Cognition and Behavior

Transcranial Direct Current Stimulation Effects on Memory Consolidation: Timing Matters

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Abstract

Transcranial direct current stimulation (tDCS) is a promising tool for modulation of learning and memory, allowing to transiently change cortical excitability of specific brain regions with physiological and behavioral outcomes. A detailed exploration of factors that can moderate tDCS effects on episodic long-term memory (LTM) is of high interest due to the clinical potential for patients with traumatic or pathological memory deficits and with cognitive impairments. This commentary discusses findings by Marián et al. (2018) recently published in *Cortex* within a broad context of brain stimulation in memory research.

Key words: anodal; brain stimulation; consolidation; dorsolateral prefrontal cortex; long-term memory; tDCS

Significance Statement

Here, we discuss the recent study of Marián et al. (2018) that demonstrated a disruption of long-term retention of remote memory after application of transcranial direct current stimulation (tDCS) over the right dorsolateral prefrontal cortex (DLPFC). We address methodological issues of tDCS application such as timing, site of stimulation, electrode montage and stimulation parameters (intensity, duration). Moreover, since tDCS effects are often under debate in terms of reliability, we point at the importance of the statistical design and at the consistency with previous evidence.

Recent studies questioned the reliability of transcranial direct current stimulation (tDCS) across different domains (e.g., perceptual, motor, cognitive functions) and brain networks (Horvath et al., 2015; Bestmann and Walsh, 2017). Among others, a recent meta-analysis focused on statistically non-significant close-to-zero effects of tDCS on episodic long-term memory (LTM; Galli et al., 2019). Indeed, tDCS effects on episodic memory accuracy are heterogeneous and require reevaluation, depending on different factors such as stimulation parameters and/or task specificity (Medvedeva et al., 2019).

Specifically, inside the LTM domain, it is important to consider timing of tDCS administration (Medvedeva et al., 2019) for two different reasons. First, the dynamic of tDCS effects depending on the duration and intensity of stimulation requires further clarification. Relatively low intensity

(up to 1 mA) and short duration (up to 13 min) of stimulation show monotonic effects (Nitsche and Paulus, 2000, 2001), whereas longer and more intense stimulation can lead to weaker (Jamil et al., 2017) or even reversed effects (Batsikadze et al., 2013). Second, as discussed below, memory consolidation unfolds in time and is maintained by a series of processes within specific time windows. Therefore, the inconsistency of tDCS effects on LTM may be due to a temporal mismatch between the experimental intervention and the process of interest.

Consolidation is a dynamic process of memory reorganization and stabilization, which includes a complex of cellular and physiologic changes unfolding in time and resulting in transfer of labile hippocampus-dependent memories to more neocortical-dependent and stable form (Bayley et al., 2005; Squire et al., 2015). While cellular consolidation occurs within hours after memory acquisition and relies more on structural changes in the hippocampus (Morris et al., 1982), the process of system consolidation requires days and results in a redistribution of the memory engrams in the neocortex (Morris, 2006). The latter is supposed to be supported by memory reactivation or reencounter (Frankland and Bontempi, 2005) which takes place during NREM sleep (Diekelmann et al., 2009; Genzel et al., 2014) and resting wakefulness (Tambini et al., 2010). Interestingly, it has been shown that in a short period of time after the reactivation (e.g., using cues), memories are susceptible to modification or reconsolidation (Nader and Hardt, 2009), thereby more easily prone to enhancement or impairment. The study of Marián et al. (2018) extended this stream of research by addressing the tDCS modulatory effects on memory in different time windows of the consolidation process. Specifically, authors examined the impact of the right dorsolateral prefrontal cortex (DLPFC) on the reactivation process and its causal role on the delayed recall. In the study, subjects were instructed to remember word pairs (encoding phase). After a 30-min break, the reactivation phase was administered. Reactivation of encoded word pairs was induced by direct reexposure of the same pairs or by cued recall, with one word from the encoded pair presented as a cue, and the other to be recalled. Reactivation was preceded (experiment 1) or followed (experiment 2) by anodal tDCS of the right DLPFC. Finally, 7 d after the encoding phase, subjects performed the final memory test in the form of a cued recall task. The final test revealed a decrease of memory recall accuracy only in the case when tDCS was applied before but not after memory reactivation (i.e., in experiment 1). Crucially for the experiment 1, while the cued recall accuracy in the reactivation task (short-term recall) was unaffected by tDCS, its detrimental effect appeared in 7 d (long-term recall). In contrast, for the experiment 2, both short-term (reactivation) and long-term recall were unaffected by stimulation. This finding seems to suggest that the increase of prefrontal activity during memory reactivation (triggered by a cue) induces a redundant input to the hippocampus which interferes with the ongoing processes of reconsolidation (Marián et al., 2018).

In summary, this evidence shows that manipulation of the DLPFC activity is effective inside a certain time window, i.e., before but not after memory reactivation. Moreover, this effect cannot be observed immediately after tDCS application (reactivation) but only after 7 d (delayed recall). This suggests that design of tDCS experiments should follow the temporal dynamics of the process of interest (i.e., in this case, episodic memory). However, despite the high potential of the general idea behind this study, there are several weak points that hamper interpretation and further implication of results.

Despite the quite intense stimulation (yet inside the existing safety guidelines; Antal et al., 2017) and relatively large sample size, the statistical design is controversial. On the one hand, the ANOVA showed a significant main effect of stimulation on recall accuracy for experiment 1. Of note, despite the interaction between the two factors, "stimulation" and "reencounter type" (i.e., reactivation task), was not significant, the authors reported significant *post hoc* comparisons.

In addition to the ANOVA, the authors performed a multiple regression analysis which showed a significant contribution of stimulation type to the recall accuracy. However, the statistical analysis was performed separately for each experiment making difficult to disentangle reliable tDCS effects. Indeed, the baseline performance (i.e., sham) in both the experiments looks to be different: the "decreased" performance for anodal condition of the experiment 1 seems equivalent to the one of anodal and sham conditions of the experiment 2. Therefore, one might interpret the significant effect reported in the experiment 1 as an increase of performance by sham rather than a decrease by anodal stimulation.

Besides the statistical analysis, there are three more issues that might have undermined the authors' findings. First, the authors' rationale to apply stimulation to the right DLPFC rather than the left is unclear. Several studies revealed that verbal memory is left-lateralized (Badre and Wagner, 2007; Spaniol et al., 2009). Though another strand of researchers demonstrated encoding-retrieval hemispheric asymmetry, implying predominant involvement of the left PFC into encoding of verbal material while the right PFC into retrieval (Cabeza and Nyberg, 2000; Sandrini et al., 2003; Innocenti et al., 2010; Medvedeva et al., 2019). Thus, considering the verbal nature of the task and the similarity between processes of encoding and reconsolidation (Javadi and Walsh, 2012), it is likely that a stronger effect could pop-out if the stimulation would have been applied on the left DLPFC.

Second, a crucial point of discussion regarding most of the tDCS studies is the electrode montage. Among different montages, tDCS is classically delivered by adopting bipolar or monopolar montages. The former implies an "active" (either cathode or anode) and a "reference" electrode placed on the scalp surface, while the latter uses a reference placed on an extracephalic target (e.g., shoulder, arm or cheek; Nasseri et al., 2015). In the study of Marián et al. (2018) a bipolar montage was applied, with the anode on F4 and the cathode on Cz according to the
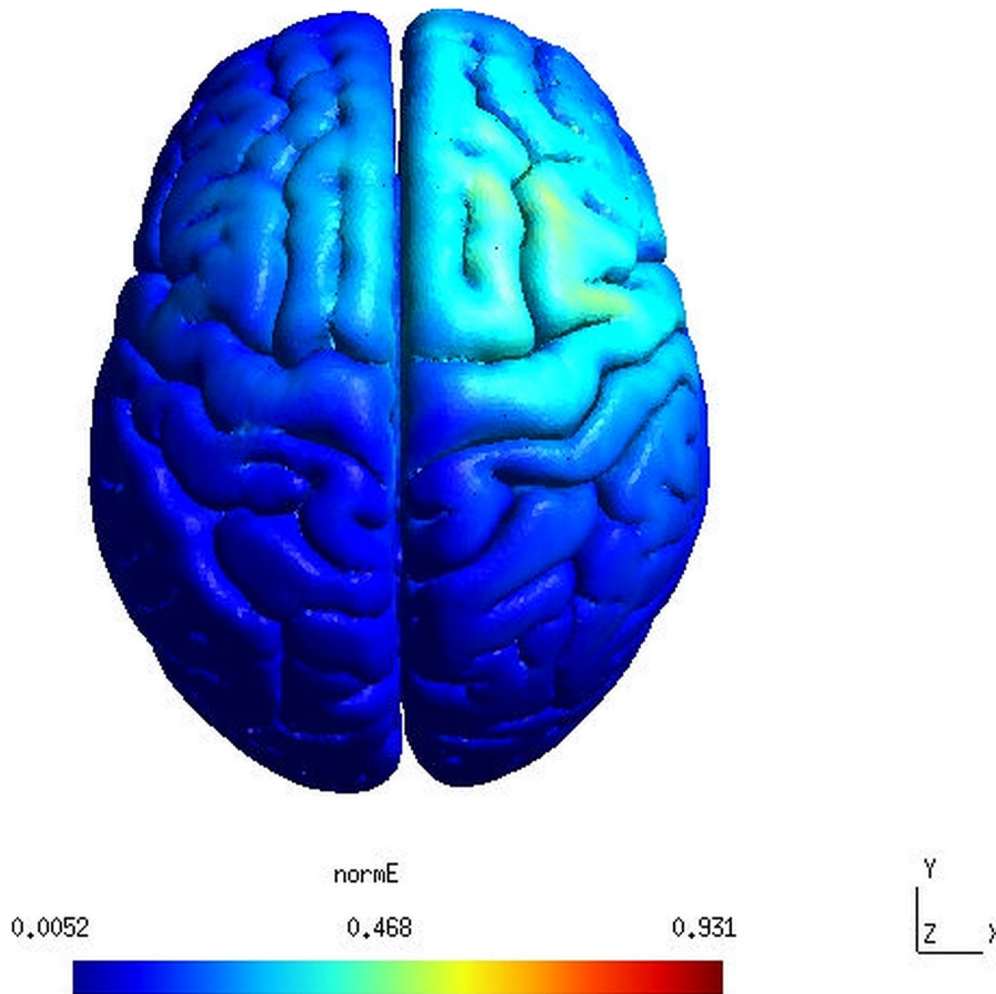
Figure 1. A realistic model of distribution of the tDCS-induced normalized electric field (normE) in the brain. The electric field modeling was based on the montage used in the experiment by Marián et al. (2018): anode is located on F4 and cathode is located on Cz according to the International 10–20 EEG system. The greatest amplitude of the electric field was mostly revealed on the posterior left superior frontal gyrus and posterior left middle frontal gyrus, i.e., nearby FC4 position. The electric field distribution was computed using a realistic finite element model as implemented in SimNIBS 2.1 free software (Thielscher et al., 2015).

10–20 EEG coordinate system. Thereby, it must be taken into account that while the target electrode was delivering anodal current to the right PFC, the reference electrode on Cz was delivering cathodal current on precentral regions thus running the risk of involving adjacent cortical areas such as the superior parietal lobule commonly involved in attention and working memory (WM) processes (Wang et al., 2015) and the right precentral gyrus involved in encoding of verbal information (Baker et al., 2001). However, a modeling approach could clarify the direction of the electrical current by taking into account different stimulation parameters such as electrode position, size, shape and current intensity. For example, according to a recent modeling tool which takes into account the electrical current spread on the cortex based on the aforementioned parameters (Thielscher et al., 2015), one may argue that the real distribution of electric field could differ from the one supposed by the authors (Fig. 1). On the one hand, the modeled electric field involves partly the right prefrontal area, meaning that the authors could eventually succeed in stimulation of their target region. On the other hand, according to the model the actual optimal hotspot (maximum intensity of the estimated electric field) of the stimulation could have been shifted slightly backward nearby FC4 electrode. This would imply a stimulation of a cortical area which is also associated to WM maintenance and attention rather than purely LTM processes (Owen et al., 2005) which could interfere with the target process. Finally, this study reveals an interesting discrepancy with previous evidence (Javadi and Cheng, 2013) which demonstrated an increase of episodic memory performance after reactivation phase combined with excitatory DLPFC stimulation. Indeed, Javadi and Cheng (2013) used anodal tDCS over the left DLPFC during memory reactivation and found an improvement of recognition performance after a 5-h interval. As noted by Marián et al. (2018), this variance of results can be explained by taking into account different encoding-retrieval intervals and task specificity (recall vs recognition).

However, the interpretation suggested by authors (i.e., activation of the right DLPFC during reconsolidation period resulted in a negative effect on memory recall) might imply that inhibition of the right DLPFC would result in a reversed (facilitatory) effect on memory recall. Interestingly, this suggestion is partly in line with findings by Sandrini et al. (2013). They applied 1-Hz repetitive transcranial magnetic stimulation (rTMS) over the right DLPFC after memory reactivation induced by a spatial-context cue. This resulted in an increase of memory recall the day after reactivation. Since 1-Hz rTMS is considered as a standard protocol for inhibition of brain activity (Chen et al., 1997; Muellbacher et al., 2000), this evidence may be considered as a reversed effect of stimulation, so that inhibition of the right DLPFC resulted in better memory performance. To be more clear, while inhibition of the right DLPFC by TMS increases memory recall, facilitation induced by tDCS of right DLPFC decreases it (Marián et al., 2018), suggesting an involvement of the same memory mechanism. However, in the study by Sandrini et al. (2013), stimulation occurred after reactivation, while in Marián et al. (2018) stimulation was effective only when was applied before but not after memory reactivation. This raises the question on the authors' conclusion that the right DLPFC activity is critical during reactivation per se but not during reconsolidation period after reactivation. Nonetheless, this discrepancy could be due to methodological differences between these two studies (tDCS vs TMS, 5 d of retention vs 1 d, cued recall vs free recall, reactivation of encoded information vs reactivation of its context, etc.). Further systematic studies including cathodal stimulation of the DLPFC could reveal a polarity-dependent effect and replicate the TMS effect found by Sandrini et al. (2013). Moreover, this would allow examination of the time window of the right DLPFC role in memory reconsolidation process with the same method as in the present study, allowing a more reliable comparison of results. Another future research direction could also use time-locked single-pulse targeted TMS of the DLPFC in a specific time window of interest. Supposedly, this would allow for inducing selective reactivation of distinct memories, as it was demonstrated for "latent working memories" (Rose et al., 2016), thereby modulating their consolidation. Additionally, simulation of the electric field distribution on the cortex based on electrode position, size, shape and current intensity would help to obtain a predictive model of the tDCS effects (Thielscher et al., 2015).

In summary, results reported in the Marián et al. (2018) do not clearly demonstrate effects of excitatory stimulation on episodic memory consolidation. This raises important issues about the use of tDCS in memory studies. Several factors that may have influenced the reliability of the study have to be taken into account, such as the statistical design, the electrode montage and the timing of stimulation. The latter has been shown to have a particular impact for the use of tDCS in LTM investigations (Medvedeva et al., 2019).

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