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Research Report

The functional relevance of right DLPFC and VMPFC in risk-taking behavior

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ABSTRACT

Background: The prefrontal cortex can be partialized in various anatomical and functional sub regions. Among those regions, both right dorsolateral prefrontal cortex (rDLPFC) and ventromedial prefrontal cortex (VMPFC) have been associated with risk-taking behavior based on neuroimaging studies. Noninvasive brain stimulation (NIBS) studies aiming at demonstrating the functional relevance of neural activity in these areas almost exclusively focused on the rDLPFC, where its experimental stimulation with a (generally) inhibitory protocol lead to a measurable increase in risk-taking behavior due to reduced cognitive control. The functional relevance of VMPFC in risk-taking behavior has not yet been addressed using NIBS, although multiple neuroimaging studies correlate this area's activity with valuation.

Objective/hypothesis: Here, we used NIBS to investigate the functional relevance of both, the rDLPFC and VMPFC in risk-taking behavior. We hypothesized that, compared to sham stimulation, VMPFC suppression leads to a reduction in risk-taking behavior by reducing the appeal to higher value options and consequently the attractiveness of riskier options, whereas rDLPFC suppression leads to an increase in risk taking, replicating previous findings.

Methods: We applied continuous theta burst stimulation (cTBS), a generally inhibitory protocol, to stimulate either VMPFC or DLPFC before the execution of the computerized Maastricht Gambling Task (MGT) in a within-subject design with 30 participants. The MGT allowed the analysis of potential brain region-specific effects of cTBS on risk-taking behavior such as participants' choices of average values, probabilities, and response time.

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Results: cTBS applied to either rDLPFC or VMPFC both led to an increase in risk-taking behavior and in the average value chosen as compared to sham transcranial magnetic stimulation. No effect on the choice of probabilities was found. A significant increase in response time was observed exclusively after suppressing rDLPFC. We speculate that these similar behavioral consequences following cTBS over DLPFC and VMPFC are likely due to the strong anatomical and functional interconnection between both brain regions.
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1. Introduction

The prefrontal cortex plays a fundamental role in high order cognitive processes, including attention, inhibitory control, decision-making and risk-taking behavior (Boggio et al., 2010; Kito, Hasegawa, & Koga, 2012; Rao, Korczykowski, Pluta, Hoang, & Detre, 2008). This region is partialized into different sub regions based on their cytoarchitecture, anatomical position or function (Carlén, 2017). Numerous imaging studies explored the relevance of these prefrontal sub regions, more specifically the dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex (VMPFC), in risk-taking behavior (Kuhnen & Knutson, 2005; Rao et al., 2008). There is currently an almost exclusive focus on the DLPFC when it comes to studying the functional relevance of prefrontal brain regions in risk-taking behavior. In contrast, systematic investigations of the functional relevance of VMPFC using NIBS, have not taken place, although neuroimaging studies repeatedly indicated that also this prefrontal area is activated during the execution and modulation of risk-taking behavior (Rudorf & Hare, 2014).

The DLPFC has been reported to be involved in self-control and executive control which directly links to risk taking behavior (Hutcherson, Plassmann, Gross, & Rangel, 2012). A number of studies using different techniques of noninvasive brain stimulation (NIBS) have successfully demonstrated that applying a (generally) inhibitory protocol to the DLPFC leads to increases in risk taking behavior, likely by the inhibition of self-control (Boggio et al., 2010; Fecteau, Pascual-Leone, et al., 2007; Koul, Soriano, Avenanti, Cavallo, & Becchio, 2019; Rao et al., 2008). A relevant example is the work of Knoch et al. (2006) where the experimental deactivation of the right DLPFC (rDLPFC) using 1 Hz repeated transcranial magnetic stimulation (TMS) caused significant increases in risk-taking behavior, whereas this was not the case after left DLPFC (lDLPFC) stimulation (Knoch et al., 2006).

Neuroimaging literature frequently linked VMPFC activation with valuation (Bartra, McGuire, & Kable, 2013; Chib, Rangel, Shimojo, & O'Doherty, 2009; Lim, O'Doherty, & Rangel, 2011), the calculation of each option's maximum expected utility (or expected value of reward). Valuation is a key component in the processing of risk. When faced with a risky choice, one integrates the available information and evaluates the presented options in terms of risk-benefit before choosing (Rudorf & Hare, 2014). This complex process, according to the economics literature, includes a calculation of an option's level of risk by considering both its probabilities of winning and its payoff (so the option's expected value) compared to the same aspects of the deferred option (Myerson, 2005). The greater the spread, thus the standard deviation, between winning and losing with the chosen option, the greater the risk of that option (Myerson, 2005).

Within this conceptualization of risk-taking behavior, the VMPFC's activation has been taken as a proxy for the value encoding component of decision-making under risk (Bartra et al., 2013; Chib et al., 2009). This assumption derives from previous studies correlating increases in VMPFC activity to the attribution of higher subjective value of presented options (Chib et al., 2009; D'Argembeau, 2013; Hiser & Koenigs, 2018). According to these findings, we may speculate that the suppression of VMPFC activity would cause a significant reduction in the subjective valuation of presented options and therefore reduce the attractiveness of riskier options with higher benefits.

However, to our knowledge no previous studies targeted the VMPFC with NIBS while directly studying risk-taking behavior. One reason may be the challenging anatomical position of VMPFC as compared to DLPFC, requiring TMS coils capable of stimulation slightly deeper regions in the brain. Only recent developments allowed the stimulation of deeper areas such as the VMPFC using double cone coil TMS technology (Roth, Zangen, & Hallett, 2002). With the use of a double cone coil, Cho et al. (2015) were able to target the VMPFC and demonstrated that after a protocol of 10 Hz repetitive TMS (rTMS), healthy participants displayed lower discounting rates in an intertemporal choices task (Cho et al., 2015). In a study including healthy participants with pathological gambling, neither 10 Hz rTMS to the VMPFC, nor continuous Theta Burst Stimulation (CTBS, an inhibitory protocol) to the DLPFC reduced participants' delay discounting (Zack et al., 2016). Nevertheless, significant reductions in bet size, game speed and subjective reinforcement were observed after DLPFC suppression only (Zack et al., 2016). Although these studies do not explore the stimulation's effect on risk-taking behavior directly, they did successfully investigate related phenomena and represent an important contribution to a better understanding of the functional relevance of VMPFC in decision-making (Cho et al., 2015; Zack et al., 2016).

Here we aimed at investigating the functional relevance of the rDLPFC and VMPFC in risk-taking behavior, with two main objectives. The first being the replication of Knoch et al.'s finding that inhibiting the DLPFC (i.e., self-control) increases risk taking behavior (Knoch et al., 2006), but with a cTBS rather than 1 Hz rTMS protocol.

The second objective is to evaluate the effects of suppressing the VMPFC with an inhibitory cTBS protocol on risk-taking behavior. To that end, we used the Maastricht Gambling Task (MGT) (Dantas, Sack, Bruggen, Jiao, & Schuhmann, 2021), which is a computerized task that elicits and measures risk-taking behavior. This task allows us to analyze potential brain region-specific effects of cTBS on risk-taking behavior, as well as additional measures of participants' choices under risk.

Risk-taking behavior is measured by the standard deviation of the chosen option, a measure of risk often used in the economics and finance literature, taking into account of the varying payoffs and probabilities. Additional measures of participants' choice pattern under risk include (1) expected value (sometimes called "bet decision" (Yazdi et al., 2019) or "betting behavior" (Clark, Bechara, Damasio, Aitken, & Sahakian, 2017)) and probability spread of the chosen option, and (2) response time.

We hypothesized that stimulating the rDLPFC with a generally inhibitory protocol leads to an increase in risk-taking behavior, due to a reduction in executive control, as previously found by Knoch et al. (2006). This effect should not be restricted to a specific aspect of risk-taking behavior since both the choice of probabilities and the average value choice would be in theory affected by a reduction in executive control.

We also hypothesized that stimulating the VMPFC with a generally inhibitory protocol leads to a reduction in average values chosen due to a lower subjective value of the presented options. This reduction of subjective value would therefore lower appeal to choose riskier options with higher payoff (Berkman, 2018; Hiser & Koenigs, 2018; Rudorf & Hare, 2014). Since our estimation of risk-taking behavior takes into account both the payoff values and the probabilities of each option offered, a significant reduction in average value would lead to a reduction in risk-taking behavior. Based on this rationale, the choice of probabilities would therefore not be affected by the VMPFC suppression.

2. Material and methods

2.1. Participants

We calculated our sample size using GPower (Universität Düsseldorf: G*Power, n.d.) using as reference the effect size obtained by Knoch et al. (2006) ($F(2,24) = 4.92$), which led to an aimed sample size of 30 participants. Thirty healthy, right-handed participants (18 females, mean age 25.4 years, range 19–44 years, SD = 6.04) participated in this study. All participants were members of the academic community of Maastricht University, had normal or corrected-to-normal vision and gave written informed consent after being introduced to the experiment. As part of the recruitment, participants were screened for TMS safety (Safety, Ethical Considerations, and Application Guidelines for the Use of Transcranial Magnetic Stimulation in Clinical Practice and Research, 2009). The study was approved by the Ethics Review Committee Psychology and Neuroscience (ERCPN) of Maastricht University, The Netherlands (ERCPN 188_07_02_2018). Participants were compensated based on the choices they made and luck in the risk-taking task in the form of vouchers with monetary value in the local commerce. Three participants reported discomfort during the stimulation and one of them reported headache after participation in session 1 and were therefore not invited to the following sessions. Their results were excluded from the analyses. We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.2. Task

To elicit and evaluate participants' risk-taking behavior and estimate their valuation and choice of probabilities, we used the Maastricht Gambling Task (MGT). This task is based on the Cambridge gambling Task (CGT) (Rogers et al., 1999), but controls for loss aversion, memory and wealth effects (Dantas et al., 2021). In the MGT, participants are asked to indicate the color of the box they believe that hides a token represented by a yellow X. They see six boxes which can be either pink or blue. The task presents independent trials in which the boxes distribution and payback offered to each option varies. The task consists of 2 repetitions of 125 unique trials, with all possible combinations of probabilities (1/6 pink and 5/6 blue to 5/6 pink and 1/6 blue) and rewards (5, 25, 50, 75 and 100 points). If the participant guesses the color that hides the token correctly, she wins the value assigned to that color. Otherwise, the participant gains zero points. Participants played the complete task twice in each session (before and after stimulation). Please refer to Dantas et al. (2021) for more details of the task.

For compensation, a random trial was selected by the participant and out of that outcome, each point gained in the task was converted to €0.1 in their final compensation to be paid by the end of the experiment. From the task we obtain four main dependent variables: risk, average value, probability scores and response time (exact calculations are presented in the Statistical analyses, section 2.5).

2.3. Procedure

In each session participants were asked to first fill in a pre-experimental check and sign a consent form confirming the absence of COVID-19 symptoms and recognizing being aware of the specific measures taken to guarantee safety from contamination, following Maastricht University's guidelines. They were then assigned to a randomized condition determining the order of stimulation.

Afterwards, the stimulations sites were determined according to the international 10–20 EEG system. To stimulate we located the coil above FpZ (VMPFC) and F4 (rDLPFC) F4. Sham stimulation was delivered either over FpZ or F4 (50% of the times in each location also in a randomized fashion). In the first session, the resting motor threshold (rMT) was determined.

Participants then received a task explanation and instructions, followed by 10 practice trials. In the sequence, they played five rounds of 50 trials each of the MGT. They then received the stimulation in the location determined according

to the protocol assigned for that day and immediately after, they played the MGT for a second time.

After playing the game twice, participants were asked to select a random number using an online random number generator and the selected number represented the trial that would be paid by the end of the experiment. We then reported the payoff obtained in that session and the participants were dismissed.

The same procedure was repeated in every session, during which participants received either VMPFC, rDLPFC or sham stimulation. By the end of the third session participants were compensated with €7.5 per hour of participation and the total gained with one random trial of the task per experimental session. After this, participants were debriefed.

2.4. Stimulation

In each session participants received either VMPFC, rDLPFC or sham stimulation immediately before the second repetition of the MGT. The stimulation position was determined using the international 10/20 EEG system, with FpZ as location for the VMPFC stimulation and F4 for rDLPFC stimulation. The sham stimulation position was randomly assigned and could be over FpZ or F4, with the coil flipped by 180°, meaning that no actual stimulation occurred in this condition.

Choosing an ideal control condition for TMS studies is difficult and which of the control conditions is the best to use is still under debate (Duecker & Sack, 2015; Loo et al., 2000). We chose to use a sham condition, during which we flipped the coil 180°. Hereby, participants are exposed to the same clicking sound, however they do not receive actual stimulation.

We used a continuous theta burst stimulation protocol (cTBS), composed by a continuous 40 sec train of 600 pulses, with short bursts (3 stimuli) of 50 Hz rTMS repeated at theta range (5 Hz) using a MagVenture ×100 stimulator (MagVenture A/S, Farum, Denmark).

To be able to reach the VMPFC we used a double cone coil (MagVenture Cool D-B80 MagVenture A/S, Farum, Denmark), which allows deeper stimulation (Cho et al., 2015). The coil was placed tangentially to the scalp with the handle pointing backwards, parallel to the midline.

Magnetic stimulation was applied at 100% individual resting motor threshold (mean stimulation intensity = 36.6% (±6.1 SD) of maximum stimulator output). The individual resting motor threshold was defined as the lowest stimulation intensity needed to elicit a visible contraction of the left abductor pollicis brevis (APB) in five out of ten pulses after stimulating the right motor cortex.

The simulation of the magnetic field for the stimulation protocol can be seen in Fig. 1, using SimNibs (Thielscher, Antunes, & Saturnino, 2015). We also ran a simulation to exclude a possible overlap between the stimulated areas in both active conditions, using a threshold of 1 V/m (Fig. 1C).

2.5. Statistical analyses

We focused on the four dependent variables obtained from the MGT (risk, value, probability scores and response time). To analyze risk, we estimated the standard deviation chosen in each trial, which takes into consideration both the probability of the chosen alternative and its payoff (Burke & Tobler, 2011; Dantas et al., 2021; Tobler, O'Doherty, Dolan, & Schultz, 2007). For each trial, participants can choose to bet on the color X (X = blue or pink), with probability p, a payoff of x and expected payoff E(X) of xp. The risk of this trial is therefore estimated by calculating the variance of payoffs from choosing color X in the trial i.

$$Var(X_i) = \sum p(x - E(X))^2 \quad (1)$$

The standard deviation is then calculated as the square root of the given variance, where:

$$Risk = SD = \sqrt{Var(X)} \quad (2)$$

Considering that this measure of risk is composed of distinct factors, we also look into the average values and probabilities chosen by participants. Average value is calculated by averaging the participants' choices of value across task repetitions. To estimate participants' choices of probabilities, similarly to what was done in previous studies (Fecteau, Knoch, et al., 2007; Knoch et al., 2006; Rogers et al., 1999), we attributed scores to the probabilities chosen. Probabilities below 50% (considered in previous studies as risky (Rogers et al., 1999)) received positive scores and probabilities above 50% receive negative scores. The probabilities chosen were then transformed into a scale ranging from −2 to 2, where −2 indicates a probability of 5/6 and 2 indicates a probability of 1/6.

Finally, response times were measured per trial in seconds, from the moment when the trial was displayed in the screen until the participants' responses. All dependent measures were obtained from the MGT and preprocessed for analyses using customized MATLAB scripts (MATLAB R2018b, 2018). Since participants responded to the exact same trial twice each time they played the game, we averaged these responses to consolidate our dataset, considering they presented 94% consistency across these repetitions. In total we have 750 observations per participant (125 unique trials × 2 blocks × 3 sessions), with a total of 22,500 observations.

The statistical analyses were done using customized R scripts (R Core team, 2015). We started the analyses by removing outliers, using custom R scripts to remove observations outside 1.5 times the interquartile range above the upper quartile and bellow the lower quartile (R Bloggers, 2011). No observations were excluded from the analyses of risk, valuation, or probability scores. 760 observations (of different participants) were excluded from the response time analyses as outliers, leaving 21,740 observations.

We then ran a series of linear mixed model analyses. All models included block (block 1 (before stimulation) or block 2 (after stimulation)), stimulation (sham, VMPFC and rDLPFC) and their interaction (block × stimulation) as factors. The variables were dummy-coded, whereby block 1, was coded as 0 (baseline) and block 2 was coded as 1. Sham was coded as 0 and hence presented the baseline to which a dummy variable for VMPFC and a dummy variable for rDLPFC were compared (please refer to the Appendices, section A.1).

Given the within subject experimental design, we used participant as a random factor. Each participant was exposed to 125 unique trials with different choice scenarios. Each of

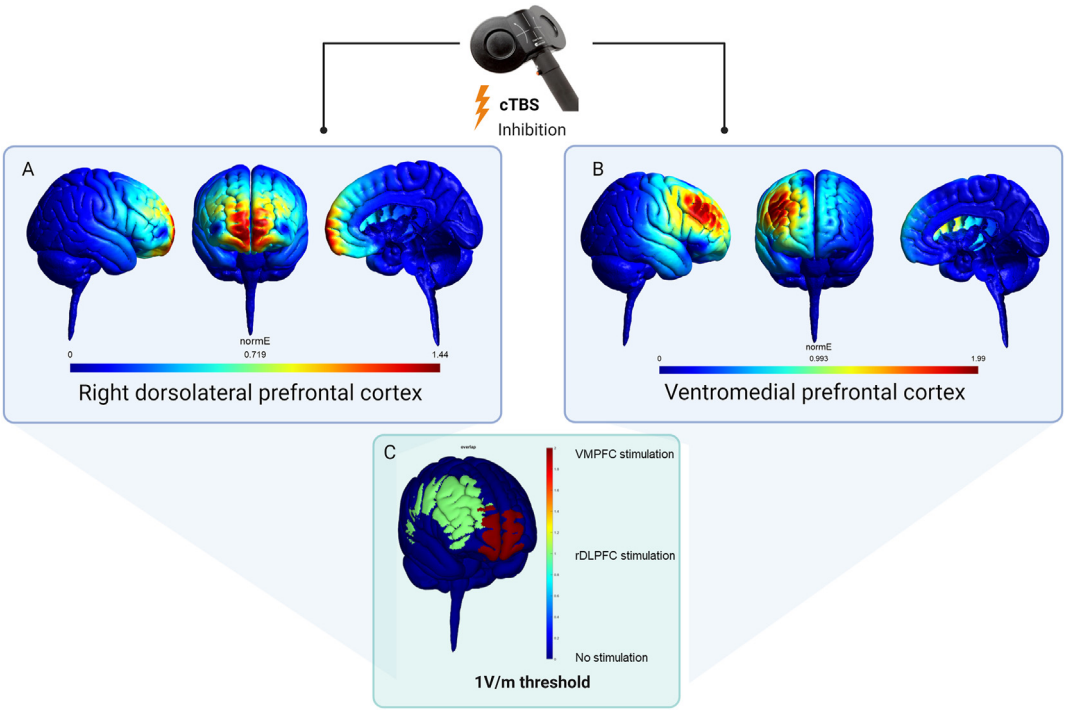

Fig. 1 – SimNibs simulations of the induced electric field for the active stimulation protocols. Simulation of the induced electric field using SIMNIBS (Thielscher et al., 2015) of VMPFC stimulation (A), rDLPFC stimulation (B) and a simulation of a possible overlap between the two stimulation protocols at a 1 V/m threshold (C), also produced using SIMNIBS (Thielscher et al., 2015).

these trials was coded in a variable named "Trial code". We used the combination of the participant and trial code as random intercept in our model, which captures individuals' baseline and accounts for individual differences to unique trials. Our model assumes that changes from this baseline are due to the factors included in the model as fixed effects and hence no random slope is included.

The effects of stimulation on risk, valuation and probability scores were estimated by fitting a linear mixed model estimated using reduced maximum likelihood (REML) and compound symmetry (CS) covariance structure. The analysis of the effects on response time used a first order autoregressive (AR1) covariance structure. To ensure transparency and reproducibility, all data and codes used for its analyses and task are available at https://data.mendeley.com/datasets/vwzz3dt3pf. No part of the study procedures or analyses was pre-registered prior to the research being conducted.

3. Results

3.1. *Risk-taking behavior*

Our results show a significant effect of the interaction block × stimulation, indicating an increase in risk-taking behavior after the suppression of both rDLPFC and VMPFC compared to sham, with a significant positive effect of block 2 × rDLPFC (beta = .46, t(23214) = 3.37, $p < .001$) and block2 × VMPFC (beta = .35, t(23214) = 2.52, $p = .01$) on risk-taking behavior. Although the rDLPFC suppression effect has a higher beta compared to the effects observed after VMPFC inhibition, the contrast between these two conditions is not significantly different (block2 × rDLPFC, beta = .12, t(15466) = .85, $p = .394$) (Fig. 2).

There was also a significant negative effect of block, indicating that overall, participants reduced their risk-taking behavior from the first (baseline, dummy coded as zero) to the second repetition of the task (beta = −.21, t(23214) = −2.21, $p = .012$) conditional on stimulation being Sham. There were no significant main effects of either rDLPFC (beta = −.16, t(23214) = −1.67, $p = .095$) nor VMPFC (beta = −.18, t(23214) = −1.90, $p = .057$) compared to sham in the first block.

3.2. *Valuation*

With respect to participants' average value chosen, the interaction of block 2 with both active stimulation protocols, rDLPFC suppression (block2 × rDLPFC, beta = .98, t(23214) = 3.16, $p = .002$) and VMPFC suppression (block2 × VMPFC, beta = .71, t(23214) = 2.29, $p = .022$) was positive and significant. This means that the average value chosen by participants after rDLPFC and VMPFC stimulation were significantly higher than after sham stimulation. The contrast between VMPFC and rDLPFC inhibition protocols is not significantly different (block2 × rDLPFC, beta = .27, t(15466) = .89, $p = .374$).

We also found a marginally significant negative effect of block with a reduction of average value from block 1 (baseline, dummy coded as zero) to block 2 (beta = −.43, t(23214) = −1.98, $p = .048$) conditional on stimulation being Sham. Hence we

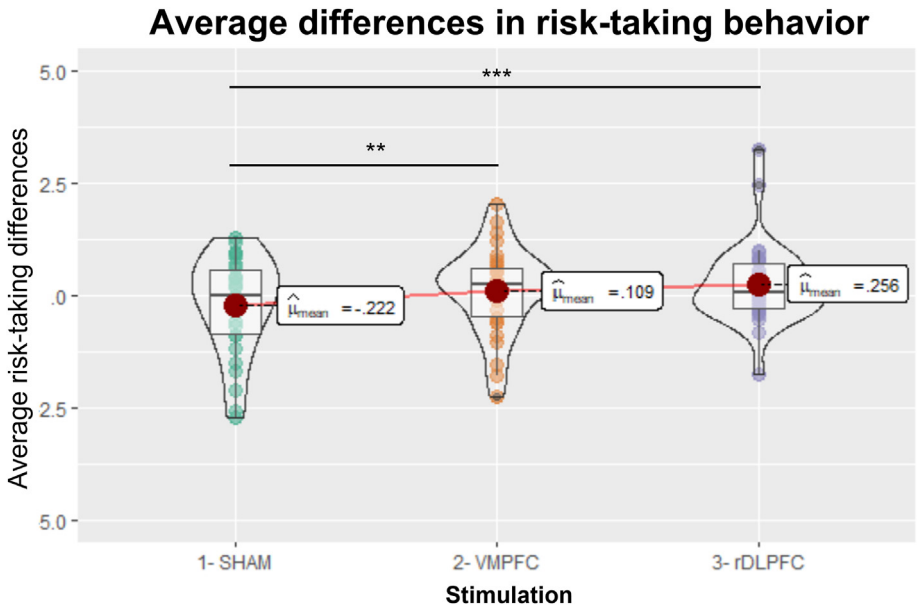

Fig. 2 – Average differences in risk-taking behavior ($n = 30$). Average differences in risk-taking estimated by the average standard deviation of each participant's choice across stimulation conditions (Sham in green, VMPFC in orange, and rDLPFC in purple) and contrasting the results obtained after stimulation from before it (Block 2 – Block 1). Dark red marks indicate the mean risk per condition. *$p < .05$; **$p < .01$; ***$p < .001$.

observed a reduction in average value chosen between the first and second repetition of the task in the sham condition (Fig. 3).

3.3. *Probability choices*

When analyzing the average probability choices obtained before and after the stimulation protocols, we found no significant effects of either the interaction of block 2 with the rDLPFC ($p = .99$) or the VMPFC stimulation ($p = .95$), meaning that there was no significant effect of the stimulation protocols.

3.4. *Response time*

The analyses of participants' response times indicated that participants were overall significantly faster in the second

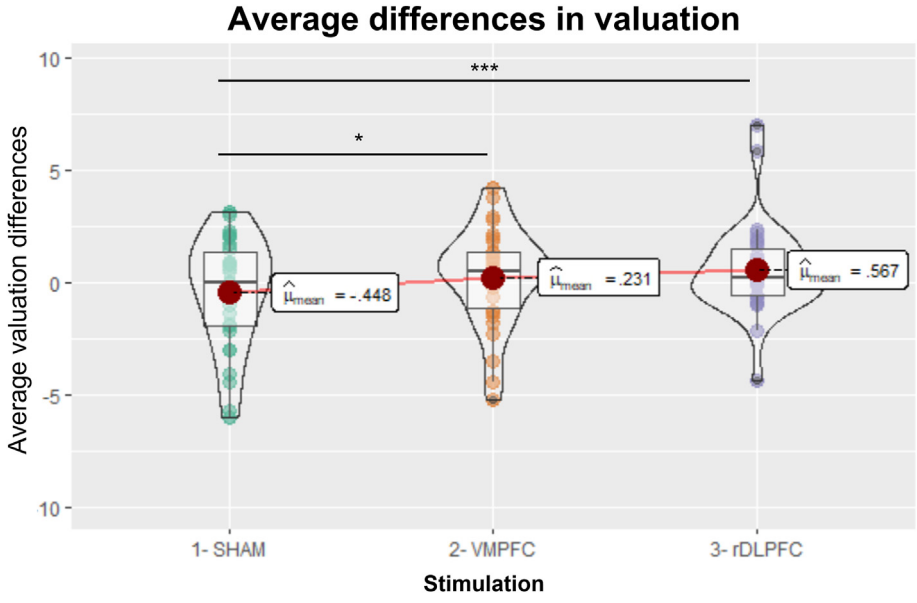

Fig. 3 – Average differences in valuation ($n = 30$). Average differences in valuation estimated by the average value chosen by participants across stimulation conditions (Sham in green, VMPFC in orange, and rDLPFC in purple) and contrasting the results obtained after stimulation from before it (Block 2 – Block 1). Dark red marks indicate the mean risk per condition. *$p < .05$; **$p < .01$; ***$p < .001$.

repetition of the task with a significant negative effect of block, comparing block 1 to block 2 (beta = −.06, t(21704) = −12.32, $p < .001$). We also found a significant positive effect of the interaction between block 2 and the rDLPFC stimulation (beta = .01, t(21704) = 2.17, $p = .03$). Albeit not significant, the interaction between block2 and VMPFC stimulation led to a decrease in response time (beta = −.009, t(21704) = −1.32, $p = .188$). These results indicate that rDLPFC stimulation (but not VMPFC or the sham stimulation) led to a significant increase in response time (Fig. 4).

4. Discussion

Here, we aimed at using cTBS to investigate the functional relevance of two important prefrontal brain regions, the rDLPFC and the VMPFC, in risk-taking behavior, during the execution of the computerized MGT. Regarding the rDLPFC stimulation, we aimed at replicating the findings of Knoch et al. (2006) by stimulating this area with an inhibitory protocol expecting to significantly increase risk-taking behavior. However, rather than using a 10 Hz rTMS protocol (Knoch et al., 2006), a cTBS protocol was adopted to reach such suppression with a shorter stimulation time. Our results show a successful replication of their findings, with a significant increase of risk-taking behavior after the cTBS-induced rDLPFC suppression.

Our second objective was to investigate the functional relevance of the VMPFC in risk-taking behavior. Recent TMS coil developments allow greater stimulation depth with the use of double-cone coils, making stimulation of deeper-lying areas, such as the VMPFC possible (Cho et al., 2015). We hypothesized that, compared to sham stimulation, VMPFC suppression would lead to a reduction in risk-taking behavior by reducing the appeal to riskier options with higher pay off. Contrary to our initial hypothesis, our results indicate that VMPFC suppression also leads to a significant increase in risk-taking behavior, although a greater effect size was observed after rDLPFC suppression.

The MGT allowed us to analyze potential brain region-specific effects of cTBS on risk-taking behavior such as participants' average probability choices, average values, and response time after both rDLPFC and VMPFC stimulation. Our results indicate a significant increase in average value choices after both protocols, while no significant changes in probability choices were observed after either.

It is interesting to observe that the effects of both stimulation protocols on risk-taking behavior were driven by participants' valuation processing, and no significant effects were observed in their probability choices. This means that, considering that risk-taking behavior is estimated by calculating the standard deviation of the participant's choice, which takes into account both the option probability and payoff (see Eqs. (1) and (2) in the statistical analyses, section 2.5) (Myerson, 2005), a significant change in risk-taking behavior would be driven by one of these factors or an interaction between them. Hence, once there is no significant change in the probability scores, the significant increase in risk-taking behavior observed must be attributed to the significant increase in average value choices.

The finding that both VMPFC and rDLPFC suppression led to an increase in the average value choices and hence risk-taking behavior, with a stronger effect for the rDLPFC suppression, indicates that the VMPFC may not the only area responsible for valuation processing. A more feasible explanation, according to our findings, would be a network processing involving both the VMPFC and the DLPFC to evaluate options and modulate risk-taking behavior.

The similar results regarding risk-taking behavior and average choice of values obtained after the stimulation of the

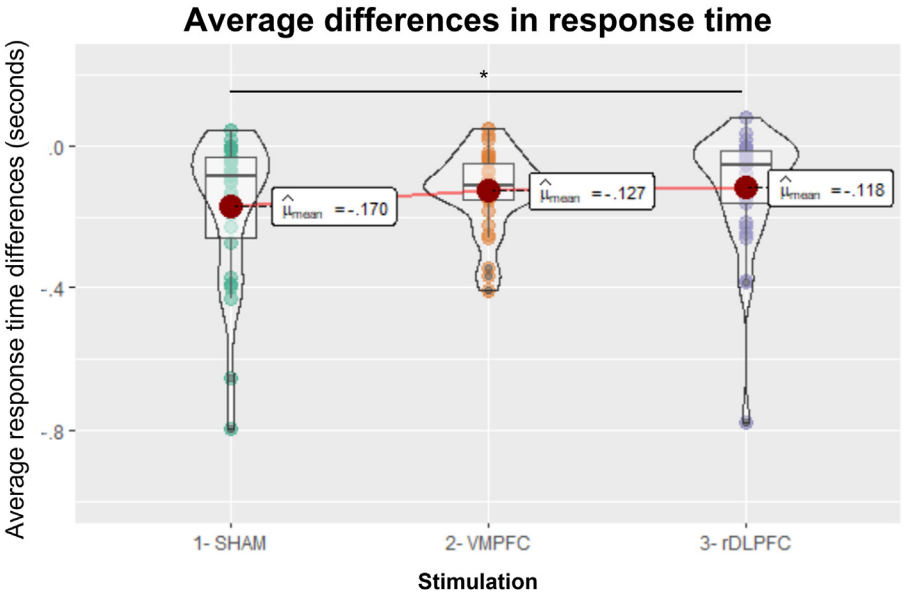

Fig. 4 − Average differences in response time ($n = 30$). Average differences in response time estimated across stimulation conditions (Sham in green, VMPFC in orange, and rDLPFC in purple) and contrasting the results obtained after stimulation from before it (Block 2 − Block 1). Dark red marks indicate the mean risk per condition. *$p < .05$; **$p < .01$; ***$p < .001$.

rDLPFC and VMPFC are also maybe not that surprising. These two areas are known to have a strong association considering their strong anatomical connectivity (Ghashghaei & Barbas, 2002). At least in the conditions of our study, it does not seem to be possible to fully dissociate the activity of the rDLPFC and VMPFC regarding risk-taking behavior and value choices using a repetitive inhibitory cTBS protocol. Our findings are in line with the results of Rudorf and Hare (2014), who demonstrated an interplay between the rDLPFC and the VMPFC during valuation in different contexts. According to the authors, varying choice contexts require more executive control for proper adjustment (Rudorf & Hare, 2014). An example of such variation is presented during the MGT, in which each trial brings different probabilities and payoffs with varying risk levels which can be more or less challenging, demanding adjustment and therefore more executive control.

Our findings are also in line with the assumption of Fecteau, Knoch, et al. (2007) that the DLPFC suppression would also affect the VMPFC and vice-versa due to their strong connectivity (Fecteau, Knoch, et al., 2007). The strong functional interplay between these two areas has been reported in several studies, for example, in the context of depression treatment (Dunlop, Hanlon, & Downar, 2017), emotional regulation in bipolar disorder (Ladouceur et al., 2011) and during self-control in healthy participants. For example, Hare, Camerer, and Rangel (2009) demonstrated the correlation between self-control during a choice task and the functional connectivity between DLPFC and VMPFC using fMRI (Hare et al., 2009).

Another possible explanation for the similar results obtained after both rDLPFC and VMPFC stimulation would be an overlap of stimulated areas. TMS is known as the NIBS method that offers greater focality. Nevertheless, considering our objective of reaching the VMPFC with our stimulation protocol, we opted for a double cone coil, which grants greater depth of stimulation (MagVenture, n.d.-b). However, this coil design offers lower focality compared to a traditional figure-of-eight coil (MagVenture, n.d.-a). To check for the possibility of stimulation overlap, we ran a simulation of the stimulated areas, with SimNibs (Thielscher et al., 2015), using a threshold of 1 V/m. The results, presented in Fig. 1 show no significant overlap, meaning that this is an unlikely explanation.

Interestingly, and confirming the independent stimulation of each area, we found a region exclusive significant increase in response time after rDLPFC suppression but not after VMPFC or sham stimulation, excluding the overlap hypothesis. Albeit not significant, the VMPFC stimulation led to a decrease in response time. These findings represent behavioral evidence for the independent stimulation of these two areas since the increase of response time observed after rDLPFC stimulation is exclusive to this condition. This increase in response time might be attributed to varied factors. Higher response times are frequently associated with longer deliberation times, while shorter response times are commonly correlated with impulsivity and anxiety (Rubinstein, 2013). Considering the role of the DLPFC on executive control, we cannot attribute the observed increase in response time after the suppression of the rDLPFC to increased deliberation. However, it is possible that the temporary disruption of the rDLPFC, leads to the recruitment of other brain areas such as the left DLPFC or even the VMPFC itself, yielding higher response times. Nevertheless, this mechanism can only be speculated at this point and still needs to be explored for example by using a combination of NIBS and neuroimaging techniques.

Potential clinical applications emerge from these findings. Abnormal risk-taking behavior is a symptom and a diagnostic criterion in a variety of neural and psychological disorders including gambling disorder, addiction, binge eating, bipolar disorder, attention-deficit/hyperactivity disorder (ADHD), and frontotemporal dementia (Dekkers et al., 2020; Giorgetta et al., 2012; Manoochehri & Huey, 2012; Pettorruso et al., 2021; Pettorruso Giovanni Martinotti et al., 2020; Reddy et al., 2013). Therefore, clarifying the underlying neural mechanisms of risk-taking behavior allows the development of more efficient treatment techniques. Using prefrontal TMS as therapeutic tool in the treatment or symptom management of patients with abnormal risk-taking is in line with previous findings (Pettorruso et al., 2021).

Decision-making under risk strongly affects people's health and wellbeing. In a clinical context, risk taking might even play a vital role, for example in suicidal ideation. TMS been applied in various clinical studies where the rates of suicidal ideation among participants with major depression disorder could significantly be reduced through prefrontal TMS (Croarkin et al., 2018; Cui et al., 2022; Weissman et al., 2018). Yet, these hypothesis and clinical applications still have to be explored in further studies.

As discussed, we found an increase in risk-taking behavior after both rDLPFC and VMPFC stimulation. A possible explanation for this could be that the results we see are caused by unspecific side effects of brain stimulation such as pain and/or unpleasantness. What in our perspective, however, speaks against this interpretation is the fact that we used a so-called TMS offline design, meaning that brain stimulation was applied outside the execution of the behavioral task. It is therefore rather unlikely that any potential unpleasant sensation during stimulation would affect task performance measures several minutes after stimulation has terminated. In addition, although risk taking behavior indeed increased after both, DLPFC and VMPFC stimulation, we also found differential effects between both brain regions with regard to response times, with an increase in response time only after rDLPFC stimulation and not after VMPFC stimulation. Therefore, we can conclude that the observed results are indeed due to strong interconnection between both VMPFC and rDLPFC that interact actively during the modulation of risk-taking behavior.

5. Conclusions

In conclusion, we here demonstrate a functional role of both, the rDLPFC and VMPFC in risk-taking behavior. We showed an increase in risk-taking behavior after right DLPFC cTBS, which replicates previous findings (Knoch et al., 2006). We also showed that cTBS applied over VMPFC also leads to increases in risk-taking behavior. Our results indicate that the increase in risky choices after stimulating both areas are likely due to

increases in average valuation, contradicting theories that attribute valuation processing solely to the VMPFC. The study contributes to a better understanding of the underlying neural mechanisms of risk-taking behavior and the functional relevance of the VMPFC within this network, and expands the knowledge on the interconnection between rDLPFC and VMPFC.

Open practices

The study in this article earned Open Data and Open Materials badges for transparent practices. Materials and data for the study are available at: https://10.17632/vwzz3dt3pf.1.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendices

A.1 Variables coding

Table A.1. Block coding:

Block	Code
Before stimulation	0
After stimulation	1

Table A.2. Stimulation condition coding:

Stimulation condition	Code
Sham	0
VMPFC	1
rDLPFC	2

A.2 Results tables

Table A.3. Risk-taking behavior

	Value	Std.Error	DF	t-value	*p*-value
(Intercept)	26.25	.35	23214	75.31	.000
Block 2	−.21	.10	23214	−2.21	.027
VMPFC	−.18	.10	23214	−1.90	.057
rDLPFC	−.16	.10	23214	−1.67	.095
Block 2 × VMPFC	.35	.14	23214	2.52	.012
Block 2 × rDLPFC	.46	.14	23214	3.37	.001

Table A.4. Average value choices

	Value	Std. error	DF	t-value	*p*-value
(Intercept)	59.53	.78	23214	76.36	.000
Block 2	−.43	.22	23214	−1.98	.048
VMPFC	−.36	.22	23214	−1.64	.101
rDLPFC	−.31	.22	23214	−1.40	.163
Block 2 × VMPFC	.71	.31	23214	2.29	.022
Block 2 × rDLPFC	.98	.31	23214	3.16	.002

Table A.5. Probability choices

	Value	Std. error	DF	t-value	*p*-value
(Intercept)	−.92	.03	23214	−33.00	.000
Block 2	.01	.01	23214	.67	.506
VMPFC	.00	.01	23214	−.05	.962
rDLPFC	.00	.01	23214	.31	.757
Block 2 × VMPFC	.00	.02	23214	−.07	.946
Block 2 × rDLPFC	.00	.02	23214	.02	.987

Table A.6 - Response time

	Value	Std. error	DF	t-value	*p*-value
(Intercept)	.86	.02	21704	35.43	.000
Block 2	−.06	.00	21704	−12.32	.000
VMPFC	−.03	.01	21704	−5.03	.000
rDLPFC	−.02	.01	21704	−3.30	.001
Block 2 × VMPFC	−.01	.01	21704	−1.32	.188
Block 2 × rDLPFC	.01	.01	21704	2.17	.030

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