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Analysis of Cognitive Flexibility in Major Depressive Disorder and the Effects of Transcranial Direct Current Stimulation

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Abstract

[Background] Cognitive dysfunction is a persistent residual symptom of major depressive disorder (MDD), among which reduced cognitive flexibility is a typical cognitive dysfunction. Patients with cognitive inflexibility have difficulty switching between tasks. This consists of two subcomponents: forgetting old tasks and adapting to new tasks. The present study aimed to examine the subcomponents of cognitive inflexibility in MDD patients separately and to determine whether they can be improved by transcranial direct current stimulation (tDCS) of the prefrontal cortex.

[Method] The study included 20 patients with MDD and 22 age-matched healthy controls (HCs). In a crossover design, participants received anodal tDCS in either the dorsomedial prefrontal cortex (DMPFC) or the dorsolateral prefrontal cortex (DLPFC). Patients performed a modified Wisconsin Card Sorting Test with explicit task rule switching, and occasional release of proactive interference from the previous task rule was administered before and after adaptation by tDCS.

[Result] 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 to that for anodal tDCS on the DLPFC in the MDD group. DLPFC tDCS increased the task-switch cost and facilitated responses under no proactive interference.

[Conclusions] These findings suggest that cognitive inflexibility in MDD is primarily explained by difficulty to adapt to a new task and environment. tDCS in MDD patients has different effects on the improvement of cognitive flexibility response time, depending on the site of stimulation.

Keywords: task switching, tDCS, dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, cognitive flexibility

Introduction

Major depressive disorder (MDD) is a mental disorder that causes a marked personal and psychological burden while impairing social and occupational functioning.^{1,2)} Consequently, it has far-reaching social and economic effects. Patients with MDD exhibit various symptoms, including depressed mood, anxiety, reduced motivation, sleep disturbances, and cognitive dysfunction. Among these symptoms, cognitive dysfunction, including reduced concentration and deficits in executive function, has long been overlooked in

MDD treatment strategies. However, in recent years, remission of cognitive dysfunction has become recognized as an important treatment goal.⁴⁾ This shift stems from recent research demonstrating that cognitive dysfunction in MDD patients persists even after depressive symptoms resolve,^{3,1)} hindering social and occupational reintegration following recovery.^{1,1)}

While antidepressants are the first-line treatment for MDD patients, their efficacy against cognitive dysfunction remains relatively limited.^{2,4)}

Vortioxetine is the only antidepressant recognized as effective against cognitive dysfunction,²⁾ but the degree of improvement remains modest.¹⁵⁾ Therefore, exploring other treatment strategies targeting cognitive dysfunction is crucial.

Non-invasive brain stimulation (NBS) methods, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have been shown to be effective in treating MDD patients.²⁸⁾ tDCS involves applying a weak direct current to the cerebral cortex using relatively simple and inexpensive equipment, thereby modulating the membrane potential of cortical neurons.

tDCS applied to the dorsolateral prefrontal cortex (DLPFC) has been shown to exert moderate antidepressant effects,²⁶⁾ but sufficient evidence supporting the treatment of patients with cognitive dysfunction using NBS, including tDCS, has not been obtained. The inconsistent results of tDCS studies targeting cognitive dysfunction stem from differences in tDCS electrode use across studies and variations in the cognitive symptoms addressed, resulting in ongoing debate.³⁾¹⁷⁾²⁴⁾ A recent meta-analysis indicated that tDCS to DLPFC is beneficial for improving working memory and processing speed in MDD patients.⁷⁾ Furthermore, one study investigated

whether tDCS to DLPFC improves the ability to resolve cognitive conflict, measured by the Stroop task, in MDD patients; however, no improvement in behavioral performance was observed.⁶⁾

Many previous studies on TMS or tDCS treatment for MDD patients targeted the dorsolateral prefrontal cortex (DLPFC), while several others targeted the dorsomedial prefrontal cortex (DMPFC).¹⁰⁾²¹⁾ The efficacy of repetitive TMS (rTMS) targeting DMPFC for depressive symptoms has yet to be fully established¹⁰⁾²¹⁾; however, one study reported that DMPFC stimulation led to superior improvement in depressive symptoms compared with DLPFC stimulation.²⁰⁾ Furthermore, DMPFC, including the rostral anterior cingulate cortex, anatomically connects with the orbitofrontal cortex, DLPFC, ventral striatum, and amygdala, and is involved in higher-order cognitive functions, particularly cognitive flexibility and emotion regulation.²¹⁾²⁵⁾ Therefore, DMPFC stimulation is considered to contribute to improving cognitive dysfunction in MDD patients, especially cognitive flexibility.

This study examined the effects of tDCS on cognitive dysfunction in MDD patients. Specifically, a task-switching paradigm was employed to assess cognitive flexibility. Task switching involves performing and switching

between two or more tasks; effective switching from one task to another requires cognitive flexibility.¹⁶⁾ It is known that immediately after switching from an old task to a new one, the influence of the old task causes delayed responses and reduced accuracy. This behavioral cost, involving response delays and accuracy declines, is termed the task-switching cost, which reportedly increases in the presence of MDD.²³⁾³¹⁾³³⁾ Task switching can be broadly divided into two cognitive processes: (1) establishing the process for performing the new task, and (2) forgetting the process for performing the old task.¹⁶⁾ If the process needed for the old task is not completely forgotten, this will interfere with performing the new task. This is called proactive interference.

This study had two objectives. First, it aimed to isolate and understand the components of task switching that are impaired in MDD patients. To achieve this, the modified Wisconsin Card Sorting Test (mWCST) was used, which explicitly specifies task-switching rules and occasionally releases proactive interference.¹⁸⁾ Second, it aimed to examine the effects of tDCS over DMPFC on cognitive dysfunction compared with tDCS to the left DLPFC. A crossover design was used, in which participants underwent a single session of tDCS over either DMPFC or the left

DLPFC. The primary outcome measures were to analyze whether impairment (presence or absence of depression) and the stimulation site affected the mWCST reaction time and accuracy. Secondary outcome measures were to assess whether medication use and MDD severity affected the mWCST reaction time and accuracy.

I. Methods and Results

1. Participants and Methods

We recruited 24 healthy controls (HC) (7 females) and 20 MDD patients (7 females) diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Note that a portion of this study, focusing on EEG data analysis, has been described in other publications.²⁹⁾ Two HC withdrew consent before the study began and were thus excluded. All participants had received at least 12 years of education. MDD patients were diagnosed by psychiatrists with over 10 years of clinical experience. The severity of depressive symptoms was assessed using the 17-item Hamilton Depression Rating Scale (HAMD-17).¹³⁾ Outpatients were the only participants included in this study, as the task difficulty was considered too high for patients with severe depressive symptoms. During the study period, there were no changes in medication prescriptions or dosages for any

participants in the MDD group. No HC had a history of mental disorders. This study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants. The study protocol was approved by the Kansai Medical University Institutional Review Board (KAN-I-RIN 1406-1).

A crossover design was employed. Each participant was randomly assigned to receive tDCS over either the left DLPFC or DMPFC during the first session. In the second session, participants received tDCS over an alternate site. An interval of at least one week was maintained between the two tDCS sessions. In each session, participants underwent tDCS and completed mWCST both before and after stimulation.

tDCS was administered using a battery-powered stimulation device (DC STIMULATOR PLUS; NeuroConn, Ilmenau, Germany). Stimulation was delivered at 1 mA through conductive rubber electrodes (20 cm², circular) attached with conductive EEG paste. Anodal stimulation was applied over either DMPFC (AFz, 10-10 EEG international electrode placement) or the left DLPFC (F5, 10-10 EEG international electrode placement). To minimize the effect of the cathode electrode on the brain, it was placed on

the left shoulder. Stimulation was performed for 20 minutes at rest.

For the cognitive flexibility task, we adopted mWCST used in previous studies, simplified for our cohort.¹⁸⁾ Specifically, we reduced the number of target cards from four to three. The task program was implemented using Cogent Toolbox (http://www.vislab.ucl.ac.uk/cogent_2000.php; RRID:SCR_015672) in MATLAB version 2014a (MathWorks, Natick, MA, USA). The procedure was as follows. Participants were presented with four cards. A cue card was displayed at the bottom center, with three choice cards positioned above it, to the right, and to the left. Each card depicted a geometric figure varying across three perceptual dimensions: color, shape, and number. The current rule (color, shape, number) was displayed at the center of the screen, and participants were instructed to select the card matching the cue card according to the rule. Each block consisted of 4 to 6 trials, after which participants moved to a new block. This block either introduced a new rule or repeated the previous rule. When switching to a new task rule, one error card was set to be correct under the previous rule. This was designed to actively induce proactive interference from the previous rule. There were two types of task-switching blocks: one was a standard task-switching block, and

the other included release from a proactive interference trial (RPI trial) on the third trial after the rule switch, where none of the response cards matched the cue card under the previous rule, thus releasing participants from proactive interference (Figure). All participants in this study practiced mWCST before the experiment began.

Statistical analysis was performed using R software (<https://www.r-project.org/>). Descriptive statistics were calculated using the psych package,³⁰⁾ and linear mixed models (LMM) were created using the lme4 package¹⁾ and lmerTest package.²²⁾

Primary outcome measures included group (MDD or HC), tDCS site (DLPFC or DMPFC), switch type (switching or repetition), presence of RPI trials, session order (first or second), whether it was the first trial of a block (1stTr), whether it was the second or later trial of a block, and task-switch cost (Switch \times 1stTr: first trial of a block where the task switched or other trials) as fixed effects. We included the following interaction effects: interaction with group for tDCS site (MDD \times DLPFC and MDD \times DMPFC), RPI trial (RPI \times MDD), and task-switch cost (MDD \times Switch \times 1stTr). We also set interaction effects between the tDCS site and RPI trial (RPI \times DLPFC or DMPFC) and task-switch cost (Switch \times

1stTr \times DLPFC or DMPFC). Additionally, we set RPI trials (MDD \times RPI \times DLPFC or DMPFC) and task-switch cost (MDD \times Switch \times 1stTr \times DLPFC or DMPFC) as interactions between the MDD group and tDCS. Random effects included participants and trial number. For accuracy analysis, trials with responses faster than 250 ms were counted as errors. For reaction time analysis, trials with responses faster than 250 ms or slower than 4,500 ms were excluded as outliers, along with error trials. Additionally, as a secondary outcome measure, we examined whether benzodiazepine (BDZ) use and depression symptom severity affected the results, using only data from the MDD group. This analysis used the model described above but excluded all fixed effects, including group, and added HAMD17 scores and BDZ dosage.

2. Results

Demographic characteristics of the study participants are shown in Table 1. No significant differences in age or sex were observed between MDD and HC groups. The MDD group had 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 used LMM to analyze the effects of tDCS, group, task-switch cost, and proactive interference on the

accuracy and response time (Tables 2 and 3).

First, we examined task-switch cost, characterized by increased errors and slower responses on the first trial after switching to a new task rule. This was modeled as an interaction between the first trial of a block and switch type in a mixed-effects model (Switch \times 1stTr).

The results showed a significant interaction between the first trial of a block and switch type (Switch \times 1stTr: Accuracy model, $\beta = -0.740$, $P < 0.001$; Reaction time model, $\beta = 26.944$, $P = 0.021$), confirming that task-switch costs occur during rule changes in mWCST.

Furthermore, only the response time model revealed a significant interaction between task-switch cost and group (MDD \times Switch \times 1stTr): accuracy model, $\beta = 0.188$, $P = 0.624$; response time model, $\beta = 42.591$, $P = 0.031$, indicating that the MDD group exhibited greater task-switch costs than the HC group.

Next, we examined responses during RPI trials. In the trials, no error cards that would induce proactive interference were present, allowing participants to respond free from proactive interference. Significant improvements in both accuracy and reaction time were observed during RPI trials (accuracy model: $\beta = 0.631$, $P < 0.001$; reaction time model: $\beta = -26.464$, $P = 0.003$), indicating improved

behavioral performance in the absence of proactive interference. However, no significant differences were noted between MDD and HC groups (Accuracy model, $\beta = 0.408$, $P = 0.256$; Reaction time model, $\beta = -2.509$, $P = 0.867$).

Furthermore, upon examining persistence errors (incorrect responses under the current rule but correct under the previous rule), there was no significant difference between MDD and HC groups (MDD: mean = 13.3, SE = 2.93; HC: mean = 11.77, SE = 1.98; $t = 0.43$, $P = 0.66$).

Regarding tDCS effects, a reduction in reaction time was observed after DLPFC and DMPFC stimulation (DLPFC: $\beta = -143.533$, $P < 0.001$; DMPFC: $\beta = -151.945$, $P < 0.001$), whereas a reduction in accuracy was observed only following tDCS to DLPFC (DLPFC: $\beta = -0.392$, $P < 0.001$; DMPFC: $\beta = -0.124$, $P = 0.149$). These results suggest a trade-off between reaction time and accuracy following tDCS to DLPFC. Furthermore, an effect of session order was observed on reaction time ($\beta = -155.744$, $P < 0.001$), suggesting that a general learning effect cannot be entirely excluded.

Furthermore, a significant interaction between DLPFC or DMPFC stimulation and group (MDD \times DLPFC or DMPFC) was observed for reaction time (DLPFC: $\beta = -27.304$, $P = 0.003$; DMPFC: $\beta = -63.655$, $P < 0.001$). In the

MDD group, the interaction effect of DMPFC stimulation was significantly larger than that of DLPFC stimulation ($P < 0.001$), indicating that the reduction in reaction time following tDCS to DMPFC was greater than that following tDCS to DLPFC. These results suggest that tDCS to DMPFC may facilitate conflict resolution during mWCST in patients with MDD.

In contrast, in the accuracy models for HC and MDD groups, only DLPFC showed a significant between-group interaction (DLPFC: $\beta = 0.316$, $P = 0.045$; DMPFC: $\beta = 0.222$, $P = 0.195$) (Table 2). However, the accuracy model for the MDD group alone showed no significant effect of tDCS on DLPFC, indicating that the reduction in accuracy following tDCS to DLPFC was minimal in the MDD group.

Furthermore, in the reaction time model, significant interactions were noted between DLPFC stimulation and task-switch cost (DLPFC \times Switch \times 1stTr) ($\beta = 59.341$, $P = 0.017$), and between DLPFC stimulation and RPI trials (DLPFC \times RPI) ($\beta = -46.678$, $P = 0.013$), indicating that DLPFC stimulation increases task-switching cost while simultaneously facilitating responses in the absence of proactive interference.

Finally, LMM was used to examine the effects of depression severity and BDZ use on reaction time. In the

accuracy model, the main effect of the HAMD17 score ($\beta = 0.053$, $P = 0.029$) was significant, whereas the main effect of BDZ use ($\beta = -0.023$, $P = 0.94$) was not. In the reaction time model, neither the main effect of HAMD17 score nor that of BDZ use was significant (HAMD17: $\beta = -1.565$, $P = 0.55$; BDZ: $\beta = 177$, $P = 0.14$).

II. Discussion-Including the Significance of This Study and Challenges/Innovations-

The significance of this study lies primarily in two main aspects: (i) it may provide conceptual support for psychological therapies targeting rumination and repetitive negative thinking in MDD, and (ii) it suggests the potential to tailor tDCS stimulation sites to improve cognitive dysfunction in MDD patients.

Regarding (i), our results showed that although the MDD group exhibited greater task-switching costs than the HC group, no difference was observed in proactive interference. This indicates that the dysfunction of cognitive flexibility in MDD patients can primarily be explained by difficulties in adapting to new tasks or environments. Furthermore, no difference was observed between HC and MDD groups in perseverative errors. This shows that evidence supporting the suggestion that rumination arises from perseveration may be weak. Instead, our findings

indicate that rumination may arise as a result of difficulty shifting to new thoughts or perspectives. This finding is consistent with clinical observations that job transfers or promotions can trigger the onset of MDD.¹⁴⁾ Moreover, a recent review on psychological therapy for MDD and anxiety disorders indicated that shifting away from repetitive negative thoughts is effective in preventing and ameliorating depressive symptoms.³⁶⁾ Therefore, the efficacy of psychological therapies targeting rumination and repetitive negative thoughts may be underpinned by the facilitation of shifting to new thoughts and perspectives.

Regarding (ii), with respect to tDCS effects, it was suggested that tDCS may improve different cognitive functions in MDD patients depending on the stimulation site. Specifically, tDCS targeting DMPFC in MDD improved conflict resolution, whereas tDCS targeting DLPFC did not improve cognitive flexibility, such as task switching, but may enhance the reaction time in non-conflict situations. Considerations for each stimulation site are described below.

First, regarding tDCS targeting DMPFC in MDD, it is considered to improve conflict resolution: the cognitive process of selecting the correct card from options that induce conflict. Recent research revealed that rTMS

targeting DMPFC improves not only overall depressive symptoms but also cognitive flexibility, attention, and processing speed.³²⁾ In this study, by employing carefully designed mWCST, we demonstrated that tDCS targeting DMPFC, although it does not improve cognitive flexibility in MDD, enhances the ability to resolve cognitive conflict.

Furthermore, regarding tDCS targeting DLPFC in the MDD group, the findings suggest an improvement in reaction time during conflict-free trials without compromising response accuracy. This contrasts with the HC group, in which tDCS targeting DLPFC tended to prioritize speed at the expense of accuracy.

The observation that the decrease in mWCST accuracy in the HC group was not present with tDCS targeting DLPFC in the MDD group, and that both groups showed improvements in switching costs and reaction times, particularly during RPI trials, can be interpreted from two perspectives. These are the perspective of resolving cognitive conflict, and that of subcortical circuits. Regarding the resolution of cognitive conflict, mWCST requires the selection of accurate responses by resolving cognitive conflict, which necessitates suppressing information unrelated to task selection. In this reactive control, if irrelevant information is not efficiently suppressed,

the left DLPFC becomes reactively activated.²⁷⁾ In the HC group, tDCS targeting DLPFC may saturate its capacity for reactive control by further activating DLPFC, potentially reducing response accuracy. Conversely, in the MDD group, baseline activity in the left DLPFC is reduced. Therefore, applying tDCS to DLPFC does not saturate its capacity for reactive inhibition.³⁵⁾ This likely explains why no decrease in mWCST accuracy was observed with tDCS targeting DLPFC in the MDD group.

Regarding the latter point, task switching is not mediated solely by cortical regions; subcortical structures are considered to significantly contribute to these processes.⁹⁾ Specifically, previous studies revealed that lesions in the basal ganglia increase error rates only when proactive interference is present.³⁷⁾ Moreover, non-invasive stimulation of DLPFC is known to increase dopamine release in the basal ganglia. Recent studies also showed that depletion of tyrosine, a dopamine precursor, increases task-switching costs, which can be ameliorated by tDCS targeting DLPFC.⁵⁾ Efficient task performance under demanding workloads requires an optimal level of dopamine release.⁸⁾³⁴⁾ Therefore, in RPI trials without proactive interference, tDCS to DLPFC is considered to facilitate responses by

activating DLPFC. Conversely, when proactive interference is present, tDCS to DLPFC may influence not only the reactive conflict resolution system but also optimal dopamine balance in the basal ganglia. This likely accounts for the improvement in task-switching costs observed in both groups, particularly the enhanced reaction speed during RPI trials.

Conclusion

Future research should aim to clarify how multiple-session stimulation protocols affect impairments in cognitive flexibility. Additionally, it remains an important unresolved question whether tDCS can ameliorate cognitive dysfunction that persists following MDD remission.

This paper is a Japanese adaptation of a recent research article published in PCN,¹⁹⁾ prepared at the request of the editorial committee and written by one of the authors, with additional commentary on its significance and future directions.

There are no conflicts of interest relevant to this paper.

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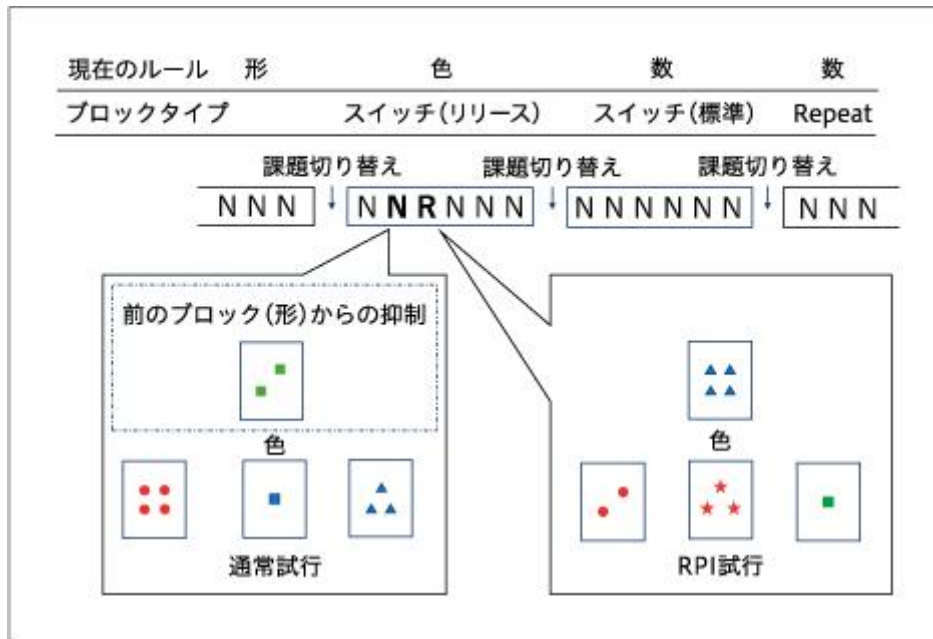


図 mWCST 課題の概要

被験者は、視覚的特徴を定義したルールに従って、キューカード（模範試行では中央下のカード）に一致する応答カードを選択するよう求められた。

Nは通常試行，RはRPI試行をそれぞれ表す。RPI試行はスイッチリリースブロックの3試行目にもみ実施。通常試行（左下）では、1枚の回答カードは常に、前のルールで示された手がかりカードと同じ視覚的特徴をもつ。この例では、正しい応答カードは3つの青い三角形が描かれた右側のカードであり、2つの緑の四角形が描かれた上のカードは、前のルールによる特徴（形状）をもち、順行抑制を引き起こす。一方、RPI試行（右）では、どの応答カードも前のルールで示された視覚的特徴（形状）をもっていない。

（文献 19 を和訳して引用）

Figure: Overview of mWCST

Participants were instructed to select a response card that matched the cue card (lower center placement during model trial) according to rules specifying visual features.

N denotes a standard trial, and R denotes an RPI trial. RPI trials were conducted only on the third trial of the switch-release block. In a standard trial (bottom left), one response card always shares the same visual feature (shape) as the cue card defined by the preceding rule. In this example, the correct response card is the right card depicting three blue triangles. The top card, depicting two green squares, possesses the feature (shape) indicated by the preceding rule and triggers proactive interference. In contrast, in the RPI trial (right), none of the response cards possess the visual feature (shape) indicated by the preceding rule.

(Translated and cited from Reference 19)

表 1 参加者背景

	MDD (n=20)	HC (n=22)	
	Average (SD)	Average (SD)	<i>P</i> (<i>t</i> test)
年齢 (歳)	46.5 (14.9)	49.5 (14.9)	0.524
HAMD17	14.5 (5.1)	0.4 (0.7)	<0.001
罹病期間 (月)	19.3 (19.3)	—	—
エピソード (回数)	2.3 (0.9)	—	—
	n	n	<i>P</i> (χ^2)
性別 (女性)	7	7	1.00
ベンゾジアゼピンの使用 (有)	14	—	—
薬物療法 (併用)	15	—	—

MDD: 大うつ病性障害, HC: 健常対照者, SD: 標準偏差, HAMD17: 17項目ハミルトンうつ病評価尺度
(文献 19 を和訳して引用)

Table 1 Participant Background

	MDD (n=20)	HC (n=22)	
	Average (SD)	Average (SD)	<i>P</i> (<i>t</i> -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 illness (months)	19.3 (19.3)	—	—
Episodes (number)	2.3 (0.9)	—	—
	n	n	<i>P</i> (χ^2)
Sex (Female)	7	7	1.00
Benzodiazepine use (Yes)	14	—	—
Medication (Concurrent)	15	—	—

MDD: Major Depressive Disorder (MDD), HC: Healthy Controls, SD: Standard Deviation, HAMD17: 17-item Hamilton Depression Rating Scale
(Translated and cited from Reference 19)

表2 主要評価項目：正確度の線形混合モデル

	Estimate	Std. Error	t-value	P-value	
固定効果					
Intercept	4.155	0.116	35.963	<0.001	***
主効果					
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 試行)	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	0.510	
3rd or later trials after task switch	0.045	0.089	0.516	0.606	
交互作用					
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 試行	0.408	0.359	1.136	0.256	
DMPFC × RPI 試行	0.542	0.479	1.131	0.258	
DLPFC × RPI 試行	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 試行	-0.068	0.963	-0.071	0.944	
MDD × DLPFC × RPI 試行	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：大うつ病性障害，Std. Error：標準誤差，DMPFC：背内側前頭前野，DLPFC：背外側前頭前野，Switch：タスク・スイッチブロック，RPI 試行：順行抑制から解放された試行，1stTr：タスク・スイッチ後1回目の試行，Task-switch cost：タスク・スイッチコスト * $P < 0.05$ ，*** $P < 0.001$

(文献 19 を和訳して引用)

Table 2 Primary Outcome Measure: Accuracy Linear Mixed Model

	Estimate	Std. Error	t-value	P-value	
Fixed Effects					
Intercept	4.155	0.116	35.963	<0.001	***
Main Effect					
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 trial)					
	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	0.510	

3rd or later trials after task switch

0.045 0.089 0.516 0.606

Interactions

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 trial

0.408 0.359 1.136 0.256

DMPFC × RPI trial

0.542 0.479 1.131 0.258

DLPFC × RPI trial

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 trial

-0.068 0.963 -0.071 0.944

MDD × DLPFC × RPI trial

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 (MDD), Std. Error: Standard Error, DMPFC: Dorsomedial Prefrontal Cortex, DLPFC: Dorsolateral Prefrontal Cortex, Switch: Task Switch Block, RPI Trial: Release From Proactive Inhibition Trial, 1stTr: First Trial After Task Switch, Task-switch Cost: Task-switch Cost *P<0.05, ***P<0.001 (Translated and cited from Reference 19)

表 3 主要評価項目：反応時間の線形混合モデル

	Estimate	Std. Error	df	t-value	P-value	
固定効果						
Intercept	1,151.951	35.775	41.801	32.200	<0.001	***
主効果						
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 試行)	-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	***
交互作用						
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	<0.001	***
MDD × DLPFC	-27.304	9.114	44301.841	-2.996	<0.01	**
MDD × RPI 試行	-2.509	14.952	44306.059	-0.168	0.867	
DMPFC × RPI 試行	-24.189	18.908	43456.552	-1.279	0.201	
DLPFC × RPI 試行	-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 試行	-10.030	36.665	44308.728	-0.274	0.784	
MDD × DLPFC × RPI 試行	-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：大うつ病性障害，Std. Error：標準誤差，DMPFC：背内側前頭前野，DLPFC：背外側前頭前野，Switch：タスク・スイッチブロック，RPI 試行：順行抑制から解放された試行，1stTr：タスク・スイッチ後 1 回目の試行，Task-switch cost：タスク・スイッチコスト * $P < 0.05$ ，** $P < 0.01$ ，*** $P < 0.001$
(文献 19 を和訳して引用)

Table 3 Primary Outcome Measure: Linear Mixed Model for Response Time

	Estimate	Std. Error	df	t-value	P-value	
Fixed Effects						
Intercept	1,151.951	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 trial)	-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	<0.001	***
MDD × DLPFC						
	27.304	9.114	44301.841	-2.996	<0.01	**
MDD × RPI trial						
	-2.509	14.952	44306.059	-0.168	0.867	
DMPFC × RPI trial	-24.189	18.908	43456.552	-1.279	0.201	
DLPFC × RPI trial	-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 trial	-10.030	36.665	44308.728	-0.274	0.784	
MDD × DLPFC × RPI trial	-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, DMPFC: Dorsomedial Prefrontal Cortex, DLPFC: Dorsolateral Prefrontal Cortex, Switch: Task-switch Block, RPI Trial: Trial Free From Proactive Interference, 1stTr: First Trial After Task-switch, Task-switch Cost: Task-switch Cost * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (Translated and cited from Reference 19)