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The right dorsolateral prefrontal cortex prevents post-error slowing

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ABSTRACT

Adjusting behavior following the detection of inappropriate actions allows flexible adaptation to task demands and environmental contingencies during goal-directed behaviors. Post-error behavioral adjustments typically consist in adopting more cautious response mode, which manifests as a slowing down of response speed. Although converging evidence involves the dorsolateral prefrontal cortex (DLPFC) in post-error behavioral adjustment, whether and when the left or right DLPFC is critical for post-error slowing (PES), as well as the underlying brain mechanisms, remain highly debated. To resolve these issues, we used single-pulse transcranial magnetic stimulation in healthy human adults to disrupt the left or right DLPFC selectively at various delays within the 30-180ms interval following false alarms commission, while participants preformed a standard visual Go/NoGo task. PES significantly increased after TMS disruption of the right, but not the left DLPFC at 150ms post-FA response. We discuss these results in terms of an involvement of the right DLPFC in reducing the detrimental effects of error detection on subsequent behavioral performance, as opposed to implementing adaptative error-induced slowing down of response speed.

INTRODUCTION

Error detection is a fundamental cognitive control process that enables flexible and adaptative behaviors. Prominent models of cognitive control advocate the involvement of the anterior cingulate cortex (ACC) in performance monitoring during goal-directed behavior (Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007). Errors yield strong reinforcement learning signals within the dorsal ACC, which in turn connect to more lateral prefrontal regions in order to timely increase executive control and adjust behavior (e.g. Botvinick, Braver, Barch, Carter, & Cohen, 2001). Among these regulatory processes, post-error behavioral adjustment translates a systematic slowing down of response time to process stimuli immediately following response errors (i.e. post-error slowing, PES; Rabbit, 1966). PES mechanisms are assumed to decrease the probability of committing consecutive errors by decreasing the activity of motor areas. In turn, the amount of information observers have to accumulate before the response threshold is met increases and consequently false alarm rate decreases.

However, this assumption is challenged by evidence that PES is not systematically associated with an increase in accuracy as a switch to more careful response mode would predict (e.g. Hajcak & Simons, 2008). Alternative accounts posited that PES merely results from attentional modulations. Accordingly, PES would follow from the effort required to refocus attention to the task after the distraction effect generated by the occurrence of an unexpected event, i.e. a deviant response error (so -called “orienting account”; Notebaert et al., 2009).

Compelling human neuroimaging data document the involvement of dorsolateral prefrontal (DLPFC) areas in PES (e.g. Kerns et al., 2004). However, previous literature failed to arbitrate between the motor deactivation or attention orienting hypotheses, notably because DLPFC is either linked to modulation in motor cortices activity or in attention control (e.g. Aron, Robbins, & Poldrack, 2004).

Furthermore, whether the left or right DLPFC is preferentially associated with post-error behavioral adjustment, as well as the timing of DLPFC involvement in PES remains controversial (Fassbender et al., 2004).

To resolve these issues and to determine whether the relationship between DLPFC activity and PES is causal or correlative, we applied single-pulse transcranial magnetic stimulation (TMS) to transiently and focally disrupt DLPFC processing following false alarms during a standard visual Go/NoGo task. TMS was applied over either the Left or Right DLPFC at various delays post-FA commission. If DLPFC support post-error shifts to more cautious response mode, TMS disruption would primarily decrease PES. By contrast, if DLPFC is involved in attentional control and compensating distraction induced by the occurrence of an unexpected error (Notebaert et al., 2009), TMS should increase the magnitude of PES. To complement the TMS data, we assessed the dynamic of left and right DLPFC activity using electrical source analysis of event-related potentials to FAs from the data of Vocat, Pourtois, & Vuilleumier (2008), in which the same Go/NoGo paradigm was used.

MATERIAL AND METHODS

Participants

Ten right-handed (Oldfield, 1971) male volunteers aged 21-44 years (mean±SEM= 26.2±2.1) participated in this study. All subjects provided written, informed consent to participate in this study and completed a TMS safety questionnaire following standard practice (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). No participant had a history of psychiatric or neurological illness, or a relative who had epileptic seizures. The experiments were approved by the Ethics Committee of the Faculty of Biology and Medicine of University of Lausanne and conducted in accordance with the TMS guidelines established by Rossi et al. (2009).

Stimuli

Visual stimuli consisted of arrow symbols presented centrally on a white background and oriented either upward or downward (see Fig. 1).

Procedure and task

Participants sat in a sound attenuated booth in front of a 19” LCD screen with their head fixed by a stabilizing chin and forehead rest in a Magstim TMS chair and responded with their right hand using a response box. The paradigm was identical to Vocat et al. (2008). Each trial started with a black arrow (upright or inverted) presented during 1000–2000ms. The black arrow was then replaced by a green or turquoise arrow with either the same or the opposite orientation. The color arrow remained on the screen until the subject's response (on Go trials) or for a maximum of 1500ms (on NoGo trials). The inter-trial intervals (ITIs) included a blank screen of 500ms.

Participants were instructed to perform a speeded color plus orientation discrimination task. They had to press the response key as fast as possible if the black arrow turned green and kept the same orientation (Go trials) and to not respond if the black arrow either turned green but changed orientation, or if it turned turquoise irrespective of orientation.

The TMS experiment was divided into 6 sessions, each starting with a calibration block (containing 14 trials: 10 Go and 4 NoGo of each type), immediately followed by 2 consecutive testing blocks (containing 96 trials each: 64 Go and 32 NoGo of each type). Trial presentation was randomized within blocks. The whole experiment included 1236 trials and lasted about 90 min.

During each calibration block, the mean RT for Go trials was calculated online and used to define an upper limit for correct Go trials in the subsequent test blocks. Participants were never informed about this procedure. For the two subsequent blocks, this upper limit was updated and set to 90% of the mean RT. This procedure required participants to respond at least 10% faster on Go trials than their average response during the calibration phase. A feedback about response speed was provided during the test blocks (on Go trials) to implement speed pressure and eventually unlock the commission of FAs on NoGo trials (unforced errors).

Stimulus presentation and response recording were controlled using E-Prime 2.0 software.

Transcranial magnetic stimulation

During the completion of the visual Go/NoGo task, TMS was applied with a Magstim Rapid2 Transcranial Magnetic Stimulator via a High Power 90mm circular coil after participants committed either color or orientation FA. TMS was applied at six delays after the FA response, from 30 to 180ms with 30ms steps (Fig. 1). The stimulation threshold was defined individually as 110% of the individual motor threshold (Schlaak, Pascual-Leone, & Siebner, 2007). TMS was delivered to the left dorsolateral prefrontal cortex (L-DLPFC) during the completion of the first half of the experiment and to the right DLPFC (R-DLPFC) during the second half. This order was counterbalanced across participants (TMS to L-DLPFC then R-DLPFC or R-DLPFC then L-DLPFC). The coil placement on the left and right DLPFC was determined using the Beam F3 locator, localizing the position of the L-DLPFC or R-DLPFC based on the scalp position of the F3 or F4 electrode, respectively, of the 10-20 EEG system relative to individual skull measurements (Beam, Borckardt, Reeves, & George, 2009).

Electrical Sources Imaging

To complement the TMS data, we assessed the dynamic of DLPFC activity using electrical source analysis of event-related potentials to FAs from the data of Vocat et al (2008), in which the same Go/NoGo paradigm was used. We estimated the electrical sources in the brain using a distributed linear inverse solution and the local autoregressive average (LAURA) regularization approach (Grave de Peralta, Gonzalez-Andino, & Gomez-Gonzalez, 2004; also Michel et al., 2004 for a comparison of inverse solution methods). Lead field calculation was based on the

Spherical Model with Anatomical Constrains method (SMAC; Spinelli, Andino, Lantz, Seeck, & Michel, 2000). Intracranial sources were estimated for each participant over the 0 to 180ms time period and then statistically compared at each time-frame between left and right DLPFC region of interest as defined in the Automated Anatomical Labeling (AAL) space (Tzourio-Mazoyer et al., 2002) using t-tests. Temporal auto-correlation was corrected through the application of an >12 contiguous data-point temporal criterion (equivalent to >12ms for data acquired at 1024Hz) for the persistence of differential significant effects (Guthrie and Buchwald, 1991).

Behavioral Data Preprocessing

Only response times (RT) to Go stimuli following color and orientation FA within the range of ±2.5 SD from the individual mean RT for each block separately were included in the statistical analyses. The mean number of FA included in each condition was 10.19±0.21.

RESULTS

Our paradigm induced a high number of FAs on NoGo trials (mean±SEM: 47.96±3.92%), replicating the results of Vocat et al. (2008). However, only eight out of the ten participants showed enough (>4) FA to be included in the analysis for the 30, 120 and 150ms TMS condition. The rates of orientation or color FAs did not statistically differ (48.32±2.26% and 51.67±2.26%, respectively; $t(9)=-0.74$; $p=0.47$). In order to increase the number of datapoints per condition both FAs were averaged for further statistical analysis. There were only few omissions (Go trial with no response: 0.44±0.21%).

Mean response time (RT) to Go trials following responded Go trials was 272.99±6.40ms (Fig 2a). At the level of electrical sources, time wise t-test between left and right DLPFC activity revealed a significantly stronger engagement of R than L DLPFC 130 to 160ms post FA commission ($t(9) \geq 4.78$, $p \leq 0.002$; Fig. 2b).

RTs to Go trials following either color or orientation FA were averaged separately for each TMS site (Left or right DLPFC) and post-FA response TMS delay (30; 60; 90; 120; 150; 180), yielding 12 experimental conditions. The resulting values were submitted to a 2 by 6 repeated measure ANOVA with TMS Site and TMS Delay as within subject factors. This analysis revealed a significant main effect of TMS site ($F_{(1,9)} = 10.65$, $p = 0.017$), indicating that RT modulated differentially when TMS was applied to the left or right DLPFC. There was also a significant TMS delay ($F_{(1,9)} = 21.81$, $p = 0.044$), indicating that the delays at which the TMS was administered had differential effects on subsequent RTs. Due to a low statistical power (i.e. factor Delay has six level and the effects of TMS were highly specific to one delay, see below), the interaction term was not significant ($F_{(1,9)} = 3.50$, $p = 0.23$), although TMS had clearly a different impact depending on the side and the delay (see Fig. 2a).

We conducted a series of post-hoc contrasts which were planned a priori based on the results of the source estimation for a differential involvement of the L- and R- DLPFC over the 130-160 time period only. Paired t-tests between RT to Go stimuli following left vs. right DLPFC post-FA TMS stimulation for each delay showed that RT following FA were significantly slower following stimulation of the right than left DLPFC for the 150ms delay only (post-left TMS RT: 284.11±14.78ms; post-right TMS RT: 334.88±17.76ms; $t(7)=-2.56$; $p=0.038$; Fig. 2a). None of the other pairwise comparisons (left vs. right DLPFC for the 5 other delays) reached significance (all p-vals above 0.28).[1]

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[1] *There were too few FAs following FAs to support a reliable statistical assessment of the effects of TMS on accuracy in the Go/NoGo task.*

DISCUSSION

Transient TMS-induced disruption of the right DLPFC 150ms after the commission of FAs during a standard visual Go/NoGo task significantly increased (but not decreased) post-error slowing effect to subsequent Go stimuli. By contrast, TMS pulses applied at other post-FA delays and on the left DLPFC had no effect on post-error slowing, indicating a site-specific as well as interval-specific interference effect. Importantly, the TMS results were highly consistent with the electrical source analyses of evoked potential to FA commission (Vocat et al., 2008), revealing a significantly stronger engagement of the right than left DLPFC 150ms post-FA onset.

These TMS results challenge traditional views holding that PES effects primarily follow from adaptative mechanisms aiming at decreasing the probability of committing consecutive errors. Based on correlative functional evidence for associations between post-error DLPFC activity and PES, this brain region was thought to support the engagement of more conservative response modes by inducing a leftward shift of the speed-accuracy tradeoff, putatively mediated by decreasing motor activation (Kerns et al., 2004). According to this influential model, a disruption of DLPFC processing should primarily decrease PES by hampering the slowing down of RTs.

By contrast, here we show that transient single pulse TMS disruption of the right DLPFC increased PES, indicating an involvement of this area in reducing, but not increasing, PES effects. Accordingly, we assume that the right DLPFC implements mechanisms preventing the detrimental consequences of error detection on subsequent behavioral performance. This hypothesis is in line with the “orienting account” recently put forward by Notebaert and colleagues (2009) advancing that the post-error slowing down of response speed merely follows from an attentional capture of an unexpected, infrequent response error (see also Nunez Castellar, Kuhn, Fias, & Notebaert, 2010). The distraction of attention away from the task would lead to increased response time due to the need for refocusing to the task at hand. In keeping with this theoretical framework, our results suggest that the increase executive control mediated by the right DLPFC might support compensatory attentional mechanisms, and consequently that TMS of this region released PES effects. In other words, right DLPFC disruption at 150 ms following error commission might have increased PES by preventing participants to compensate for the attentional interference induced by the occurrence of distracting error trials.

That TMS disruption of the right but not left DLPFC modulated PES further supports an interpretation of our effects in terms of attentional orienting. In line with neuroimaging studies documenting a right hemispheric specialization in attention, the right but not left DLPFC has been involved in implementing top-down attentional control (Banich et al., 2000) and in updating and maintaining task-set (MacDonald, Cohen, Stenger, & Carter, 2000). Consistent with this view, lesion data reported that right but not left prefrontal damage has a reliable impact on the magnitude of post-error slowing (e.g. Molenberghs et al., 2009).

The precise timing of the TMS interference effect (150ms post-response onset) within the right DLPFC is also compatible with an orienting account of PES in our study. Right DLPFC disruption modulated PES when applied 150ms post-FA response, an interval corresponding to the peak latency of PES-related ERP components (error positivity, Pe; P3; Ridderinkoff, Ramautar, & Wijnen, 2009). These ERP deflections have been advanced to index attentional capture by new events (Friedman, Cycowicz, & Gaeta, 2001) and maintaining the attentional resources towards task-relevant stimulus (Polich, 2007). While no definitive conclusion on the underlying neural generators can be drawn based on the locus of electrode sites, it is worth mentioning that larger P3 amplitudes in right than left prefrontal areas have been linked to the processing of rare events in oddball tasks (Alexander et al., 1996), which would support the preferential implication of R-DLPFC in maintaining attention to the task.

Importantly, our TMS results for a right DLPFC involvement are strongly supported by the time-wise statistical analysis of DLPFC activity based on distributed electrical source estimations of event-related potential to FAs recorded from another cohort of healthy participants (Vocat et al., 2008) who completed the same Go/NoGo task. Our results reveal that the right DLPFC was more engaged than the left DLPFC 130-160ms post FAs onset, i.e. during the period when TMS had the most effective impact on PES.

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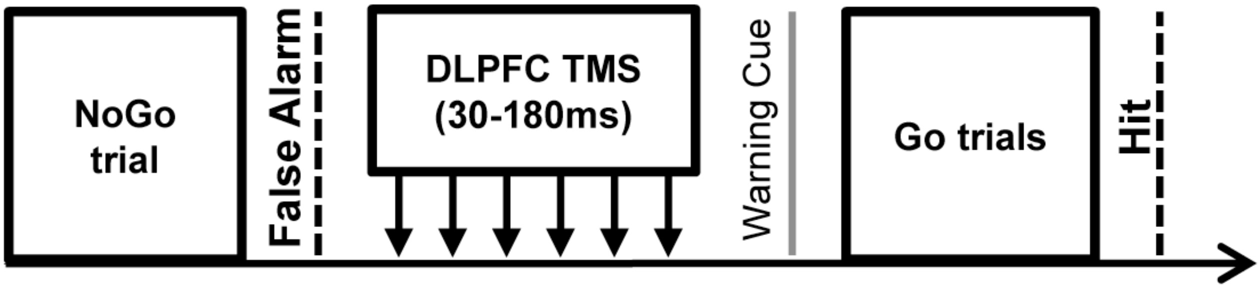
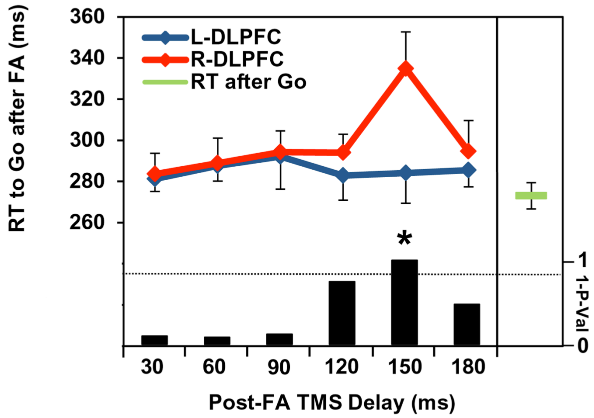


Fig.1

a. Behavioral Results



b. Distributed LAURA Electrical Sources

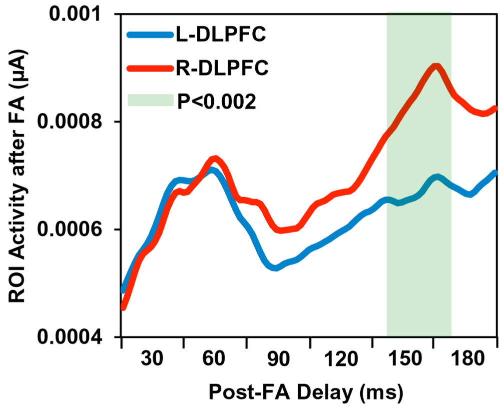


Fig. 2. a. & b.

Figure Legend

Fig. 1. Experimental design. Single transcranial magnetic stimulation (TMS) pulses were applied to the right or left dorsolateral prefrontal cortex (DLPFC) at six delays following the commission of false alarms (FAs). Post-error slowing effects were assessed by recording response time to responded go trials (Hits) following FA.

Fig. 2. **a**. Mean response time (RT) to Go trials following false alarms (FA) as a function of TMS site and delay. As compared to the left dorsolateral prefrontal cortex (DLPFC) cortex condition, only transcranial magnetic stimulation (TMS) of the right DLPFC significantly increased response time to go trials following false alarms (FA). 1-Pval of the left vs. right DLPFC condition for each TMS delay are indicated in black. The asterisk indicates a p-val < 0.04. The dotted line indicate the p<0.05 significance threshold. **b**. Distributed LAURA electrical source estimation of the left and right dorsolateral prefrontal cortex (DLPFC) after false alarm (FA) commission. Time-wise statistical comparison reveal significantly stronger activity within the right than left DLPFC activity 130-160ms post FA.