 | |
| | | Reencounter success | 0.83 | 0.06 | 0.90*** |
| | Step 2 | Constant | -0.04 | 0.04 | |
| | | Reencounter success | 0.83 | 0.06 | 0.89*** |
| | | Stimulation | 0.01 | 0.03 | 0.02 |

**Table 2.** Regression analyses for recall success in the final test phases of Experiment 1 and 2. *Notes.* Experiment 1: Coefficient values when only reencounter success was included in the regression model (Step 1) and when both reencounter +success and stimulation were included (Step 2). Note. $R^2 = .81$ for Step 1; $\Delta R^2 = .02$ (*p*s < .05). * $p < .05$, *** $p <. 001$. Experiment 2: Coefficient values for when only reencounter success was included in the regression model (Step 1) and when both reencounter success and stimulation were included (Step 2). Note. $R^2 = .79$, $p < .001$ for Step 1, $\Delta R^2 = .00$, $p = .82$. *** $p <. 001$.

## 3. Experiment 2

### 3.1. Materials and Methods

#### 3.1.1. Participants

Fifty-three Hungarian undergraduate students participated in Experiment 2. One participant was excluded from the sample due to a low level of performance in the final test phase of the

memory task (overall recall rate of 5%). We analyzed the data of 52 participants (20 men; age: 19-28 years, $M$ = 23.2, $SD$ = 2.5). Subjects were randomly assigned to either an anodal ($N$ = 27; 10 men) or a sham ($N$ = 25; 10 men) stimulation condition.

### 3.1.2. Procedure

The procedure of Experiment 2 was equivalent to the procedure of Experiment 1 with only one exception. Whereas in Experiment 1 the stimulation occurred before the reencounter phase of the memory task, in Experiment 2 stimulation occurred after memory reencounters. Just as in Experiment 1, the stimulation was executed over the right DLPFC with 2 mA for 15 min in the anodal group and with 2 mA for 30 s in the sham group. The experimental procedure is illustrated in Figure 1.

### 3.1.3. Statistical analysis

For both the reencounter phase and the final test phase, recall success (Table 1) and RTs (Table 1) were analyzed in a similar way as in Experiment 1. Also similarly to Experiment 1, we conducted a multiple linear regression analysis with REENCOUNTER SUCCESS and STIMULATION as independent variables and recall success on the final test as a dependent variable to reveal any significant unique contribution of stimulation effects to recall success on the final test for items previously reencountered by retrieval.

## 3.2. Results

### 3.2.1. Reencounter Phase: Short-Term Recall

The ANOVA indicated that there was no STIMULATION main effect on recall success, $F(1, 50) = 0.009$, $p = .924$, $\eta^2_p < .10^{-3}$, and that there was no BLOCK x STIMULATION interaction, $F(4, 200) = 0.288$, $p = .886$, $\eta^2_p = .006$. These results indicate that there was no initial difference between the anodal and sham stimulation groups. BLOCK had a main effect on recall rate, $F(4, 200) = 7.757$, $p < .001$, $\eta^2_p = .134$. For RTs, similar results were found with a main effect of BLOCK, $F(4, 200) = 74.584$, $p < .001$, $\eta^2_p = .599$, and with no

significant BLOCK x STIMULATION interaction, $F(4, 200) = 0.123$, $p = .974$, $\eta^2_p = .002$, and no main effect of STIMULATION, $F(1, 50) = 0.211$, $p = .648$, $\eta^2_p = .004$.

As in Experiment 1, post hoc analyses were conducted for the entire sample, because STIMULATION had no effect either on recall success or on RTs[2]. Recall success was better in the last than it was in the first, $F(1, 51) = 22.901$, $p < .001$, $\eta^2_p = .310$, and second retrieval block, $F(1, 51) = 15.574$, $p < .001$, $\eta^2_p = .234$. The RT in the last block was lower than it was in each previous block (all $F$s $\geq 4.841$, all $p$s $< .05$).

In sum, a similar pattern of results was found in the retrieval blocks of the reencounter phase as in Experiment 1 (both for recall success and RTs). That is, recall success improved while RTs decreased during the retrieval blocks.

### 3.2.2. Final Test Phase: Long-Term Recall

As in Experiment 1, REENCOUNTER TYPE had a main effect on recall success, $F(1, 50) = 59.403$, $p < .001$, $\eta^2_p = .543$, and the STIMULATION x REENCOUNTER TYPE was not significant, $F(1, 50) = 0.115$, $p = .736$, $\eta^2_p = .002$. However, this time, STIMULATION had no main effect on recall rate, $F(1, 50) = 0.002$, $p = .966$, $\eta^2_p = 10^{-4}$, see Figure 3. As in Experiment 1, recall rate for word pairs of the retrieval condition was higher than recall rate for word pairs in the re-presentation condition – anodal: $t(26) = 5.168$, $p < .001$, $d = 0.995$; sham: $t(24) = 5.765$, $p < .001$, $d = 1.153$ –, but this time, no reliable difference was found between the anodal and sham stimulation conditions.

[2] When post hoc analyses were conducted for the two groups (anodal, sham) separately, a similar pattern of results was found, i.e., increasing recall success and decreasing reaction times during the retrieval blocks of the reencounter phase.

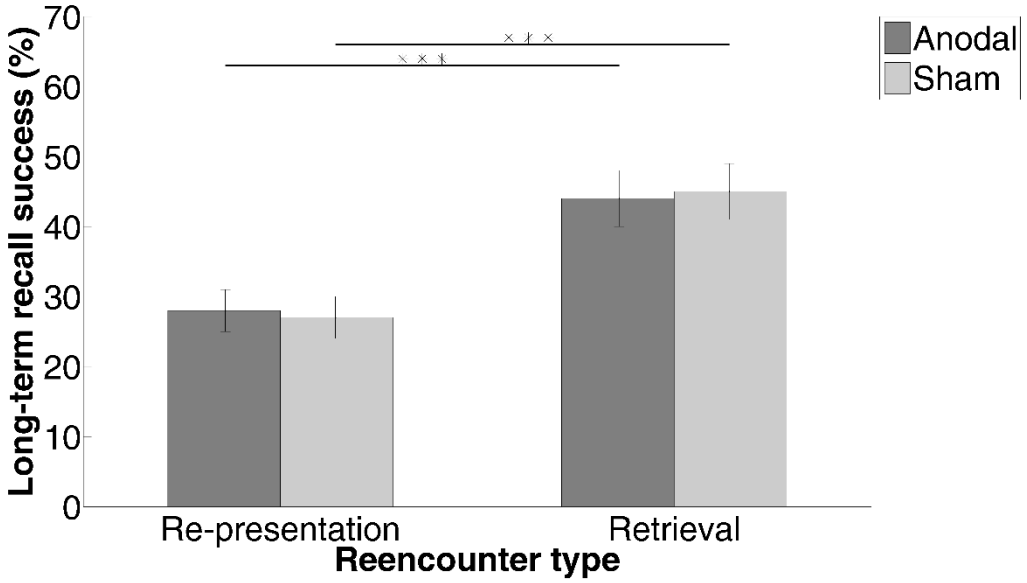


**Figure 3.** Recall success in the final test phase of Experiment 2.

*Notes.* When memory reencounter (re-presentation and retrieval) was followed by the anodal tDCS of the right DLPFC, it had no effect on long-term recall success (seven days after the reencounter phase). *** Significant within-subjects difference at the level of $p < .001$. Error bars represent the standard error of the mean.

As in Experiment 1, for RTs, the main effect of REENCOUNTER TYPE was significant, $F(1, 49) = 21.027$, $p < .001$, $\eta^2_p = .300$, indicating that response speed was lower for the retrieval than it was for the re-presentation condition both in the anodal (retrieval: $M$ = 2021.0 ms, $SEM$ = 89.6; re-presentation: $M$ = 2463.3 ms, $SEM$ = 127.7), $t(26) = 3.091$, $p <$ .01, $d = 0.595$, and the sham group (retrieval: $M$ = 2036.2.0 ms, $SEM$ = 99.2; re-presentation: $M$ = 2719.2 ms, $SEM$ = 159.5), $t(23) = 3.336$, $p < .01$, $d = 0.684$. The main effect of STIMULATION, $F(1, 49) = 1.498$, $p = .227$, $\eta^2_p = .030$, and the STIMULATION x REENCOUNTER TYPE, $F(1, 49) = 0.757$, $p = .388$, $\eta^2_p = .015$, interaction were not significant – just as in Experiment 1.

As a result of the multiple regression analysis, a significant regression equation was found $F(2, 49) = 93.60$, $p < .001$, $R^2 = .793$. REENCOUNTER SUCCESS significantly

predicted recall success on the final test $F(1, 50) = 190.75$, $p < .001$, $R^2 = .792$. STIMULATION did not have a significant unique contribution to recall success on the final test: inclusion of stimulation condition as a predictor variable in the model did not result in better prediction of recall success on the final test, $\Delta R^2 = .00$ $p = .82$. Coefficient values of this regression analysis are included in Table 2.

## 4. Discussion

Reencountering memories is a key process that affects long-term memory retention. In two experiments we investigated the role of the DLPFC in the long-term retention of repeatedly encountered memories by using tDCS. When memory reencounter was preceded by the excitatory stimulation of the right DLPFC (Experiment 1), stimulation had no immediate effect either on recall success or on response speed shortly after the stimulation (i.e., during the reencounter phase of the memory task). However, stimulation had a detrimental impact on the long-term retention of the reencountered memories.

In a second experiment, we investigated whether stimulation exerted its effect during reencounter or during the consolidation period. Therefore, in Experiment 2, the reencounter phase was followed by the anodal stimulation of the right DLPFC. This time, stimulation had no effect on long-term memory performance.

Taken together, these results indicate that the excitatory stimulation of the right DLPFC disrupts the long-term retention of memories by exerting its effect during memory reencounter. Furthermore, we replicated the well-established phenomenon of the testing effect (Karpicke & Roediger, 2008; Roediger & Karpicke, 2006), that is, repeated retrieval led to better long-term memory than the re-presentation of the study material. This effect was present regardless of the stimulation condition (anodal, sham), which corroborates the robustness of the testing effect.

### 4.1. Maintaining prefrontal activity disrupts retention

Our results are in line with the findings of previous functional neuroimaging studies showing that decreasing PFC activity during memory reencounters is associated with better long-term memory retention (Karlsson Wirebring et al., 2015; Keresztes et al., 2014; Kuhl et al., 2007; van den Broek et al., 2013). Accordingly, when the control network remained active during memory reencounter following the excitatory stimulation of the right DLPFC (in our first experiment), it diminished long-term memory performance. Recently, it has been suggested that some kind of automatization occurs during repeated retrieval meaning that repeated retrieval decreases the involvement of effortful attentional control processes resulting in superior long-term memory retention (Racsmány et al., 2018). Since in our study stimulation affected long-term memory performance irrespective of the type of reencounter (re-presentation of the study material and cued recall), our results point to a broader role of the DLPFC in processes that occur when associative memories are reencountered.

Our results are also in line with findings of studies demonstrating an overall decrease in PFC activity during sleep (Braun et al., 1998; Maquet et al., 1996), known to play a role in memory retention. In contrast, the hippocampus shows increased activity both during the REM phase and at memory reactivation in SWS, a sleep phase assumed to benefit the long-term retention of memories. Notably, it is widely recognised that the PFC and the hippocampus interact via the bidirectional frontohippocampal path (Jin & Maren, 2015; Jones & Wilson, 2005; Xu & Südhof, 2013) to execute, among other functions, memory tasks such as episodic retrieval (Preston & Eichenbaum, 2013; Simons & Spiers, 2003). Altogether these results indicate that interactions between the PFC and the hippocampus are implicated in memory retrieval and subsequent stabilization. There is also evidence that transcranial magnetic stimulation of the PFC during memory processes can alter its connectivity with the hippocampus (Bilek et al., 2013). It is thus assumable that maintaining activity in the PFC

during reencounters by stimulation might hinder memory stabilization processes by way of affecting frontohippocampal connectivity. During memory reencounters, the PFC putatively projects to the hippocampus via the frontohippocampal path, and at repeated reencounters this prefrontal cortical input to the hippocampus gradually decreases, as activity in the prefrontal cortical region lowers. Since this decrease in PFC activity is associated with better memory retention, it is plausible that maintaining PFC activity during reencounter overstimulates the hippocampus, which in turn leads to demolished memory performance. Without stimulation, the normally occurring decrease in PFC activity during repeated reencounter might result in gradually decreasing input to the hippocampus, and this decreased prefrontal cortical input can be assumed to benefit retention of individual episodic memories.

### 4.2. Novelty of results and limitations

Important novelties of our study include the investigation of long-term effects of stimulation and of repeated reencounters on memory retention. To the best of our knowledge, only two previous tDCS studies examined the impact of stimulation over the DLPFC on memory reencounters. In one of these studies, anodal tDCS occurred over the left DLPFC (Javadi & Cheng, 2013), while in the other study, the right DLPFC was stimulated by direct current during memory reencounters (Penolazzi, Stramaccia, Braga, Mondini, & Galfano, 2014). Just as in our first experiment, stimulation had neither an effect on recall success (Javadi & Cheng, 2013; Penolazzi et al., 2014) nor on response speed (Javadi & Cheng, 2013) in the reencounter phase of the memory task. However, the anodal stimulation of the left DLPFC improved later memory performance (Javadi & Cheng, 2013). At a first glance, this latter result and our finding suggest that the left and the right DLPFC might play different roles during memory reencounter, however, it must be noted that there are important methodological differences between these studies as well. Whereas in the former study

(Javadi & Cheng, 2013), the authors used a recognition task and a relatively short delay of five hours following the reencounter phase, we applied a cued recall task and tested memory following a longer retention interval of seven days.

As a novelty, we decided to use a stimulation method (tDCS) in the present study, since this method allows the researcher to introduce a controlled independent variable in the experimental design making it possible to examine the difference between stimulated and unstimulated groups, which has clear advantages to the analysis of purely correlational data. A limitation of the study, however, should be pointed out: despite convincing evidence for the effectiveness of tDCS (Ruhnau et al., 2018; Stagg, Lin, Mezue, Segerdahl, Kong, & Xie, 2013), there is no consensus regarding its mechanisms of action or the extent of its effects. Several alternative explanations have been proposed over the years (Bikson & Rahman, 2013; Liebetanz, Nitsche, Tergau, & Paulus, 2002), although research using this technique mostly relies on behavioral data and observed changes in electric potentials in stimulated brain areas. It is important to emphasize, however, that behavioral data, especially regarding anodal stimulation, supports the view that tDCS can effectively modulate excitability in stimulated areas (Ambrus, Zimmer, Kincses, Harza, Kovács, & Antal, 2011; Boggio et al., 2007; Boggio et al., 2008; Ferrucci, 2008; Habich et al., 2017; Javadi, Cheng, & Walsh, 2012).

## 5. Conclusion

To the best of our knowledge, this is the first study investigating the effect of excitatory stimulation over the right DLPFC on memory retention following a relatively long retention interval of seven days. We showed that stimulation had a detrimental impact on long-term memory only when stimulation preceded the reencounter of memories. Our findings suggest that when the DLPFC remains active during memory reencounters, it disrupts long-term memory retention. In other words, these results support the assumption that the decreasing

involvement of DLPFC and possibly its decreasing input to the hippocampus at repeated memory reencounters are beneficial for long-term memory retention.

## Acknowledgements

This work was supported by the 2017-1.2.1-NKP-2017-00002 Research Grant (National Brain Research Program, Hungary) and by the NKFI K124094 Research Grant. We thank Tamás Káldi for his useful comments on a previous version of the manuscript. We thank Ádám Markója for his help with the statistical analysis. We thank Márta Zimmer and Dezső Németh for their technical help. We thank Attila Keresztes for his help in the initial phase of the study.

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