

Is Alpha Wave Neurofeedback Effective with Randomized Clinical Trials in Depression? A Pilot Study

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Key Words

Neurofeedback · Depression · Clinical psychophysiology · EEG biofeedback · Frontal EEG asymmetry

Abstract

Frontal asymmetric activation has been proposed to be the underlying mechanism for depression. Some case studies have reported that the enhancement of a relative right frontal alpha activity by an asymmetry neurofeedback training leads to improvement in depressive symptoms. In the present study, we examined whether a neurofeedback training designed to increase the relative activity of the right frontal alpha band would have an impact on symptoms of depressive subjects suffering from emotional, behavioral, and cognitive problems. Our results indicated that the asymmetry neurofeedback training increased the relative right frontal alpha power, and it remained effective even after the end of the total training sessions. In contrast to the training group, the placebo control group did not show a difference. The neurofeedback training had profound effects on emotion and cognition. First, we replicated earlier findings that enhancing the left frontal activity led to alleviation of depres-

sive symptoms. Moreover, cognitive tests revealed that the asymmetry training improved performance of executive function tests, whereas the placebo treatment did not show improvement. We preliminarily concluded that the asymmetry training is important for controlling and regulating emotion, and it may facilitate the left frontal lobe function.

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Introduction

Depressed patients show relative hypoactivation in the left prefrontal area, which differs from that found in normal people who show relative hyperactivation in the left prefrontal area compared to the right frontal area [1–3]. This phenomenon was observed in remitted depressed patients [1] and children of a depressive mother [4]. This observation suggests that an impairment in the left prefrontal function may indicate susceptibility to depression [5].

Some scientists have attempted to modulate the susceptibility by increasing left frontal activity. Repetitive transcranial magnetic stimulation (rTMS) and neuro-

feedback have frequently been chosen to modulate cortical activity. Some rTMS studies have reported favorable results. The studies found that rTMS facilitated the activity in the left prefrontal cortex and also reported improvement in patients' mood symptoms [6–8].

The positive findings in the rTMS studies have raised the possibility that neurofeedback, which is a safer way to modulate brain activity, could be an alternative treatment option for depression. Rosenfeld et al. [9] were the first researchers who developed a neurofeedback protocol (called 'asymmetry protocol') for modifying brain asymmetry. Some case studies [10, 11] and an experimental study [12] have been conducted for altering frontal asymmetry. Baehr et al. [13] reported 2 cases of depressive women who received neurofeedback using the asymmetry protocol. Their scores on the depression scale of the Minnesota Multiphasic Personality Inventory, second edition [14] decreased to a normal range after the training session. The same authors [11] followed the change of depressive symptoms of patients who completed the training. They found that 50% of participants maintained treatment outcomes at 5-year follow-ups. Allen et al. [12] modulated the frontal asymmetry of normal subjects with 5 neurofeedback sessions. The randomly assigned 'left group', in which the left frontal activity was enhanced relative to the right frontal activity, showed an increase in positive mood and a decrease in negative mood in response to emotionally evocative films. These results suggest potential effectiveness of the asymmetry protocol, but the existing studies have some limitations.

First, Baehr et al. [10, 11] adopted a single-case design, which was not able to control for nonspecific treatment factors [15]. The existing case reports could not rule out the possibility that the positive outcome was merely due to participants' belief that they were being treated.

Second, Allen et al. [12] controlled for nonspecific treatment factors by employing a group experimental design. However, the subjects were not patients suffering from depression. Therefore, there is some doubt as to whether their results can be generalized to a clinical population.

In the present study, we investigated the psychophysiological and behavioral effects of the asymmetry training. We adopted a randomized control group design to control for nonspecific treatment factors. We recruited participants suffering from depression to evaluate clinical efficacy of the asymmetry protocol. We hypothesized that the asymmetry training will increase the relative left frontal activity and alleviate depressive symptoms.

Methods

Subjects

Participants were recruited from May 2006 to September 2006. All patients met the DSM-IV criteria for depressive disorders. Diagnoses were based on a semi-structured clinical interview (Structured Clinical Interview for DSM-IV Axis I Disorders) [16] by a clinical psychologist. Persons who had organic disorders or who had been treated with psychoactive drugs for at least 2 months prior to the study were excluded.

All patients gave informed consent for participation in the study. Twenty-four right-handed subjects with depressive mood were randomly assigned to two groups (EEG biofeedback/psychotherapy placebo) by a block randomization. Twenty-three participants completed the training. One participant from the psychotherapy placebo group dropped out after week 1 because of sudden relocation. The remaining members of both groups were comparable with respect to age, gender, education and symptom severity (table 1).

The number of remitted people in the training group was 5, and only 1 of them met the full remission criteria. The number of remitted people in the control group was 2, and everyone met the criteria of partial remission. In both groups, no subject had a history of hospitalization for psychiatric illness. Two persons had been treated by psychiatrists in outpatient settings, one of whom belonged to the training group and the other to the control group. Further, no one reported suicide attempts at any point in their life history.

Participants attended the clinic during the interview, baseline assessments and 5-week training, and at the 1-month follow-up. The Institutional Review Board of the Kyunghee University approved the study protocol.

Neurofeedback Training

The neurofeedback training was administered for 5 weeks. In all of our clinical training sessions, the neurofeedback system 'Procomp Infiniti' (Thought Technology Ltd.) and the 'asymmetry protocol' were used. The 'asymmetry protocol' had originally been developed by Rosenfeld [17]. Subjects who are treated with this protocol can be reinforced when the left midfrontal alpha power is decreased or when the right midfrontal alpha power is increased.

For the neurofeedback, EEGs from F3 and F4, both referenced to Cz, were recorded. The calculated index for measuring frontal asymmetry is $A_2 = (R - L)/(R + L)$, where R is alpha power at the cortical site F4 and L is that at F3 [17]. When this value exceeded 0, characters shown on the screen signaled the subjects a successful trial with classical music (Franz von Suppé 'Light Cavalry Overture') the volume of which varied with the A_2 value. The participants were told to try to keep the sound on and to try to continuously raise its volume. Subjects received training for 10 sessions (twice per week). Each training session consisted of 6 four-minute trials followed by 5 thirty-second rest periods.

Psychotherapy Placebo Training

Psychotherapy placebo sessions were provided for 5 weeks. The participants in this group did not receive neurofeedback. Instead, they participated in the psychotherapy placebo training. These sessions consisted of psychological assessment, interpretation of the test results, and providing information on the course

Table 1. Group characteristics and clinical data

	Training group (n = 12)	Placebo group (n = 11)	t/ χ^2
Age, years	28.46 ± 9.69	28.54 ± 6.84	-0.022
Education, years	15.83 ± 1.70	14.00 ± 2.00	2.377
Handedness	89.58 ± 8.38	89.55 ± 9.07	0.010
Number of depression episodes	1.54 ± 0.99	1.18 ± 0.87	0.922
Duration of total episodes, months	7.79 ± 11.21	11.00 ± 19.18	-0.495
Baseline stress score	25.58 ± 12.30	34.11 ± 12.13	-1.582
Sex (males/females)	2/10	4/7	1.155
Clinical status (current/remitted)	7/5	9/2	1.495
MMPI-2 depression scale score	62.08 ± 12.61	67.00 ± 16.07	-0.820

Handedness was measured by the Edinburgh Handedness Inventory. MMPI-2 = Minnesota Multiphasic Personality Inventory, second edition.

and treatment of mood disorders. They were told that it was part of the formal treatment session.

Self-Training

After subjects completed the neurofeedback training, they participated in a 1-month (twice per week) self-training session to maintain a similar mental state as during the neurofeedback training sessions but without the feedback system's assistance. In contrast to the EEG biofeedback training group, subjects who had finished psychotherapy placebo training were referred to other therapists who provided a conventional therapy for depression as needed.

Before and after Testing

The participants and evaluators were not blinded to the group assignments. Clinical ratings were administered by a clinical psychologist using the Hamilton Depression Inventory (HAM-D) [18]. The clinical ratings were recorded by a video camera, and 2 independent clinical psychologists verified the ratings. Interrater reliability was 0.99.

All participants completed self-report questionnaires, such as the Daily Stress Scale [19], the Automatic Thought Questionnaire-Positive (ATQ-P) [20], the Automatic Thought Questionnaire-Negative (ATQ-N) [21], and the Beck Depression Inventory II (BDI-II) [22].

Cognitive functions were assessed by the Semantic Fluency Test (SFT), the Phonological Fluency Test (PFT) and the Stroop Test (ST). The ST had been programmed in Superlab version 2.0 by the first author of this paper. The items of the ST were neutral (colored strings of a symbol), congruent (color names matching the written color), or incongruent (color names different from written color). The subjects were asked to push the corresponding colored key on the keyboard when color words were presented on a computer screen. The response latencies for the trials with incorrect responses were excluded from the response latency analyses. The response latencies for the trials were determined for each group and for each item (congruent, neutral, incongruent) from the individual median reaction times (RTs).

EEG was recorded by a Grass QP511 amplifier and Grass Ag-AgCl electrodes at 3 scalp locations: F3, F4, and Cz according to the international 10/20 system. All placements were referenced to the vertex (Cz), and an electrode attached to the forehead was used for ground. The vertex (Cz) is a popular reference site, which most of the asymmetry studies [1, 5, 10, 12, 23–27] employed. It is known to efficiently detect the difference of activities between two active sites [28]. Electrode impedances were all under 5,000 Ω .

Eye movement (electrooculogram, EOG) was recorded from electrodes placed above and below the right eye to allow for the removal of artifacts from the EEG. After preparing for recording, the participants were seated in a comfortable chair. Resting EEG was recorded for 8 min. One of two randomly generated sequences of four 1-minute blocks of eyes-open (O) and four 1-minute blocks of eyes-closed (C) resting EEG was recorded during each session (either O-C-C-O-C-O-O-C or C-O-O-C-O-C-C-O), with the sequence counterbalanced across the subjects. The subjects heard one tone signaling the beginning of each 60-second recording. A 30-second interval followed between the blocks.

These outputs were sent through Grass QP511 amplifiers set to pass signals from 3 to 100 Hz (3 dB cutoff at 3 and 100 Hz). Amplification was 20,000 for EEG leads and 5,000 for EOG leads. The signals were then passed through NI PCI 6024E DAQ hardware to a Pentium 1.2 GHz computer with Labview 6.1 software. We processed four eyes-open blocks and four eyes-closed blocks separately. Each of the four 1-minute EEGs was divided into 59 × 2-second epochs with 50% overlap.

Data windows exceeding an EOG amplitude of 80 μ V were deleted from the analysis. Due to EOG artifacts, an average of 15% (eyes open: 19%, and eyes closed: 11%) EEG epochs were rejected. We monitored the face of subjects during the EEG recording since facial expressions can distort the EEG signal. Five subjects made facial expressions and this affected EEG recordings. During those instances, we reminded the subjects of the instructions and recorded again. Other than EOG and facial electromyography elimination, all data were inspected visually to detect unidentified ar-

Table 2. Pre- and post-training comparisons of quantitative EEG in the eyes-open condition

Frequency band	Training		Placebo	
	Pre	Post	Pre	Post
<i>F3</i>				
Delta	5.88 (0.63)	6.00 (1.01)	5.83 (0.82)	6.17(1.38)
Theta	4.14 (0.72)	4.23 (0.70)	4.22 (0.48)	4.32 (0.65)
Alpha	4.04 (1.04)	4.17 (0.99)	3.82 (0.86)	3.98 (0.80)
Low beta	2.90 (0.85)	2.99 (1.05)	2.64 (0.61)	2.79 (0.65)
Mid beta	2.20 (0.90)	2.33 (0.85)	2.19 (0.53)	2.28 (0.68)
<i>F4</i>				
Delta	5.67 (0.48)	6.20 (1.05)	5.58 (0.65)	5.93 (1.06)
Theta	4.07 (0.70)	4.27 (0.63)	4.05 (0.49)	4.15 (0.52)
Alpha	3.72 (1.11)	4.14 (0.98)	3.66 (0.71)	3.78 (0.76)
Low beta	2.70 (0.87)	3.01 (1.01)	2.44 (0.49)	2.66 (0.58)
Mid beta	2.15 (0.86)	2.46 (0.72)	2.07 (0.56)	2.31 (0.58)

Figures are means of natural log-transformed EEG with standard deviations in parentheses. A significant group \times time \times hemisphere interaction was found ($p < 0.01$) in the training group.

tifacts. There was one occurrence and in this case we stopped recording and re-recorded the next day.

Artifact-free 2-second epochs were converted to 2-second Hamming windows and subjected to a fast Fourier transform algorithm for calculation of absolute (μV^2) powers. For each EEG frequency band, delta (0.2–3.9 Hz), theta (4–7.9 Hz), alpha (8–11.9 Hz), low beta (12–14.9 Hz) and mid beta (15–17.9 Hz), voltage values were calculated by the periodogram function of Matlab version 6.5 (Mathworks, Natick, Mass., USA). These values were natural log transformed to resolve the non-normal distribution of the EEG data, which is called natural log-transformed power.

Like most of the research that studied the frontal asymmetry, we selected the alpha band because it showed a good test-retest reliability [29]. As alpha power is inversely related to the activity of the brain, decreased alpha power could be interpreted as an increase in the activity of the corresponding brain area [30, 31].

Interhemispheric alpha power asymmetry, called A score, was computed for homologous sites F3–F4 as described by Tomarken et al. [27]. An asymmetry metric (A score) was computed for each epoch by subtracting log-transformed alpha power of the left midfrontal site from log-transformed alpha power of the right site ($\log R - \log L$).

All clinical instruments were applied twice (before and after training) with the measurement approximately 6 weeks apart. For the neurofeedback training group, a 1-month follow-up assessment was done.

Statistics

For pre- and post-training comparisons of EEG, group (training, placebo) \times time (before training, after training) \times hemisphere (left, right) analyses of variance (ANOVAs) with repeated measures were performed. For pre- and post-training compari-

sons of asymmetry score and cognitive measures, group (training, placebo) \times time (before training, after training) ANOVAs with repeated measures were performed.

Data measured by self-report questionnaires could be affected by life stress change [32–34]. To control the confounding effect of life stress change, all self-report data were analyzed using repeated-measures analyses of covariance, which added a stress change score (post-test score minus pre-test score of the Daily Stress Scale) as a covariate. In case of significant group \times time interactions, post hoc paired t tests were computed for each group separately.

As 2 scales (BDI-II and ATQ-P) did not satisfy the parametric assumption, the rank transformation procedure [35] was employed for these variables. The procedure is a nonparametric analysis substituting mixed-design ANOVAs. In case of significant group \times time interactions, Mann-Whitney tests were computed for each group separately.

To evaluate change from post-treatment to 1-month follow-up, we used a paired t test.

Categorical measures were compared with χ^2 and Fisher's exact tests. Himadi et al.'s [36] criteria were adopted to classify the participants as responders. According to their criteria, a responder should be free of depressive episodes after the treatment and show at least a 20% decrease in score from the pretest on 75% of outcome measures. For all statistical procedures, significance was set at $p < 0.05$.

Results

Pre- and post-training comparisons of EEG activities are presented in table 2 and table 3. For alpha activity, the repeated-measures ANOVA revealed a group \times time \times hemisphere interaction in the eyes-open condition [$F(1, 21) = 14.39$; $p < 0.01$]. To interpret the meaning of the interaction effect, a two-way ANOVA followed in each group. There was a significant time \times hemisphere interaction in the training group [$F(1, 11) = 46.50$; $p < 0.001$], but not in the control group. Although a log-transformed alpha power difference between the pre- and post-tests was found in the training group [$t(11) = -2.74$, $p < 0.05$], such a difference was not found in the control group.

Three-way interaction effects of the alpha activity were not found in the eyes-closed condition. For other frequency bands (delta, theta, low beta and mid beta), no significant effects containing the factors group \times time \times hemisphere were obtained.

Pre- and post-training comparisons of the asymmetry scores are summarized in figure 1. For the A_1 score, a significant group \times time interaction was obtained in the eyes-open condition [A_1 : $F(1, 21) = 15.53$; $p < 0.01$], but no interaction was found in the eyes-closed condition. Although, in the eyes-open condition, there were no pre-training differences for the A_1 score between the two

Fig. 1. Pre- and post-training comparisons of asymmetry score. A significant group \times time interaction was found ($p < 0.01$) in the eyes-open condition. There were significant post-training differences in both conditions. * $p < 0.05$, ** $p < 0.01$.

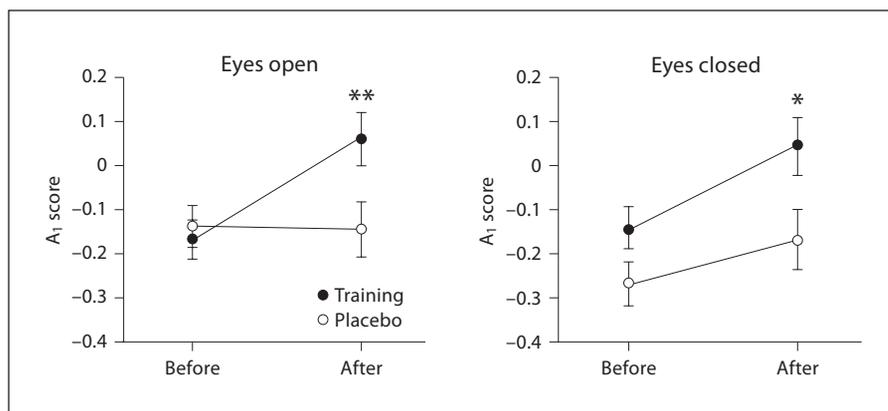
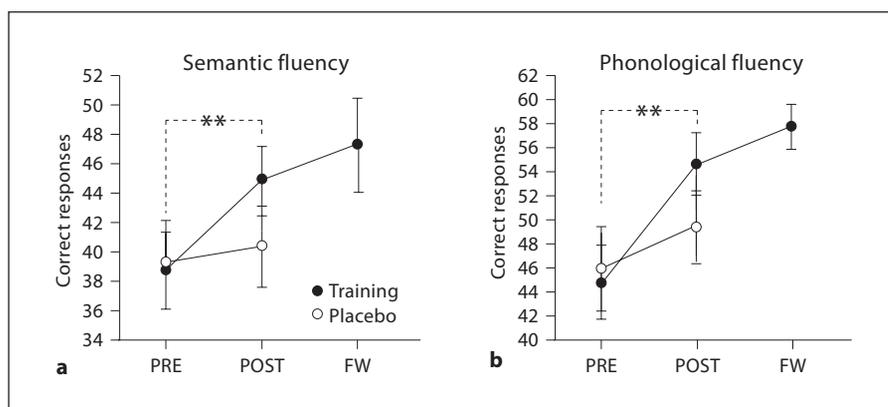


Fig. 2. Pre-training (PRE), post-training (POST) and 1-month follow-up (FW) comparisons of the Verbal Fluency Test. Dotted lines show the changes of the correct responses of the SFT (a) and of the PFT (b). $p < 0.01$.



groups, there were post-training differences between the scores of the two groups [A_1 : $t(21) = 2.32$, $p < 0.01$].

Pre- and post-training comparisons of clinical assessments are summarized in table 4. For the BDI-II, ATQ-N, and HAM-D, significant group \times time interactions were found [BDI-II: $F(1, 20) = 6.87$, $p < 0.05$; ATQ-N: $F(1, 20) = 6.02$, $p < 0.05$; HAM-D: $F(1, 20) = 5.96$, $p < 0.05$]. For ATQ-P, a trend toward significance was observed [$F(1, 20) = 4.00$, $p = 0.059$]. In BDI-II, ATQ-N, HAM-D, and ATQ-P, although there were no pre-training differences between the two groups, there were post-training differences between them [ATQ-N: $t(21) = -2.27$, $p < 0.05$; HAM-D: $t(21) = -2.70$, $p < 0.05$; BDI-II: $U = 31.00$, $p < 0.05$; ATQ-P: $U = 32.50$, $p < 0.05$].

Pre- and post-training comparisons of verbal fluency functions are summarized in figure 2. For the number of correct responses in the SFT, a significant group \times time interaction resulted [$F(1, 21) = 9.45$; $p < 0.01$]. In the SFT, the average score of the training group increased after the training [$t(11) = -3.48$, $p < 0.01$]. The placebo group did not show a significant increase in the score. For the

Table 3. Pre- and post-training comparisons of quantitative EEG in the eyes-closed condition

Frequency band	Training		Control	
	Pre	Post	Pre	Post
<i>F3</i>				
Delta	6.37 (0.85)	6.70 (0.58)	6.33 (1.08)	6.49 (1.24)
Theta	4.13 (0.77)	4.44 (0.72)	4.33 (0.61)	4.51 (0.70)
Alpha	4.64 (1.02)	4.72 (0.91)	4.64 (0.87)	4.54 (0.90)
Low beta	3.09 (0.97)	3.12 (1.10)	2.89 (0.68)	3.07 (0.88)
Mid beta	2.34 (0.95)	2.58 (0.82)	2.34 (0.58)	2.47 (0.69)
<i>F4</i>				
Delta	6.04 (1.05)	6.84 (0.78)*	6.12 (0.84)	6.27 (0.78)
Theta	4.13 (0.96)	4.49 (0.71)	4.10 (0.58)	4.31 (0.67)
Alpha	4.53 (1.01)	4.79 (0.93)	4.33 (1.02)	4.35 (1.07)
Low beta	2.93 (0.99)	3.22 (0.97)	2.74 (0.81)	2.64 (1.03)
Mid beta	2.26 (0.82)	2.47 (0.77)	2.14 (0.73)	2.45 (0.84)

A significant increase in natural log-transformed delta power was found at the F4 site of the training group (* $p < 0.05$). Figures are means of natural log-transformed EEG with standard deviations in parentheses.

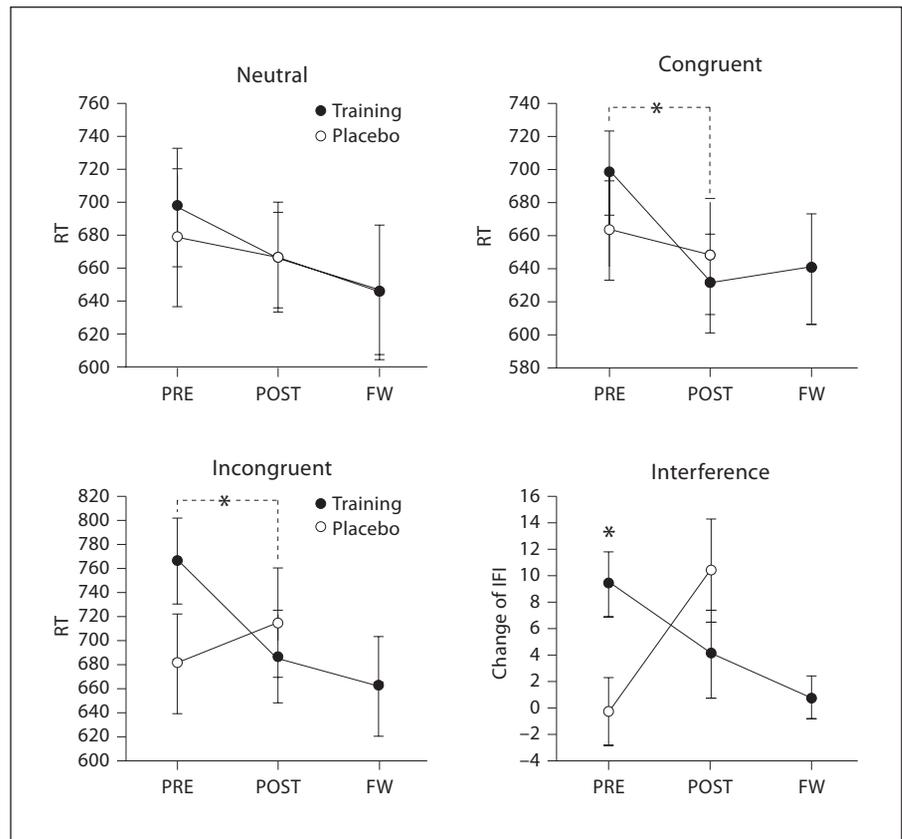


Fig. 3. Pre-training (PRE), post-training (POST) and 1-month follow-up (FW) comparisons of the ST. Dotted lines show RT changes of the training group in the congruent condition and incongruent condition. Group difference in IFI was found in the pre-treatment assessment. * $p < 0.05$.

Table 4. Means (standard deviations) on clinical assessments

	Training group (n = 12)		Placebo group (n = 11)		Statistics ^a
	Pre	Post	Pre	Post	
BDI-II	22.75 (12.35)	9.08 (6.92)	26.18 (16.21)	21.27 (15.86)	G × T: $p < 0.05$; T: $p < 0.001$
ATQ-P	74.83 (14.70)	85.08 (9.31)	76.22 (32.88)	76.11 (31.44)	G × T: $p < 0.05$; T: $p < 0.05$
ATQ-N	84.67 (24.13)	59.00 (20.15)	87.44 (33.59)	78.11 (28.83)	G × T: $p < 0.05$; T: $p < 0.001$
HAM-D	11.33 (7.52)	4.08 (4.14)	12.36 (7.67)	11.08 (7.91)	G × T: $p < 0.05$; T: $p < 0.05$

G = Group; T = time. ^a d.f. = 1, 21.

number of correct responses in the PFT, a trend in group × time interaction was found [$F(1, 21) = 4.02$; $p < 0.1$]. In the PFT, the average score of the training group increased after the training [$t(11) = -4.70$, $p < 0.01$]. The placebo group did not show a significant increase in the score.

We then compared the RT of the pre-training ST with that of the post-training ST. Figure 3 shows the change of

RT of the neutral, congruent, and incongruent condition and the change of the interference index (IFI). A group × time ANOVA did not reveal any main and interaction effects in the neutral condition.

A group × time ANOVA on the congruent condition revealed a significant main effect of time [$F(1, 21) = 4.98$; $p < 0.05$]. In this condition, the average RT of the training group decreased after the training [$t(11) = 2.57$, $p < 0.05$].

The placebo group did not show a significant reduction in the RT.

A group \times time ANOVA on the incongruent condition revealed a significant group \times time interaction [$F(1, 21) = 4.98$; $p < 0.05$]. In the training group, the RT in the incongruent condition decreased [$t(11) = 2.88$, $p < 0.05$] after the training but the placebo group did not show any performance change.

A group \times time ANOVA on the IFI revealed a significant interaction effect [$F(1, 21) = 5.99$; $p < 0.05$]. Although there were significant pre-training differences between the two groups [$t(21) = 2.69$, $p < 0.05$], there were no post-training differences between them.

Subsequent analysis showed that differences in all physiological, clinical, and neuropsychological assessment scores between the post-training and 1-month follow-up were not significant.

In the training group, the number of responders was 6, which means 50% of the participants improved to a clinically meaningful level. In the placebo group, no one was classified as a responder. No participants reported significant side effects.

Discussion

To the best of our knowledge, this is the first attempt to examine the efficacy of an asymmetry training in depression by adopting an experimental design. In the present pilot study, the effects of 10-session asymmetry training were investigated in subjects with depressive symptoms compared to a psychotherapy placebo group.

The neurofeedback training induced left frontal dominance. Alpha absolute power of the right frontal area increased, and asymmetry scores increased in the training group exclusively. The training effect was only observed in the alpha band, which was originally a target of the neurofeedback training. As alpha power inversely correlates with the activity of the corresponding brain area [30, 31] and the increase in the asymmetry score meant relative dominance on the left frontal area, these results can be interpreted that neurofeedback relatively weakened the right frontal activity.

The change of asymmetric brain activity pattern was only found in the eyes-open condition. This finding is consistent with previous research [37, 38] which found that an alpha enhancement effect had been easily observed in a specific condition in which visual input was presented. The training effect accomplished in the eyes-closed condition could not exceed a mere alpha increase

of eyes closed [37]. Our findings suggest that the alpha enhancement training effect should be measured in the eyes-open (or similar 'alpha blocking') condition.

From a behavioral perspective, the training decreased depressive symptoms and enhanced executive functions of participants. Moreover, 50% of the subjects showed clinically meaningful changes, which were not found in the psychotherapy placebo group. Taken together, these findings can lead to the conclusion that the increased activity of the left frontal cortex may suggest a neurophysiological correlate of mitigated depressive symptoms.

The results of the current study were consistent with previous case reports [10, 11] and rTMS studies [6–8]. In addition, we found that the effect of neurofeedback was greater than that of psychotherapy placebo which contained most of nonspecific treatment factors. It means that the effectiveness of neurofeedback treatment could not entirely be explained by the nonspecific treatment factors.

It should be noted that the result of our study suggested a causal relationship between the asymmetric frontal activity and depressive symptoms. Depression had been characterized by the hypoactivation in the left prefrontal cortex and hyperactivation in the right frontal cortex [3, 39], which raised the possibility that the imbalance of the bilateral prefrontal activity was a biological cause of depression. Although previous neurofeedback studies [10–12, 17, 40] partially supported this assumption, most of them just showed a cross-sectional relationship between two variables. Only Allen et al.'s [12] study revealed that alteration of the asymmetric frontal activity could change human emotional response. Our research extended Allen et al.'s [12] finding to the area of pathophysiology of an emotional disorder.

The asymmetry training is thought to play a key role in the treatment of depression, but the internal mechanism by which depressive symptoms are alleviated is uncertain. Recent findings from the information process study of normal persons give us a broader view on the mechanism of neurofeedback. According to the report by Cohen and Shaver [41], the left hemisphere holds an advantage in processing positive emotional information, whereas the right hemisphere holds an advantage in processing negative emotional information. Decreased negative-biased processing associated with decreased right frontal activity (induced by neurofeedback) may diminish negative cognition and emotion in depressive subjects. Further research is required to precisely elucidate the brain mechanism responsible for the treatment outcome we obtained.

Another important finding of our study is that the changes of frontal asymmetry and depressive symptoms were maintained for more than 1 month, which indicates that the change induced by neurofeedback can be generalized across time. Given that depression frequently relapses [42], a longitudinal follow-up study should be conducted to determine whether generalization of training prevents a recurrence of depression.

Despite the favorable results of the asymmetry training, the present study has limitations. First, 12 subjects are an insufficient number to generalize the efficacy of training. Second, a single-blind design might evoke a rater bias although this possibility seemed to be minimal as there was a high concordance between independent raters who did not know subject allocation. Additional research with a sham randomized controlled double-blind study is recommended to overcome this limitation. Third, our EEG recording method is not sufficient to investigate the change of brain activity. Two-channel recording cannot examine how a change in the frontal activity affects other brain areas. Fourth, reference montage using the vertex electrode has its own limitation. Though vertex montage is of a great advantage to a researcher who wants to assess the frontal asymmetry with a small number of

electrodes, there is a possibility that variations in power at Cz can distort the magnitude and direction of asymmetry recorded from lateral sites [43]. Davidson [39], the frontier of asymmetry research, recommended to use computer-derived average reference using a large number of active electrodes. The use of multichannel EEG recording or neuroimaging techniques (e.g. fMRI, PET) is likely to yield data that truly advance our understanding of asymmetry training.

Our pilot study raises the possibility that EEG biofeedback might be a promising alternative treatment for depressive patients who cannot comply with a biological treatment due to side effects. A study with a sufficiently large number of subjects and a placebo-controlled design, and repetitive replications will improve the validity of the asymmetry neurofeedback training.

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