Diminished Risk-Aversion After Right DLPFC Stimulation: Effects of rTMS on a Risky Ball Throwing Task

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(RECEIVED March 8, 2018; FINAL REVISION August 30, 2018; ACCEPTED September 4, 2018; FIRST PUBLISHED ONLINE December 6, 2018)

Abstract

Objectives: Several studies on human risk taking and risk aversion have reported the involvement of the dorsolateral prefrontal cortex (DLPFC). Yet, current knowledge of the neural mechanisms of risk-related decision making is not conclusive, mainly relying on studies using non-motor tasks. Here we examine how modulation of DLPFC activity by repetitive transcranial magnetic stimulation (rTMS) affects risk-taking behavior during a motor response task. **Methods:** One-Hertz rTMS to the right DLPFC was applied to monitor risk-taking and risk-aversion performance during a goal-directed risky task with motor response. Healthy participants were instructed to aim for a high score by throwing a ball as close to the ceiling as possible, while avoiding touching the ceiling with the ball. **Results:** One-Hertz rTMS stimulation. **Conclusions:** Our results suggest that the right DLPFC is a valid target for manipulating risky behavior in tasks with a motor-response. Following rTMS stimulation participants' preference shifts toward immediate awards, while becoming significantly less sensitive to potential negative consequences. The results confirm that the right DLPFC is involved in impulse control in goal-directed executive tasks. (*JINS*, 2019, *25*, 72–78)

Keywords: Dorsolateral prefrontal cortex, DLPFC, Repetitive transcranial magnetic stimulation, Executive functions, Risk taking, Risk aversion, Decision making

INTRODUCTION

Weighing risks and benefits in complex decision-making situations while keeping the end goal in mind, likely involves the prefrontal cortex (PFC; Bechara, Damasio, Damasio, & Anderson, 1994). Namely the dorsolateral part of the PFC (DLPFC) appears to play a prominent role in executive control, goal maintenance, and impulse inhibition (Fuster, 1991; Miller & Cohen, 2001), keeping a focus on long term consequences of options of choice (Hutcherson, Plassmann, Gross, & Rangel, 2012). Several theories specifically emphasize the role of the DLPFC in active value-related, win/loss situations, where adaptive strategy execution is needed for maximizing gains (Camus et al., 2009; Manes et al., 2002).

Performing the Balloon Analogue Risk Task (BART), a computerized risk-taking task, triggers a significant bilateral DLPFC activation in active win/loss situations, whereas no or minimal activation is seen in passive modes (Rao, Korczy-kowski, Pluta, Hoang, & Detre, 2008). Accordingly, patients

with DLPFC lesions demonstrate impairments in making optimal choices in risky situations (Fellows & Farah, 2003; Manes et al., 2002).

Treatment and intervention practices for decreasing adaptive vulnerability in cases of increased chances of behavioral risk-taking resulting from neurological or neuropsychiatric pathology can be successfully developed if we learn how DLPFC functionality can be reliably manipulated. Noninvasive methods of manipulation with PFC functionality have become one of the promising venues of treatment and rehabilitation. However, findings from direct or alternating current stimulation of DLPFC aimed at manipulation of risk-involving behavior have remained inconclusive, delivering mixed results regarding lateralization of function and the role of motivational involvement (e.g., Pripfl, Neumann, Köhler, & Lamm, 2013; Sela, Kilim, & Lavidor, 2012). Research on noninvasive intervention methods of functionality manipulation can benefit also from application of different methods such as transcranial magnetic stimulation (TMS). The aim of the present study was to use repetitive transcranial magnetic stimulation (rTMS) in combination with a game model of risk for these purposes.

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Considering the lateralization of neural mechanisms involved in decision making, Camus et al. (2009) have reported that specifically the right DLPFC participates in computation of stimuli values at the time of choice. Consistent with this finding, Knoch et al. (2006) demonstrated that suppression of the right (not the left) PFC by rTMS reduces inhibitory control, leading to overly risky decision making and a selective neglect for negative consequences.

However, in addition to its significance for cognitive control processes, the PFC also serves as a motor area, relevant for planning and execution of motor behavior (Fuster, 1997). Curtis and D'Esposito (2003) suggest that addressing motor aspects of working memory tasks is essential to understanding PFC function. Thus, sustained DLPFC activity in delayed working memory tasks represents a signature of actively stored cognitive representations, but likely also accounts for motor preparations and selection processes subserving motor plans. Consistent with this notion, Pochon et al. (2001) report that DLPFC activation in delayed response tasks is only maintained when the subject is mentally preparing for a memory-guided sequence of actions, but not when simply maintaining visuospatial information. Therefore, including motor aspects to the study design is crucial for understanding the integrative role of the DLPFC in goal directed decision making. If we consider behavior involving risk then, obviously, the most consequential and dangerous behaviors presuppose certain forms of chosen overt actions as a consequence of the preceding covert decision making.

The notion of right DLPFC as the principal part of the impulse control system has been supported by experimental results showing that inhibitory transcranial direct current stimulation of the right DLPFC causes an increase in risk taking (Cheng & Lee, 2016; Gorini, Lucchiari, Russell-Edu, & Pravettoni, 2014). These results prompt testing of TMS as the suitable means to manipulate the level of behavioral risk taking in tasks involving non-symbolic, overt motor actions. TMS can be used non-invasively to alter the functionality of the stimulated cortical region and associated neural circuits transiently to study their contribution to cognitive and perceptual processing (Pascual-Leone & Hallett, 1994; Ruff, Driver, & Bestmann, 2009).

This understandably applies also to the mechanisms implicated in risk-related behavior. TMS has previously been used to confirm the role of the DLPFC in adaptive, nonveridical decision making (Tulviste, Goldberg, Podell, & Bachmann, 2016). The neural effect of rTMS depends on the frequency of stimulation, as well as on the intensity of stimulation and the cortical state of the subject at the time of the procedure (Silvanto & Pascual-Leone, 2008). Generally, low frequency rTMS (at rates of 1 Hz or less) leads to reduced excitability of the underlying neural tissue (Chen et al., 1997; Romero, Anschel, Sparing, Gangitano, & Pascual-Leone, 2002) similarly to the cathodal current effect.

The BAS/BIS theoretical model of frontal functions (Carver & White, 1994) suggests that left-hemisphere frontal areas are involved in approach behavior and disinhibition

while right-hemisphere frontal areas are involved in impulse control and behavioral inhibition.

If the right DLPFC is involved in impulse control and behavioral inhibition, as proposed by the BAS/BIS model (Carver & White, 1994; Gable, Neal, & Threadgill, 2018; Reckless, Bolstad, Nakstad, Andreassen, & Jensen, 2013), then disruptive rTMS to the right DLPFC is expected to increase proneness to risky decisions and emphasize risk aversion as one of the functions of this cortical area and the systems connected to it. We predicted that action outcomes which can be interpreted as a result of proneness to take risk in a game of skill will be increased after rTMS of the right DLPFC.

METHODS

Participants

Twelve subjects (7 female; mean age = 33.7 years; SD = 6.9; range, 23-49) participated in the experiment (mean years of education = 17.9; SD = 2.9). All subjects were right-handed and had normal or corrected-to-normal vision. Age ranges for females (mean age = 35.8 years; SD = 8.0) and males (mean age = 30.6 years; SD = 4.1) were similar. Participants were considered right handed if their individual score on the Briggs and Nebes (1975) handedness questionnaire was 41 or greater of a possible 48. The subjects were new to the ballgame concept, and the sample did not include professional athletes or representatives of professions known to be related to higher levels of behavioral risky decision making with harmful consequences. None of the participants had any history of neurological or psychiatric illness. All subjects were checked for TMS exclusion criteria (Wassermann, 1998). Written informed consent was obtained from all participants before the experiments. The study was approved by the Research Ethics Committee of the University of Tartu and was conducted according to the principles set in the Declaration of Helsinki.

Materials and Measures

Game of skill task

Game of Skill - Minimum-TB[®], a ballgame used in the current study, combines fine motor action with an element of risk, challenging the player to obtain a high total score by balancing the potential to gain or lose points on individual throws (Otsa, Paaver, Harro, & Bachmann, 2016). The basic theme of the game is to throw a tennis ball as close to the ceiling as possible, but refrain from letting the ball touch the ceiling. The scoring scale for the game is nonlinear, determined by distance from the ceiling. Thus, to achieve a good score, the player throws a ball high, as close to the ceiling as possible, but has to avoid touching the ceiling by the ball. The increment of the score accelerates with decrease of the distance between the ball and ceiling. For example, if the ball reaches its highest elevation at 30 cm from ceiling the corresponding score is 5 points, whereas at 20 cm from ceiling the corresponding score is 15 points. By getting closer to the ceiling by 10 cm the score increases by 10 points.

However, at the distances closer to ceiling the increment is larger so as to motivate some risk-taking to gain more points. Thus, when the highest elevation the ball trajectory reaches is 10 cm from ceiling, the increment of points for this (compared to 20 cm from ceiling elevation) is not 10 but 30 points, for example. The steepest score value increases characterize ball distances of few cm and mm from ceiling. The automatic sensor measures the smallest achieved distance between the ball and the ceiling and allows to carry out measurements according to the game score rule: the smaller the distance between the ball and the ceiling, the higher the score (max 100 points) awarded for the trial.

Previously, performance on the Game of Skill task has been correlated with biomarkers indicating risk proneness, relatively low platelet monoamine oxidase (MAO) activity levels, as well as with sensation seeking personality traits (Otsa et al., 2016). Lowered MAO activity in turn has been shown to relate to higher risk proneness in real life situations such as traffic behavior and use of alcohol and tobacco (see Harro & Oreland, 2016 for a review).

Procedure

Each experimental treatment block included four games (two "Normal", two "Risky" varieties of the game risk level), each game consisting of 21 throws. In total, each player performed three blocks (Baseline without TMS coil involved, rTMS, Sham), completing a total of 252 throws as well as 10 practice throws before the game. The blocks were administered in counterbalanced order and the participants were blinded to the treatment assignment. In the "Normal" mode, any throw that hit the ceiling counted as "0" points, but the accumulated overall score from the previous trials was sustained. In the "Risky" condition, however, hitting the ceiling would reset the overall accumulated score from completed trials back to "0". For each condition (Baseline, TMS, Sham) and risk mode ("Normal", "Risky"), the number of ceiling hits, the total score, as well as the number of points lost due to ceiling hits were determined (per game averages).

rTMS

Before each block, the TMS coil placed against the participants' scalp, the subject received low-frequency (1 Hz; 360 pulses in total) rTMS for 6 min, targeted at the right DLPFC. Stimulation protocols with similar length and intensity have been successfully used to trigger neuromodulatory changes in the cortex (e.g., Fitzgerald et al., 2006). For Sham conditions, the same stimulation protocol was used, but the coil was tilted 90° off the scalp. The goal of sham TMS is to be indistinguishable from real TMS by matching the sensory effects experienced by the subject without triggering an actual magnetic field (Duecker & Sack, 2015). While placing the stimulation coil in a tilted position on the head is a commonly used Sham method, preserving the acoustic and somatosensory artefacts experienced with real TMS (Wassermann & Lisanby, 2001), the resulting magnetic field can still be potentially sufficient to result in unwanted somato-sensory effects and nerve stimulation leading to residual brain stimulation (Lisanby, Gutman, Luber, Schroeder, & Sackeim, 2001).

However, the intensity and precision of stimulation is by far superior in the main experimental condition compared with Sham. Participants remained blinded to the treatment assignment order (rTMS or Sham). The experiment was performed in a single session, each subject completing three blocks of ballgames. The order of risk levels in the game (Normal, Risky) and stimulation conditions (rTMS/Sham), was counterbalanced across subjects to avoid order effects.

Offline rTMS as applied before the experimental game-ofskill tasks, was delivered using a Nexstim Navigated Brain Stimulation (Nexstim Ltd., Helsinki, Finland) MRI-assisted TMS system with a figure-of-8-shaped coil. Stimulation intensity was set to 100% of individual motor threshold (measured as a barely noticeable twitch of thumb), ranging between 34% and 43% of maximal stimulator output for individual participants. The stimulation site was determined by using the Beam F3 system (Beam, Borckardt, Reeves, & George, 2009), which allows to locate the DLPFC in the absence of structural brain scans, while taking into account individual variability in skull sizes. The BeamF3 algorithm determines the DLPFC location by 3 scalp measurements: the nasion-inion distance, the left tragus-right tragus distance through the scalp vertex, and the head circumference. The coil in the real rTMS condition was positioned tangential to the scalp and the handle pointing back and away from the midline at 45°. No rTMS adverse effects were observed in the participants.

Statistical Analysis

The data met the assumption of normality. Repeated measures analyses of variance (ANOVAs) and paired samples ttests were used to compare differences in the number of ceiling hits and points earned before (at Baseline) and after receiving rTMS or Sham treatment. For the "Risky" condition, we also determined the number of points lost due to ceiling hits.

RESULTS

Ceiling Hits

A two-way repeated measures ANOVA with factors risk and stimulation type was conducted to assess any systematic effects on how often participants erroneously hit the ceiling. The main effect of risk was significant (F(1,11)=13.39; p=.004; $\eta P2=.549$), confirming that the game of skill is sensitive to the level of risk experienced by the players. On average, participants performed more ceiling hits in the

"Normal" game mode (M = 4.75; SD = 2.79) compared to the "Risky" game mode (M = 2.86; SD = 2.00).

The main effect for stimulation type was not significant $(F(2,22) = 1.63; p = .220; \eta P2 = .129)$, but the interaction between risk and stimulation type showed a trend $(F(2,22) = 2.85; p = .079; \eta P2 = .206)$. Planned pairwise comparisons confirmed that, in accordance with our main hypothesis, disruptive rTMS stimulation of the right DLPFC decreased risk aversion in the "Risky" game mode. The number of ceiling hits after rTMS (M = 3.92; SD = 2.23) was systematically higher compared to baseline (M = 2.33; SD = 1.97; t(12) = 2.66; p = .022; Cohen's d = 0.76) and Sham-stimulation (M = 2.33; SD = 1.44; t(12) = 3.38; p = .006; Cohen's d = 0.98).

As shown in Figure 1, risk taking increased in the "Risky" rTMS condition by 1.58 (SD = 2.07) ceiling hits per game, but remained unchanged after Sham stimulation. Consequently, in the rTMS condition, ceiling hits in the "Risky" mode (M = 3.92; SD = 2.23) became virtually as frequent as in the "Normal" mode (M = 4.66; SD = 2.87), indicating a lack of significant effect of risk level on behavior (t(12) = 0.87; p = .399; Cohen's d = 0.25). In contrast, awareness of risk ("Normal" vs. "Risky") still yields systematically less ceiling hits in the Baseline (t(12) = 4.10; p = .002; Cohen's d = 1.18) and Sham (t(12) = 3.19; p = .009; Cohen's d = 0.92) conditions.

Total Points Score

Repeated measures ANOVA returned a significant main effect of risk for total points gathered (F(1,11) = 42.31; p < .001;



Fig. 1. Ceiling hits during a game (21 throws in each game), mean \pm SEM. Sensitivity to risk level is evident in the Baseline and Sham conditions, whereby significantly less ceiling hits occur in the "Risky" game mode compared to "Normal" mode. However, in the rTMS condition, the influence of risk on game performance is almost eliminated.

 $\eta P2 = .794$). The total points scores were included in the results analysis, as the study participants were instructed to gather as many points in the game as possible, while avoiding hitting the ceiling. Participants scored more points in the "Normal" mode (M = 447.35; SD = 210.75) compared to the "Risky" game mode (M = 178.71; SD = 120.41). The main effect for stimulation type (F(2,22) = 1.65; p = .215; $\eta P2 = .130$) and risk × stimulation type interaction (F(2,22) = 0.39; p = .692; $\eta P2 = .034$) were not significant. Pairwise comparisons indicated that rTMS intervention led to a marginally higher total score in the "Normal" condition (M = 460.29;SD = 118.20) compared to baseline (M = 400.25; SD = 194.36; t(12) = 1.212; p = 0.251; Cohen's d = 0.35). In the "Risky" game mode, despite the added risk of losing all points in the ongoing game due to a ceiling hit, the scores were virtually the same for Baseline (M = 169.42; SD = 121.54) and rTMS (M = 162.75; SD = 125.73; t(12) = 0.152; p = .882; Cohen'sd = 0.04) conditions (Figure 2).

Points Lost

To further explore the effects of rTMS stimulation on gameplay, we determined the number of points lost due to hitting the ceiling in all "Risky" conditions. Despite lack of a significant main effect of risk on number of points lost $(F(2,22) = 2.216; p = .133; \eta P2 = .168)$, pairwise comparisons indicated that more points were lost in the rTMS condition (M = 203.38; *SD* = 116.27), compared to Baseline



Fig. 2. Number of points earned per game (21 throws in each game), mean $(n = 12) \pm \text{SEM}$. In all conditions (Baseline, Sham, rTMS), subjects earned less points in the "Risky" game mode compared to "Normal". In the "Baseline" and "Sham" conditions, the subjects scored less points in the "Risky" mode due to a more conservative throwing style aimed at avoiding ceiling hits (penalty). However, in the rTMS condition, the lower total score can be explained by more frequent ceiling hits which decreased the total score achieved in the game.

(M = 137.33; SD = 105.23) and Sham (M = 139.04; SD = 91.68).

DISCUSSION

The game of skill model allowed us to study the effects of DLPFC manipulation on risk taking behavior in situations where strategic decision making and motor control were both involved. We expected low-frequency right DLPFC rTMS stimulation to affect subjects' self-control, triggering a shift to strategically riskier behaviors, resulting in more ceiling-hits per game. More frequent ceiling-hits would indicate elevated risk taking, likely explained by an uninhibited preference for immediate awards (Camus et al., 2009) and a decreased sensitivity to negative consequences.

As DLPFC is assumed to support cognitive ability to take into account the nature of recent trials while regulating behavior on the current trial (Boschin, Mars, & Buckley, 2017), our game of skill was expected to be valid also in terms of its strategical design. Thus, disruption of this adaptive skill would impair subjects' ability to avoid risky, closerto-the-ceiling, throws toward later trials in the "Risky" mode to avoid nullifying the total accumulated score if hitting the ceiling. Our results supported the hypothesis by showing increase in risky actions as a result of disrupting right DLPFC by rTMS.

Consistently with the hypothesized role of right DLPFC in strategic decision making, its disruption likely resulted in a failure to keep focus on long-term goals, triggering a tendency to reach for immediate awards on single trials. TMS stimulation eliminated the loss-sensitive, conservative strategy practiced by participants at Baseline, avoiding ceiling hits in the "Risky" mode, and the number of ceiling hits in the "Normal" (4.66 ceiling hits, on average) and "Risky" (3.92) conditions was virtually the same (t(12) = 0.87; p = .399; Cohen's d = 0.25).

Although rTMS stimulation caused participants to take the risk of hitting the ceiling, the occasional score-resetting throws did not bring down the substantially large scores obtained from successful high-trajectory throws, the frequency of which increased due to a riskier motor behavior), contributing generously to the accumulated score. Despite higher point losses (203 points per game lost due to ceiling hits, on average) compared to Baseline (169 points lost) and Sham (139) conditions, the final score in the "Risky" game was virtually the same in the rTMS and Baseline conditions (163 *vs.* 169, respectively).

Our results are consistent with the theoretical model proposed by Stuss and Alexander (2007), proposing that goal-directed behavior is executed by three independent supervisory functions of the frontal lobes: energization, task setting, and monitoring. Later, Stuss (2011) localized the monitoring functions to the right DLPFC, assigning it the responsibility for checking performance and adjusting behaviors when needed. Consistent with this theory, disruption of the right DLPFC impaired behavioral adjustment in the "risky" game mode, whereby the subjects opt for immediate higher payoffs, ignoring the potential negative consequences of high losses. Accordingly, a ceiling hit should make the subject more cautious to avoid further throws too close to the ceiling. Interruption of the right DLPFC likely impairs the ability to modulate ongoing activity and switch to a more conservative throwing style to not end up with a low total score.

There are of course several limitations to this exploratory study. The small sample size reduces the reliability of the results. As the game of skill task is executed by motor actions, and because DLPFC connects to higher level and primary motor cortical areas, the influence of rTMS may have affected the motor subparts of the integrated cognitiveexecutive system, reaching beyond the strategic decision making and monitoring systems. Further research involving selective manipulations of different cortical areas as well as non-motor risky decision-making tasks (e.g., the Iowa Gambling Task or the BART task) must be carried out to answer this question.

Another problem is related to the fact that DLPFC stimulation did not have a relatively smaller effect on the overall scores between the "Normal" and "Risky" conditions when rTMS was used, compared to Baseline and Sham conditions. Possibly the participants acquired the skill of throwing the ball high enough to obtain a good enough score without risking too much. Alternatively, the subjects may deliberately have chosen a riskier strategy after rTMS stimulation, resulting in more throws with more points awarded for reaching close to the ceiling, but not touching it. Thus, contrary to the common assumption, the riskier strategy may even reflect successful adaptive behavior: the participants, despite producing more ceiling hits than in the Baseline and Sham condition, achieved a similar total score. Alternative explanations to the increased total score need to be addressed directly in future research.

Another obvious future task would be to use a facilitative TMS protocol instead of the disruptive one, with a prediction that boosting the right DLPFC should lead to highly cautious performance, with very few throws touching the ceiling. Using both facilitative and inhibitory TMS protocols may provide further insights into the specific role of the right and left DLPFC in risk-related decision making processes. Finally, as activation of the left DLPFC is involved in counteracting the control function of the right DLPFC related BIS system (Liu & Feng, 2017), specifically left DLPFC stimulation effects must also be tested.

CONCLUSION

In conclusion, we found evidence that disruption of the right DLPFC produces a change in subjects' risk related behavior in a motor response task specifically in terms of how frequently actions leading to counterproductive results were taken. Apparently, after rTMS, the subject becomes less sensitive to considerations of chance of loss and more

focused on immediate gains. The results suggest that the right DLPFC plays a role in executing and monitoring risk-related decision making in tasks with a motor response. The second main result of this study showed that a game of skill in its two risk level modes that we used here proved to be a useful model case for studying information processing and action execution where risk is adaptively inconsequential.

ACKNOWLEDGMENTS

We thank Kadi Tulver, René Randver, Renate Rutiku, and Geili Pais for their help at various stages of this study. Research presented in this article was supported by Estonian Research Agency (ETAG) institutional research support scheme IUT20-40 (subaccount TSVPH14140I). J.T. and T.B. developed the concept, J.T. collected and analyzed the data and designed the study, both authors interpreted the results and wrote the study (first draft by J.T.). The authors declare no competing financial interests.

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