

The Efficacy of Neurofeedback Among Patients with Major Depressive Disorder: Preliminary Study

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Abstract

Introduction: Alpha asymmetry of the left and right frontal hemisphere is a potential biomarker for major depressive disorder (MDD). Neurofeedback (NFB) is a clinical intervention program for regulating brain activity and decreasing alpha asymmetry. The purpose of this study was to explore the efficacy of NFB among patients with MDD. **Methods:** Fourteen patients with MDD were randomly assigned to a NFB group that received neurofeedback training 1 hr weekly for 6 weeks and to a control group that was treated without training. A 5-min resting baseline of electroencephalogram (EEG) was recorded at F3 (left) and F4 (right) before and after NFB, and the alpha power was analyzed as an asymmetry index (A1). **Results:** The A1 of the control group decreased from pre- to post-interventions while the A1 of the NFB group increased from pre- to post-interventions. Anxiety and depression scores of the responder group decreased from pre- to post-interventions, while the scores of the non-responder group increased from pre- to post-interventions. **Conclusion:** Patients who respond to the NFB training showed a decrease in anxiety and depression scores compared to those who do not. This study indicated that NFB could improve left frontal hypoarousal or right frontal hyperarousal among patients with MDD.

Keywords: major depressive disorder; neurofeedback; electroencephalogram; alpha asymmetry

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Introduction

Major depressive disorder (MDD) is one of the common mental disorders that cause individual physical discomfort and emotional suffering, as well as interpersonal problems, and impaired social and career functioning. Depression is usually treated with antidepressant medications; however, recent research suggests that for children and teenagers with major depression, 13 out of the 14 antidepressant drugs do not work and can increase teenage suicide rates (Le Noury et al., 2015). Even in adults, selective serotonin reuptake inhibitors, such as Prozac, may not work any better than placebo; in addition, almost all studies that have demonstrated positive pharmaceutical effects have been directly or indirectly sponsored by

pharmaceutical companies (Ebrahim, Bance, Athale, Malachowski, & Ioannidis, 2016). To avoid antidepressant side effects and offer patients MDD treatment, neurofeedback (NFB) is a promising new approach.

Electroencephalographic (EEG) studies have found greater alpha power over the left than the right frontal regions among patients with MDD (Debener et al., 2000; Gotlib, Ranganath, & Rosenfeld, 1998). Davidson (1984) indicated that the frontal alpha asymmetry with an active left frontal lobe is related to the behavioral approach system (BAS), leading to more positive emotions, motivation, and behavioral approaches. On the other hand, an active right prefrontal lobe is related to behavioral inhibition system (BIS), leading to more negative emotions,

escape-related motivation, and behavioral withdrawal.

Davidson (1998) calculated the alpha asymmetry score (A score) from the alpha power at the left frontal (L or F3) and right frontal (R or F4) lobes. Baehr, Rosenfeld, and Baehr proposed two equations for the A score: $A1 = \log(R) - \log(L)$ and $A2 = (R - L) / (R + L)$ (Baehr, Rosenfeld, & Baehr, 1997; Rosenfeld, Baehr, Baehr, Gotlib, & Ranganath, 1996). When the alpha power at the right frontal lobe is higher than that in the left frontal lobe, the A1 score is positive and is associated with more positive emotions (such as happiness and joy), motivation, and approach behavior from the BAS system. When the alpha power at the right frontal lobe is lower than that in the left frontal lobe, the A1 score is negative and is associated with more negative emotions (such as fear, disgust, and sadness), escape-related motivation, and behavior withdrawal from the BIS system (Davidson, 1984). The prefrontal alpha asymmetry suggests brain lateralization (hemispheric laterality; Davidson, 1984, 1993, 1998).

Patients with MDD show lower alpha asymmetry scores as compared to healthy adults (Cantisani et al., 2015; Coan and Allen, 2004; Debener et al., 2000; Kemp et al., 2010). Similar alpha asymmetry was also observed in patients with remission from MDD (Stewart, Coan, Towers, & Allen, 2011).

Based on the concept that alpha asymmetry is a potential biomarker for depression, Baehr et al. (1997) developed a neurofeedback protocol, the Alpha Asymmetry (ALAY) protocol, to train patients to change the frontal alpha asymmetry as neurofeedback training for depression. The goals were to decrease the left frontal alpha power at F3 to improve positive emotion and increase the right frontal alpha power at F4 to decrease depression. Case reports found that the ALAY protocol could improve the frontal alpha asymmetry and decrease depressive symptoms (Baehr et al., 1997; Dias & van Deusen, 2011; Rosenfeld et al., 1996). The treatment effectiveness was maintained through 1- to 5-year follow-ups (Baehr, Rosenfeld, & Baehr, 2001).

Several studies have shown that neurofeedback has long-term benefits and show significant improvement in the frontal alpha asymmetry and depressive symptoms. Choi et al. (2011) conducted a randomized sham control group study comparing a 1-hr twice a week for 10 weeks NFB group (ALAY protocol) with a psychotherapy group. The NFB

group as compared to the psychotherapy group showed higher A1 scores, increased positive autonomic thoughts, decreased negative autonomic thoughts, and improved performance of the executive function tests, such as semantic and phonological fluencies. Peeters, Oehlen, Ronner, van Os, and Lousberg (2014) confirmed that the neurofeedback with the ALAY protocol did decrease the depression score, but did not decrease the A1 score after 10 sessions for decreasing left frontal alpha power.

Previous studies have found that the average number of sessions of the NFB protocol were between 10 and 36 sessions (Baehr et al., 1997, 2001; Choi et al., 2011; Peeters et al., 2014; Rosenfeld et al., 1996). The average treatment sessions to complete the NFB protocol are 20–22 sessions (Hammond, 2005). After 3–6 sessions of 30-min each of NFB, patients may feel the difference between pre- and post-interventions. After 10–12 sessions, patients feel a significant improvement. For sustained, long-term changes and clinical benefits of neurofeedback, 30 to 60 sessions may be required, which depends on compliance and motivation (Linden, Habib, & Radojevic, 1996). Hammond (2005) indicated that patients might feel the differences after 3–6 sessions of neurofeedback; however, this has not been systematically explored. The purpose of this study was to examine: (1) a short-term six-session ALAY protocol of NFB among patients with MDD, and (2) the efficacy of the ALAY protocol in increasing the alpha asymmetry score and decreasing depressive symptoms among patients with MDD in Taiwan.

Methods

Participants

Fourteen patients with MDD were referred by psychiatrists based on the criteria of Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) at an outpatient clinic of Kaohsiung Medical University Hospital (American Psychiatric Association, 2013). Patients with MDD with serious physical and mental disorders (e.g., cancer, heart disease, kidney disease, Alzheimer's disease, Parkinson's disease, schizophrenia, bipolar disorder, substance abuse, etc.) were excluded from this study. The institutional review board approval was obtained from the ethics committee of the Kaohsiung Medical University Hospital (KMUH-IRB-20110063), and written informed consent was obtained from each participant before the experiment.

All participants were assigned randomly to the NFB group and the control group. There was no

significant difference between the two groups in age, sex, Beck Anxiety Inventory (BAI), Beck Depression Inventory-II (BDI-II), and duration of disorder. Participants in both groups received medications by psychiatrists; however, there was no group difference in the categories of medications (Table 1). All participants in both groups received neither psychotherapy nor other nonpharmacological treatment at the same time. The equal group design was confirmed in this study. Participants in the NFB

group received 1 hr per week for 6 weeks of neurofeedback that was based on the ALAY protocol (Baehr et al., 1997). The ALAY protocol included down-training of the alpha power (8–12 Hz) at F3 and up-training of the alpha power (8–12 Hz) at F4, and the treatment goal was to increase the A1 score (Baehr et al., 1997; Baehr, Rosenfeld, Baehr, & Earnest, 1998). Participants in the control group received the pharmacological treatment only.

Table 1
The Demographic Characteristics of All Participants

Variable	NFB group (<i>n</i> = 7)	Control group (<i>n</i> = 7)	<i>t</i> / χ^2
Age (years)	49.86 (3.98)	47.43 (13.84)	-0.45
Sex			
Women	5	6	
Men	2	1	0.42
Beck Anxiety Inventory	17.86 (10.51)	16.00 (9.92)	-0.34
Beck Depression Inventory-II	30.14 (10.25)	22.86 (13.03)	-1.16
Duration of disorder (years)	8.83 (2.71)	6.68 (5.37)	-0.88
Medications			
Benzodiazepine	6	5	0.42
Selective serotonin reuptake inhibitors	1	2	0.42
Atypical antidepressants	5	4	0.31
Sedative-hypnotic	4	2	1.17

Psychological questionnaires

All participants completed self-report questionnaires that covered demographic characteristics (such as age, sex, and years of disorder), BAI, and BDI-II at pre- and post- interventions of neurofeedback. The BAI and BDI-II are self-report questionnaires that measure the symptoms of anxiety and depression disorder over the course of a period, respectively.

EEG equipment and measurement

The BrainAvatar Version 4.0 (BrainMaster Technologies, Inc., Bedford, OH) EEG system was used for EEG data collection, with a 19-channel EEG cap which was placed on the participants' scalps, and linked-ear was the reference to collect EEG raw signals. All participants were measured for a 5-min baseline with eyes closed at pre- and post-NFB intervention. The BioGraph Infiniti Version 6.1.1 (Thought Technology Ltd., Montreal, QC,

Canada) was used with a bipolar-channel at F3 and F4 based on the International 10-20 system, Cz was the reference, and the left earlobe served as ground (Baehr et al., 1997). The impedances of the electrode were set below 5 k Ω ; band-pass was 1–30 Hz, notch filter was at 60 Hz, and the sampling rate was 256 Hz.

Data reduction and statistical analysis

The EEG raw signal was analyzed using MATLAB R2008a (The Math Works, Natick, MA), and the EEG power spectrum was transformed to the alpha power (8–12Hz) by EEG insight software (Delorme & Makeig, 2004). The frontal alpha asymmetry score (A1 index) was computed with the natural logarithms (ln) by subtracting the left alpha power from the right alpha power, $A1 = \log(R) - \log(L)$ (Baehr et al., 1997).

The t -tests and χ^2 test were used to examine the equal group design on the demographic characteristics. The paired t -tests were used to examine the differences in the A1 score, BAI, and BDI-II at pre- and post-intervention for the NFB group and control group. In addition, the change-score of A1 = (A1 at post-intervention – A1 at pre-intervention) was used to separate participants in the NFB group and control group into a responder group and non-responder group. Participants in the responder group showed an increased A1 score; the non-responders had no change in the A1 score. In addition, this study also examined the differences in the A1 score, BAI, and BDI-II at pre- and post-interventions between the responder group and the non-responder group.

Results

The treatment effectiveness of neurofeedback on the A1 score

The A1 score was increased slightly in the NFB group from pre-intervention ($M = 0.11$, $SD = 0.13$) to post-intervention ($M = 0.12$, $SD = 0.13$); the A1 score was decreased slightly in the control group from pre-intervention ($M = 0.04$, $SD = 0.07$) to post-intervention ($M = 0.02$, $SD = 0.07$; Table 2). Although an overall increase in the alpha power at F3 and F4 was observed from pre- to post-intervention in both NFB and control groups. However, there was no significant difference between the two groups in the A1 score.

Table 2

The Changes in the Alpha Power from Pre- to Post-interventions in the NFB Group and the Control Group

Alpha Power	Pre-intervention	Post-intervention	t
NFB group ($n = 7$)			
F3	10.10 (4.58)	12.77 (5.23)	-1.07
F4	10.91 (4.27)	14.42 (5.75)	-1.26
A1	0.11 (0.13)	0.12 (0.13)	-0.24
Control group ($n = 7$)			
F3	5.51 (3.95)	7.27 (5.42)	-1.18
F4	5.80 (4.14)	7.57 (5.76)	-1.24
A1	0.04 (0.07)	0.02 (0.07)	0.63

The responders showed an increased A1 score as compared to the non-responders in the NFB group.

This study used the change-score of A1 to separate participants in the NFB group into a responder group and a non-responder group. Although the A1 score

was not different between the two groups, four participants (57.14%) showed increased A1 score from pre- to post-interventions; however, three of them (42.86%) showed decreased A1 score after neurofeedback training (Figure 1).

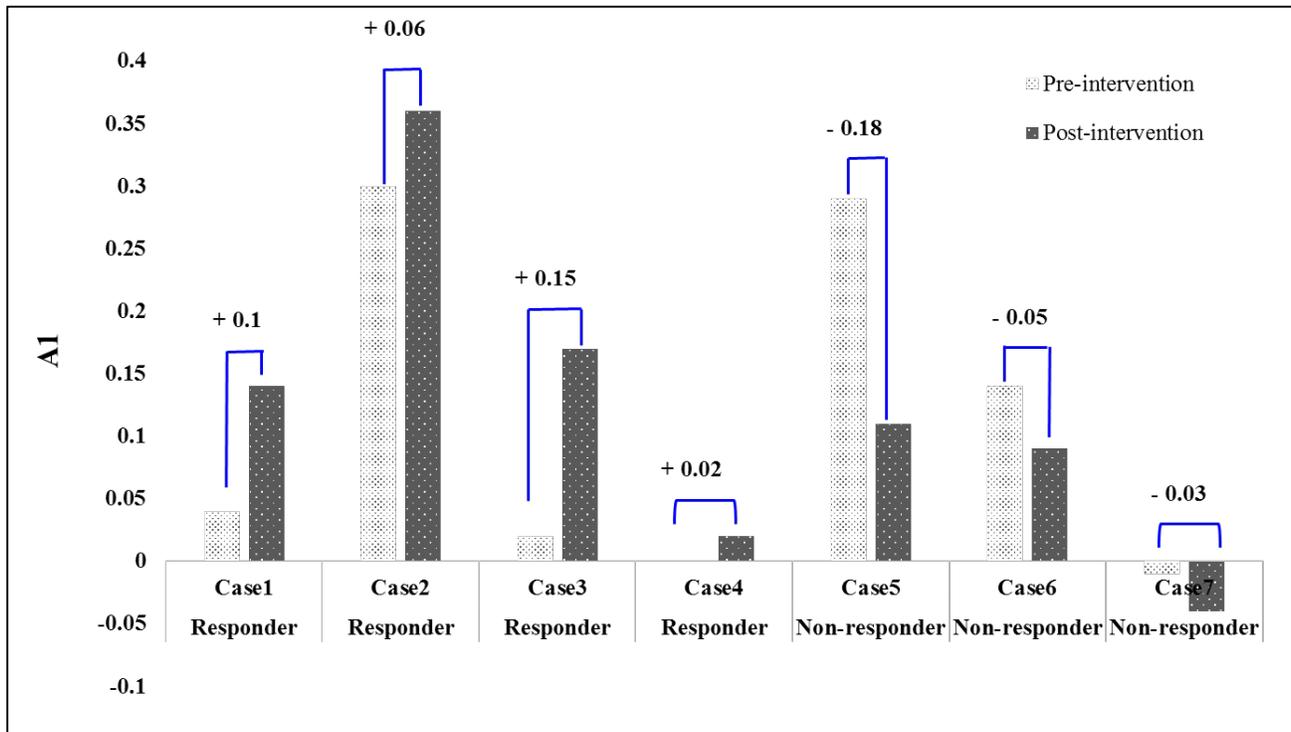


Figure 1. The A1 score at pre- and post-interventions between the responders and non-responders in the NFB group. Note: Change-score of A1 = (A1 at post-intervention) – (A1 at pre-intervention).

The responders showed a decrease in anxiety and depression scores as compared to the non-responders in the NFB group.

In the NFB group, anxiety and depression scores were decreased slightly from pre- to post-interventions (BAI: 23.00 to 18.00; and BDI-II: 35.75 to 29.25, respectively) in the responder group ($t = 0.99$, $p > 0.05$; and $t = 1.32$, $p > 0.05$); otherwise, anxiety and depression scores were increased slightly from pre- to post-interventions (BAI: 11.00 to 24.67; and BDI-II: 22.67 to 28.33, respectively) in the non-responder group ($t = -1.39$, $p > 0.05$; and $t = -0.87$, $p > 0.05$; Figure 2).

In addition, we used similar analysis of the responder group and non-responder group for the control group. The results showed that in the control group, the scores of anxiety and depression decreased slightly from pre- to post-interventions in the responder group (BAI: 15.00 to 10.75; and BDI-II: 19.00 to 13.75, respectively); otherwise, anxiety and depression scores were increased or did not change from pre- to post-interventions (BAI: 17.33 to 19.33; and BDI-II: 28.00 to 28.00, respectively) in the non-responder group (Figure 2).

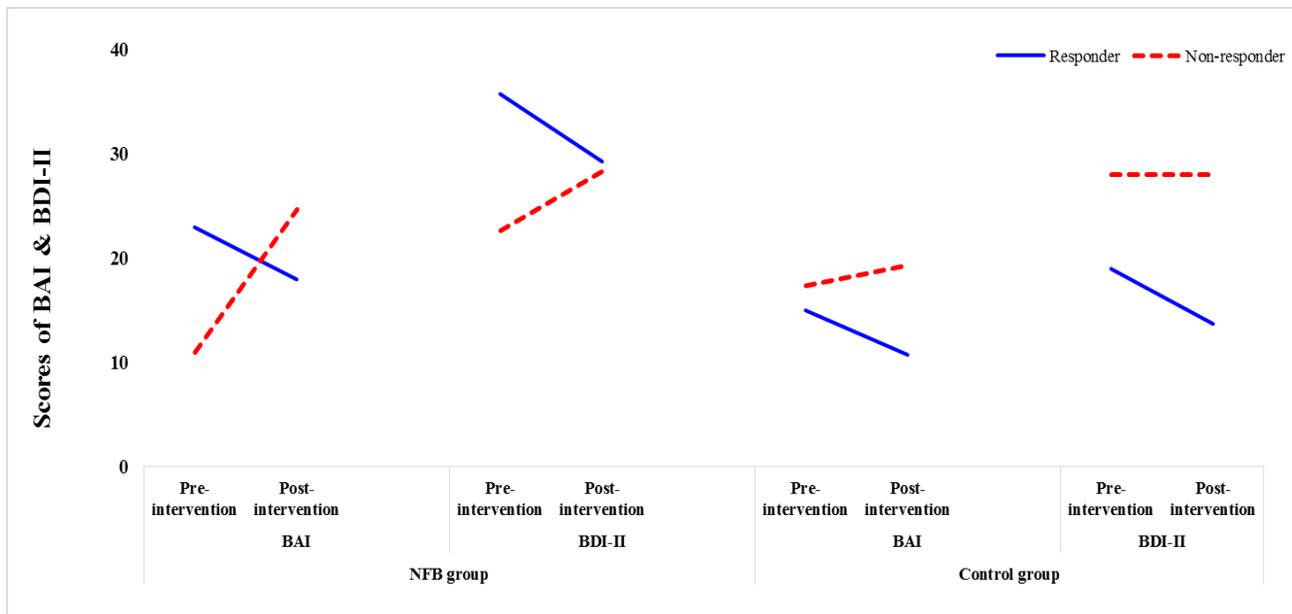


Figure 2. The scores of BAI and BDI-II at pre- and post-interventions between the responders and non-responders for the NFB and control groups.

Discussion

Preliminary results show that patients with MDD showed increased A1 score after neurofeedback training in the NFB group. The responder group responded to the neurofeedback with more improvement in anxiety and depression than the non-responder group. By separating the responders and non-responders, the study points out that it is not the number of training sessions that is important, but whether the skill mastery has been achieved. Clinical conclusions should only be drawn from those participants who mastered the skill. These results suggest that six training sessions were either insufficient for the non-responders and they needed more sessions to develop mastery or that the training protocol was inappropriate and they needed a different type of intervention (Shellenberger & Green, 1986).

This study indicated that neurofeedback training increases the A1 score by improving frontal alpha asymmetry because of two reasons: (1) increased right frontal alpha power means decreased right frontal activity, and (2) decreased left frontal alpha power means increased left frontal activity. This result was consistent with previous studies that showed decreased depressive symptoms after neurofeedback training (Baehr et al., 1997; Baehr et al., 2001; Choi et al., 2011; Dias et al., 2011; Peeters et al., 2014; Rosenfeld, 2000). We found that patients with MDD with increased A1 score after

neurofeedback training (responder) also showed decreased anxiety and depression; on the other hand, patients with MDD with decreased A1 score after neurofeedback training (non-responder) showed increased anxiety and depression.

However, this study found that not all patients with MDD increased A1 score after neurofeedback training. Even though the ALAY protocol of neurofeedback was followed to address frontal alpha asymmetry, not all patients with MDD had A1 score lower than zero. Some patients with MDD had A1 score higher than zero. Overall, this study found that increased A1 score was related to decreased symptoms of anxiety and depression ($r = -0.27$). However, this result may be due to the placebo effect and needs to be reassessed in the same experimental conditions.

Depressive disorder is a heteroscedastic disorder, the pathophysiological mechanisms of which are still controversial. Some depressive disorders are comorbid with anxiety disorder or anxiety symptoms (Bruder et al., 1997), with melancholia or non-melancholia (Quinn, Rennie, Harris, & Kemp, 2014), and psychomotor retardation (Cantisani et al., 2015). These heteroscedastic characteristics may reflect different EEG patterns in different brain regions. For example, patients with MDD with comorbid anxiety had higher activity in the right parietal-temporal lobe than those with MDD without anxiety (Bruder et al., 1997).

Several limitations should be noted in this study. First, only 14 patients with MDD were included in this present study. The insufficient sample size may decrease the statistical power and cause no significant finding. Second, the neurofeedback protocol for patients with MDD needed at least 10–36 sessions in the previous studies (Baehr et al., 1997; Choi et al., 2011; Peeters et al., 2014; Rosenfeld et al., 1996); however, our participants in the NFB group only received 1 hr per week for 6 weeks of neurofeedback training which may limit the efficacy of neurofeedback. More practice may improve neuroplasticity (Malkowicz & Martinez, 2009). Third, the pathophysiological mechanism of alpha asymmetry was not confirmed for all patients with MDD, even though there was higher alpha asymmetry score among patients with MDD than in the healthy controls (Debener et al., 2000; Kemp et al., 2010). Fourth, because of the heterogeneity of depressive disorders, some patients with MDD with comorbid mild anxiety symptoms in our study showed a BAI score of 17.86 in the NFB group and 16.00 in the control group. Previous studies found hyperactivity in the right posterior regions in patients with comorbid MDD and anxiety symptoms (Bruder et al., 1997; Heller, Etienne, & Miller, 1995), and the pathophysiological mechanism of EEG patterns may differ between MDD with anxiety and MDD without anxiety (Bruder et al., 1997). Therefore, the individualized neurofeedback protocol should be set up for these patients. Fifth, depressive symptoms in some patients were caused by stressful life events or adjustment problems and some patients with MDD improved significantly after few sessions of neurofeedback; however, some of them showed increased severity of depression during neurofeedback training. Hammond (2005) indicated that not all individuals with frontal alpha asymmetry will be depressed, and some persons can experience negative life events and still become depressed in the absence of frontal alpha asymmetry. Some patients did not improve significantly because of other stressful life events during neurofeedback training, such as a loss in their family (Hammond, 2005). Therefore, stressful life events may be a confounding factor in the outcome evaluation. Sixth, some studies examined the learning curve across and within neurofeedback sessions (Baehr et al., 1997; Zuberer, Brandeis, & Drechsler, 2015) to confirm a linear trend of EEG changes. However, this study did not measure the scores of frontal alpha asymmetry under each session, and hence, the trend of treatment effectiveness is still unknown.

In conclusion, there was partial support for the efficacy of neurofeedback among patients with MDD, especially for those who were responders. Patients in the responder group showed decreased symptoms of anxiety and depression, as well as improved frontal alpha asymmetry. However, some of them did not improve significantly and probably needed more training sessions. Finally, the sample size should be increased in future studies.

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