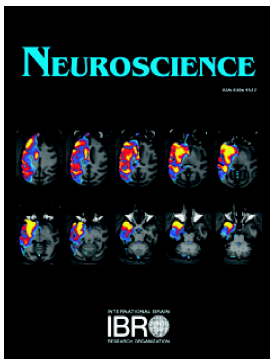

High Definition Transcranial Direct Current Stimulation Does Not Modulate Implicit Task Sequence Learning and Consolidation

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High definition transcranial direct current stimulation does not modulate implicit task sequence learning and consolidation

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Abstract

The incidental acquisition of a succession of tasks is termed implicit *task* sequence learning. Patients with dorsolateral prefrontal cortex (DLPFC) lesions are strongly impaired in this ability. However, recent results of conventional transcranial direct current stimulation (tDCS) above the prefrontal cortex showed no modulation of implicit task sequence learning and consolidation. One explanation for these null findings is that conventional tDCS has non-focal effects on the cortex. Thus, the aim of the present study was to use a focal type of tDCS, namely high definition tDCS (HD-tDCS), to influence implicit task sequence learning and consolidation. Participants received stimulation during implicit task sequence learning and, 24 hours later, consolidation was measured. The results showed that sequence learning was present in all conditions and sessions. Furthermore, consolidation was robust. However, both sequence learning and consolidation were not modulated by stimulation. Thus, this study corroborates previous findings by showing that even focal HD-tDCS is not sufficient to modulate implicit task sequence learning and consolidation.

Keywords: implicit task sequence learning; memory consolidation; high definition transcranial direct current stimulation; dorsolateral prefrontal cortex

Introduction

A plethora of studies showed the involvement of the prefrontal cortex for many cognitive functions, such as learning, memory, and the ability to switch between tasks (Hardwick, Rottschy, Miall, & Eickhoff, 2013; Nyberg et al., 2003; Wager, Jonides, & Reading, 2004). Specifically for procedural learning, several studies showed that the prefrontal cortex is critical for acquiring motor and perceptual sequences without intention (Hazeltine, Grafton, & Ivry, 1997; Honda et al., 1998; Peigneux et al., 2000), that is, implicit sequence learning (Abrahamse, Jiménez, Verwey, & Clegg, 2010; Cleeremans, Destrebecqz, & Boyer, 1998). However, so far few studies have explored the neural structures involved in implicit learning of abstract sequences of tasks in which motor response and stimulus features are random, an ability otherwise termed implicit *task* sequence learning (Heuer, Schmidtke, & Kleinsorge, 2001; Kemény & Meier, 2016; Meier & Cock, 2010; Weiermann, Cock, & Meier, 2010).

One informative study compared performance in different groups of patients with the task sequence learning paradigm (TSL) (Meier et al., 2013). The results indicated that while amnestic patients showed intact learning, patients with dorsolateral prefrontal cortex (DLPFC) lesions did not show any sequence learning in the TSL. Based on these findings, in a previous study we aimed to influence the TSL by applying conventional transcranial direct current stimulation (tDCS) above the DLPFC of healthy individuals (Savic, Müri, & Meier, 2017). Conventional tDCS consists of two rectangular electrodes with opposite polarities placed on participants scalp (Nasseri, Nitsche, & Ekhtiari, 2015; Polanía, Nitsche, & Ruff, 2018). Part of the direct current flowing between the electrodes supposedly penetrates to neurons and modulates the probability of action potentials

(Krause, Márquez-Ruiz, & Kadosh, 2013). Anodal and cathodal tDCS should increase and decrease the probability of action potentials, respectively, and in turn improve and impair behavior (Nitsche et al., 2003; Nitsche & Paulus, 2000). Contrary to our expectations, neither anodal nor cathodal conventional DLPFC tDCS influenced TSL (Savic et al., 2017). As we suspected that the bimanual design that we have used may have been the reason for these null-findings, in a follow-up study we used a modified version of the TSL with unimanual responses and the same conventional tDCS-montage (Savic, Cazzoli, Müri, & Meier, 2017). However, again we found no evidence of tDCS modulation on learning or consolidation, suggesting that a lack of effectiveness of conventional tDCS rather than the response effectors was the reason for the null-finding.

Importantly, these results are in line with numerous findings showing that conventional tDCS is not as effective as originally thought, and that it is susceptible to several sources of variability (Horvath, Carter, & Forte, 2016; Lukasik et al., 2018; Mancuso, Ilieva, Hamilton, & Farah, 2016; Medina & Cason, 2017; Meier & Sauter, 2018; Tremblay et al., 2016; Westwood & Romani, 2017). Recently, to increase the precision of tDCS and in turn its effectiveness, high definition tDCS (HD-tDCS) was developed (Bikson, Rahman, & Datta, 2012; Datta et al., 2009; Datta, Elwassif, Battaglia, & Bikson, 2008). Hence, the aim of the present study was to influence TSL performance by applying HD-tDCS on the DLPFC.

Specifically, HD-tDCS was applied via five round electrodes with smaller surfaces than the one used for conventional tDCS. Previous neurophysiological and modelling results showed that the effects of HD-tDCS on the cortex seem stronger, last longer, and are more focal than conventional tDCS (Edwards et al., 2013; Kuo et al.,

2013). In addition, HD-tDCS seems to be effective on perception, learning, and memory (Chua, Ahmed, & Garcia, 2017; Nikolin, Loo, Bai, Dokos, & Martin, 2015; Pixa, Steinberg, & Doppelmayr, 2017; Zito et al., 2015). However, it has to be highlighted that the quantity of HD-tDCS studies so far is limited. Among this small amount, we used a specific stimulation protocol for two reasons. Firstly, the protocol was shown to be effective on behavior and DLPFC excitability (Chua & Ahmed, 2016; Nikolin et al., 2015). Secondly, the protocol had a duration of 20 minutes, which previous findings suggested to be more effective on cortical excitability than longer stimulation durations (Vignaud, Mondino, Poulet, Palm, & Brunelin, 2018). Last but not least, as empirical results of DLPFC tDCS effects showed that different intensities seem not decisive to influence reaction times and accuracy (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016; Nikolin, Martin, Loo, & Boonstra, 2018), stimulation intensity was not a crucial criteria for the selection of the protocol.

Moreover, although it was not the primary goal of the study, we evaluated HD-tDCS impact on the set of memory transformations taking place after learning (Dudai, Karni, & Born, 2015). This set of transformations, referred to as memory consolidation, are commonly measured by repeating a task in two sessions separated by a period of time in which participants are not exposed to the task (Robertson, Pascual-Leone, & Miall, 2004).

Thus, in a first session, participants received HD-tDCS above the left or right DLPFC during the TSL. Twenty-four hours later, to evaluate the impact of HD-tDCS on consolidation, participants re-performed the TSL. As neurostimulation of the left DLPFC seems to influence both implicit sequence learning and memory tasks (Javadi & Walsh,

2012; Nikolin et al., 2015; Pascual-Leone, Wassermann, Grafman, & Hallett, 1996), anodal and cathodal left DLPFC HD-tDCS were expected to modulate sequence learning. Similarly, since in the TSL different types of information are integrated together in the same task and the right hemisphere seems dominant in integrating different kinds of information (Geschwind & Galaburda, 1985; Thiebaut de Schotten et al., 2011), anodal and cathodal right DLPFC HD-tDCS were also expected to modulate sequence learning. In addition, because executive functions, such as task switching, are involved in the TSL, and converging results showed the DLPFC to be critically involved in these functions (Aron, Monsell, Sahakian, & Robbins, 2004; Miyake et al., 2000; Tayeb & Lavidor, 2016), here task switching was taken as a control parameter to evaluate whether the DLPFC was properly stimulated.

Method

Participants and design

Participants were recruited via word of mouth. All participants were right handed, did not self-report past or present psychiatric or neurologic disease, and were not taking psychoactive medications. In total, 96 participants took part to the experiment. We conducted a power analysis with G*Power to obtain the sample size for the present study (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007). The effect size was estimated based on HD-tDCS effects on learning rate ($\eta^2 = 0.29$) by Nikolin et al. (2015) from which the HD-tDCS protocol was adopted. The power analysis with an alpha of 0.05 and a beta (power) of 0.95, indicated that approximately 72 participants would be needed. All participants gave their written informed consent before the start of the experiment and were blind to the design. Four participants were excluded

because they had an accuracy below 80% in blocks in which the sequence was embedded (i.e., blocks 5-12), three participant were excluded because of technical problems. The final sample consisted of 89 participants (25 woman, mean age = 23, *SD* = 6). The number of participants for each experimental condition was: 16 participants for anodal left DLPFC, 15 for anodal right DLPFC, 16 for cathodal left DLPFC, 11 for cathodal right DLPFC, 16 for sham left DLPFC, and 15 for sham right DLPFC. The experiment had a mixed design, with stimulation type (anodal vs. cathodal vs. sham) and hemisphere (left DLPFC vs. right DLPFC) manipulated between subjects and blocks manipulated within subject. The experiment was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of the Canton of Bern.

Materials

The TSL paradigm was adopted from Weiermann, Cock, & Meier (2010) (cf. Heuer et al., 2001). The stimuli were the digits 1, 2, 3, 4, 6, 7, 8, 9, and the letters a, e, i, u, c, n, r, s. They were presented in either green or red color on the center of a black background screen in 32-point Arial.

HD-tDCS tDCS was delivered with a DC stimulator plus (neuroConn, Ilmenau, Germany) connected to five round electrodes that had a diameter of 12 millimeters (mm). The electrodes were compatible with electroencephalography (EEG) caps, meaning that they could be directly inserted in the EEG channels. Figure 1 depicts the electrodes placements used to stimulate the left and the right DLPFC. For anodal and cathodal stimulation, current was delivered with an intensity of 2 milliamperes (mA) for 20 minutes. The current was ramped up and down gradually through 30 seconds (s). For sham, the parameters were the same as in anodal and cathodal except that stimulation

lasted 30 seconds (Nikolin et al., 2018). To reduce impedance, an electro conductive gel was placed directly inside the EEG channels between the surface of the electrodes and the scalp. Impedance was kept below 10 kilo-Ohms (kΩ).

Procedure

Figure 2 depicts the procedure. In Session 1, HD-tDCS was installed on participants' head. Afterwards, participants received the instructions in which it was written that they would perform a simple reaction time task. The TSL procedure was identical to the initial study, that is, with bimanual responses. Participants were instructed to respond as fast and accurate as possible and were not informed about the presence of a sequence. The task consisted of deciding whether a number was smaller (1, 2, 3, 4) or bigger than five (6, 7, 8, 9), or whether a letter was a vowel (a, e, i, u) or a consonant (c, n, r, s). In addition, the color of the stimuli determined the response mapping. Green was compatible and red incompatible response mapping. Compatible response mapping indicated pressing keyboard button "1" with the left index finger for digits smaller than five and vowels, and pressing keyboard button "5" with the right index finger for digits bigger than five and consonants. Incompatible response mapping was the opposite, therefore pressing keyboard button "1" with the left index finger for digits bigger than five and consonants, and keyboard button "5" with the right index finger for digits smaller than five and vowels. Compatible response mapping was indicated by fixed instructional reminders displayed in white color and in 26-point Arial font on the left and right of the stimuli. Figure 3 depicts two examples of trials. Sixteen eight-element sequences of task type (digit vs. letter) and response mapping (compatible vs. incompatible mapping) combinations were created according to Heuer et al., (2001).

Each combination consisted of the four possible trial-to-trial relations (task type repeated vs. task type switched and response mapping repeated vs. response mapping switched). It is important to stress that in the TSL the order of responses and stimuli features is random and, thus, sequence learning in the TSL is based on a sequence of tasks rather than a sequence of motor responses (Weiermann et al., 2010). Each participant trained with one of these sequences. After making sure that participants understood the instructions, HD-tDCS was given either for 30 s (i.e., sham) or for 20 minutes (i.e., actual). At the end of Session 1, participants were asked to rate the pain and unpleasantness felt during HD-tDCS. Pain was rated on a scale from "0" (e.g., "I feel no pain") to "10" (e.g., "I cannot continue the task because of pain"), for each point of the scale a corresponding description was available. Unpleasantness was rated on a scale from "1" (i.e., very pleasant) to "6" (i.e., very unpleasant) with "4" indicating a neutral sensation.

Eighteen blocks composed Session 1. Blocks 1-4 were practice blocks in which a pseudorandom order of task type-response mapping combinations was presented (see Supplementary material S1 for complete description on how the pseudorandom order was created). Blocks 5-14 were sequenced blocks, in which an eight-element sequence of task type-response mapping combinations was presented. In blocks 15 and 16 the sequence was changed to pseudorandom. In blocks 17 and 18 the sequence was re-established. In each sequenced block the eight-elements sequence was repeated 13 times resulting in 104 trials. In each trial a digit or a letter, either in green or red color, would appear on the screen. The stimulus remained on the screen until one of the two response buttons (i.e., keyboard button "1" or "5") was pressed. The inter-stimulus interval was 200 milliseconds (ms).

Seven blocks composed Session 2. Block one was pseudorandom followed by two sequenced blocks, two pseudorandom blocks, and two sequenced blocks. The TSL was programed with E-Prime version 2.0 (Psychology Software Tools, Pittsburgh, PA).

At the end of session 2 participants were informed that there was a repeating sequence of task type-response mapping combinations embedded. They were asked whether they noticed something and to guess a sequence. The number of consecutive elements reproduced was used as a measure of explicit knowledge. Additionally, participants were informed that there were two conditions of stimulation (i.e., actual and sham), and were asked to guess which one they received.

Data analysis

The first trial of each block, trials in which an error was committed, trials after an error, and trials with reaction times (RTs) lower than 100 ms were excluded from the analysis. Sequence learning was measured by calculating disruption scores. For Session 1, disruption scores were the mean RTs of pseudorandom blocks 15 and 16 minus the mean RTs of sequenced blocks 13, 14, 17, and 18. For Session 2, disruption scores were the mean RTs of pseudorandom blocks 4 and 5 minus the mean RTs of sequenced blocks 2, 3, 6, and 7. Thus, large disruption scores indicated large RTs increases in pseudorandom blocks 15-16 and 4-5 of Session 1 and 2, respectively. Consolidation was evaluated by comparing the disruption scores of the two sessions. Task switching was measured in switch costs that are the RTs difference between trials in which the task was switched and trials in which it was repeated (Heuer et al., 2001; Rogers & Monsell, 1995). The switch costs analysis was restricted to pseudorandom blocks 15-16 and 4-5 in Session 1 and 2, respectively. Additional analyses were conducted on the reported level

of pain and unpleasantness, on the explicit knowledge test, and on participants' guess regarding which stimulation condition they received (actual vs. sham). For all statistical analysis an alpha value of 0.05 was used. Effect sizes are indicated in partial η^2. Due to violations of normality, the data were log-transformed (Whelan, 2008). Levene's tests of equality indicated that the homogeneity of variances assumption was met.

Results

Sequence learning and consolidation

Figure 4 depicts RTs across all blocks for each experimental condition. During blocks 5 to 12 there was a continuous decrease in RTs reflecting a general learning effect. When the sequence order was switching to pseudorandom, performance slowed down which is an indirect indication of sequence learning. A similar pattern of disruption was found in Session 2. In order to analyze sequence learning and consolidation across HD-tDCS conditions we performed a mixed analysis of variance (ANOVA) on the disruption scores with the two sessions as within subject factor and stimulation type (anodal vs. cathodal vs. sham) and hemisphere (left DLPFC vs. right DLPFC) as between subjects factors. The ANOVA revealed no significant result (*ps* > 0.086) (see Table 1, top half) indicating that disruption scores did not change across sessions and that HD-tDCS influenced neither sequence learning nor consolidation. Figure 5 depicts the disruption scores of both sessions for each experimental condition. T-tests revealed that the grand means of the disruption scores were significantly differed from zero, t (88) = 7.64, p < 0.001 and t (88) = 10.10, p < 0.001 for Session 1 (77 ms; *SE* = 9) and 2 (58 ms; *SE* = 6), respectively.

Table 1

Outputs of the mixed ANOVAs conducted to evaluate HD-tDCS effects on disruption scores and switch cost.

Source	df	Mean Square	F	P	Partial η2
Disruption scores					
Between-Subjects					
Stimulation type	2	0.000	0.415	0.662	0.010
Hemisphere	1	0.001	1.015	0.317	0.012
Stimulation type * Hemisphere	2	0.002	1.504	0.228	0.035
Error	83	0.001			
Within-Subject					
Sessions	1	0.001	1.295	0.258	0.015
Sessions * Stimulation type	2	0.000	0.377	0.687	0.009
Sessions * Hemisphere	1	0.002	3.013	0.086	0.035
Sessions * Stimulation type * Hemisphere	2	0.000	0.473	0.625	0.011
Error (Sessions)	83	0.001			
Switch costs					
Between-Subjects					
Stimulation type	2	0.002	0.768	0.467	0.018
Hemisphere	1	0.000	0.068	0.795	0.001
Stimulation type * Hemisphere	2	0.001	0.442	0.644	0.011
Error	83	0.002			
Within-Subject					
Sessions	1	0.008	7.786	0.007	0.086
Sessions * Stimulation type	2	0.001	0.676	0.511	0.016
Sessions * Hemisphere	1	0.002	1.813	0.182	0.021
Sessions * Stimulation type * Hemisphere	2	0.002	1.758	0.179	0.041
Error (Sessions)	83	0.001			

As sample size influences heavily *p*-values, the null findings reported above were not able to disentangle whether the null hypothesis was true or the evidence inconclusive (Biel & Friedrich, 2018). In other words, the analysis conducted so far could not give any insight on the genuineness of the null findings. To explore this critical point, we conducted Bayesian statistics to compute the probability of H_1 and H_0 (Biel & Friedrich, 2018; Dienes, 2011). The free software JASP (Wagenmakers et al., 2018, Version 0.8.6.0; cf. 2017) was used to calculate Bayes Factors (*B*). *B* values indicate the probability of H_1 relative to H_0 (Wagenmakers et al., 2017). A *B* above 3 indicates evidence for H_1; a *B* below 1/3 indicates evidence for H_0; importantly, all values between 1/3 and 3 indicate data insensitivity to distinguish the hypotheses (Dienes, 2014). A Bayesian mixed ANOVA on the disruption scores with the two sessions as within subject factor and stimulation type (anodal vs. cathodal vs. sham) and hemisphere (left DLPFC vs. right DLPFC) as between subjects factors indicated support for the null hypothesis as all *B*s were below 1/3 (see Table 2 top half). Therefore, the Bayesian analysis supported the findings that disruption scores did not change across sessions and HD-tDCS did not influence sequence learning and consolidation.

Table 2

JASP output table of the Bayesian ANOVAs

Effects	P(incl)	P(incl|data)	$BF_{Inclusion}$
Disruption scores			
Sessions	0.737	0.242	0.114
Stimulation type	0.737	0.133	0.055
Hemisphere	0.737	0.317	0.165
Sessions * Stimulation type	0.316	0.005	0.010
Sessions * Hemisphere	0.316	0.046	0.105
Stimulation type * Hemisphere	0.316	0.016	0.035
Sessions * Stimulation type * Hemisphere	0.053	0.000	0.002

Switch costs			
Sessions	0.263	0.734	4.256
Stimulation type	0.263	0.152	0.188
Hemisphere	0.263	0.171	0.227
Sessions * Stimulation type	0.263	0.028	0.210
Sessions * Hemisphere	0.263	0.067	0.457
Stimulation type * Hemisphere	0.263	0.010	0.230
Sessions * Stimulation type * Hemisphere	0.053	0.000	0.659

Note. P (incl) = prior inclusion probability, P(incl|data) = posterior inclusion probability, $BF_{Inclusion}$ = Bayes Factor (i.e., change from prior to posterior inclusion)

Switch costs

A mixed ANOVA with the switch costs of the two sessions as within subject factor and stimulation type (anodal vs. cathodal vs. sham) and hemisphere (left DLPFC vs. right DLPFC) as between subjects factors revealed only a main effect of switch costs F (1, 83) = 7.78, $p < 0.05$, $\eta^2 = .086$ (see Table 1 bottom half), an indication that switch costs decreased across sessions (task switch costs Session 1 = 127 ms, *SE* = 19; task switch costs Session 2 = 75, *SE* = 10). T-tests revealed that these switch costs significantly differed from zero, t (88) = 9.20, $p < 0.001$ and t (88) = 8.70, $p < 0.001$ for Session 1 and 2, respectively.

Due to the non-significant effects of HD-tDCS, switch costs were analyzed with a Bayesian mixed ANOVA with the two sessions as within subject factor and stimulation type (anodal vs. cathodal vs. sham) and hemisphere (left DLPFC vs. right DLPFC) as between subjects factors. The main effect of switch costs produced a high *B* (4.256) indicating evidences for the alternative hypothesis. Most relevant, the *B*s regarding HD-tDCS effects were smaller than 1/3 and between 1/3 and 3 (see Table 2 bottom half), indicating suggestive evidence for the null hypothesis. Thus, the Bayesian analysis

supported the findings that switch costs decreased across sessions and there was no influence of HD-tDCS.

Additional results

One participant did not rate the pain and participants did not rate unpleasantness felt during HD-tDCS. The mean reported level of pain was 1.7 (*SD* = 1.5) and 0.7 (*SD* = 1) for actual and sham tDCS, respectively. An independent-samples *t*-test revealed that the level of reported pain was higher when actual tDCS was given compared to sham, $t(82) = 3.58$, $p = 0.001$. The level of reported unpleasantness was 4.1 (*SD* = 1.2) and 4 (*SD* = 1.1) for actual and sham tDCS, respectively. An independent-samples *t*-test showed no significant difference between actual and sham tDCS ($p = 0.7$).

One participant did not complete the explicit knowledge test at the end of the experiment. The mean number of correctly generated elements of the sequence was 3.5 (*SD* = 1.6), 3.4 (*SD* = 1.6), 3.1 (*SD* = 1), 3.2 (*SD* = 1.3), 3.2 (*SD* = 1), and 3.7 (*SD* = 1) for anodal right DLPFC, anodal left DLPFC, cathodal right DLPFC, cathodal left DLPFC, sham right DLPFC, and sham left DLPFC, respectively. A two-factorial ANOVA with the between subject factors stimulation type (anodal vs. cathodal vs. sham) and hemisphere (left DLPFC vs. right DLPFC) showed no significant effect ($ps > 0.6$). Participants who generated more than four elements were suspected of having explicit knowledge of the sequence. In total, 13 participants generated more than four elements. Excluding these participants did not change the sequence learning effects.

When asked whether they thought that they were in the actual stimulation condition or not, the same number of participants guessed correctly and wrongly (i.e., 43

participants), indicating that blinding was successful and that the judgement was on chance level.

Discussion

Patients with DLPFC lesions are strongly impaired in implicit TSL. However, recent results showed that conventional tDCS of the DLPFC does not modulate task sequence learning and consolidation (Savic, Müri, & Meier, 2017). As HD-tDCS is more precise than conventional tDCS, we expected that DLPFC HD-tDCS would modulate TSL performance. In order to maximize the chances of stimulation effects, we applied an HD-tDCS protocol that successfully modulated DLPFC activity and learning in previous studies (Chua & Ahmed, 2016; Nikolin et al., 2015). Nevertheless, the results showed no DLPFC HD-tDCS influence on performance. Sequence learning was present in both sessions and across all conditions, corroborating the finding that implicit learning of abstract sequences of tasks is robust and it can be reliably measured with the TSL (Meier & Cock, 2010).

Notably, a post-hoc computer simulation of the electric fields produced by the conventional tDCS-montage used in our previous studies (Savic, Cazzoli, et al., 2017; Savic, Müri, et al., 2017) and by the HD-tDCS montage used in the present study (Dmochowski, Datta, Bikson, Su, & Parra, 2011; Kempe, Huang, & Parra, 2014) shows that, compared to conventional tDCS, the electric fields produced by HD-tDCS were circumscribed to the area of the DLPFC (see Figure 6). Moreover, according to Figure 6, the electric field strength reached above the left and right DLPFC during HD-tDCS was 0.087 volts (V)/meters (m) and 0.107 V/m, respectively. The parameter that most probably produced these electric fields strengths is the position of the return electrodes.

Indeed, a recent study published after the present one was conducted, showed no DLPFC HD-tDCS effects on memory and attention (Nikolin, Lauf, Loo, & Martin, 2019). Critically, the authors used the same protocol as the present study, and one of the interpretation was that the space between the electrodes was too small (see Figure 1). This interpretation is supported by modeling results suggesting that the position of the return electrodes is critical for the efficacy of stimulation (Bikson, Datta, Rahman, & Scaturro, 2010; Kabakov, Muller, Pascual-Leone, Jensen, & Rotenberg, 2012), and that more distance between the electrodes increases electric field strength and reduces focality (Alam, Truong, Khadka, & Bikson, 2016). Thus, the present null findings may have been provoked by the electric field strengths that, in turn, are dependent from the position of the return electrodes.

This interpretation is partially corroborated by the lack of effects on switch costs. Actually, patients and neuroimaging data suggested a critical involvement of the DLPFC in the ability to switch between tasks (Aron et al., 2004; Tayeb & Lavidor, 2016). Nonetheless, previous results showed that DLPFC involvement might be apparent only at lower statistical thresholds (Wager et al., 2004). In addition, changes in paradigm parameters seem to activate different parts of the network involved in task switching (Witt & Stevens, 2013). Therefore, it might be that DLPFC HD-tDCS did not influence switch costs because task switching, in the TSL, did not sufficiently engage the DLPFC.

The insufficiency of HD-tDCS and TSL alone, or the combination of both to engage the DLPFC is supported from the Bayesian analysis. The latter showed that in most cases the results favored the null over the alternative hypothesis, suggesting an unsuccessful stimulation protocol or an unsuccessful combination of stimulation protocol

and task (Biel & Friedrich, 2018). By combining tDCS with neuroimaging and electrophysiological methods (e.g., Pisoni et al., 2018; Romero Lauro et al., 2016; Varoli et al., 2018), future studies should investigate the cortical reactivity induced by the combination of the present protocol and task.

In the same vein, future studies could probe whether stimulation of other brain areas might modulate TSL performance. For example, converging results showed that the cerebellum contributes to motor and non-motor aspects of behavior (Caligiore et al., 2016; Stoodley & Schmahmann, 2009; Timmann et al., 2010). Moreover, modelling results suggested that the cerebellum seems particularly responsive to tDCS (Rampersad et al., 2014), and its stimulation seems to influences perception, learning, and memory (Ferrucci & Priori, 2014; Grimaldi et al., 2016; Jongkees et al., 2019). Thus, there are sufficient evidences indicating that cerebellar tDCS could modulate TSL performance. Likewise, since the primary motor cortex (M1) seems to be as well particularly responsive to tDCS compared to other cortical areas (Radman, Ramos, Brumberg, & Bikson, 2009; cf. Savic & Meier, 2016), and the TSL requires a motor response, M1 tDCS could influence TSL performance.

Although investigating consolidation of the TSL per se was not the main goal of the study, the present results are important. In line with previous findings, the results showed that memory traces of sequences in the TSL are maintained across sessions (Savic, Cazzoli, Müri, & Meier, 2017; Savic, Müri, & Meier, 2017). This contrasts to a prominent model based on neuroimaging data suggesting that consolidation of abstract sequences should result in improvement rather than maintenance (Albouy et al., 2015; Albouy, King, Maquet, & Doyon, 2013). To widen our understanding of consolidation

taking place after sequence learning, future studies should investigate consolidation trajectories for different kinds of sequences (cf. Meier & Cock, 2014).

In conclusion, previous results showed that conventional tDCS does not influence TSL performance probably due to its non-focal effect. The present study extends these findings by showing that even a more focal stimulation method of the DLPFC, namely HD-tDCS, was not sufficient to influence implicit learning and consolidation of abstract sequences of tasks.

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Disclosure statement

No potential conflicts of interest were reported from the authors.

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Figure legends

*Figure 1***.** Electrodes placement used for stimulation of the left (A), and stimulation of the right DLPFC (B). For anodal stimulation, the light grey electrode was the anode and the four dark grey electrodes cathodes. For cathodal stimulation, the light grey electrode was the cathode and the four dark grey electrodes anodes.

Figure 2. Experimental procedure. In the TSL, "R" stands for random block and "S" for sequenced block. The blocks colored in grey represent ongoing HD-tDCS.

Figure 3. Two trials of the TSL (Weiermann, Cock, & Meier, 2010). The actual background was black. Instructions reminders, indicating compatible response mapping, were constantly presented left and right from the stimuli. The correct response for "3" green was pressing keyboard button "1" with the left index finger. The correct response for "a" red was pressing keyboard button "5" with the right index finger (see text for details).

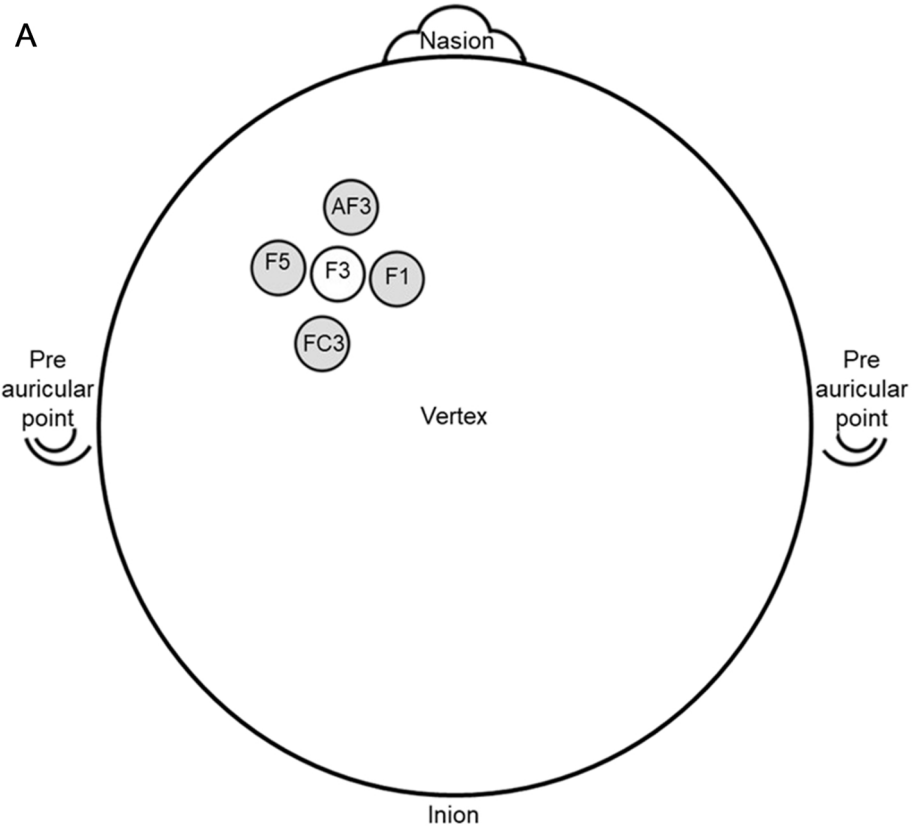
Figure 4. RT trajectories across blocks. "A" and "B" depict left and right DLPFC conditions, respectively. "R" = random block; "S" = sequenced block. Bars represent standard errors.

Figure 5. Disruption scores separately for Session 1 and Session 2 and each experimental condition, respectively. Bars represent standard errors.

Figure 6. Simulation distributions of the electric fields produced by conventional tDCS (top) and HD-tDCS (bottom) on left and right DLPFC of a healthy adult male. Blue and red colors depict low and high electric field strength, respectively. The white circles depict the target areas, Montreal Neurological Institute (MNI) positions x = -46, y = 38, z = 8, and x = 43, y = 38, z = 12, for left and right DLPFC, respectively. The simulation was obtained using HDExplore™.

Highlights

- We used focal brain stimulation to modulate implicit task sequence learning.
- Sequence learning was present in all conditions and sessions.
- However, focal brain stimulation was not sufficient to modulate performance.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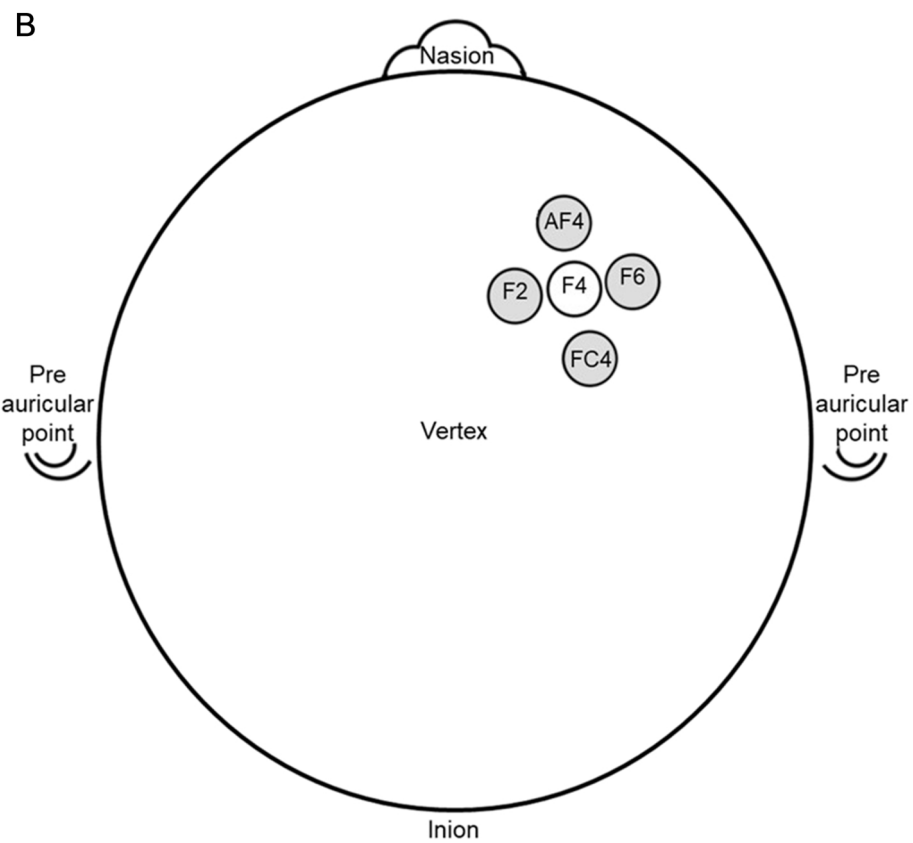
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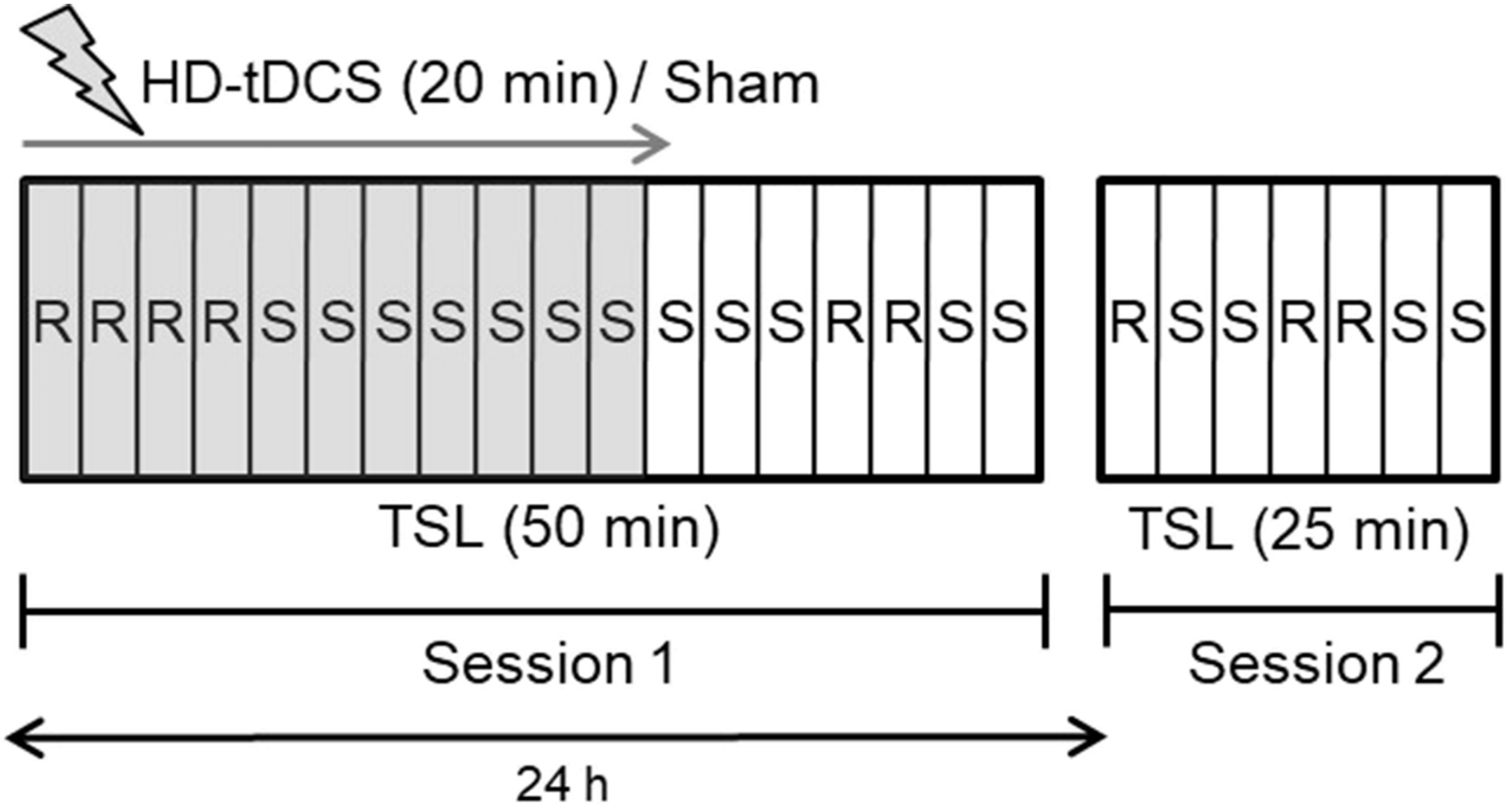
Figure 1


HD-tDCS (20 min) / Sham
R R R R S S S S S S S S S S R R S S
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TSL (50 min)
TSL (25 min)
Session 1
Session 2
24 h

Figure 2

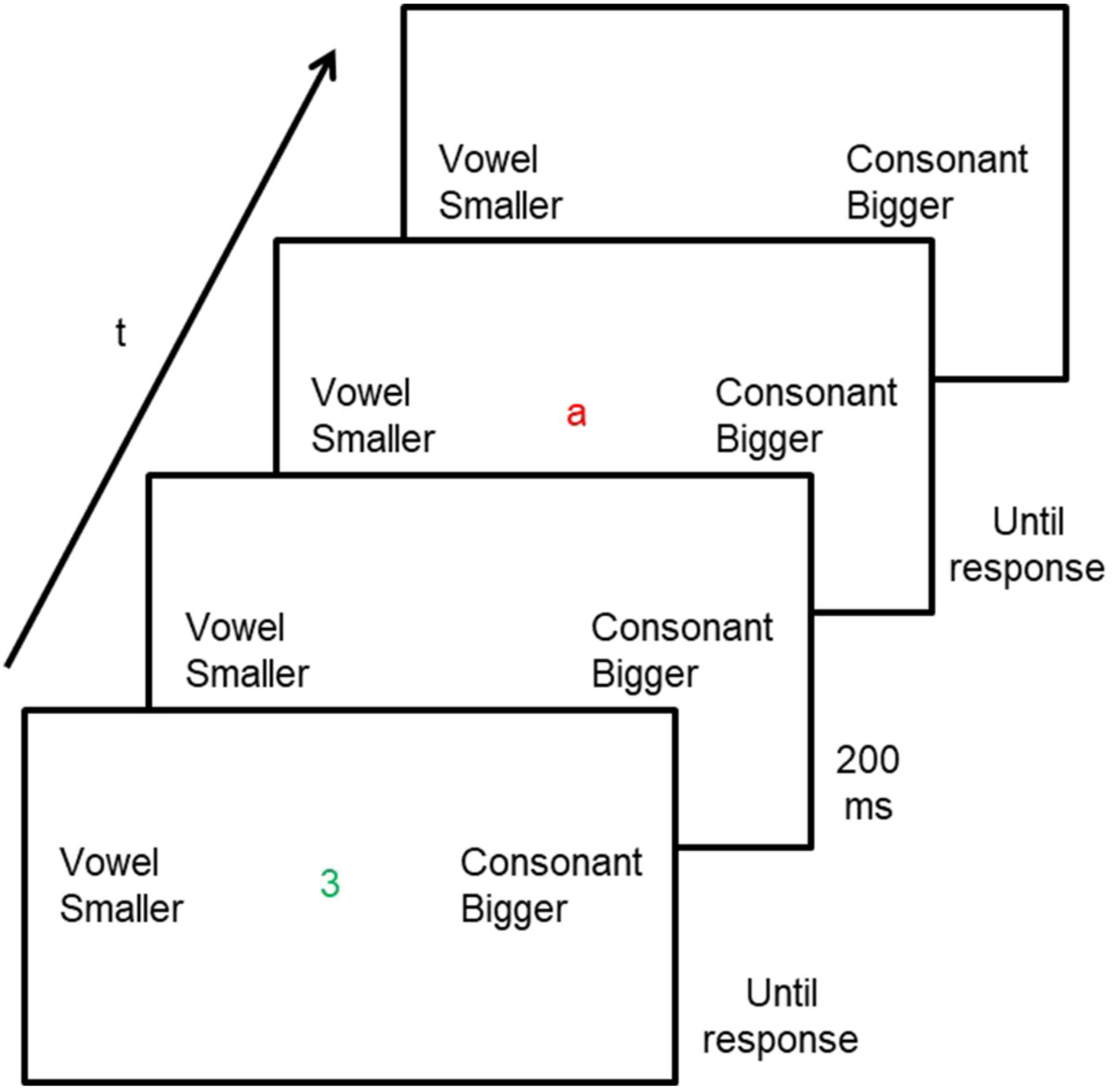
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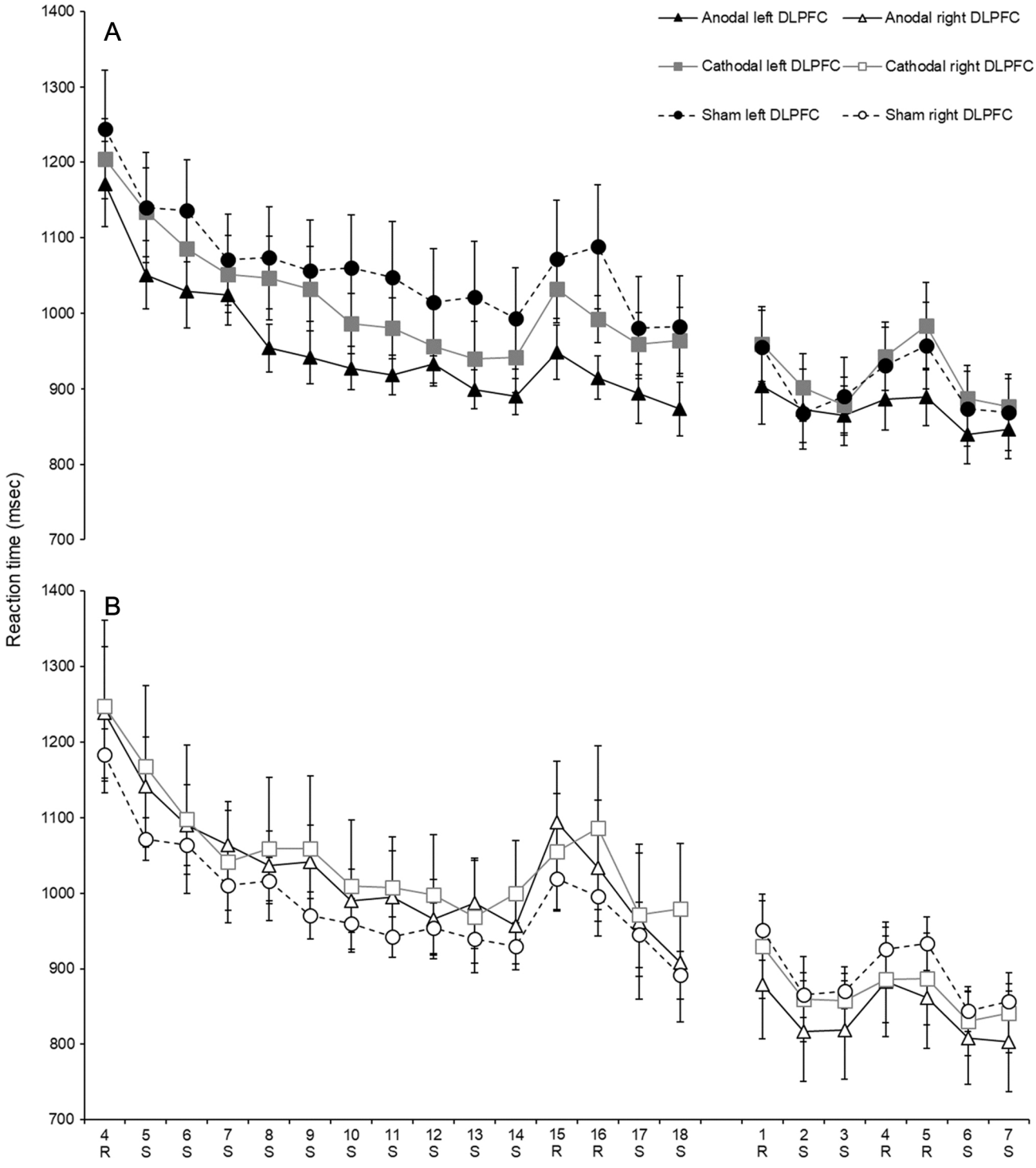
Figure 3


A
B
Anodal left DLPFC
Anodal right DLPFC
Cathodal left DLPFC
Cathodal right DLPFC
Sham left DLPFC
Sham right DLPFC
Reaction time (msec)
1400
1300
1200
1100
1000
900
800
700
4 R
5 S
6 S
7 S
8 S
9 S
10 S
11 S
12 S
13 S
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6 S
7 S

Figure 4

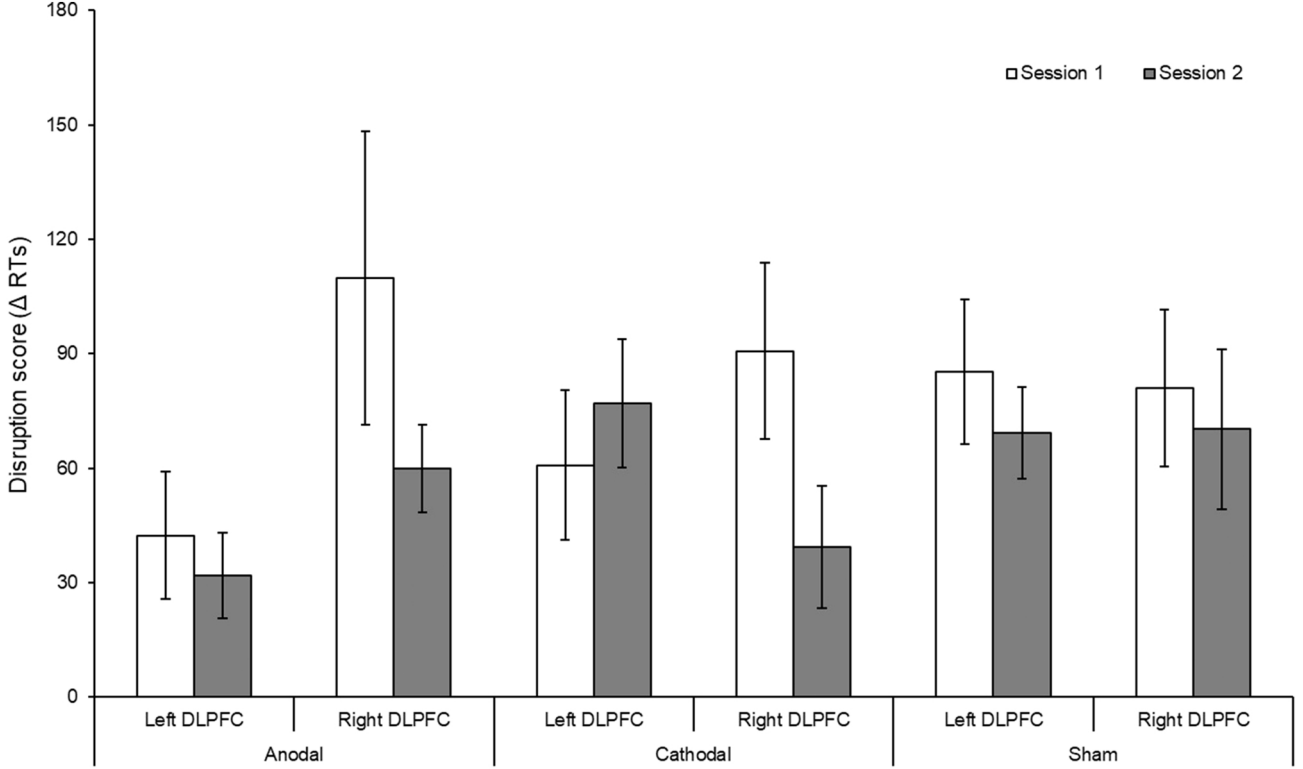
180
150
120
90
60
30
0
Disruption score (Δ RTs)
Session 1
Session 2
Left DLPFC
Right DLPFC
Left DLPFC
Right DLPFC
Left DLPFC
Right DLPFC
Anodal
Cathodal
Sham

Figure 5

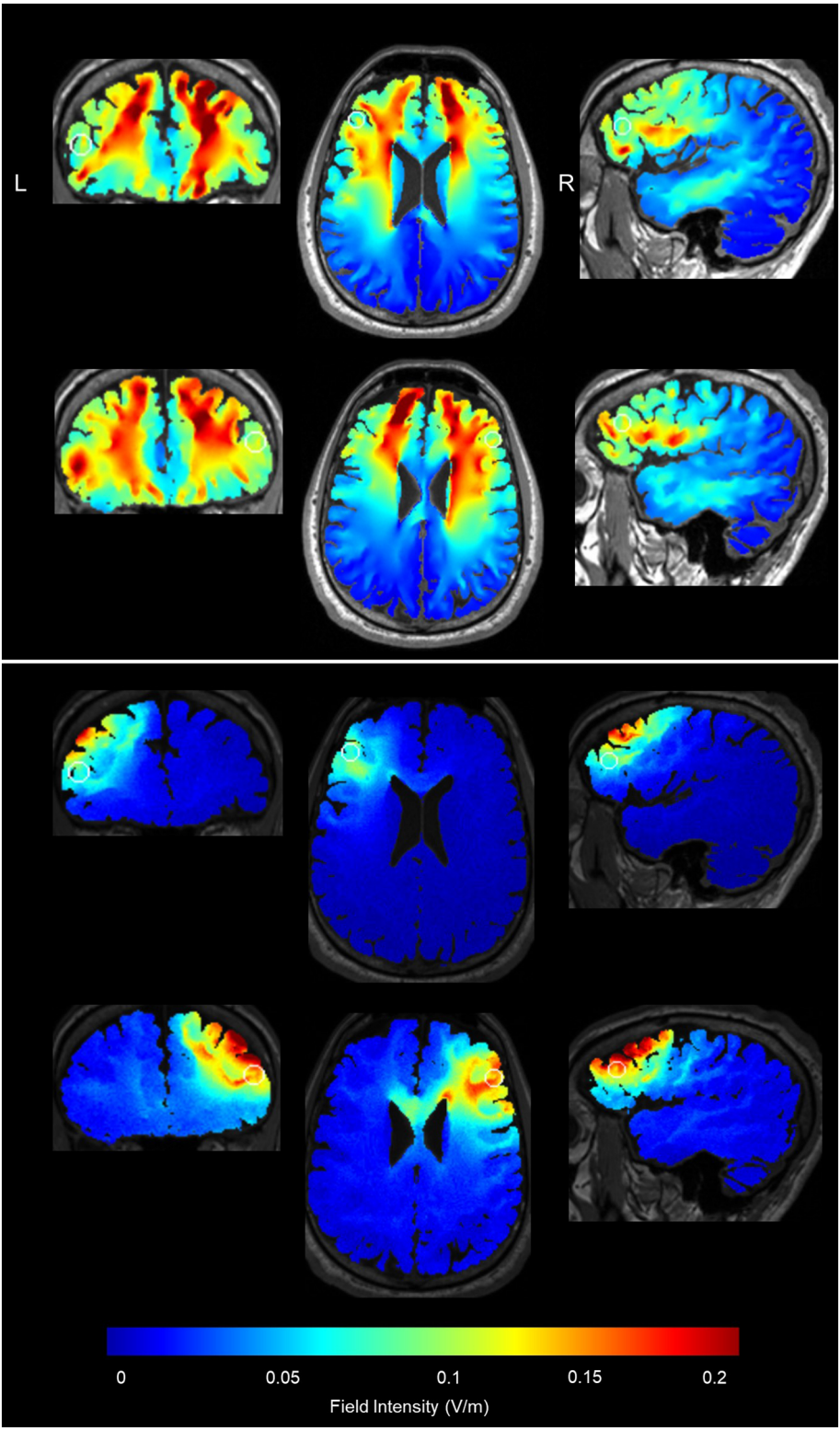

Figure 6