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Perturbation of the right prefrontal cortex disrupts interference control

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ABSTRACT

Resolving cognitive interference is central for successful everyday cognition and behavior. The Stroop task is a classical measure of cognitive interference. In this task, participants have to resolve interference on a trial-by-trial basis and performance is also influenced by the trial history, as reflected in sequence effects. Previous neuroimaging studies have associated the left and right prefrontal cortex with successful performance in the Stroop task. Yet, the causal relevance of both regions for interference processing remains largely unclear. We probed the functional relevance of the left and right prefrontal cortex for interference control. In three sessions, 25 healthy participants received online repetitive transcranial magnetic stimulation (rTMS) over the left and right dorsolateral prefrontal cortex, and sham stimulation over the vertex. During each session, participants completed a verbal-response Stroop task. Relative to sham rTMS and rTMS over the left prefrontal cortex, rTMS over the right prefrontal cortex selectively disrupted the Stroop sequence effect (i.e., the congruency sequence effect; CSE). This effect was specific to sequential modulations of interference since rTMS did not affect the Stroop performance in the ongoing trial. Our results demonstrate the functional relevance of the right dorsolateral prefrontal cortex for the processing of interference control. This finding points towards process-specific lateralization within the prefrontal cortex. The observed process- and site-specific TMS effect provides new insights into the neurophysiological underpinnings of Stroop task performance and more general, the role of the prefrontal cortex in the processing of interference control.

1. Introduction

A core aspect of goal-oriented behavior is the ability to select the 'correct' responses to the selected objects and thus elicit the anticipated sensory effects of the correct reaction (e.g. when we press the correct button on a remote control and the TV turns on). In a world full of objects, which are equipped with numerous interaction and response possibilities, selecting the 'correct' responses can be hard. Yet, in everyday life humans often seem to overcome this problem quite easily. We reach for a particular object (maybe a cup of coffee) from amongst a number of different objects and we write our emails and papers despite the fact that our smartphones (or children) are drawing our attention. In different circumstances, one might be asked by a police officer to ignore the meaning of a road sign to circumvent a roadblock. Yet later down the road it might be harder to properly react to that sign, after being told to ignore it. In other words, we can control our actions and cognitive processing and shield them against interference. Consequently, in most models of human information processing this ability, interference control, is a core concept.

In the laboratory, the Stroop task is one of the best established, interference-inducing experimental paradigms of cognitive psychology (MacLeod, 1991; Stroop, 1935). In this task, participants have to respond to the print color of a color word while ignoring its meaning. For instance, if the word "green" was printed in blue, participants should respond with "blue" and not "green". Cognitive interference in the Stroop task is investigated with two performance indices. Firstly, the classical Stroop effect reflects the difference in performance between congruent (e.g. the word "red" displayed in red color) and incongruent (e.g. the word "red" displayed in blue color) trials, with incongruent trials typically leading to worse performance compared to congruent ones. Cognitive models assume that the irrelevant meaning of the word is processed automatically and correctly responding to the print color requires cognitive effort to overcome this automatic process (MacLeod, 1991). Secondly, independent of the trial-wise interference, sequential effects

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across trials can be analyzed in the Stroop task. The basic idea is that the performance in trial n is influenced by its trial history (i.e. the trial n-1), such that after congruent trials performance for incongruent trials is worse; a finding known as the Gratton or congruency sequence effect (CSE) (Blais et al., 2014; Gratton et al., 1992). Conversely, after incongruent trials, performance for incongruent trials is improved. The congruency sequence effect is argued to reflect adaptive control, indicating that the cognitive system tries to adapt to conflicting information (i.e., an incongruent trial) to reduce future conflict (Braem et al., 2019; Braem and Egner, 2018).

To date, numerous neuroimaging studies have investigated the neural correlates of the Stroop effect (e.g. Laird et al., 2005; Milham et al., 2003; Nee et al., 2007). Specifically, the left and right inferior and middle frontal gyrus (IFG and MFG, respectively) as well as the dorsolateral prefrontal cortex (DLPFC) show consistent activation during the Stroop task across studies. Note that the labeling of prefrontal areas is inconsistent across studies. For example, the DLPFC has been labeled as Brodmann areas 6, 8, 9, 10 and 46, which overlaps with the middle frontal gyrus (MFG) (Burruss et al., 2000; Cieslik et al., 2013; Hoshi, 2006; Mylius et al., 2013). To avoid confusion, the present study defines the DLPFC as a part of the MFG, overlapping with areas BA 9 and 46 (Fuster, 2001; Miller and Cohen, 2001; Nee et al., 2007). In contrast, the IFG (sometimes also labeled as ventrolateral PFC) mainly overlaps with areas BA 44 and 45 (Aron et al., 2004; Klaus and Hartwigsen, 2019; Miller and Cohen, 2001). There is some evidence pointing towards a more left-lateralized activation with regards to the verbal Stroop task (Liu et al., 2006; MacDonald et al., 2000). Since the classical Stroop task employs written word stimuli and sometimes even verbal responses, these results might be partially traced back to the involvement of the left IFG in language processing (Klaus and Hartwigsen, 2019; Kuhnke et al., 2017). In contrast, the left MFG is not only recruited by the Stroop task, but also by other processes requiring cognitive control (Blasi et al., 2006; Owen et al., 2005; Sylvester et al., 2003). Likewise, the right PFC has also been implicated in cognitive control and executive functions aside from Stroop task performance. For example, the right IFG has been implicated in domain-general perceptual processing and cognitive control (Baumgaertner et al., 2013) as well as response stopping (Aron et al., 2014, 2004) and the MFG has been associated with response inhibition across domains (Depue et al., 2016; Zhang and Li, 2012).

Based on these results, some researchers have argued for a lateralization within the PFC and tried to further disentangle the different subprocesses related to interference processing. Particularly, the DLPFC has been assigned a key role in updating task-rules and keeping them accessible in the face of interference. This notion is based on the observation of increased left DLPFC activity during the response period regardless of the trial type, with stronger left DLPFC activity being associated with smaller Stroop interference effects (MacDonald et al., 2000; Vanderhasselt et al., 2009). With respect to the specific role of the left and right DLPFC in conflict resolution, it was argued that the left DLPFC is responsible for up-regulating the attentional set based on the expectation of conflict, whereas the contribution of the right DLPFC is only necessary when a response conflict is experienced (Vanderhasselt et al., 2009). It has further been proposed that the left DLPFC strategically prepares for conflict processing by loading the attentional set into working memory. These adjustments are not based on the amount of conflict but purely represent an overall strategical bias towards the relevant dimension (Egner, 2007; Liu et al., 2008). During cognitive processing of the Stroop task, this biases information processing towards the word color. On the other hand, right DLPFC activation seems to be conflict-driven and reduces interference from the irrelevant stimulus dimension following conflict (Egner and Hirsch, 2005a; Gratton et al., 1992; Kerns et al., 2004).

Non-invasive brain stimulation (NIBS) can be used to probe the functional relevance of both left and right DLPFC in conflict resolution and establish causal relationships between neural activation and behavior (Bergmann and Hartwigsen, 2020). Indeed, a number of NIBS studies applied repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) over the left and right DLPFC, providing evidence for a causal role of both areas in the processing of interference control (Friehs et al., 2019; Frings et al., 2018; Lowe et al., 2014; Vanderhasselt et al., 2007, 2006) and response inhibition (Chambers et al., 2007; Friehs and Frings, 2019, 2018; Yang et al., 2018). Yet, these results remain equivocal as some of the previous studies report increased performance while others show decreased performance in various performance measures under different NIBS protocols.

Moreover, to the authors' best knowledge, only few studies probed the role of the PFC in Stroop task performance with "online" stimulation directly during task processing. In short, online TMS refers to stimulation during task performance, which usually includes a single pulse or a short burst of a few pulses administered around the time of stimulus processing. Online TMS bursts typically affect cortical activity at the stimulated area for a period outlasting the stimulation for about half the duration of the stimulation train (Rotenberg et al., 2014) and thus provide a temporal resolution in the range of hundreds of milliseconds. In contrast, offline TMS refers to stimulation before the task. The plastic after-effects of offline TMS usually outlast the stimulation for several minutes (e.g. Parkin et al., 2015). This means that while offline TMS somewhat indiscriminately affects the processing in the stimulated area after stimulation, online TMS provides the opportunity to target specific processes with a higher temporal resolution. However, the specific temporal resolution depends on the specific TMS protocol at hand and should cover several 100 milliseconds in the present study. Importantly, during online TMS, there is no time for functional reorganization to occur, while offline TMS elicits plastic after-effects (for a review, see Bergmann and Hartwigsen, 2020).

In the present study we use online TMS to investigate the functional relevance of the left and right DLPFC in cognitive interference and trial history processing as measured with the congruency sequence effect during Stroop task performance (Guse et al., 2010; Olk et al., 2015; Yang et al., 2018). A recent study investigated the effect of left DLPFC stimulation on performance in an interference task similar to the classical Stroop task (Muhle-Karbe et al., 2018). The authors had participants categorize the gender of faces, while ignoring an overlaid gender-descriptive word (e.g. the word "WOMAN" overlaid on top of a female face represented a congruent trial). During the task the proportion of incongruent trials in different experimental blocks was varied unbeknownst to the participants. Their results showed that, when 10 Hz TMS over the left DLPFC was applied just before the to-be-classified stimulus (i.e. during the period of adaptive regulation of cognitive control), adaptive control was diminished.

The present study aims to investigate the functional relevance of both right and left DLPFC by stimulating both areas and analyzing the Stroop interference effect as well as the CSE. To this end, we applied focal 10 Hz rTMS bursts over left and right DLPFC, respectively, to actively disrupt interference control. Online TMS may have several effects on task processing in the stimulated area (Bergmann and Hartwigsen, 2020). While the exact physiological mechanisms of action remain unclear, online TMS is assumed to induce neuronal noise, due to the excitation of random neural elements in the stimulated circuits. The artificial induction of noise can hinder or delay task-relevant processing in the stimulated area by decreasing the signal-to-noise ratio. Additionally, neuronal excitation results in subsequent suppression of activity for short time periods after stimulation. As a consequence of the excitation and the subsequent suppression in the stimulated area, certain activation patterns are reduced, which further disrupts task-relevant neuronal computations. Importantly, previous studies have demonstrated the effectiveness of 10 Hz online rTMS to modulate task performance in different cognitive task (e.g. Gough et al., 2005; Hartwigsen et al., 2010; Kuhnke et al., 2017; Preston et al., 2010).

Since both the left and right DLPFC seem to be involved in interference, rTMS over both regions was expected to disrupt performance (Nee et al., 2007). Based on the above-discussed neuroimaging studies,

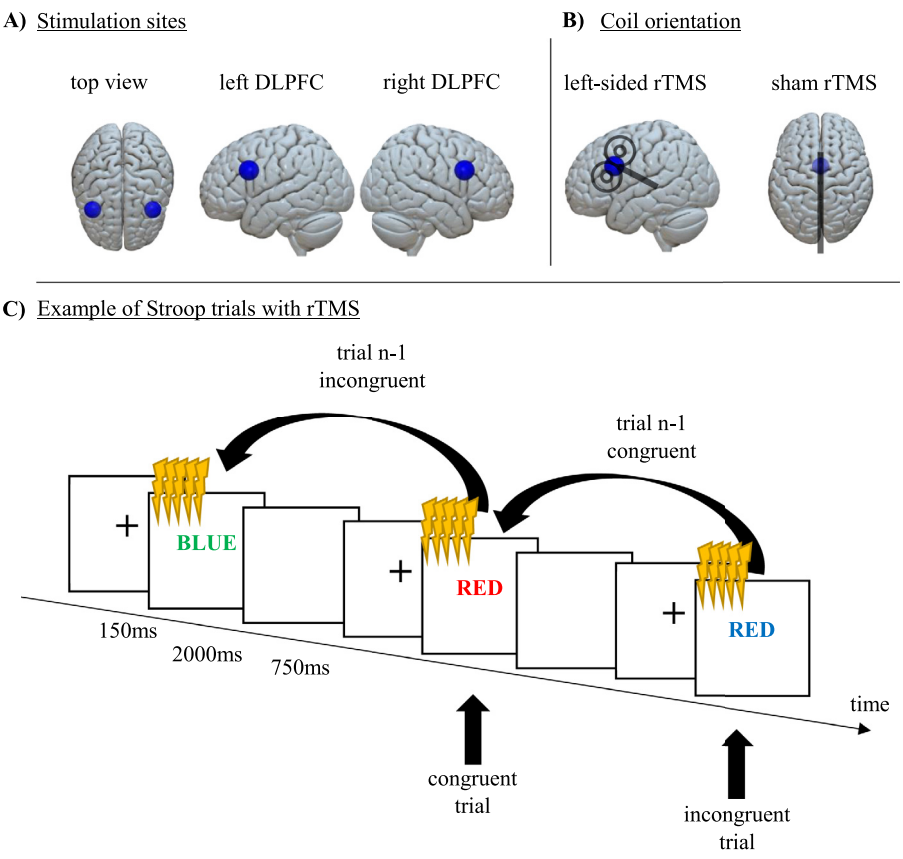

Fig. 1. Experimental Design. A) Stimulation sites for left and right DLPFC. Stimulation sites were mirrored across hemispheres (MNI; $x = \pm 42$, $y = 16$, $z = 28$). B) Coil orientation. The coil was positioned tangentially to the cortex and oriented 45° to the sagittal midline (orientation for left DLPFC displayed). During sham TMS, the coil was oriented at 90° over the vertex; note that the coil wings are not visible. **C)** Example of Stroop trials. In congruent trials, print color matches the word meaning, in incongruent trials, there is a mismatch between both. Lightning bolts depict the TMS pulses; five TMS pulses were applied at a frequency of 10 Hz at stimulus onset.

we expected that rTMS over the left DLPFC should increase the Stroop effect as measured by larger differences between congruent and incongruent trials in error rates and/or reaction times. In contrast, rTMS over the right DLPFC should result in a larger congruency sequence effect. Furthermore, in contrast to other studies, we used a verbal Stroop variant instead of a keypress version. Previous evidence revealed a compatibility effect of response modality and the ordinary processing route of the (ir)relevant stimuli, arguing that interference is increased if the normal processing route of the irrelevant dimension matches the normal response mode for the relevant dimension (MacLeod, 1991). Specifically, since words are processed to be spoken aloud and the required response is overt speech, stimulus-response compatibility is given and the irrelevant dimension (i.e. word meaning) interferes more strongly with the relevant stimulus dimension (i.e. word color).

2. Materials and methods

2.1. Sample

Twenty-five healthy, right-handed participants (12 female) aged 19 – 32 (mean age = 26.00 ± 4.80) were recruited for the study. All participants were native German speakers, had normal or corrected to normal vision and no prior neurological, psychiatric or cardiovascular disease. Written informed consent was obtained, the study protocol was in accordance with the guidelines of the Declaration of Helsinki and approved by the local ethics committee.

2.2. Experimental design and procedure

Each participant underwent three experimental sessions that varied in TMS site (right prefrontal vs. left prefrontal vs. sham stimulation over the vertex, Fig. 1A and B). After preparation and a practice block, each participant performed two experimental blocks of the Stroop task. Each session lasted approximately 2–3 h.[1] The individual resting motor threshold was determined in the first session. Sessions were separated by at least 7 days to prevent carry-over effects. The order of sessions was counterbalanced across participants to the best possible degree. Our design resulted in six possible stimulation sequences. We aimed to gather four participants per sequence and an additional participant for safety in case some data had to be excluded. Due to complications during data collection, three sequences were completed by four participants, two sequences by five participants and one sequence by three participants.

2.3. Task

In each trial, participants were asked to verbalize the print color of color words presented on a white computer screen (RGB values 215, 215, 215). The words ROT, BLAU, GRÜN, GELB (red, blue, green and yellow in German) were used as stimuli and presented using the font Times New Roman (font size 55). Thus, the letters were about 2.67cm high, with the German Umlaut "Ü" in "GRÜN (Green)" standing a bit taller. The viewing distance between the participant and the monitor was approximately 1 meter, leading to a visual angle of approximately 1.146°. Stimuli were presented either in green (RGB values 0, 128, 0), blue (RGB values 0, 0, 255), red (RGB values 255, 0, 0) or yellow (RGB values 255, 255, 0). In congruent trials, print color and word meaning corresponded, whereas in incongruent trials they did not (Fig. 1C). During the practice block, 12 congruent and 12 incongruent trials were presented. Afterwards, two experimental blocks followed with 60 congruent and 60 incongruent trials each. Thus, each participant had to perform 240 experimental Stroop trials in a single session. Each possible stimulus combination was presented equally often with an equal

[1] After the Stroop experiments a negative priming experiment was run in each session (Frings et al., 2015). This data is not reported here.

share of congruent and incongruent trials. More precisely, 120 congruent trials contained 30 trials each, where the color and the meaning matched (i.e. 30 trials where red/green/blue/yellow was printed in red/green/blue/yellow). We included twelve different color meaning x print color combinations, which resulted in incongruent trials. Consequently, each possible combination was presented ten times during 120 incongruent trials. All trials were presented in random order. Thus, each block contained a random order of 60 congruent and 60 incongruent (i.e. five trials for each of the possible twelve combinations) trials. A trial started with the presentation of the fixation cross for 1500 ms, followed by the presentation of the color-word stimulus for 2000 ms and a blank screen for 500 ms. With the onset of each color-word stimulus, a 10Hz rTMS train of five pulses was applied. Such a stimulation using short rTMS bursts perturbs processing in the area for several 100 milliseconds. Note that the duration of single word processing should last 300–500 ms (Bentin et al., 1999; Pylkkänen and Marantz, 2003) and our rTMS train was applied within this time frame. This was crucial because response selection and execution can only take place after the processing of the stimulus (Rangelov et al., 2012; Zehetleitner et al., 2012). Consequently, our rTMS train should impact stimulus processing rather than response selection. Stimuli were presented with Presentation software (Neurobehavioral Systems Inc., Berkley, CA) and response recording was performed via microphone (Rode NT55).

2.4. Repetitive transcranial magnetic stimulation (rTMS)

We used neuronavigated rTMS (TMS Navigator, Localite, Sankt Augustin, Germany) based on co-registered individual T1-weighted MRI images to navigate the TMS coil and maintain its exact location and orientation throughout all sessions. T1-weighted images were taken from the inhouse database or acquired at a 3-Tesla MRI (Siemens Healthcare, Germany) using a magnetization prepared rapid gradient echo (MPRAGE) sequence in sagittal orientation (MPRAGE; inversion time = 650 ms, repetition time = 300 ms, flip angle = 10°, field of view = 256 mm × 240 mm, voxel-size = 1 mm × 1 mm × 1.5 mm). TMS was performed using the average mean Montreal Neurological Institute (MNI) coordinates for the right DLPFC (right MFG, $x = 42$, $y = 16$, $z = 28$) and the left DLPFC (left MFG, $x = -42$, $y = 16$, $z = 28$) from previous fMRI studies and a meta-analysis (Laird et al., 2005; MacDonald et al., 2000; Nee et al., 2007; Niendam et al., 2012). Individual stimulation sites were obtained by using the inverse of the normalization procedure in SPM 8 (Welcome Trust Center for Neuroimaging, University College London, UK) and transforming the coordinates from standard MNI space to individual space for each participant in Matlab (The Mathworks, Inc., version 9.3). The vertex was determined as the midpoint between the lines connecting the nasion and inion and tragi of the left and right ear. During each experimental session, participants were co-registered to their structural T1. Stimulation intensity was set to 90% of a participant's individual resting motor threshold (RMT) as in our previous studies (Hartwigsen et al., 2015, Hartwigsen et al., 2010; Hartwigsen et al., 2010). RMT was defined as the lowest stimulation intensity producing a visible motor evoked potential of 50 μV (peak-to-peak amplitude) or greater in the relaxed first dorsal interosseus muscle in 5 out of 10 trials with single pulse TMS given over the motor hand area in the left primary motor cortex (Kaelin-Lang, 2007). The motor hot spot was determined functionally by estimating its position approximately 1 cm anterior and 4–5 cm lateral from the vertex (Kaelin-Lang, 2007) and starting with a fixed intensity of 50% total stimulator output. We additionally marked the anatomical M1 on the individual MRI. The coil position was adjusted until the optimal functional motor hotspot was located and stimulation intensity was gradually adapted during the individual motor threshold determination (see Hartwigsen et al., 2015 for a similar procedure). The coil was placed tangentially on the head with the handle pointing at 45° to the sagittal plane. RMT was determined in the first session and kept constant across all sessions to stimulate all targeted areas with the same intensity (for similar designs see Klaus and Hartwigsen, 2019; Kuhnke et al., 2017). We relied on the individual resting motor threshold obtained from the primary motor cortex because for cognitive areas, no measurable overt response like the motor evoked potential can be elicited and the use of the motor threshold can be considered as the standard procedure to calibrate stimulation intensity (Bergmann and Hartwigsen, 2020). The average stimulation intensity used for stimulation was 41.08 (SD = 6.78), thus the average RMT was approximately 45.64. A figure-of-eight-shaped coil (CB-60; double 60 mm) connected to a MagPro X100 stimulator (MagVenture, Denmark) was used in all rTMS conditions, and the overall application of TMS pulses was within recommended safety limits (Rossi et al., 2009; Rossini et al., 2015). During the individual session, the coil was held in place by the experimenter. Accurate coil positioning and maintenance was achieved with a neuronavigation system, which was placed behind the participant but visible for the experimenter. Participants were asked to lean against a custom-made headrest with the back of their head and avoid movements during the experiment. All participants tolerated this procedure and completed the whole experiment. Note that in case of discomfort we reduced the stimulation intensity by 1–2%. This did not result in significant differences between sessions. Facial muscle contraction did not interfere with the visual perception or verbalization of the stimuli, as the location of the stimulation target caused more lateral contractions, if any. For the sham condition, the coil was oriented parallel to the sagittal plan and placed across the vertex (Fig. 1B); a setup which has been used in previous TMS studies (e.g. Kuhnke et al., 2017). Importantly, the coil was tilted away from the head in the sham condition to avoid any effective stimulation of the underlying brain tissue.

3. Results

3.1. Data analysis

Naming latencies and error rates were measured using Praat software (Boersma and Weenink, 2018). Erroneous or missing responses were excluded from reaction time (RT) analysis. Overall participants performed 19,800 trials; the 1800 practice trials were excluded from the analysis, because during this time the participant was familiarized with the task and the rTMS procedure. Out of the remaining 18000 experimental trials only 54 errors were recorded. Due to the low number of errors (< 1% on average, range = 0–1.167%), error rates were not analyzed. RTs were analyzed using SPSS Statistics for Windows (version 26, SPSS INC., Chicago, USA). The congruency of trial n-1 and its interaction with the congruency of trial n is considered for analysis. Thus, if red printed in red follows blue printed in green, a congruent trial followed an incongruent one. Refer to Fig. 1C for a visual representation. All analysis includes a within-participants factor TMS condition with three levels (rDLPFC vs. lDLPFC vs. sham). Since repeated measures designs are inherently multivariate, MANOVAs were calculated. One advantage of using a MANOVA compared to a simple repeated-measures ANOVA is that while the univariate approach requires sphericity, the multivariate approach does not – the MANOVA can thus be regarded a more robust method. (for details on the use of MANOVA for repeated measures designs see Tabachnick and Fidell, 2012). However, before any TMS effects on behavior can be analyzed, first we had to establish a significant Stroop and congruence sequence effect. For the main results Bayesian follow-up analysis was conducted. In contrast to frequentist analysis, Bayesian statistics can generate evidence not only for the alternative hypothesis or the absence of it, but also for the null hypothesis (Keysers et al., 2020; Rouder et al., 2009).

3.2. Stroop reaction times

RTs were averaged across both Stroop blocks for each participant. The classical Stroop effect is based on the comparison of congruent and incongruent trials; typically performance is slower and worse in incongruent compared to congruent trials (MacLeod, 1991; Stroop, 1935).

Table 1
Mean correct response times in seconds for the different trial types (Stroop effect) and trial sequences (current and previous trial, Stroop congruency sequence effect) for all three TMS conditions. The reaction times were additionally split by block, regardless of the participant's individual session order. Standard deviations are given in brackets below. con = congruent; inc = incongruent; con-inc = congruent trial *n*-1 came before an incongruent trial n.

	Stroop effect		Stroop congruency sequence effect			
	congruent	incongruent	con-con	con-inc	inc-con	inc-inc
overall						
rDLPFC	0.715	0.789	0.692	0.795	0.718	0.785
	(0.155)	(0.143)	(0.121)	(0.120)	(0.128)	(0.117)
lDLPFC	0.711	0.779	0.694	0.765	0.710	0.770
	(0.159)	(0.152)	(0.151)	(0.147)	(0.159)	(0.153)
Sham	0.701	0.770	0.712	0.784	0.726	0.779
	(0.138)	(0.135)	(0.172)	(0.156)	(0.171)	(0.168)
block 1						
rDLPFC	0.701	0.774	0.686	0.793	0.709	0.777
	(0.152)	(0.139)	(0.126)	(0.117)	(0.124)	(0.113)
lDLPFC	0.699	0.769	0.682	0.757	0.698	0.756
	(0.151)	(0.148)	(0.144)	(0.146)	(0.151)	(0.151)
Sham	0.693	0.760	0.679	0.760	0.709	0.764
	(0.139)	(0.137)	(0.168)	(0.149)	(0.168)	(0.172)
block 2						
rDLPFC	0.792	0.804	0.698	0.797	0.727	0.794
	(0.162)	(0.154)	(0.122)	(0.126)	(0.137)	(0.127)
lDLPFC	0.723	0.790	0.706	0.773	0.721	0.783
	(0.169)	(0.159)	(0.161)	(0.150)	(0.168)	(0.159)
Sham	0.708	0.779	0.726	0.807	0.744	0.794
	(0.141)	(0.137)	(0.179)	(0.169)	(0.178)	(0.171)

The analysis of RTs was based on a 3 (TMS condition: rDLPFC vs. lDLPFC vs. sham) x 2 (trial type: congruent vs. incongruent) factorial repeated measures MANOVA. Analysis revealed a main effect of trial type ($F(1, 24) = 94.49$, $p < .0001$, $\eta_p^2 = .80$) reflecting a significant overall Stroop effect of approx. 70 milliseconds, with incongruent trials leading to significantly longer RTs compared to congruent ones (0.779 sec, SD = .193 vs. 0.709 sec, SD = .183). The overall Stroop effect was significantly different from 0 ($t(24) = 9.72$, $p < .0001$). Neither the main effect of TMS ($F(2, 23) = .55$, $p = .59$, $\eta_p^2 = .05$) nor the interaction of TMS x trial type ($F(2, 24) = .35$, $p = .70$, $\eta_p^2 = .03$) were significant. This suggests that TMS did not modulate the overall Stroop effect. Bayesian analysis revealed a Bayes Factor of $BF_{01} = 5.99$ in favor of the null hypothesis. This can be interpreted as moderate evidence in favor of the null hypothesis (Wagenmakers et al., 2018, 2011). Importantly, this pattern of results was identical in both experimental blocks and not influenced by the order of TMS application. In detail, when the Stroop effect itself was submitted to analysis, there was no significant two-way interaction of TMS condition x block ($F(2, 18) = 0.54$, $p = .59$, $\eta_p^2 = .058$), indicating that the Stroop effect was comparable across blocks. However, while there was an interaction of TMS condition x order for the Stroop effect ($F(10, 38) = 2.83$, $p < .05$, $\eta_p^2 = .43$), this effect was due to practice and a general performance increase over time. Accordingly, participants showed an average Stroop effect of 83 ms in their first and 62 ms in their third session. The main effect of block ($F(1, 19) = 0.002$, $p = .97$, $\eta_p^2 < .001$) and the main effect of order ($F(5, 19) = 1.54$, $p = .22$, $\eta_p^2 = .289$) were not significant. Furthermore, there was no significant interaction of TMS condition x block x order ($F(10, 38) = 0.89$, $p = .55$, $\eta_p^2 = .188$) for the Stroop effect. Please refer to Fig. 2A for the main results and Table 1 for the descriptive data.

3.3. Congruence sequence effect

RTs were averaged across both Stroop blocks for each participant. The first trial of each block was excluded. The analysis of RTs was based on a 3 (TMS condition: rDLPFC vs. lDLPFC vs. sham) x 2 (trial n: congruent vs. incongruent) x 2 (trial n-1: congruent vs. incongruent) factorial repeated measures MANOVA. The analysis revealed a main effect of trial n ($F(1, 24) = 10.90$, $p < .01$, $\eta_p^2 = .31$) as well as a main effect of trial n-1 ($F(1, 24) = 96.31$, $p < .0001$, $\eta_p^2 = .80$). This indicates the presence of a Stroop effect in trial n as well as the influence of congruency in trial n-1 on RTs in trial n. Crucially, the two-way interaction of trial n x trial n-1 was significant ($F(1, 24) = 34.12$, $p < .0001$, $\eta_p^2 = .59$), reflecting a significant congruency sequence effect. The main effect of TMS ($F(2, 23) = 0.54$, $p = .59$, $\eta_p^2 = .045$) and the two-way interaction of TMS x trial n ($F(2, 23) = 0.81$, $p = .46$, $\eta_p^2 = .066$) were not significant. There was a significant two-way interaction of trial n-1 x TMS ($F(2, 23) = 7.62$, $p < .01$, $\eta_p^2 = .40$) and a three-way interaction of trial n-1 x trial n x TMS ($F(2, 23) = 5.60$, $p < .05$, $\eta_p^2 = .33$). To decipher this latter interaction pattern, we computed the Stroop effect in trial n and entered it into a 3 (TMS: rDLPFC vs. lDLPFC vs. sham) x 2 (trial n-1: congruent vs. incongruent) repeated measures MANOVA. Helmert contrasts were used to specify the significant interaction. There was no difference between sham and lDLPFC TMS ($F(1, 24) = 1.17$, $p = .29$, $\eta_p^2 = .046$), but the average of those two conditions was significantly different from the rDLPFC TMS condition ($F(1, 24) = 9.37$, $p < .01$, $\eta_p^2 = .28$). This was confirmed using Bayesian analysis. Entering the difference in Stroop effects into a repeated-measures Bayesian ANOVA revealed an effect of TMS condition with a Bayes Factor in favor of the alternative hypothesis of $BF_{10} = 8.01$ when tested against the null model. Further testing revealed no significant difference between rTMS over the lDLPFC and sham rTMS ($BF_{10} = 0.36$; $BF_{01} = 2.81$). Taken together, Bayesian analysis indicated that rTMS over the rDLPFC significantly affected performance compared to lDLPFC stimulation or sham rTMS. Together, complementary evidence from both conventional ANOVAs and Bayes analyses show that the Stroop congruency sequence effect was significantly increased under rDLPFC TMS after congruent trials which can be traced back to increased RTs in incongruent trials after congruent ones. Importantly, this pattern of results was identical in both experimental blocks and did not interact with the order of TMS application. In detail, the previous analysis was repeated and the order of TMS sessions and blocks were added to the analysis. Results show that there was no interaction of TMS condition x trial n-1 x trial n with block ($F(2, 23) = 2.88$, $p = .08$, $\eta_p^2 = .20$) and no interaction with order ($F(10, 38) = 0.58$, $p = .82$, $\eta_p^2 = .13$). Please refer to Fig. 2B for a visualization of the main result and Table 1 for the descriptive data.

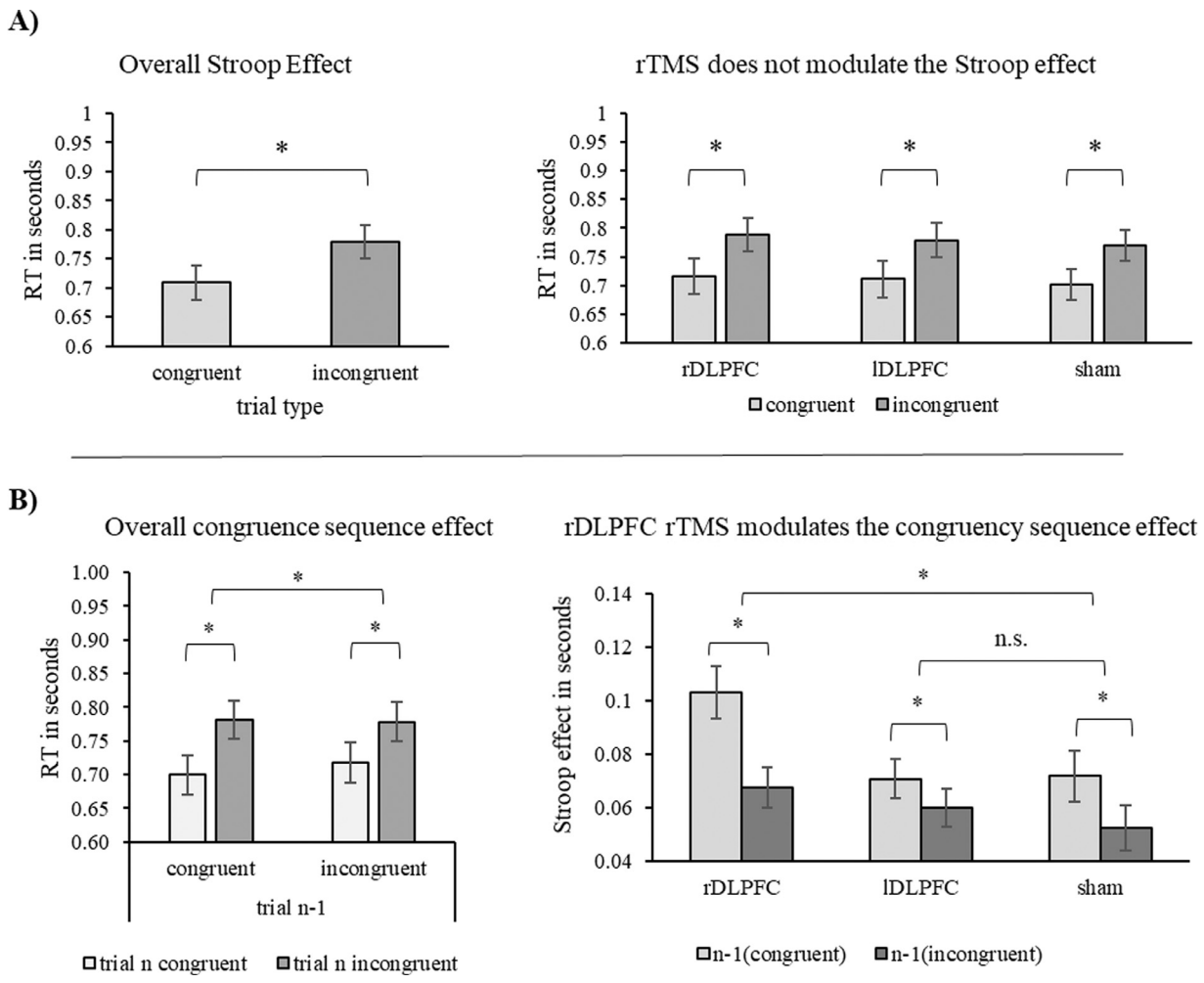

Fig. 2. Key results of the study. Error bars indicate the standard error of the mean. A) Significant behavioral Stroop effect (pooled across conditions). B) Significant congruency sequence effect and modulation of this effect for rTMS over the right DLPFC. The interaction was significant on a p-level of $p = 0.01$, $\eta_p^2 = .33$ (* $p < 0.05$).

4. Discussion

In this study, we probed the functional relevance of left and right dorsolateral prefrontal cortex for interference processing. As a main finding, we observed a process-specific disruption of adaptive control when focal perturbations induced by rTMS bursts were applied to the rDLPFC. Consequently, response times were significantly delayed with rTMS over the rDLPFC; specifically, the Stroop effect was larger after congruent trials. This effect was site-specific, as rTMS did not impair processing when applied to the lDLPFC. Process-specificity was also demonstrated since perturbation selectively interfered with the congruency sequence effect, without modulating the overall Stroop effect. These results provide first evidence for a key contribution of the rDLPFC to interference processing.

Adaptive control – as measured by the congruency sequence effect – refers to the dynamic adjustment of processing priority in response to changes in the environment (Braem et al., 2019; Braem and Egner, 2018). Our results hint at the causal involvement of the rDLPFC in this type of adaptive cognitive control, which conforms with existing neuroimaging results (Egner and Hirsch, 2005). These results support the notion that the rDLPFC is involved in cognitive control processing by shielding task-relevant processing against irrelevant distractors (Milham et al., 2001). Moreover, this region is associated with implementing top-down control after receiving input from the anterior cingulate cortex (Botvinick et al., 2004, 2001). Notably, in our study, the disruptive effect of rTMS over rDLPFC was selectively observed for the congruency sequence effect, pointing towards the impact of trial history. Congruent trials, which follow congruent ones benefit from a facilitation of irrelevant distractor processing, whereas incongruent trials following congruent ones have to overcome the momentary focus on the (unexpected) task-irrelevant dimension. The observed impairment of adaptive control in our study during rTMS over the rDLPFC reflects the difficulty to adapt an appropriate task strategy. Corresponding evidence comes from patients with rDLPFC damage, who have difficulties in developing appropriate response strategies (Cipolotti et al., 2016; Hornberger and Bertoux, 2015; Robinson et al., 2015). Furthermore, right PFC lesions have been associated with worse performance for incongruent Stroop trials (Stuss et al., 2001; Vendrell et al., 1995). These results have been interpreted as evidence for the involvement of the rDLPFC in attentional control. Our results extend these studies, showing that the deficit in adaptive interference control is tied to a specific cortical area within the PFC.

Our results show that the employed online rTMS protocol induced additional noise in the system (Siebner et al., 2009), thereby hindering the targeted area from adjusting processing priorities and suppressing distracting information. If a congruency sequence effect is observed, the information of the previous trial was actively held in working memory and retrieved in the present one. After incongruent trials, the Stroop effect is usually smaller because the cognitive system is already prepared for interference (and vice versa for congruent trials). This results from the fact that congruent trials are not associated with interference

and therefore do not result in the temporary up-regulation of cognitive control. Thus, the level of cognitive control is low in the following trials, leading to a larger Stroop interference effect. During online rTMS over the rDLPFC, we observed a significantly increased reaction time-based Stroop effect selectively after congruent trials. This might reflect the increased difficulty to bias the processing in favor of current task demands, when additional noise is induced through TMS. In a way, incongruent trials following congruent ones are particularly difficult to handle because they lack the temporal up-regulation of cognitive control after incongruent trials in addition to producing inherent interference. This might indicate that rTMS perturbance during this period is especially hard to compensate, which could also explain the lacking rTMS effect on the regular Stroop effect without consideration for trial sequences. Notably, our results show no significant differences between rTMS conditions for the Stroop effect after incongruent trials, likely reflecting the fact that the rTMS induced interference is limited to conditions, which require strong cognitive control. This would further stress the functional relevance of the rDLPFC for interference processing. This interpretation is in line with other theories suggesting that the rDLPFC is responsible for macro-level adjustments of cognitive control and converge with evidence of the rDLPFC being active after the initial conflict occurs (Blasi et al., 2006; Egner et al., 2008; Ukai et al., 2002; Vanderhasselt et al., 2009). The cortical amplification hypothesis suggests that in tasks where interference arises due to conflicting stimulus information, adaptive cognitive control is implemented by the rDLPFC and entails an attentional biasing towards the task-relevant information (Egner, 2008; Egner and Hirsch, 2005). Consequently, we propose that rTMS over the rDLPFC disrupted adaptive control by introducing additional noise to the information biasing process.

Together with the previous results by Muhle-Karbe et al. (2018), the present results findings may inform a framework of prefrontal adaptive control processes. We propose that while the left DLPFC is involved in anticipatory regulation of control, the right DLPFC is responsible for reactive control adjustments. The reliance on right DLPFC activity and the reactive adjustments is especially high when interference resolution is required in situations with low anticipatory control (i.e. when a congruent trial is followed by an incongruent one). Consequently, the right DLPFC has to select the correct response in the face of increased interference after the stimulus has already been processed. This would be in line with the notion that the left DLPFC is important for the conflict resolution itself, while the right DLPFC is responsible for response selection after the stimulus has been processed (Nee et al., 2007). However, while this framework of DLPFC lateralization can integrate the present and previous results (Muhle-Karbe et al., 2018), some specific assumptions remain to be tested. For example, a future chronometric study could address the time course of DLPFC engagement in both hemispheres. If the left DLPFC is responsible for a more proactive control adjustment and the right DLPFC acts more reactively, the disruptive TMS effect should depend on the timing of the stimulation.

A number of previous NIBS studies have looked at the involvement of left and right DLPFC in interference control. Yet, studies report inconsistent results for polarity-dependent tDCS or high-frequency offline TMS over the lDLPFC. NIBS can lead to better (Friehs et al., 2019; Vanderhasselt et al., 2006) or worse performance (Frings et al., 2018; Masina et al., 2018; Vanderhasselt et al., 2007; Zack et al., 2016) in tasks requiring interference control. In particular, for the Stroop task, it seems that applying high-frequency offline TMS over the lDLPFC can improve performance (Kim et al., 2012; Vanderhasselt et al., 2006), but similar protocols over the rDLPFC impair performance (Vanderhasselt et al., 2007). In contrast, continuous theta burst stimulation over neither the left or right DLPFC produced any modulation of the Stroop effect (Lowe et al., 2014; Tupak et al., 2013; Wagner et al., 2006). For example, Vanderhasselt et al. (2006) applied suprathreshold high-frequency offline rTMS over the lDLPFC to modulate performance in a keypress Stroop task. They report a general facilitation of response speed after rTMS, regardless of the trial type. Interestingly, the Stroop interference effect itself was not impacted by rTMS and the authors did not analyze trial sequence effects. Other studies examined the effect of high-frequency offline rTMS over the rDLPFC on verbal Stroop task performance. For instance, offline rTMS at 100% of the resting motor threshold over the rDLPFC did not interfere with the Stroop effect (Wagner et al., 2006). This is congruent with the observed absence of a modulation of the general Stroop effect by rTMS over the rDLPFC in our study. However, the congruency sequence effect was not analyzed in the previous studies and it thus remains unclear whether offline rTMS interfered with the trial history. We wish to emphasize that our study differs from the previous TMS studies discussed above in several aspects. Firstly, the use of short online rTMS bursts allowed us to target specific processes directly during task performance. Secondly, we used a verbal Stroop variant to increase the interference effect (MacLeod, 1991). Yet, the use of a verbal Stroop task might have influenced the results besides increasing the overall interference effect, since the left PFC in general has been associated with verbal processing (Liu et al., 2006; MacDonald et al., 2000). Consequently, we would have expected a significant modulation of the Stroop effect with TMS over the left DLPFC, which was not present in our results. To further solidify the present results, a comparison of response modalities in a future study is required. Nevertheless, we are confident that the main result of the present study should not be affected by response modality. Thirdly, we used a complete within-participant design, with each participant undergoing all three stimulation conditions. Fourthly, in contrast to previous work, our study used a relatively precise localization of the target areas based on individualized MNI-coordinates. The absence of any modulatory effects of rTMS over the rDLPFC in previous work might be partly explained by insufficient localization. Finally, to the best of our knowledge, our study represents the first comparison of the impact of online rTMS over the left and right DLPFC on adaptive control as measured by the congruency sequence effect in the Stroop task. In summary, our results provide novel insight into the role of the rDLPFC in interference control.

However, there is a potential alternative explanation for our results, since the right DLPFC has been shown to be involved in working memory processes (Barbey et al., 2013; Curtis and D'Esposito, 2003) and this area was stimulated in every trial (i.e. on trial n-1 and trial n). While we cannot completely rule out this alternative explanation, we believe that this explanation cannot account for the present results since the present results show that rTMS over the rDLPFC selectively affected performance *after a congruent trial,* pointing towards a strong specificity. Nevertheless, since we cannot answer this question conclusively, a future study might manipulate the stimulation timing during the task (i.e. stimulation of every second trial) to disentangle the differential contribution of TMS on trial n and n-1.

Additionally, the present task design has some shortcomings, because congruent stimuli were presented more frequently compared to the incongruent combinations. In detail, during a 120 trial block, the 60 congruent stimuli included 15 stimuli per one of four possible congruent color-word combination, whereas the 60 incongruent trials contained 12 different incongruent color-word combinations, which were each presented five times. Such a design can lead to contingency learning effects (Braem et al., 2019; Schmidt, 2013) and it is thus not completely clear which process was modulated by TMS over the right DLPFC. It is safe to conclude that our results provide evidence for an important role of the right DLPFC in cognitive control, although the exact process that were affected by our TMS intervention (e.g. learning, feature binding, feature overlap induced retrieval) are unclear (for a discussion see a recent framework by Frings et al., 2020). A future study should change the task to a 2 alternative force-choice design to disentangle these effects.

Furthermore, it should be noted that, contrary to our hypothesis, we did not observe any impact of left-hemispheric TMS on Stroop task performance. A possible explanation for the absence of disruption is that either the lDLPFC itself increased its activity to maintain a sufficient level of activity or the contribution of the contralateral, homologous region aided in fulfilling task demands, thereby compensating

for the TMS induced disruption (Hartwigsen, 2018). These explanations are not mutually exclusive and would be in line with previous neuroimaging studies demonstrating increased activation for the Stroop effect in both hemispheres, with a stronger upregulation of the lDLPFC being negatively related to the Stroop interference effect (Banich, 2009; MacDonald et al., 2000; Nee et al., 2007; Van Veen and Carter, 2005). Given the low stimulation intensity employed in our study (90% of the individual resting motor threshold) that was necessary to avoid unpleasant side effects of prefrontal stimulation (Hartwigsen et al., 2010), compensatory upregulation of either left or right DLPFC seems plausible. However, the present study cannot conclusively answer this question. To uncover potential compensation between homologous regions or other nodes in the network for interference control processing, future studies will have to combine TMS with fMRI. Indeed, some previous studies combining TMS and neuroimaging in a subsequent fashion have demonstrated that stimulation of the DLPFC modulates neuronal plasticity in a larger network. For example, stimulation of the right DLPFC changed functional connectivity between the target site and other network nodes during working memory and Flanker task performance (Bilek et al., 2013; Esslinger et al., 2014). Furthermore, a study combining TMS and positron emission tomography reported that after TMS over the right DLPFC, cerebral blood flow was increased in the stimulated area as well as in the ipsilateral, ventrolateral PFC (Eisenegger et al., 2008). However, only few studies investigated prefrontal interference control in a combined TMS-neuroimaging approach. One study did not find plastic after-effects of theta burst stimulation over the right IFG (Anderkova et al., 2018), while another reported bilateral decreases in cerebral blood flow after stimulation of the left DLPFC (Tupak et al., 2013). More evidence for TMS-induced short-term neuronal plasticity within the prefrontal cortex comes from research on speech and language processing (Hartwigsen, 2018; Hartwigsen et al., 2013). Such adaptive short-term plasticity may help to compensate for the disruption of neural key regions for specific processes (Hartwigsen, 2018) and may have prevented behavioral disruption after left DLPFC stimulation in our study. Notably, combined TMS-fMRI studies have further demonstrated strong remote effects in distant connected regions (Bestmann and Feredoes, 2013; Hallett et al., 2017; Ruff et al., 2009). For example, in a recent study, it was shown that TMS over the left DLPFC modulated activity in the anterior cingulate cortex (Vink et al., 2018). The functional relevance of such remote effects has also been demonstrated by combining offline TMS with fMRI (e.g. Hartwigsen et al., 2017). While remote inhibition could contribute to the disruptive effect of right DLPFC TMS, we believe that the observed effects are unlikely to be fully explained by inhibition of distant nodes because the strongest effect of online rTMS should be observed at the targeted region. Moreover, if disruption of the right DLPFC resulted in inhibition of the contralateral homologous region, then we would have expected even stronger impairment when directly targeting the left DLPFC.

In conclusion, we show for the first time that the right but not left DLPFC is causally relevant for the processing of the congruency sequence effect in the Stroop task. In congruent-incongruent trial pairs, the induced cognitive conflict is particularly high, which typically results in a higher overall interference effect after congruent trials. rTMS over the rDLPFC increased this sequence-modulated interference effect, which provides evidence for a crucial involvement of this region in adaptive, cognitive control, which is highly relevant for goal-oriented behavior.

Declaration of Competing Interest

The authors have no conflicts of interests to disclose.

Credit authorship contribution statement

Maximilian A. Friehs: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Data curation. **Jana Klaus:** Investigation, Software, Formal analysis, Writing - review & editing, Supervision. **Tarini Singh:** Software, Writing - review & editing. **Christian Frings:** Writing - review & editing, Supervision, Methodology. **Gesa Hartwigsen:** Writing - review & editing, Supervision, Resources, Funding acquisition, Methodology.

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