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Application of functional connectivity neurofeedback in patients with treatment-resistant depression: A preliminary report

Masahiro Takamura [a,b], Go Okada [a,*], Toshiharu Kamishikiryo [a], Eri Itai [a], Miyuki Kato [a], Tomokazu Motegi [c], Jessica Elizabeth Taylor [c], Toshinori Yoshioka [c,d], Mitsuo Kawato [c,d], Yasumasa Okamoto [a]

[a] Department of Psychiatry and Neurosciences, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-Ku, Hiroshima 734-8553, Japan
[b] Department of Neurology, Faculty of Medicine, Shimane University, Izumo, Japan
[c] Brain Information Communication Research Laboratory Group, Advanced Telecommunications Research Institute International, Kyoto, Japan
[d] XNef Inc., Kyoto, Japan

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ABSTRACT

Functional connectivity neurofeedback (FCNef) is a technique that modulates synchronous neural activity through training and is being investigated as a potential novel treatment for patients suffering from treatment-resistant depression (TRD). An FCNef protocol, based on the analysis of resting-state functional imaging data from a large cohort of depressed individuals, has been proposed to promote negative functional connectivity between the dorsolateral prefrontal cortex and the posterior cingulate cortex (DLPFC-PCC FC). This study aimed to assess the therapeutic efficacy and practicality of the protocol in a small sample of TRD patients. Of the six patients recruited, five completed the FCNef sessions. Depression and rumination scores significantly improved post-treatment, however, there were no significant changes in DLPFC-PCC FC. The study demonstrated efficacy of FCNef in ameliorating depressive symptoms, yet, it also indicated that the training itself may be burdensome for depressed patients, as evidenced by participants reporting fatigue (one of whom dropped out). Thus, a more efficient and less burdensome protocol is needed for future investigations and applications.

1. Introduction

Depression is characterized by severe symptoms and high morbidity that significantly impacts the quality of life, and overcoming depression is an important social challenge. Specifically, addressing the heterogeneity of the condition, including the treatment of drug-resistant patients, is crucial (Rush et al., 2006). Recent advances have led to the development of several promising approaches for the diagnosis and treatment of depression. These include studies utilizing functional magnetic resonance imaging (fMRI) to identify the neural basis of various symptoms in depressed patients (Hamilton et al., 2012). Additionally, efforts have been made to generate fMRI-based biomarkers for diagnosis through the accumulation of large datasets and the application of machine learning techniques (Patel et al., 2016; Gao et al., 2018). In our previous study (Ichikawa et al., 2020), we employed machine learning algorithms to extract patterns of brain functional connectivity (FC) during resting-state that can discriminate melancholic depression from healthy subjects. As a result, a small number of resting-state FCs were determined, including an FC between the left dorsolateral prefrontal cortex (DLPFC) and the posterior cingulate cortex (PCC) / precuneus. In addition, the study examined changes in the FC before and after antidepressant treatment and found that drug treatment did not normalize the DLPFC-PCC FC. Previous neuroimaging research on depression has suggested that this functional coupling reflects a loss of control from the prefrontal cortex to the default mode network (DMN) region, which has been interpreted as being specifically related to ruminative symptoms (Bartova et al., 2015; Williams, 2016).

In terms of treatment strategy other than pharmacological intervention, a promising approach is the use of neurofeedback technology, in which brain activity is fed back to the individual for self-regulation (Pindi et al., 2022). There have been reports suggesting that functional connectivity neurofeedback (FCNef), which modulates functional

* Corresponding author.
E-mail address: goookada@hiroshima-u.ac.jp (G. Okada).

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connectivity (Watanabe et al., 2017), can have effects on a variety of psychiatric disorders (Pindi et al., 2022). Recently, Taylor et al. (2022) conducted a pilot study in subthreshold depressed populations to treat depression by promoting the anti–correlation of DLPFC-PCC FC. The study yielded promising results, including changes in functional connectivity and improvements in depression and rumination. The present study reports on the preliminary results of an FCNef training program designed to enhance the DLPFC-PCC anti-correlation in a small number of patients with treatment-resistant depression.

2. Methods

2.1. Participants

Patients with depression attending or hospitalized at University Hospital or a nearby medical facility were recruited. Inclusion criteria were age (20–80 years old), current diagnosis of a major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), and a recent major depressive episode with medication resistance (17-item Hamilton rating scale for depression (HRSD, (Hamilton, 1960)) score of 14 or higher after at least 4 weeks of adequate antidepressant medication) or low tolerance to medication (inability to take adequate doses due to adverse drug reactions). Exclusion criteria included a mental status making it difficult to understand the purpose of the study, a physical illness that makes it difficult to tolerate the examination, and conditions that are not amenable to MRI testing.

From 2019/5 to 2022/2, six patients enrolled. Participants were explained the details of the experiment in advance, and informed consent was obtained from all participants. One of the six participants withdrew on the third day due to fatigue. Finally, five participants completed the experimental procedure (two males and three females, mean age, 38.8 ± 6.3 years). The protocol of the current study was approved by Hiroshima University Certified Review Board (No. CRB6180006) and registered as jRCTs062180027.

2.2. Measures

The Beck Depression Inventory-II (BDI, (Beck et al., 1996)) and HRSD were used as depression severity scores. The Ruminative Response Styles (RRS) scale (Nolen-Hoeksema and Morrow, 1991) was administered to measure rumination symptoms. The RRS has subscores for Reflection, Brooding, and Depression. The RRS-Brooding was used as a measure of maladaptive rumination severity in this study based on previous reports (Taylor et al., 2022; Misaki et al., 2020).

2.3. Experimental procedure

The overall flow of this experiment of the FCNef training procedure are based on our previous study (Taylor et al., 2022) and the details are described in the supplementary materials.

On the first day of the experiment, psychological scores were measured and resting-state fMRI, structural MRI, and fMRI tasks were administered. Regions of interest (ROIs) for FCNef were then created based on activation and inhibition patterns in the two-back task, with the coordinates of the sphere determined for each individual from the activated DLPFC and inhibited precuneus regions during task execution.

Next, a sham session was conducted, during which participants were fed back random values instead of the values based on their own functional connectivity. The average functional connectivity of the participants in the sham session was then used to calculate the feedback score in the actual FCNef session. The actual FCNef session was then conducted for 4 days, starting with the next session. Resting-state fMRI was taken after the sham and real FCNef sessions. At the end of the final FCNef training day, psychological scores were measured. Follow-up examinations were also conducted at 1 week and 1 month after the final FCNef day to assess psychological scores.

2.4. FCNef training

FCNef training began with a resting state of 150 s, followed by four 62-second trials. The initial resting state was provided for signal stabilization and body movement compensation. One trial consisted of a 14-second resting state, a 42-second control period, and a 6-second feedback presentation. Changes in the FCNef training phase were indicated by cue stimuli on the screen. Participants remained in a resting state while the equal sign was presented. When the plus sign was presented, they were instructed to control their brain activity to increase the size of the feedback circle using a free strategy. Feedback was indicated by a green disk centered on the fixation point; the baseline value based on SHAM-FCNef session was indicated by a red circle. At the end of each run, participants were asked to rate their sleepiness and report the strategy used during the induction period.

2.5. MRI acquisition and analysis

Image acquisition was performed on a 3.0 Tesla Siemens MRI (MAGNETOM Skyra-fit). Functional images of the resting state, FCNef, and localization task were taken with the following parameters: slice number, 60; matrix size, 100 * 100; voxel size, 2.0 * 2.0 * 2.0 mm; TR, 1000 ms; TE, 28 ms; flip angle, 65°; and multiband factor, 6. Each resting state, FCNef, and localizer task session lasted 600 s, 512 s, and 590 s, respectively. T1-weighted structural images (MPRAGE) for spatial normalization of functional images were obtained with the following parameters: slice number, 240; matrix size, 256 * 256; FOV, 256 mm; voxel size, 1.0 * 1.0 * 1.0 mm (no slice gap); TR, 2300 ms; TE, 3.06 ms; and flip angle, 9°.

Matlab was used for image analysis. FCNef trial, localization task, and resting-state fMRI data were analyzed using the same procedures and the same scripts as in previous studies (Taylor et al., 2022), and the DLPFC-PCC FC during FCNef trial and resting-state fMRI were calculated.

2.6. Statistical analyses

To examine the treatment effect of FCNef, the depression symptom scores and DLPFC-PCC FCs during resting state and FCNef induction periods were analyzed by repeated-measured ANOVA with the Huynh-Feldt ε correction. In the post-hoc comparisons, p-values were corrected for multiple testing with the Holm method. The significance threshold was set to $P < 0.05$. Statistical analyses were conducted with JASP version 0.16.4 (JASP Team, 2022).

3. Results

Five patients completed the FCNef training session and the 1-week and 1-month follow-ups. Subjective and objective depression scores, as well as rumination scores, showed significant improvement after FCNef (Fig. 1). The effect of time was significant for BDI ($F(3, 12) = 5.10$, $p = 0.018$, $\varepsilon = 0.97$ $\eta^2 = 0.56$), HRSD ($F(3, 12) = 48.34$, $p < 0.001$, $\varepsilon = 1.00$ $\eta^2 = 0.92$), and RRS-Brooding ($F(3, 12) = 4.88$, $p = 0.025$, $\varepsilon = 0.87$ $\eta^2 = 0.55$). The post-hoc multiple comparisons revealed significant changes between Pre and Post FCNef in BDI, HRSD, and RRS-Brooding (Fig. 1). For long-term effects, only HRSD was significantly lower at 1 week and 1 month later compared to Pre. The course of change in the anti-correlation of DLPFC-PCC FC during FCNef training varied for each patient. It was observed that it tended to head off in the middle of the training, rather than monotonically becoming more negative (Fig. 2a). There was no significant effect of time on DLPFC-PCC FC in FCNef training ($F(4, 16) = 1.24$, $p = 0.334$, $\varepsilon = 0.97$ $\eta^2 = 0.28$) and resting-state ($F(4, 16) = 0.63$, $p = 0.644$, $\varepsilon = 1.00$ $\eta^2 = 0.14$) (Fig. 2b). Comparing the

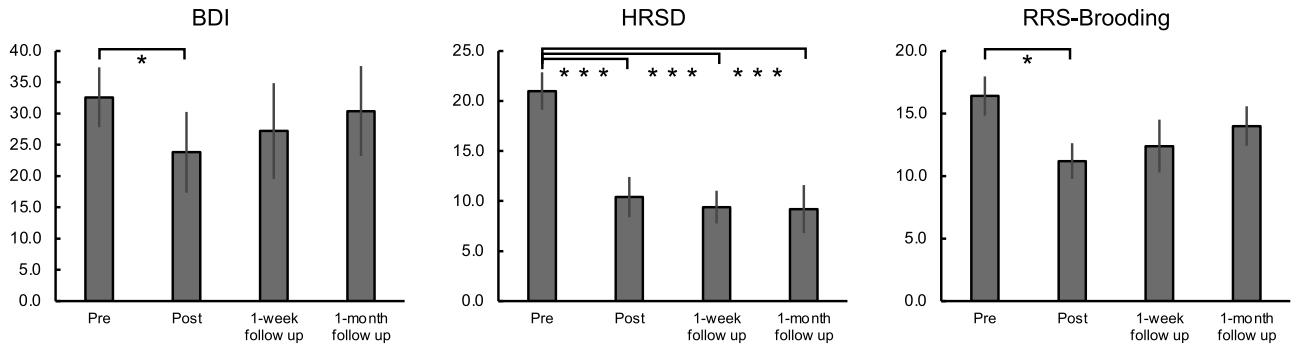

Fig. 1. FCNef training effect on depression symptom scores. BDI, Beck Depression Inventory-II; HRSD, Hamilton Rating Scale for Depression; RRS, Ruminative Response Styles scale. * $p_{corrected} < 0.05$, *** $p_{corrected} < 0.01$. Bar graph and error bars indicate mean ± standard error.

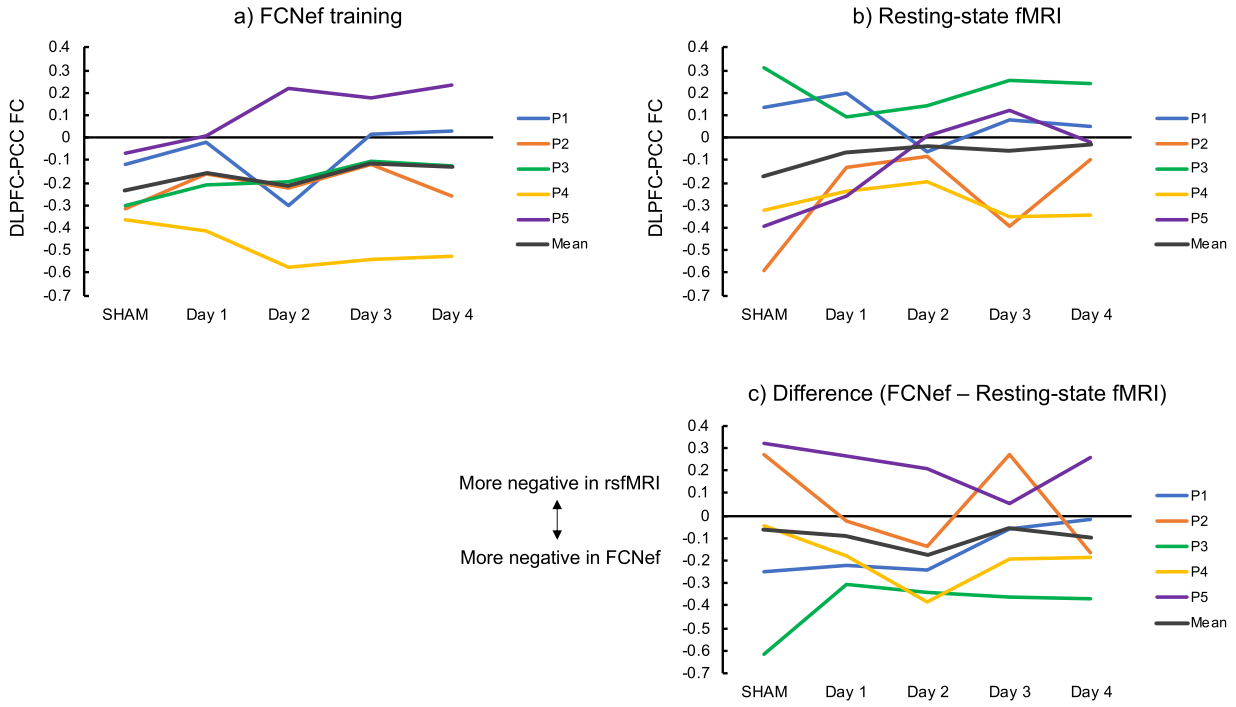

Fig. 2. FCNef training effect on DLPFC-PCC functional connectivity during (a) induction periods of the FCNef training, (b) resting-state fMRI and (c) difference between the training and resting-state conditions. Line graphs depict each individual's data and mean. rsfMRI, resting-state fMRI.

two conditions, in most cases the anti-correlation of DLPFC-PCC FC was more intense during FCNef training than during resting-state on inspection (Fig. 2c).

4. Discussion

This study was conducted to examine the treatment efficacy and tolerability of FCNef training, which enhances DLPFC-PCC anti-correlation (Taylor et al., 2022), in patients with treatment-resistant depression. Results showed significant improvement in depression severity after the training, as well as improvement in ruminative symptoms. Ruminative symptoms were considered to be associated with the DLPFC-PCC network, and the results were compatible with those of previous study (Taylor et al., 2022). A major limitations of this study is the limited sample size and single group. It was not possible to control for placebo effects or to fully examine the association between treatment effects and FC changes. Considering that sham neurofeedback has the risk of confusing patients and that neurofeedback itself imposes a burden on patients, it may be necessary to conduct an RCT comparing neurofeedback that targets neural circuits associated with different symptoms of depression in future work. Regarding the persistence of the treatment effect in this study, persistence was observed only for HRSD and not for BDI and RRS. It is known that clinician-assessed and self-reported results do not always agree (Uher et al., 2012), and it is possible that the discrepancy between HRSD, BDI, and RRS may be due to differences in the content and weighting of the assessments, in addition to the differences in whether they are clinician-led or self-report assessments. In any case, the persistence of the treatment effect cannot be clearly mentioned in this study and needs to be discussed in future studies. Although the anti-correlation of DLPFC-PCC FC was generally enhanced during the FCNef training, there was no observable group-mean improvement in DLPFC-PCC FC after FCNef intervention, either at resting state or during FCNef training. The baseline FC of some subjects in this study was already negative, and, therefore, may not have been able to change easily. The selection of intervention method based on the baseline assessment is an issue for future study. In addition, while the neurofeedback training affected clinical symptoms, the neurofeedback training itself may be burdensome for depressed patients with diminished interest and pleasure and easy fatigue as evidenced by participants' self-report after training

(Supplementary materials). More than half of the patients in this study reported at least mild fatigue, and one patient discontinued training on the third day due to fatigue. This suggests the need for an efficient protocol that is less burdensome for patients. Finally, although this study targeted DLPFC-PCC FC identified in the data-driven approach, future studies may also examine functional connectivity between the DLPFC and anterior cingulate cortex, which has been reported in neurostimulation studies (Baeken et al., 2014; Fox et al., 2012; Ge et al., 2020; Pizzagalli, 2011). In conclusion, the present study suggests that the FCNef training of the DLFPCC-PCC FC is a promising treatment for resistant depression, but improvements in the methodology are needed for further applications.

CRediT authorship contribution statement

Masahiro Takamura: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Go Okada:** Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Toshiharu Kamishikiryo:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Eri Itai:** Data curation, Writing – review & editing. **Miyuki Kato:** Writing – review & editing. **Tomokazu Motegi:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Jessica Elizabeth Taylor:** Formal analysis, Methodology, Writing – review & editing. **Toshinori Yoshioka:** Formal analysis, Methodology, Writing – review & editing. **Mitsuo Kawato:** Conceptualization, Formal analysis, Methodology, Data curation, Writing – review & editing. **Yasumasa Okamoto:** Conceptualization, Methodology, Writing – review & editing.

Declaration of Competing Interest

None

Data availability

The data that support the findings of the current study are not available due to ethical restrictions.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jadr.2023.100644.

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