Koshikawa Yosuke (Orcid ID: 0000-0002-6736-092X)
Ishii Ryouhei (Orcid ID: 0000-0002-4245-0953)

Disentangling Cognitive Inflexibility in Major Depressive Disorder: A Transcranial Direct Current Stimulation Study

Short running title: Task-switching and prefrontal tDCS in MDD

Yosuke Koshikawa[a], PhD, Keiichiro Nishida[a], PhD, Tomonari Yamane[b], M.A., Masafumi Yoshimura[c], PhD, Ai Onohara[d], M.A., Satsuki Ueda[a], M.A., Ryouhei Ishii[e], PhD, Toshihiko Kinoshita[a], PhD, Yosuke Morishima[f], PhD

[a] Department of Neuropsychiatry, Kansai Medical University, Osaka, Japan

[b] Graduate School of Psychology, Kansai University, Osaka, Japan

[c] Department of Occupational Therapy, Faculty of Rehabilitation, Kansai Medical University, Osaka, Japan

[d] Social Welfare Corporation Uminoko Gakuen Ikejimaryo, Osaka, Japan

[e] Osaka Prefecture University Graduate School of Comprehensive Rehabilitation Habikino, Osaka, Japan

[f] Translational Research Center, University Hospital of Psychiatry, University of Bern, Bern, Switzerland

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pcn.13364

Corresponding author: Yosuke Koshikawa, PhD

Department of Neuropsychiatry, Kansai Medical University,

10-15 Fumizono-cho, Moriguchi-city, Osaka 570-8506, Japan

Tel: +81 06 6992 1001 (49215); Fax: +81 06 6992 7756

E-mail: koshikay@takii.kmu.ac.jp

Numbers of figures: 2

Number of tables: 5

Word count for the manuscript: 4370

Word count for the abstract: 243

This manuscript is being submitted to *Clinical Neurophysiology*.

Abstract (243 words)

Background: Cognitive dysfunction is a persistent residual symptom in major depressive disorders (MDDs) that hinders social and occupational recovery. Cognitive inflexibility is a typical cognitive dysfunction in MDD and refers to difficulty in switching tasks, which requires two subcomponents: forgetting an old task and adapting to a new one. Here, we aimed to disentangle the subcomponents of cognitive inflexibility in MDD and investigate whether they can be improved by transcranial direct current stimulation (tDCS) on the prefrontal cortex.

Methods: The current study included 20 patients with MDD (7 females) and 22 age-matched healthy controls (HCs) (7 females). The participants received anodal tDCS on either the dorsomedial prefrontal cortex (DMPFC) or dorsolateral prefrontal cortex (DLPFC) in a crossover design. Before and after the application of tDCS, the participants performed a modified Wisconsin Card Sorting Test, in which the task-switching rules were explicitly described and proactive interference from a previous task rule was occasionally released.

Results: We found that the behavioral cost of a task switch was increased in patients with MDD, but that of proactive interference was comparable between patients with MDD and HCs. The response time for anodal DMPFC tDCS was decreased compared with that for anodal tDCS on the DLPFC in MDD.

Conclusions: These findings suggest that cognitive inflexibility in MDD is primarily explained by the

difficulty to adapt to a new task and environment, and that tDCS on the DMPFC improves behavioral performance during cognitively demanding tasks that require conflict resolution.

Keywords: Task-switching, Dorsolateral prefrontal cortex, Dorsomedial prefrontal cortex, Cognitive control, Wisconsin Card Sorting Task

Trial registration: This study was registered to UMIN-CTR (https://www.umin.ac.jp/ctr/; registration Nr. UMIN000015046).

Introduction

Major depressive disorder (MDD) is a psychiatric disorder that not only involves a severe personal psychological burden, but also impairs social and professional functionality[1]. Therefore, it has broad social and economic impacts. Patients with MDD manifest a variety of symptoms, such as depressive mood, anxiety, decreased motivation, sleep disturbance, and cognitive dysfunction. Among these symptoms, cognitive dysfunction, such as impaired concentration and executive function, has been overlooked in treatment strategies for MDD. In recent years, the remission of cognitive dysfunction has been recognized as an important treatment goal[2], as recent studies have revealed that cognitive dysfunction in MDD persists after the remission of depressive symptoms[3] and impairs social and vocational reintegration after recovery[4].

Antidepressants are the first-line treatment for MDD, but their effectiveness in treating cognitive dysfunction remains relatively poor[5]. Vortioxetine is the only agent known to be effective in treating cognitive dysfunction[6], but the magnitude of improvement is still only slight[7]. Therefore, it is important to search other treatment strategies to target cognitive dysfunction.

Noninvasive brain stimulation (NBS) methods such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been shown to be effective for treating MDD[8]. tDCS applies a weak direct electronic current to cortical areas to modulate the membrane potentials of cortical neurons using simple and inexpensive devices[9]. While tDCS on the dorsolateral prefrontal

cortex (DLPFC) has moderate antidepressant efficacy[10], little evidence is available in regard to treating cognitive dysfunction using NBS, including tDCS. The results of tDCS studies targeting cognitive dysfunction have been mixed and controversial, as each study employed a different montage of tDCS electrodes and targeted different cognitive symptoms[5, 11, 12]. In a recent meta-analysis, tDCS on the DLPFC was shown to be beneficial for improving working memory and processing speed in MDD[13]; one study examined whether DLPFC tDCS improved the capability to resolve cognitive conflicts in MDD as measured by the Stroop task, but did not improve behavioral performance[14].

Most previous studies on treating MDD with TMS and tDCS have targeted the DLPFC as the stimulation site, while several others have targeted the dorsomedial prefrontal cortex (DMPFC) [15, 16]. While the effectiveness of DMPFC repetitive TMS (rTMS) in treating depressive symptoms is not well established[15, 16], one study reported that DMPFC stimulation exhibited better improvement of depressive symptoms than did DLPFC stimulation[17]. In addition, the DMPFC, including the rostral anterior cingulate, is anatomically connected with the orbitofrontal prefrontal cortex, DLPFC, ventral striatum, and amygdala, and is involved in higher cognitive function, especially cognitive flexibility and emotion regulations[15, 18]. Therefore, DMPFC stimulation could help improve cognitive dysfunction, especially cognitive flexibility, in MDD.

In the present study, we examined the impact of tDCS on cognitive dysfunction in MDD. More specifically, to examine cognitive flexibility, we employed a task-switching paradigm. Task-switching

involves switching among two or more tasks, and requires cognitive flexibility to switch effectively from one task to another[19]. It is known that behavioral response takes more time and becomes less accurate immediately after a switch from an old task to a new one. This behavioral cost, a slower and less accurate response, is referred to as the task-switch cost, which is increased in MDD[3, 20, 21]. Task-switching can be fractionated into two major cognitive processes[19]: the first is configuring a process to conduct a new task, and the second is erasing a process to conduct an old task. When the latter process is not effectively activated, the residual processes of the execution of a previous task interfere with the execution of a new one; this is referred to as proactive interference or task-set inertia.

The aim of the present study was twofold. First, we aimed to disentangle the impaired components of task-switching in MDD. To this end, we employed a modified Wisconsin Card Sorting Test (mWCST), in which the task-switching rules are explicitly described and proactive interference is occasionally released[22]. Second, we aimed to examine the impact of DMPFC tDCS on cognitive dysfunction compared with left DLPFC tDCS. We applied single-session tDCS on either the DMPFC or left DLPFC using a crossover design. As a primary outcome, we analyzed whether disorder or the stimulation site would affect response times on the mWCST. As a secondary outcome, we analyzed whether medication and the severity of MDD would affect response times on the mWCST.

Methods

Participants

We recruited 24 healthy controls (HCs) (7 females) and 20 patients with MDD (7 females) diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Parts of this study focusing on the analysis of electroencephalogram (EEG) data have been described elsewhere[23]. Before the study began, two HCs withdrew consent, and were therefore excluded. All participants had at least 12 years of education and had been diagnosed by experienced psychiatrists (> 10 years). We also measured 17 items on the 17-item Hamilton Depression Rating Scale (HAMD17) [24] to assess the severity of depressive symptoms. We excluded patients with a history of dementia, schizophrenia, substance dependence, epilepsy, or head trauma. All patients with MDD who participated in the present study were followed by the outpatient clinic of Kansai Medical University, and 15 of 20 received medication. We included only outpatients, as we considered the cognitive demand of the task to be too high for patients with severe depressive symptoms. No changes were made in drug prescriptions or dosages during the study period. No HCs had a history of psychiatric disorders. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. Participants were recruited from September 2014 to April 2017. The study protocol was approved by the Institutional Ethics Review Committee of Kansai Medical University (関医倫 KAN-I-RIN 1406-1).

Timeline

We adopted a between-subjects crossover design (Figure 1). The order of stimulation was counterbalanced. Each participant was randomly assigned to receive either left DLPFC or DMPFC tDCS in the first session. In the second session, the participants received tDCS on the other site. An interval of at least 1 week was provided between the two tDCS sessions. For each session, the participant performed a pre-tDCS mWCST, received tDCS, and then performed a post-tDCS mWCST.

Transcranial Direct Current Stimulation (tDCS)

We administered tDCS using a battery-driven stimulator (DC Stimulator Plus; NeuroConn, Ilmenau, Germany). The electrical current was applied at 1 mA via electrically conductive rubber electrodes (20 cm^2, circular in shape) attached with an adhesive conductive EEG paste. Anodal stimulation was administered over the DMPFC (AFz, 10–10 EEG international electrode placement) or the left DLPFC (F5, 10–10 EEG international electrode placement) with the cathodal electrode placed on the left shoulder to minimize the effects of cathodal stimulation on the brain. Direct current was administered for 20 min during the resting state.

Modified Wisconsin Card Sorting Test (mWCST)

We employed an mWCST originally used in a previous study[22], and simplified it to our cohort. More

specifically, we reduced four possible target cards to three (Figure 2). To implement the task program, we used the Cogent Toolbox (http://www.vislab.ucl.ac.uk/cogent_2000.php; RRID:SCR_015672) in MATLAB version 2014a (MathWorks, Natick, MA, USA). The participants were presented with four cards. A cue card was presented at the bottom center, and three response cards were presented above, to the right or left side of the cue card. For each card, geometric figures that varied according to three perceptual dimensions (color, form, or number) were depicted. At the middle of the screen, the current rule (color, form, or number) was presented. The participants were required to select a response card that matched the cue card according to the rule. Each block consisted of four to six trials, and then moved to a new block, either switching to a new rule or repeating the previous one. When switching to a new task rule, one wrong response card matched the cue card according to the previous rule. We intended to cause proactive interference from the previous rule. There were two different task-switch blocks: one was a standard task-switch block, and the other included a trial released from proactive interference (RPI trial), in which none of the response cards matched the cue card according to the previous rule in the third trial after the rule switch (Figure 2). All participants practiced the mWCST before starting the experiments.

Statistical Analysis

We used R software (https://www.r-project.org/) for the statistical analysis. We used the psych package

for descriptive statistics[25] and the lme4[26] and lmerTest[27] packages for linear mixed-effect modeling (LMM). As a primary outcome measure, we constructed an LMM including the following fixed effects: group (MDD or HC), tDCS site (DLPFC or DMPFC), switch type (Switch: switch or repeat), RPI trial, session order (day 1 or day 2), first trial of a block (1stTr), trials after the second trial of a block, task-switch cost (Switch × 1stTr: interaction between the first trial and switch type and change in response time (RT) for the first trial of switch blocks compared with the other blocks), interaction effects of group with tDCS site (MDD × DLPFC or DMPFC), RPI trial (RPI × MDD), or task-switch cost (MDD × Switch × 1stTr), interaction effects of tDCS with RPI trial (DLPFC or DMPFC × RPI) or task-switch cost (Switch × 1stTr × DLPFC or DMPFC), and interaction effects of tDCS and group with RPI trial (MDD × DLPFC or DMPFC × RPI) or task-switch cost (MDD × DLPFC or DMPFC × Switch × 1stTr). We included participants and trial numbers as random effects. For the accuracy analysis, we counted premature responses (< 250 ms) as errors. For the response time analysis, we excluded trials with a premature response (< 250 ms) or a prolonged response (> 4500 ms) as outliers, as well as error trials. As secondary outcome measures, we also examined the effects of benzodiazepines (BDZ) and the severity of depressive symptoms using only data from the MDD group. Here, we used the model described above, but excluded all fixed effects, including group, and added HAMD17 scores and BDZ use.

Results

The demographics of the study participants are listed in Table 1. No significant differences in age or gender were found between the MDD and HC groups. The MDD group showed significantly higher HAMD17 scores than the HC group (MDD group: 14.5 ± 5.1, HC group: 0.4 ± 0.7, $U = 440$, $p < 0.001$).

Next, we analyzed the effects of tDCS, group, task-switch cost, and proactive interference on accuracy and response times using an LMM (Tables 2, 3). We first looked at task-switch cost, characterized by an increased number of errors and slower responses in the first trial after switching to a new task rule, modeled as the interaction effect between the first trial of a block and switch type in the mixed-effect models (Switch × 1stTr). We found a significant interaction effect between the first trial of a block and switch type (Switch × 1stTr: accuracy model, beta = –0.740, $p = 0.0005$; RT model, beta = 26.94, $p = 0.0205$) and confirmed the task-switch cost when switching rules during the mWCST. We also found a significant interaction effect between the task-switch cost and group (MDD × Switch × 1stTr) in the RT model only (accuracy model, beta = 0.18507, $p = 0.62$; RT model, beta = 42.59, $p = 0.031$), indicating that the MDD group exhibited a larger task-switch cost than did the HC group. Next, we examined the response in RPI trials. In the present mWCST, there is one response card, which is wrong in the current task rule, but correct in the previous task rule before switching to the current rule. This card could interfere with the selection of a correct card, and it results in slower

and less accurate responses. We call this phenomena proactive interference, interference from the previous task rule. In RPI trials, there is no such interfering wrong response card. Therefore, the participants were free from proactive interference. We confirmed significant improvements in accuracy and response time in RPI trials (accuracy model, beta = 0.630, p = 0.0007; RT model, beta = –26.46, p = 0.0030), indicating that behavioral performance was improved in the absence of proactive interference. However, no significant difference was observed between the MDD and HC groups (accuracy model, beta = 0.408, p = 0.25; RT model, beta = –2.50, p = 0.86). We also examined perseverative errors, which refer to an erroneous response based on the current rule, but a correct response according to the previous rule. The number of perseverative errors was not significantly different between the MDD and HC groups (MDD: mean = 13.3, SE = 2.93; HC: mean = 11.77, SE = 1.98; t = 0.43, p = 0.66).

Concerning the effects of tDCS, we found a reduction in response times after DLPFC and DMPFC stimulation (DLPFC: beta = –143.53, p < 0.00001; DMPFC: beta = –151.94, p < 0.00001), but accuracy was decreased only after DLPFC tDCS (DLPFC: beta = –0.392, p < 0.0001; DMPFC: beta = –0.123, p = 0.149). We observed a trade-off between response speed and accuracy after DLPFC tDCS. We also found a session order effect in response time (beta = –155.74, p < 0.00001), suggesting that general learning effects cannot be excluded. We also confirmed a significant interaction of group with DLPFC or DMPFC stimulation in response time (MDD × DLPFC or DMPFC) (DLPFC: beta

= –27.30, p = 0.0027; DMPFC: beta = –63.65, p < 0.00001). In addition, the interaction effect of DMPFC stimulation was significantly larger than that of DLPFC stimulation in the MDD group (p = 0.00017), indicating that response time reduction after DMPFC tDCS was larger than DLPFC tDCS in MDD. These results suggest that DMPFC tDCS on the MDD helps conflict resolution in the mWCST. By contrast, for the accuracy model with the HC and MDD groups, we found a significant interaction of group only with DLPFC (MDD × DLPFC or DMPFC) (DLPFC: beta = 0.316, p = 0.045; DMPFC: beta = 0.222, p = 0.19) (Table 2); no significant effect was found with DLPFC tDCS in the accuracy model only with MDD (Table 4). These results indicate that decreased accuracy after DLPFC tDCS was minimal in the MDD group.

We also found significant interaction effects between DLPFC stimulation and task-switch cost (DLPFC × Switch × 1stTr) (beta = 59.34, p = 0.017) and between DLPFC stimulation and RPI trial (DLPFC × RPI) (beta = –46.67, p = 0.013) in the RT model, indicating that DLPFC stimulation increased the task-switch cost and facilitated responses under no proactive interference.

Finally, we examined the influence of the severity of depressive symptoms and BDZ use on response times using an LMM. For the accuracy model, we found significant main effects of HAMD17 score (beta = 0.053, p = 0.029), but no significant main effect of BDZ use (beta = –0.023, p = 0.94) (Table 4). For the RT model, we did not find any significant main effects of HAMD17 score and BDZ use (HAMD17: beta = –1.565, p = 0.55; BDZ: beta = 177, p = 0.14) (Table 5).

Discussion

The present study investigated cognitive dysfunction, focusing particularly on cognitive flexibility in MDD. We employed mWCST to disentangle the task-switch cost and proactive interference, and measured response times while applying tDCS to the DMPFC and DLPFC. At the baseline pre-stimulation level, we found a significantly larger task-switch cost, slower responses, in the MDD than in the HC group, but no difference in proactive interference between groups. We also found that the reduction in response times after tDCS was significantly larger in the MDD than in the HC group, and that the reduction in response times after DMPFC tDCS was larger than that after DLPFC tDCS in the MDD group. However, DLPFC tDCS was associated with more errors in both the HC and MDD groups. Moreover, we found that DLPFC tDCS increased the task-switch cost, whereas it quickened response times in the absence of proactive interference. Regarding the secondary outcomes, we found that the severity of MDD symptoms was associated with more accurate responses, whereas BDZ use did not affect accuracy, and neither BDZ use nor the severity of MDD symptoms affected response times.

Humans adaptively select optimal actions according to environmental demands and flexibly change their actions when the environments change. Such adaptive behavior is impaired in many psychiatric disorders, including MDD. Previous research using task-switching paradigms has revealed

that cognitive flexibility is impaired in MDD[3, 20, 21, 28]. Studies on task-switching components have shown that efficient task-switching requires not only configuring new task execution processes, but also erasing old task execution processes. The present study aimed to elucidate the detailed psychopathology of cognitive flexibility in MDD by disentangling proactive interference and task-switch costs. We found larger task-switch costs in MDD, but no difference in proactive interference, indicating that the dysfunction of cognitive flexibility in MDD can mainly be explained by the difficulty in adapting to new tasks or environments. Furthermore, the results of the perseverative error analysis revealed no differences between HC and MDD, less supporting the rumination account due to perseveration. This finding is consistent with those of clinical observations reporting that relocation or promotion triggers the onset of MDD[29]. However, this is in contrast to a widely accepted belief that rumination is associated with MDD[30, 31]. Rumination is negative self-referential process that reverberates and consolidates negative ideas[32]. Increased task-switch costs in MDD would account for rumination as behavioral perseverance in an old state; however, the present results suggest that rumination could occur as a result of difficultly in shifting to new thoughts or perspectives. In fact, a recent review on psychotherapy for MDD and anxiety disorders found that shifting from repetitive negative thought is effective to prevent and improve depressive symptoms[33]. Our findings could provide conceptual support for psychotherapy targeting rumination and repetitive negative thoughts.

In the present study, as secondary outcomes, we found that the severity of MDD symptoms was

positively correlated with accuracy. One possible reason for this is that error-related signals are larger in MDD[3433] and more severe patients responded more carefully to avoid error-related signals. By contrast, we found no significant impact of BDZ use or the severity of MDD symptoms on response times or accuracy. Previous studies have shown that BDZ use generally decreases performance on many cognitive tasks[35] and attenuates tDCS-induced cortical excitability[36]. BDZ use has also been reported on the lower tDCS treatment effects on MDD[37]. In the present study, BDZ use appeared to prolong response times, but not significantly, owing to the large variance (confidence interval of the estimate: 60.58–294.5). This is probably because BDZ prescriptions are highly heterogeneous across participants, dosages, timing, and target symptoms, such as anxiety and/or insomnia. Future studies are needed to elucidate how BDZ use modifies the effects of tDCS on cognitive flexibility in MDD.

Concerning the tDCS effect, tDCS on either DLPFC or DMPFC improved response times in both groups, and the improvement was greater in MDD. However, the design of the present study did not include a sham condition, and response times were shorter on the second experimental day regardless of the stimulation site. Therefore, we presume that general learning effects would significantly contribute to a reduced response time after tDCS. However, in the present study, we employed a crossover design, and the order of the tDCS sites was counterbalanced across the participants. The difference in the tDCS effect between DMPFC and DLPFC can be simply explained by the tDCS intervention. Indeed, we observed additional reductions in overall response times after DMPFC tDCS

compared with DLPFC tDCS in the MDD group; however, we did not observe a DMPFC tDCS effect on task-switch cost. Interestingly, this difference between DLPFC and DMPFC tDCS was not observed in HCs. Therefore, DMPFC tDCS effects in MDD cannot be simply explained by the learning effect. Instead, DMPFC tDCS in MDD improved the cognitive process to select a correct card among conflicting options, that is, conflict resolution. Recent research has shown that rTMS on the DMPFC improves not only overall depressive symptoms, but also cognitive flexibility, attention, and processing speed[38]. By introducing carefully designed mWCST, our study revealed that DMPFC tDCS improves the capability to resolve cognitive conflicts in MDD, but does not improve cognitive flexibility.

In addition, the MDD group showed an additional reduction in response times after tDCS compared with the HC group. These results indicate that the effects of tDCS on response times are larger in patients with MDD than in HCs. Indeed, cognitive functions in many domains are impaired in MDD, especially dysfunctions of cognitive flexibility[3, 20, 21, 39]. In line with previous findings, the MDD group showed slower responses, but this difference was not significant, which implies that the MDD group may have more capacity to improve response times.

In contrast to DMPFC tDCS, DLPFC tDCS in HC decreased response accuracy and task-switch cost, slowing response after switching a rule, whereas it improved response times, especially in RPI trials. These results suggest that DLPFC tDCS prioritizes speed by sacrificing accuracy in HC. By

contrast, DLPFC tDCS in MDD did not affect response accuracy or task-switch cost, while it improved response time, especially in RPI trials. These results suggest that DLPFC tDCS improved response speed of no conflicting trials without sacrificing response accuracy in MDD. In the present study, we applied single-session tDCS on the prefrontal cortex to study whether prefrontal tDCS could improve cognitive dysfunction. We assumed that the effect of single-session tDCS would not last more than the day of intervention, and that the states of depressive symptoms would be comparable between sessions. To confirm a comparable baseline between the two sessions, we performed two-way analysis of variance (time × tDCS order) for the HAMD17 total score as well as each item of the HAMD17; the results revealed no significant main effect of time or significant interaction effect between time and tDCS order ($p > 0.05$). Therefore, we consider that the tDCS intervention in the present study affected the participants only immediately after application.

Regarding the current intensity of tDCS, we used 1 mA with 20 cm^2 of the anodal stimulation electrode. The effect of tDCS depends on the current density applied instead of the absolute current intensity[40]. Our protocol corresponds to 1.75 mA of tDCS with a standard 35 cm^2 electrode. Recent studies have tended to use a higher current intensity of tDCS, occasionally even more than 2 mA. Therefore, we might achieve larger intervention effects with a higher current intensity.

Neurobiological accounts for the complex pattern of DLPFC tDCS effects in the present study can be explained as follows. First, DLPFC tDCS can facilitate responses without cognitive conflicts.

This is consistent with previous studies showing that activation in the DLPFC is associated with faster and more accurate responses in various cognitive tasks[41, 42]. By contrast, mWCST requires resolution of cognitive conflict to select an accurate response. There are two modes of conflict resolution. One mechanism is proactive control, where the DLPFC amplifies neural representation relevant to a behavioral goal in advance[43]. The other is reactive control, where the left DLPFC reactively activates when irrelevant neural representation is not efficiently suppressed[44]. In HC, DLPFC tDCS may saturate the DLPFC capacity for reactive control, and as a result, reduce the response accuracy. By contrast, DLPFC tDCS in MDD did not saturate that capacity, as the baseline activity of the left DLPFC was decreased in MDD[45]. Another possible mechanism can be explained through the subcortical circuit. Task-switching processes are not simply achieved through the cortical areas; subcortical structures contribute substantially to these processes[46]. In particular, in a previous study, a lesion in the basal ganglia increased the error rate only in the presence of proactive interference[47]. In addition, noninvasive stimulation on the DLPFC is known to increase the release of dopamine in the basal ganglia. More recent research has shown that the task-switch cost was increased when tyrosine, a source of dopamine synthesis, was depleted, but was ameliorated by DLPFC tDCS[48]. For efficient task performance during demanding tasks, an optimal amount of dopamine needs to be released[49, 50]. Therefore, we speculate that during RPI trials without proactive interference, tDCS on the DLPFC may facilitate responses by activating the DLPFC. By contrast, in the presence of proactive

interference, tDCS on the DLPFC may interfere with the reactive conflict resolution system as well as the optimal dopamine balance in the basal ganglia.

In summary, tDCS on the prefrontal cortex could be beneficial for improving cognitive dysfunction in MDD in a distinct manner. DMPFC tDCS in MDD improves conflict resolution, but without improving cognitive flexibility, such as task-switching, while DLPFC tDCS in MDD improves response speeds without conflict.

The present study did have some limitations. First, as we identified the main effect of experimental days, general learning effects affected the response times. In addition, we did not include a sham condition, which made it difficult to disentangle the tDCS effects from the learning effects. However, we still observed a significant difference in tDCS effects on response times between the HC and MDD groups, and a significant improvement in response times after DMPFC tDCS compared with DLPFC tDCS in the MDD group. Second, the sample size was relatively small. We set the current sample size based on previous research, but our results need to be replicated in a larger cohort. Finally, the present study protocol used a single-session intervention. In the present study, we examined cognitive inflexibility in MDD through a single-session prefrontal tDCS intervention in a crossover design. As reviewed in a recent article[13], most previous studies have examined the effects of brain stimulation, including tDCS, on cognitive dysfunction with a single-session intervention. It is important to study whether cognitive dysfunction can be improved by a standard protocol of brain stimulation treatment

for MDD.

In future research, it will be important to investigate how cognitive inflexibility is improved through standard NBS treatment protocols with repeated brain stimulation sessions. Another important open question is whether tDCS can improve residual persistent cognitive dysfunction after remission in MDD. Lastly, it is important to explore brain stimulation approaches to facilitate shifting from repetitive negative thoughts.

Conclusion

The results of the present study suggest that the primary cause of cognitive inflexibility in MDD is difficulty in adapting to new rules, as opposed to proactive interference from previous rules. Furthermore, tDCS on the DMPFC improved cognitive conflicts in MDD.

Acknowledgments

YK, KN, TY, MY, SU, RI, and TK received funding from the Osaka University Centre of Innovation (COI) program of the Japan Science and Technology Agency (JST, No. JPMJCE1310). KN received the Translational Research program; Strategic PRomotion for practical application of INnovative medical Technology from Japan Agency for Medical Research and Development (TR-SPRINT, A129), and a Grant-in-Aid for Early-Career Scientists by JSPS KAKENHI (18K15499) and Grant-in-Aid for Young Scientists (B) (KAKEN 26860950). MY received a Grant-in-Aid for Scientific Research (C) (KAKEN 19K08056). YM was supported by the Japan Science and Technology Agency PRESTO program (10238). The research was independently planned and carried out by the principal investigator, and the funding did not affect the results or analysis.

Disclosures statement

KN was named as the inventor of national patent application No. 2019-17927, filed September 24, 2019. Except for this patent, KN declares no potential conflict of interest. The other authors declare that they have no conflict of interest in relation to this study.

Author contributions

All authors contributed to the conception and design of the study. KN and YM conducted the search processes. YK, KN, AO, and ST participated in the screening, assessments, and data extraction processes. YK, KN, TY, and YM performed the statistical analyses. YK, KN, TY, and YM discussed the results and wrote the manuscript. All authors read and approved the finalized manuscript.

Figure legends

Figure 1.

mWCST; modified Wisconsin Card Sorting Test, tDCS; transcranial direct stimulation, DMPFC; dorsomedial prefrontal cortex, DLPFC; dorsolateral prefrontal cortex.

Figure 2.

The participants were required to select a response card that matched the cue card (middle bottom card in exemplar trials) according to a rule defining a visual feature. "N" and "R" represent a normal and release trial, respectively. The release trial is implemented only in the third trial of a switch release block. In the normal trial (left bottom), one response card always has the same visual feature of the cue card indicated by the previous rule. In this example, the correct response card is the right card with three blue triangles, whereas the top card with two green squares holds the distracting feature from the previous rule (shape) to create proactive interference. On the other hand, in the release trial (right), none of response cards has the same visual feature indicated by the previous rule (shape).

References

1. G. B. D. Disease Injury IP, Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018**; 392**: 1789-1858.
2. Bortolato B, Miskowiak KW, Köhler CA, Maes M et al. Cognitive remission: a novel objective for the treatment of major depression? *BMC Med* 2016**; 14**: 9.
3. Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med* 2014**; 44**: 2029-40.
4. Ekman M, Granstrom O, Omerov S, Jacob J, Landen M. The societal cost of depression: evidence from 10,000 Swedish patients in psychiatric care. J Affect Disord 2013; **150**: 790-7.
5. Miskowiak KW, Ott CV, Petersen JZ, Kessing LV. Systematic review of randomized controlled trials of candidate treatments for cognitive impairment in depression and methodological challenges in the field. *Eur Neuropsychopharmacol* 2016**; 26**: 1845-67.
6. Baune BT, Brignone M, Larsen KG. A network meta-analysis comparing effects of various antidepressant classes on the digit symbol substitution test (DSST) as a measure of cognitive dysfunction in patients with major depressive disorder. *Int J Neuropsychopharmacol* 2018**; 21**: 97-107.
7. Jaeger J. Digit Symbol substitution test: the case for sensitivity over specificity in neuropsychological testing. *J Clin Psychopharmacol* 2018**; 38**: 513-9.
8. Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. BMJ 2019; **364**: l1079.
9. Brunoni AR, Nitsche MA, Bolognini N et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul 2012; **5**: 175-95.
10. Moffa AH, Martin D, Alonzo A et al. Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: An individual patient data meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2020; **99**: 109836.
11. Knight MJ, Baune BT. Cognitive dysfunction in major depressive disorder. Curr Opin Psychiatry 2018; **31**: 26-31.
12. Bennabi D, Haffen E. Transcranial direct current stimulation (tDCS): a promising treatment for major depressive disorder? *Brain Sci* 2018**; 8**: 81.
13. Ciullo V, Spalletta G, Caltagirone C et al. Transcranial Direct Current Stimulation and Cognition in Neuropsychiatric Disorders: Systematic Review of the Evidence and Future Directions. Neuroscientist 2021; **27**: 285-309.

14. Brunoni AR, Tortella G, Bensenor IM, Lotufo PA, Carvalho AF, Fregni F. Cognitive effects of transcranial direct current stimulation in depression: Results from the SELECT-TDCS trial and insights for further clinical trials. J Affect Disord 2016; **202**: 46-52.
15. Kreuzer PM, Downar J, de Ridder D, Schwarzbach J, Schecklmann M, Langguth B. A Comprehensive Review of Dorsomedial Prefrontal Cortex rTMS Utilizing a Double Cone Coil. Neuromodulation 2019; **22**: 851-66.
16. Dunlop K, Sheen J, Schulze L et al. Dorsomedial prefrontal cortex repetitive transcranial magnetic stimulation for treatment-refractory major depressive disorder: A three-arm, blinded, randomized controlled trial. Brain Stimul 2020; **13**: 337-40.
17. Kreuzer PM, Schecklmann M, Lehner A et al. The ACDC pilot trial: targeting the anterior cingulate by double cone coil rTMS for the treatment of depression. Brain Stimul 2015; **8**: 240-6.
18. Mitchell DG. The nexus between decision making and emotion regulation: a review of convergent neurocognitive substrates. Behav Brain Res 2011; **217**: 215-31.
19. Kiesel A, Steinhauser M, Wendt M et al. Control and interference in task switching—A review. Psychological Bulletin 2010; 136: 849-74.
20. Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. Psychol Bull 2013; **139**: 81-132.
21. Liu H, Funkhouser CJ, Langenecker SA, Shankman SA. Set shifting and inhibition deficits as potential endophenotypes for depression. *Psychiatry Res* 2021**; 300**: 113931.
22. Konishi S, Chikazoe J, Jimura K, Asari T, Miyashita Y. Neural mechanism in anterior prefrontal cortex for inhibition of prolonged set interference. Proc Natl Acad Sci U S A 2005; **102**: 12584-8.
23. Nishida K, Koshikawa Y, Morishima Y et al. Pre-stimulus Brain Activity Is Associated With State-Anxiety Changes During Single-Session Transcranial Direct Current Stimulation. Front Hum Neurosci 2019; **13**: 266.
24. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967; **6**: 278-96.
25. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria, 2021.
26. Bates D, Maechler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. Journal of Statistical Software 2015; **67**: 1-48.
27. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest package: tests in linear mixed effects models. *J Stat Soft* 2017**; 82**: 1-26.
28. Marian M, Filimon L. Cognitive restructuring and improvement of symptoms with cognitive-behavioural therapy and pharmacotherapy in patients with depression. *Ann Gen Psychiatr* 2010**; 9**.

29. Hammen C. Stress and depression. Annu Rev Clin Psychol 2005; 1: 293-319.
30. Ingram RE. Self-focused attention in clinical disorders: review and a conceptual model. *Psychol Bull* 1990**; 107**: 156-76.
31. Nolen-Hoeksema S. Responses to depression and their effects on the duration of depressive episodes. *J Abnorm Psychol* 1991**; 100**: 569-82.
32. Koster EHW, Lissnyder DE, Derakshan N, Raedt RD. Understanding depressive rumination from a cognitive science perspective: the impaired disengagement hypothesis. *Clin Psychol Rev* 2011**; 31**: 138-45.
33. Watkins ER, Roberts H. Reflecting on rumination: consequences, causes, mechanisms and treatment of rumination. *Behav Res Ther* 2020**; 127**: 103573.
34. Holmes AJ, Pizzagalli DA. Spatiotemporal dynamics of error processing dysfunctions in major depressive disorder. *Arch Gen Psychiatry* 2008**; 65**: 179-88.
35. Crowe SF, Stranks EK. The residual medium and long-term cognitive effects of benzodiazepine use: an updated meta-analysis. *Arch Clin Neuropsychol* 2018**; 33**: 901-11.
36. Nitsche MA, Liebetanz D, Schlitterlau A, Henschke U et al. GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. *Eur J Neurosci* 2004**; 19**: 2720-6.
37. Goerigk SA, Padberg F, Buhner M, Sarubin N et al. Distinct trajectories of response to prefrontal tDCS in major depression: results from a 3-arm randomized controlled trial. *Neuropsychopharmacology* 2021**; 46**: 774-82.
38. Schulze L, Wheeler S, McAndrews MP, Solomon CJ, Giacobbe P, Downar J. Cognitive safety of dorsomedial prefrontal repetitive transcranial magnetic stimulation in major depression. *Eur Neuropsychopharmacol* 2016**; 26**: 1213-26.
39. Vidrascu EM, Robertson MM. Inhibitory corticotropin-releasing factor neurons in the dorsomedial prefrontal cortex promote stress-resilient behavior in male rodents. *J Neurophysiol* 2021**; 125**: 533-6.
40. Nitsche MA, Doemkes S, Karakose T, Antal A et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. *J Neurophysiol* 2007**; 97**: 3109-17.
41. Preston G, Anderson E, Silva C, Goldberg T, Wassermann EM. Effects of 10 Hz rTMS on the neural efficiency of working memory. *J Cogn Neurosci* 2010**; 22**: 447-56.
42. Baumert A, Buchholz N, Zinkernagel A, Clarke P et al. Causal underpinnings of working memory and Stroop interference control: testing the effects of anodal and cathodal tDCS over the left DLPFC. *Cogn Affect Behav Neurosci* 2020**; 20**: 34-48.
43. Egner T, Hirsch J. Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. *Nat Neurosci* 2005**; 8**: 1784-90.
44. Morishima Y, Okuda J, Sakai K. Reactive mechanism of cognitive control system. *Cereb Cortex* 2010**; 20**: 2675-83.

45. Videbech P. PET measurements of brain glucose metabolism and blood flow in major depressive disorder: a critical review. *Acta Psychiatr Scand* 2000**; 27**: 285-309.

46. Crone EA, Wendelken C, Donohue SE, Bunge SA. Neural evidence for dissociable components of task-switching. *Cereb Cortex* 2006**; 16**: 475-86.

47. Yehene E, Meiran N, Soroker N. Basal ganglia play a unique role in task switching within the frontal-subcortical circuits: evidence from patients with focal lesions. *J Cogn Neurosci* 2008**; 20**: 1079-93.

48. Borwick C, Lal R, Lim LW, Stagg CJ, Aquili L. Dopamine depletion effects on cognitive flexibility as modulated by tDCS of the dlPFC. *Brain Stimul* 2020**; 13**: 105-8.

49. Cools R, D'Esposito M. Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biol Psychiatry* 2011**; 69**: e113-25.

50. Vaillancourt DE, Schonfeld D, Kwak Y, Bohnen NI, Seidler R. Dopamine overdose hypothesis: evidence and clinical implications. *Mov Disord* 2013**; 28**: 1920-9.

Table 1. Demographic data

	MDD (n = 20)	HC (n = 22)	
	Average (SD)	Average (SD)	*p* (*t* test)
Age (years)	46.5 (14.9)	49.5 (14.9)	0.524
HAMD17	14.5 (5.1)	0.4 (0.7)	< 0.001
Duration of morbidity (months)	19.3 (19.3)	-	-
Episode (times)	2.3 (0.9)	-	-
	n	n	*p* (χ^2)
Sex (female)	7	7	1.00
Benzodiazepine use (yes)	14	-	-
Drug therapy (multiple)	15	-	-

MDD; major depressive disorder, HC; healthy control, SD; standard deviation, HAMD17; 17-item Hamilton Depression Rating Scale.

Table 2. Main outcome: linear mixed-effect model of accuracy

	Estimate	Std. Error	*t*-value	*p*-value	
Fixed Effects					
Intercept	4.155	0.116	35.963	< 0.001	***
Main Effects					
Group ID (= MDD)	–0.087	0.224	–0.390	0.697	
DMPFC tDCS (= DMPFC)	–0.124	0.086	–1.443	0.149	
DLPFC tDCS (= DLPFC)	–0.392	0.079	–4.965	< 0.001	***
Task-switch block (= Switch)	–0.378	0.084	–4.487	< 0.001	***
Release from proactive interference trial (= RPI)	0.631	0.187	3.370	< 0.001	***
Session order	0.090	0.066	1.360	0.173	
1st trial after task switch (= 1stTr)	–0.073	0.108	–0.672	0.51	
3rd or later trials after task switch	0.045	0.089	0.516	0.606	
Interaction					
Switch × 1stTr (= Task-switch cost)	–0.740	0.212	–3.486	< 0.001	***
MDD × DMPFC	0.222	0.172	1.296	0.195	
MDD × DLPFC	0.316	0.158	2.004	<0.05	*
MDD × RPI	0.408	0.359	1.136	0.256	
DMPFC × RPI	0.542	0.479	1.131	0.258	
DLPFC × RPI	0.382	0.414	0.923	0.356	
MDD × Switch × 1stTr (= MDD × Task-switch cost)	0.188	0.384	0.490	0.624	

DMPFC × Switch × 1stTr (= DMPFC × Task-switch cost)	–0.296	0.485	–0.609	0.542
DLPFC × Switch × 1stTr (= DLPFC × Task-switch cost)	0.215	0.445	0.483	0.629
MDD × DMPFC × RPI	–0.068	0.963	–0.071	0.944
MDD × DLPFC × RPI	0.844	0.878	0.960	0.337
MDD × DMPFC × Switch × 1stTr (= MDD × DMPFC × Task-switch cost)	0.861	0.967	0.890	0.373
MDD × DLPFC × Switch × 1stTr (= MDD × DLPFC × Task-switch cost)	0.923	0.831	1.111	0.266

MDD; major depressive disorder, Std. Error; standard error, DMPFC; dorsomedial prefrontal cortex, DLPFC; dorsolateral prefrontal cortex, Switch; task-switch block, RPI; release from proactive interference, 1stTr; 1st trial after task switch, Task-switch cost; task-switch block and 1st trial after task switch.

Table 3. Main outcome: linear mixed-effect model of response times

	Estimate	Std. Error	df	*t*-value	*p*-value	
Fixed Effects						
Intercept	1151.951	35.775	41.801	32.200	< 0.001	***
Main Effects						
Group ID (MDD)	64.882	70.842	40.001	0.916	0.365	
DMPFC tDCS (= DMPFC)	–151.945	4.560	44313.769	–33.321	< 0.001	***
DLPFC tDCS (= DLPFC)	–143.533	4.555	44316.947	–31.514	< 0.001	***
Task-switch block (= Switch)	6.976	6.017	3339.626	1.159	0.246	
Release from proactive interference trial (= RPI)	–26.464	8.923	26941.209	–2.966	< 0.01	**
Session order	–155.744	3.720	44301.846	–41.864	< 0.001	***
1st trial after task switch (= 1stTr)	206.613	6.420	35402.399	32.182	< 0.001	***
3rd or later trials after task switch	32.867	5.343	35173.638	6.151	< 0.001	***
Interaction						
Switch × 1stTr (= Task-switch cost)	26.944	11.630	20619.380	2.317	< 0.05	*
MDD × DMPFC	–63.655	9.131	44301.848	–6.971	< 0.01	***
MDD × DLPFC	–27.304	9.114	44301.841	–2.996	< 0.01	**
MDD × RPI	–2.509	14.952	44306.059	–0.168	0.867	
DMPFC × RPI	–24.189	18.908	43456.552	–1.279	0.201	
DLPFC × RPI	–46.678	18.958	43164.816	–2.462	< 0.05	*
MDD × Switch × 1stTr (= MDD × Task-switch cost)	42.591	19.825	44307.976	2.148	< 0.05	*

DMPFC × Switch × 1stTr (= DMPFC × Task-switch cost)	31.809	24.923	43717.048	1.276	0.202	
DLPFC × Switch × 1stTr (= DLPFC × Task-switch cost)	59.341	25.010	43489.951	2.373	< 0.05	*
MDD × DMPFC × RPI	–10.030	36.665	44308.728	–0.274	0.784	
MDD × DLPFC × RPI	–33.049	36.604	44306.729	–0.903	0.367	
MDD × DMPFC × Switch × 1stTr (= MDD × DMPFC × Task-switch cost)	2.478	48.579	44308.621	0.051	0.959	
MDD × DLPFC × Switch × 1stTr (= MDD × DLPFC × Task-switch cost)	19.408	48.566	44305.259	0.400	0.689	

MDD; major depressive disorder, Std. Error; standard error, df; degrees of freedom, DMPFC; dorsomedial prefrontal cortex, DLPFC; dorsolateral prefrontal cortex, Switch; task-switch block, RPI; release from proactive interference, 1stTr; 1st trial after task switch, Task-switch cost; task-switch block and 1st trial after task switch.

Table 4. Secondary outcome: linear mixed-effect model of accuracy with benzodiazepine use in MDD

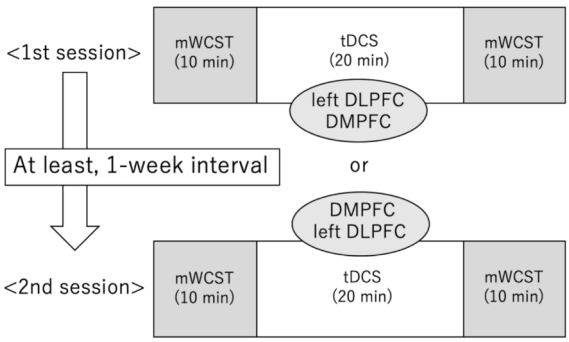
	Estimate	Std. Error	*t*-value	*p*-value	
Fixed Effects					
Intercept	4.122	0.144	28.526	< 0.001	***
Main Effects					
HAMD17	0.054	0.025	2.176	<0.05	*
Benzodiazepine	–0.024	0.322	–0.074	0.941	
DMPFC tDCS (= DMPFC)	–0.012	0.125	–0.096	0.924	
DLPFC tDCS (= DLPFC)	–0.223	0.115	–1.941	0.052	
Task-switch block (= Switch)	–0.345	0.118	–2.916	<0.01	**
Release from proactive interference trial (= RPI)	0.872	0.292	2.988	<0.01	**
Session order	0.065	0.099	0.655	0.512	
1st trial after task switch (= 1stTr)	–0.002	0.152	–0.015	0.988	
3rd or later trials after task switch	0.094	0.125	0.754	0.450	
Interaction					
Switch × 1stTr (= Task-switch cost)	–0.610	0.296	–2.060	<0.05	*
DMPFC × RPI	0.964	0.778	1.239	0.215	
DLPFC × RPI	0.832	0.665	1.251	0.211	
DMPFC × Switch × 1stTr (= DMPFC × Task-switch cost)	–0.258	0.694	–0.372	0.710	
DLPFC × Switch × 1stTr (= DLPFC × Task-switch cost)	0.732	0.629	1.165	0.244	

MDD; major depressive disorder, Std. Error; standard error, HAMD17; 17-item Hamilton Depression Rating Scale, DMPFC; dorsomedial prefrontal cortex, DLPFC; dorsolateral prefrontal cortex, Switch; task-switch block, RPI; release from proactive interference, 1stTr; 1st trial after task switch, Task-switch cost; task-switch block and 1st trial after task switch.

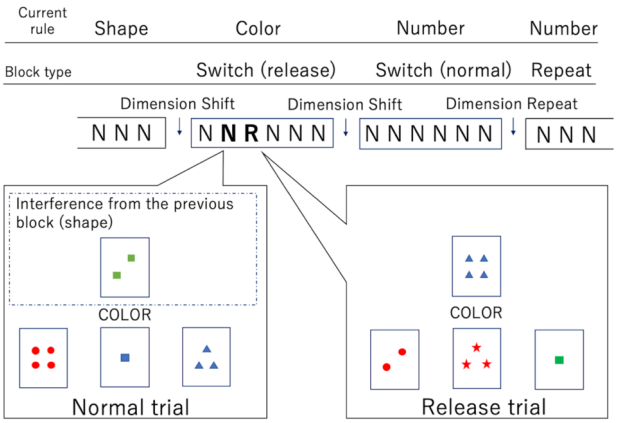
Table 5. Secondary outcome: linear mixed-effect model of response times with benzodiazepine use in MDD

	Estimate	Std. Error	df	*t*-value	*p*-value	
Fixed Effects						
Intercept	1186.609	50.855	18.378	23.333	< 0.001	***
Main Effects						
HAMD17	–1.565	2.661	4435.888	–0.588	0.556	
Benzodiazepine	177.539	116.961	18.073	1.518	0.146	
DMPFC tDCS (= DMPFC)	–185.380	7.071	21000.506	–26.217	< 0.001	***
DLPFC tDCS (= DLPFC)	–157.440	7.035	21000.896	–22.380	< 0.001	***
Task-switch block (= Switch)	9.860	8.624	1221.608	1.143	0.253	
Release from proactive interference trial (= RPI)	–21.867	13.569	9702.122	–1611.000	0.107	
Session order	–154.270	6.873	15944.068	–22.446	< 0.001	***
1st trial after task switch (= 1stTr)	210.716	9.865	14067.413	21.360	< 0.001	***
3rd or later trials after task switch	26.340	8.187	14117.360	3.217	< 0.01	**
Interaction						
Switch × 1stTr (= Task-switch cost)	49.156	17.589	7367.386	2.795	< 0.01	**
DMPFC × RPI	–25.508	29.266	19955.190	–0.872	0.384	
DLPFC × RPI	–60.234	29.122	19979.835	–2.068	< 0.05	*
DMPFC × Switch × 1stTr (= DMPFC × Task-switch cost)	38.996	38.589	20326.063	1.011	0.312	
DLPFC × Switch × 1stTr (= DLPFC × Task-switch cost)	74.763	38.522	20346.506	1.941	0.052	

MDD; major depressive disorder, Std. Error; standard error, df; degrees of freedom, HAMD17; 17-item Hamilton Depression Rating Scale, DMPFC; dorsomedial prefrontal cortex, DLPFC; dorsolateral prefrontal cortex, Switch; task-switch block, RPI; release from proactive interference, 1stTr; 1st trial after task switch, Task-switch cost; task-switch block and 1st trial after task switch.



PCN_13364_Figure_1.tiff



PCN_13364_Figure_2.tiff