Evidence for a Role of the Right Dorsolateral Prefrontal Cortex in Controlling Stimulus-response Integration: A Transcranial Direct Current Stimulation (tDCS) Study

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A B S T R A C T

Background: Acting coherently upon stimuli requires some kind of integration of stimulus and response features across various distinct cortical feature maps (one aspect of the binding problem). Although the process of feature binding proper seems rather automatic, recent studies revealed that the management of stimulus-response bindings is less efficient in populations with impaired cognitive-control processes.

Objective: Here, we investigated whether the cognitive control of stimulus-response feature bindings ("event files") in healthy participants is affected by non-invasive brain stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC)—a main component of the cognitive-control network.

Method: In different sessions, participants received anodal, cathodal, or sham tDCS (2 mA, 20 min) while performing an audio-visual event-file task assessing the creation and retrieval of stimulus—stimulus and stimulus-response feature bindings. The general findings from this task indicate that performance suffers when some, but not all of the features are repeated (the so-called partial repetition cost).

Results: Stimulation over the right, but not the left DLPFC reduced control of stimulus-response bindings and produced outcome patterns similar to those previously observed in autistic children, people with lower fluid intelligence, and older adults.

Conclusions: This finding provides empirical support for a role of the right DLPFC in feature-binding management, which might consist in preventing the stimulus-induced activation of previously created, but now task-irrelevant, episodic bindings. From a methodological perspective, the finding may suggest that tDCS could be used as a temporary, reversible "brain lesion" generator in healthy subjects, enabling experimental investigation of how the brain works.

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Introduction

The human brain processes different features of perceived events in distributed, modality-specific brain regions [1] (e.g., visual information in the occipital lobes, auditory information in the temporal lobes, etc.). However, in order to create a unified event representation, this distributed information from distinct cortical regions needs to be integrated in one way or another—the notorious binding problem [2]. The binding problem is not restricted to the perceptual domain, as initially defined, but extends to the integration of perception and action. Indeed, Hommel [3,4] has demonstrated that perceptual features and action-related information are integrated into multimodal event representations, so-called event files [4].

Evidence for the spontaneous binding of stimulus and response features into event-files comes from tasks in which perceptual features and response features vary from trial to trial. In one version of such a task (which we will refer to as event-file task), two stimuli defined by combinations of two to three perceptual features and two (spatially defined) responses are presented [3]. Participants work through pairs of trials, of which the first trial is thought to induce the episodic binding of features while the second serves to assess whether the binding was created. Each trial (see Fig. 1) starts with the presentation of a response cue for the first response (R1),
which has to be carried out after the presentation of the first stimulus (S1). The second stimulus (S2) is composed of the same, partly the same or different perceptual features than S1. The participants have to respond (R2) to one of S2’s perceptual features, with the same or different response as R1. The main interest is whether the performance on S2/R2 is affected by the preceding event (S1/R1). The general finding is that performance (reaction time and/or accuracy) is better for complete repetition or alternation than for partial repetition, and hence there is a cost (in terms of reaction time and/or accuracy) if some but not all features are repeated (the so-called partial repetition cost; for review see [5]).

The neural mechanism that underlies the binding of perceptual and action features is not entirely clear; it has been proposed that features are bound via synchronous firing of the neurons from distinct sensory-motor areas such as the occipital, temporal, parietal, and frontal lobes [6–9]. Moreover, attentional and cognitive control processes play an important role in modulating this effect [5,10,11]. The available evidence indicates that stimulus features (within or across modalities), and stimulus and response features are spontaneously integrated in a more or less automatic, presumably context-independent fashion [10], while the likelihood of the retrieval of bindings depends on the task-relevancy of, and attention devoted to the respective feature dimensions [3,12]. Interestingly, significantly elevated partial repetition costs of stimulus-response bindings have been observed in individuals with low fluid intelligence [13], in children and older adults [14], and in autistic children [11]. As all these populations are suspected to have impaired cognitive-control abilities and less efficiently functioning prefrontal cortices, this pattern suggests that cognitive-control operations, relying on the prefrontal cortex, have a role in preventing the stimulus-induced retrieval of previously stored stimulus-response bindings.

This suggestion fits with the traditional assumption that the dorsolateral prefrontal cortex (DLPFC) plays a central role in cognitive control, and in the separation of task-relevant and irrelevant information in particular (e.g. [15,16]). And it is further supported by a recent neurofeedback study demonstrating that up-regulating gamma power (but not beta) in the frontal cortex through neurofeedback training leads to a significant reduction of partial stimulus-response repetition costs [17]. If we assume that the frontal cortex uses the gamma frequency band to communicate with episodic-memory modules, this would support the idea that the prefrontal cortex has a key role in managing stimulus-response bindings. Further evidence for the role of the DLPFC comes from a study emphasizing the role of the cortico-striatal circuits in binding sensory features with action features [18]. In this study, Toni and colleagues suggested that cortico-striatal circuits assist the transformation of sensorimotor integration, which in turn reduces the demand for prefrontal resources and enables this region to respond to a new event. Furthermore, several TMS and neuroimaging studies suggest different roles of the two prefrontal hemispheres in episodic memory (the hemispheric encoding-retrieval asymmetry model [19]). In particular, the left DLPFC is assumed to play an important role during the encoding of novel episodes, while the right DLPFC is apparently more involved in episodic retrieval (for review, see Ref. [20])—the process targeted in this study.

The aim of the present study was to provide more direct evidence for a managing role of the (right) prefrontal cortex by means of transcranial direct current stimulation (tDCS). tDCS is a non-invasive brain stimulation technique that has been applied successfully in patients for clinical purposes [21] and with healthy participants for cognitive neuroscience research [22,23]. It uses low amplitude direct currents targeting a specific area of the skull, which results in the modification of the transmembrane neural potential at the underlying brain region, which again influences the level of excitability in a polarity-dependent fashion. Anodal stimulation increases excitability while cathodal reduces excitability in the targeted brain region [25,26]. Many studies have reported modulation effects on various cognitive functions after tDCS stimulation; in particular, enhancement appears to be more associated with anodal stimulation [23]—even though the specific impact of anodal and cathodal stimulation can vary with targeted areas, functions [27], polarities [28], duration and intensity [29]. Over the past decade, a vast body of research has examined this brain stimulation technique, further exploring the action mechanisms during and after stimulation, the effect of the various parameters, the magnitude induced by the electric current fields (for reviews see Refs. [24,25]) as well as safety and ethical concerns [26]. As pointed out by various authors, tDCS has a research and therapeutic potential and has recently received growing interests and popularity [30].
If we assume that the DLPFC prevents or at least modulates the stimulus-induced activation of irrelevant, just-created stimulus-response bindings, we would expect that targeting this structure with tDCS has an impact on the size of the partial-repetition cost related to stimulus-response bindings. While recent studies have demonstrated that tDCS stimulation over the left DLPFC can modify cognitive-control functions as well [31,32], the hemispheric encoding-retrieval asymmetry model [19] considers the right DLPFC as a main agent involved in the control of episodic retrieval. If so, one would expect that stimulation over the right DLPFC has the strongest impact on the management of stimulus-response bindings, as reflected in partial-repetition costs.

Methods and materials

Experimental design

A randomized sham-controlled experiment was conducted on healthy volunteers. The experiment comprised of two separate experimental groups: one receiving stimulation over the right DLPFC and another receiving stimulation over left DLPFC. Each participant underwent three sessions of tDCS stimulation (anodal, cathodal, or sham), with the order being counterbalanced across participants. In order to minimize carryover effects, the interval between the different sessions was at least 48 h. The study conformed to the ethical standards of the declaration of Helsinki and was approved by the Ethical Committee of Leiden University.

Participants

Twenty-six Leiden University students (17 women; mean age = 20 years; age range: 18–24 years) took part in the study for course credits or a financial reward. The participants were assigned randomly to one of the two groups (stimulation over left DLPFC, n = 13, or stimulation over right DLPFC, n = 13) and were naïve to the experimental procedure and purpose of the study. All participants were right handed as assessed by the Edinburgh Inventory [33] with normal or corrected-to-normal vision. Exclusion criteria included: history of psychiatric disorders, drug abuse, active medication, pregnancy, or susceptibility to seizures. Participants gave their written informed consent to participate in the study.

Stimuli and procedure

A multimodal version of the event file task was adapted from Zmigrod and Hommel [34]. The bimodal stimuli S1 and S2 were composed of two pure tones of 1000 Hz and 3000 Hz (duration 50 ms) presented at approximately 70 dB SPL, accompanied by two colored circles, which varied across the sessions to prevent learning effects (blue and red; brown and green; yellow and purple). Responses to S1 and S2 were made by clicking the right or left mouse click with the same hand. Response cues for S1 were left- and right-pointing arrowheads in the middle of the screen indicating a left or right mouse click, respectively.

Each session started with tDCS stimulation, the task began with a practice block of 15 trials. After the task was well understood and the tDCS was on for at least 5 min, the experimental block with 96 trials began. The order of the trials was randomized. Participants were to carry out two responses per trial: a left or right mouse click (R1) to the onset of S1 (ignoring its identity) and a left or right mouse click to S2 (R2) (according to the identity of the pitch, ignoring the color). The sequence of events in each trial is shown in Fig. 1. A response cue appeared for 1000 ms to signal R1, which was to be carried out as soon as S1 appeared. S2 came up 500 ms later, with the pitch signaling the second response (R2). In case of incorrect or missing responses an error message was presented.

Transcranial direct current stimulation

tDCS was delivered by means of a DC Brain Stimulator Plus (NeuroConn, Ilmenau, Germany) and was applied through a saline-soaked pair of surface sponge electrodes (5 × 7 cm). The active electrode was placed over F3 or F4 (depend on the participant’s group), a location atop the DLPFC, according to the international 10–20 system for EEG electrode placement; the reference electrode was placed over the contralateral supraorbital area. The stimulation lasted 20 min with a constant current of 2 mA and with a 15 s fade-in and fade-out. For sham stimulation, the electrodes were placed at the same position but the stimulator was automatically turned off after 30 s fade in fade-out phase of stimulation.

Results

All participants completed the three sessions without major complaints or discomfort as measured by the tDCS Adverse Effects Questionnaire [35]. After excluding trials with missing (RT > 1500 ms) or anticipatory response (RT < 100 ms), mean accuracy and RTs of the correct responses of the second response (R2) were analyzed as function of five variables: brain region stimulated (right vs. left DLPFC), stimulation type (anodal, cathodal, or sham), the relationship between R1 and R2 (repetition vs. alternation), the relationship between S1 and S2 with regards to the task-relevant auditory feature pitch (repetition vs. alternation), and the relationship between the task-irrelevant visual feature color (repetition vs. alternation). Mixed five-way ANOVAs for repeated measures were performed with brain region as between-subject factor and the other four variables as within-subject factors.

Effects of brain stimulation

The standard cross-over stimulus-response interactions between the repetition/alternation of the task-relevant stimulus feature (pitch) and the repetition/alternation of the response was observed in RTs, \( F(1,24) = 64.85, P < .0001, n^2_p = .730 \), as well as with accuracy, \( F(1,24) = 38.61, P < .0001, n^2_p = .617 \). As to be expected, performance was better if the relevant stimulus and the response were both repeated or alternated than if one was repeated but the other was not (the partial-repetition cost), replicating earlier findings [3,4,36]. Most importantly for the present purposes, the RT pitch-by-response interaction was modified by a four-way interaction including stimulated brain region and stimulation type, \( F(2,48) = 4.86, P < .05, n^2_p = .169 \). As revealed by further analyses, split by brain region, a significant three-way interaction between stimulation type, pitch, and response was observed under right-DLPFC stimulation, \( F(2,24) = 4.28, P < .05, n^2_p = .263 \), but not under left-DLPFC stimulation, \( P > .10 \), suggesting that the manipulation of the tDCS was effective only when applying direct current over the right-DLPFC but not over left-DLPFC.

In order to further explore the source of the stimulus-response interaction with regards to the brain stimulation manipulation, we calculated individual sizes of the partial-repetition cost for pitch/response combinations by subtracting the mean RTs from complete repetitions (pitch and response) and...
alternations from the means of partial repetitions (see Footnote 1). Paired-samples t-tests confirmed significant differences between anodal and sham stimulation, $t(12) = 2.66$, $P < .05$, and between cathodal and sham stimulation, $t(12) = 2.75$, $P < .05$, indicating higher partial repetition costs with anodal (72.2) and cathodal (69.9) stimulation than with sham stimulation (42.2; see Fig. 2).

In addition, the five-way omnibus ANOVA revealed a 3-way interaction in RTs between region stimulated, stimulation type, and color, $F(2,48) = 4.08$, $P < .05$, $n_{p}^2 = .145$. Separate ANOVAs, split by stimulation type, revealed a significant interaction between brain region stimulated and color repetition/alternation in the anodal stimulation only, $F(1,24) = 8.39$, $P < .01, n_{p}^2 = .259$; indicating faster responses for color repetitions (483 ms) than alternations (499 ms) under right-DLPFC anodal stimulation but faster responses for color alternations (453 ms) than repetitions (465 ms) under left-DLPFC anodal stimulation, indicating hemispheric differences in color processing.

### Additional feature integration effects

The five-way omnibus ANOVAs revealed additional effects that were unrelated to the brain stimulation manipulation. Firstly, there was a significant interaction between pitch and color in RTs, $F(1,24) = 12.45$, $P < .005$, $n_{p}^2 = .342$. The effect followed the typical crossover pattern with better performance for pitch repetition if color was also repeated than if it was alternated, but worse performance for pitch alternation if color was repeated than if it was alternated—a replication of previous results [36]. Secondly, significant effects of response repetition were observed in RTs, $F(1,24) = 5.83$, $P < .05$, $n_{p}^2 = .195$, and accuracy, $F(1,24) = 15.14$, $P < .001$, $n_{p}^2 = .387$, indicating better performance for alternating than for repeated responses. Also, a main effect of pitch repetition was obtained in RTs, $F(1,24) = 12.25$, $P < .005$, $n_{p}^2 = .338$, and accuracy, $F(1,24) = 5.49$, $P < .05$, $n_{p}^2 = .186$, indicating better performance with pitch repetitions than alternations.

### Discussion

The aim of this study was to examine the role of cognitive-control functions in mediating stimulus-response integration using non-invasive brain stimulation as a manipulation tool in healthy individuals. The targeted brain region was the DLPFC, which is commonly associated with various cognitive-control functions. Our findings replicate previous observations showing that repeating only one element of a just-experienced stimulus—response combination impairs performance as compared to repeating all or none of these elements (the partial-repetition cost) [3,36]. This response pattern was observed in all conditions, providing evidence for the existence of episodic event representations—event files that is [4]. More interesting for present purposes, we found a significant modulation of the partial-repetition cost (i.e., the effect of stimulus-response integration) by stimulation site and stimulation type: only stimulating the right DLPFC had significant impact and this impact was comparable for anodal and cathodal stimulation. Given that the partial-repetition cost increased, rather than decreased, when the right DLPFC was stimulated, these observations suggest that both anodal and cathodal stimulation impaired the efficiency of managing episodic stimulus-response bindings.

Given that our task does not require, suggest, or benefit from retrieving previous stimulus-response bindings, the most efficient strategy would be to prevent the activation of such bindings altogether. As the presence of robust partial-repetition cost demonstrates, this does not seem to be possible, and neuroimaging findings indeed suggest that the presentation of a stimulus is sufficient to automatically reactivate previously bound stimulus and/or response features [10,37]. Nevertheless, the degree of this reaction seems to be under at least partial cognitive control, as suggested by the observation that partial-repetition costs are particularly pronounced in populations with reduced control abilities, like individuals with low fluid intelligence [13], autistic children [11], and older adults [14], and can be reduced through neurofeedback training targeting the frontal cortex [17,38]. Along these lines, our present findings would suggest that the right DLPFC is involved in suppressing stimulus-induced stimulus-response episodes at least to some degree—a function that seems to be impaired by any sort of targeted brain stimulation. Such a scenario would fit previous suggestions of a role of the right DLPFC in cognitive inhibition processes [39] and in episodic retrieval [20].

Moreover, our results indicate that both anodal and cathodal tDCS hinder healthy participants’ performance. The literature seems to favor the conjecture that anodal stimulation enhances performance and cathodal diminishes it, as was observed in studies stimulating mainly the motor area [40]. However, this assumption appears to be challenged by studies that stimulated other regions (for review see [28]). In some cases, only anodal stimulation seems to have a significant effect on performance [41]: while in other cases, the effect is achieved regardless of polarity. This was exemplified by Dockery and colleagues (2009), who found that both polarities (anodal and cathodal) enhance planning performance [42]. One may postulate that stimulating a specific region (either with positive or negative direct current) in healthy young participants might cause a disruption of well-tuned cognitive processes, as was manifested in our study.

Another interesting but rather surprising finding was the interaction effect between color processing and brain lateralization in the anodal stimulation, i.e. faster responses for color repetitions vs. alternations during right-DLPFC anodal stimulation but slower...
responses during left-DLFP anodal stimulation. This observation cannot be explained with the theory of feature integration. However, an fMRI study found hemispheric asymmetries in color perception, where the right hemisphere seems to have a more prominent role than the left hemisphere [43]. More research is needed in order to understand this observation, and tDCS may be a promising tool for such investigation.

In conclusion, the present findings provide first evidence for a role of the right DLPCF in managing episodic stimulus-response bindings. Moreover, from a more methodological perspective, it is interesting to note that stimulating the right DLPCF turned the performance of healthy, young university students into behavior that is otherwise only visible in autistic, low-intelligent, or elderly individuals as was observed in other studies using the same task [11,13,14]. This suggests that tDCS might be used to create temporary, reversible “frontal lesions” in a noninvasive fashion, at least in principle and at least in some tasks, and can assist designing and developing therapeutic interventions in a rather pure and experimental manner that can be applied to populations where feature integration does not operate in the most resourceful manner.

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References
