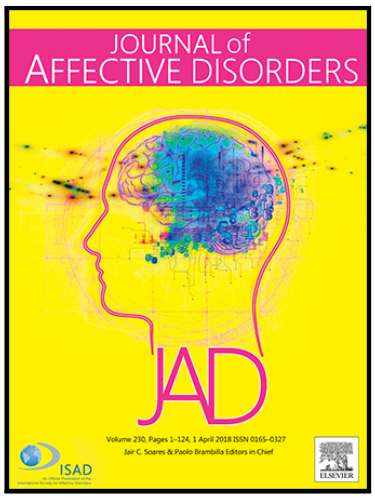

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Full length article

The effects of alpha asymmetry and high-beta down-training neurofeedback for patients with the major depressive disorder and anxiety symptoms

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Running title: Neurofeedback for depressive disorder

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Highlights

- Neurofeedback is a technologically advanced, non-invasive and professional psychological intervention.
- Both ALAY and high-beta down-training neurofeedbacks improved the symptoms of depression and anxiety.
- High-beta down-training neurofeedback significantly decreased high-beta power in the respective participants' electroencephalogram.

Abstract

Background: Alpha-asymmetry neurofeedback (ALAY) was applied to patients with major depressive disorder (MDD) based on the theory of frontal alpha asymmetry. Neurophysiological studies have found a higher high-beta activity of electroencephalography (EEG) at the posterior cortex among patients with comorbid MDD and anxiety symptoms. The present study examined the effects of ALAY and high-beta down-training (Beta) neurofeedback in symptoms of depression and anxiety and EEG parameters.

Method: Eighty-seven patients with comorbid MDD and anxiety symptoms were allocated to the ALAY, Beta, or control groups. Both neurofeedback groups received ten-session neurofeedback. All participants completed the Beck Depression Inventory II (BDI-II), Beck Anxiety Inventory (BAI), and five minutes resting EEG

recording at pre-test and post-test. EEG raw signals were transformed into an A1 score [log (F4 alpha) - log (F3 alpha)], P3 and P4 high-beta power.

Results: BDI-II and BAI scores decreased at post-test in both ALAY and Beta groups, but no significant difference between the two groups. No significant interaction effect in A1 score at pre-test and post-test between the ALAY, Beta, and control groups. The P3 high-beta was significantly decreased in the Beta group, an increase in the control group, and no change in the ALAY group at post-test compared to the pre-test.

Conclusions: Both neurofeedback groups decreased symptoms of depression and anxiety. The Beta group was more effective in decreasing high-beta power at the parietal cortex compared to other groups. This non-invasive psychological intervention can be used in the future for patients with comorbid MDD and anxiety symptoms.

Key words: major depressive disorder; anxiety symptoms; electroencephalography; alpha asymmetry neurofeedback; high-beta down-training neurofeedback

Introduction

1. *Electroencephalographic patterns among patients with major depressive disorder*

Richard Davidson proposed the theory of frontal alpha asymmetry (FAA) as a neurophysiological mechanism for patients with major depressive disorder (MDD) (Davidson, 1992). FAA identifies the difference between left and right alpha activity in the frontal regions during electroencephalographic (EEG) recording. The left frontal hemisphere relates to the behavioral activation system (BAS), associated with approach motivation and positive emotions (Stewart et al., 2011). Alternatively, the right frontal hemisphere relates to the behavioral inhibition system (BIS), which is associated with withdrawal or avoidance motivation, negative emotions, and comorbid depression and anxiety (Mathersul et al., 2008; Stewart et al., 2011; Thibodeau et al., 2006). Based on FAA theory, Baehr et al. (1997) developed the frontal alpha asymmetry score (A1 score) to represent the FAA. This was calculated by subtracting the common logarithm (log) of left-alpha power from the log of right-alpha power [A1 = log F4 –log F3]. The A1 score has been used to study depression and brain activity during resting state and task conditions in patients with MDD (Kaiser et al., 2016; Smith et al., 2017; Stewart et al., 2011). Prior studies using the A1 score have identified diminished alpha activity in the right frontal

region as compared to the left frontal region, or increased alpha activity in the left frontal region as compared to the right frontal regions. This is a trait marker for patients with MDD (Davidson, 1992; Davidson & Tomarken, 1989; Henriques & Davidson, 1990, 1991; Kemp et al., 2010; Wheeler et al., 1993).

Some inconsistencies have been reported in recent findings; however, these studies failed to identify the association between FAA and MDD, possibly due to several factors (Arns et al., 2016; Kaiser et al., 2016; Quinn et al., 2014; Stewart et al., 2011). First, there may have been methodological problems, such as choice of EEG reference, EEG recording length, and the stability of FAA within and across sessions (Smith et al., 2017). Second, disorder characteristics, such as MDD comorbidity with or without anxiety disorder or symptoms, heterogeneity (such as anhedonia, melancholia, psychomotor retardation, or anxious apprehension), and depression severity (remission or severe depression) may have also been factors (Bruder et al., 1989; Cantisani et al., 2015; Quinn et al., 2014; van der Vinne et al., 2017). In these studies, MDD patients with or without anxiety symptoms showed hypo- or hyper-activations in the associated brain regions (Bruder et al., 1997; Heller, 1993).

Hypo- and hyper-activation in the parietal-temporal cortex were found in patients with MDD comorbid with anxiety symptoms without the calculation of

FAA (Bruder et al., 1997, 1989; Heller, 1993). Heller conducted a series of studies to explore the EEG patterns associated with comorbid depression and anxiety. The results showed that depression correlated with hypoactivation of the left prefrontal and right parietal-temporal cortices, while anxiety correlated with hyperactivation of the left prefrontal and right parietal-temporal cortices (Heller, 1993; Heller et al., 1995, 1997). Several studies have confirmed that patients with MDD and anxiety symptoms have specific EEG patterns, such as higher beta-power at the right prefrontal cortex, right prefrontal-temporal cortex, and parietal, central, and occipital lobes, all of which indicate an aroused brain state (Hammond, 2010; Koberda et al., 2014; Neubrander et al., 2012). Because there is a 60% chance of comorbid MDD and anxiety disorder (Kessler et al., 2003), some researchers have focused on EEG recording associated with comorbid MDD and anxiety symptoms. Most research has revealed greater activations in the right frontal region in the comorbid group over patients with MDD without anxiety symptoms or in healthy controls (Bruder et al., 1997; Engels et al., 2010; Herrington et al., 2010; Pizzagalli et al., 2002). Inconsistent findings have been reported, however, including greater activation of the right prefrontal and posterior cortices (Bruder et al., 1997) and greater high-beta power (20-40 Hz) at the frontal cortex (F3/F4) in the comorbid group (Yamada et al., 1995), and higher high-beta power (18-30 Hz) in the left and right frontal-temporal

area (including FP1, FP2, F3, F4, F7, F8, and T4) when measured by quantitative EEG and low-resolution electromagnetic tomography (LORETA) (Paquette et al., 2009). In addition, some studies have found higher low-beta power (13-20 Hz) at the parietal (P3/P4) and occipital cortices (O1/O2) in the comorbid group (Yamada et al., 1995). Our preliminary studies enrolled patients with comorbid MDD and anxiety symptoms and compared 19 channels of EEG data with healthy controls. The results revealed that the comorbid group had higher beta activity (12-32 Hz) over the whole brain compared with the healthy controls. The results did not support the significant difference between two groups on the FAA of F3 and F4. The results revealed that the comorbid group had higher beta activity (12-32 Hz) over the whole brain compared with the healthy controls (Lin et al., 2019; Hung et al., 2016). Therefore, patients with comorbid depression and anxiety present right prefrontal hyperarousal (supporting the FAA theory), but either hyper- or hypo-arousal in the posterior area (supporting the Burder and Heller et al.'s theory), which reflects high-beta power instead of alpha or theta power. In addition, few studies have found the differences in EEG patterns among MDD subtypes of anhedonia, melancholic or psychomotor retardation, (Cantisani et al., 2015; Ouinn et al., 2014), or severity of MDD, such as current depression, remission, or a history of depression (Koberda et al., 2014; Reid et al., 1998; Stewart et al., 2011).

2. Neurofeedback protocols for major depressive disorder

Baehr et al. (1997) developed a FAA neurofeedback protocol, or ALAY neurofeedback, based on the FAA theory. The aim of ALAY neurofeedback was to increase the A1 score and thereby reduce depressive symptoms among patients with major depressive disorder (Baehr et al., 1997, 2001; Rosenfeld, 2000). Several studies have concluded that increased A1 scores after ALAY neurofeedback training are associated with decreased depressive symptoms (Baehr et al., 1997, 2001; Choi et al., 2011; Dias & van Deusen, 2011; Rosenfeld, 2000), improved cognition and executive function (Choi et al, 2011), and long-term effects based on one- to five-year follow-ups (Baehr et al., 2001).

Recent studies, however, have found a reduction in depressive symptoms after ALAY neurofeedback without an increase in A1 scores (Cheon et al., 2016; Peeters et al., 2014). Hammond (2000) found that the effect of ALAY neurofeedback was limited to patients with MDD and anxiety symptoms. Hammond (2000) switched the ALAY neurofeedback protocol to Roshi protocol for a patient with severe MDD who had difficulties increasing his A1 score. This patient felt nervous, anxious, and ruminated on training goal failures. The electrodes placement of the Roshi protocol were at the F3 and F4 with photic stimulation, and the frequencies of photic stimulation varied by patient's dominant brainwave. The target of the Roshi

protocol was to reinforce sensorimotor rhythm (15-18 Hz) while simultaneously inhibiting alpha (8-13 Hz) and theta (4-7 Hz) frequencies. After 30 training sessions, depression, somatic symptoms, anxiety, and rumination had significantly decreased. In addition, Cheon et al. (2016) revised an eight-week ALAY neurofeedback protocol to increase beta power at the left frontal cortex (F3) for depression and decreased alpha while increasing theta (alpha/theta ratio) at the parietal cortex (Pz). The results showed a significant decrease in symptoms of depression and anxiety, as well as a decrease in clinical severity of psychiatric symptoms over eight weeks. However, the A1 score did not increase after eight weeks of ALAY neurofeedback. In a preliminary study of ALAY neurofeedback, 14 patients with MDD were enrolled for six weekly sessions. No improvement in depressive symptoms and A1 scores were found, possibly due to non-intensive, limited sessions (Wang et al., 2016).

Few studies have conducted neurofeedback training on patients with MDD by observing the neurophysiology of excessive beta. One such study showed that high-beta power decreased to the normal range after high-beta down-training neurofeedback, which coincided with a significant decrease in depressive symptoms, including rumination, negative thoughts, anxiety, and behavioral inhibition (Paquette et al., 2009). To reduce excessive beta power in the right prefrontal and limbic

regions, depressive patients were able to self-regulate left amygdala hemodynamic activity and improve depressive symptoms through real-time functional magnetic resonance imaging (fMRI) neurofeedback training (Zotev et al., 2014). There are too few empirical results to date, however, to confirm the treatment effectiveness of the high-beta down-training protocol. Therefore, based on EEG neurophysiology of MDD, this study used a case-control design to examine the effects of an ALAY neurofeedback protocol and high-beta down-training neurofeedback protocol by comparing symptoms of depression and anxiety and EEG changes with a control group. The training sessions and frequencies were based on studies of Choi et al. (2011) and Dias et al. (2011) that set up the same treatment plan of ten sessions for both neurofeedback groups

Methods

Research design

This study used a 3 Group (CRST, RT, and C groups) × 2 Time (pre-test and post-test) research design. The sample size was estimated by G*Power prior to the study (Faul et al., 2007). Parameters for this study were set at the following: power at 0.80, alpha error probability at 0.05, the effect size of the partial eta-square at 0.18 (Mennella et al., 2017), number of groups at 3, and repeated measures at 2. The estimation of the total sample was 78, and a dropout rate of 10% was set. Finally, 86

participants were required for the statistical analysis; 28 each for three groups. The primary outcomes were changed on the symptoms of depression and anxiety and target EEG parameters.

Participants

A total of 1752 patients with a diagnosis of MDD were screened from medical records in the outpatient clinics of XXX Hospital, XXX Hospital, and XXX Hospital. The inclusion criteria were: (1) a diagnosis of MDD based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5; American Psychiatric Association, 2013); (2) scores on the Beck Depression Inventory-II (BDI-II) and Beck Anxiety Inventory (BAI) of more than 14 and 8, respectively; and (3) right-handedness, as prior studies indicated that handedness was related to resting EEG alpha power (Harmon-Jones and Allen, 2006; Propper et al., 2012). Participants were excluded if they had severe physical illness (such as cancer, Alzheimer's disease, or Parkinson's disease) or a mental disorder excluding MDD or an anxiety disorder. A total of 200 participants were referred by psychiatrists and completed the pre- and post-test experimental procedures. There were 113 participants excluded at pre-test due to a BDI-II or BAI score lower than 14 or 8, respectively (n = 63), damaged EEG raw data (n = 2), an outlier in EEG (n = 7), or a refusal to participate in neurofeedback (n = 41). Finally, 87 patients with

comorbid MDD and anxiety symptoms were assigned to the ALAY neurofeedback group (ALAY group; n = 24), the high-beta down-training neurofeedback group (Beta group; n = 23), or the control group (n = 23; Fig. 1). The groups were matched in terms of age and gender.

Institutional review board approvals were obtained from the ethics committees of XXX (Number-XXXXXX) and XXX (Number-XXXXXX), and willing participants provided informed consent. After completing all research procedures, the participants received approximately $20 USD for pre-test and post-test measurements, and approximately $33 USD for neurofeedback training.

Fig. 1 here

Psychological questionnaires

All participants completed self-report questionnaires that included demographic characteristics, the Beck Depression Inventory II (BDI–II), and the Beck Anxiety Inventory (BAI) at pre-test and post-test. The demographic characteristics included age, gender, history related to MDD (e.g., number of readmissions, frequency of suicidal ideation, and number of suicide attempts).

The BDI-II is a 21-item questionnaire that was used to assess cognitive and somatic depression in a period of two weeks prior to the commencement of the study. The score range of the BDI-II is from 0 to 63 (Beck et al., 1996). The internal

consistency (Cronbach's alpha) was between .92-.93, and one-week test-retest reliability was .93 (Beck et al., 1996; Steer et al., 1998). The Chinese version of BDI-II was translated by Chen (2000), where the coefficient of internal consistency was found to be .94 and split-half reliability was .91 (Lu et al., 2002). The internal consistency of this study was .85.

The BAI is a 21-item questionnaire that was used to assess symptoms of anxiety in a period of one week prior to the study. The score range of the BAI is from 0 to 63. The internal consistency (Cronbach's alpha) was .92, and one-week test-retest reliability was .75 (Beck et al., 1988). The Chinese version of BDI-II was translated by Lin (2000), where the internal consistency was found to be .95 and split-half reliability was .91 (Che et al., 2006). The internal consistency of this study was .90.

Instruments

The continuous EEG raw signals were recorded with the BrainAvatar (BrainMaster Technologies, Inc., Bedford, OH) and a 19-channel EEG cap (Electro-cap International Inc., Eaton, OH). The electrode placement was based on the International 10-20 system, included FP1, FP2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, T5, T6, Pz, P3, P4, O1, and O2. The linked-ear reference (A1/A2) and ground (A2) were placed on participants' ears. All participants were assessed with

five minutes resting baseline with eyes closed at pre-test and post-test (Baehr et al., 1998).

In the neurofeedback training, the BioGraph Infiniti (Thought Technology Ltd., Montreal, Quebec, Canada) with two-channel EEG-Z sensors were placed on the F3 and F4 for the ALAY group and the P3 and P4 for the Beta group. The linked-ear electrodes were placed on participants' ears, using the right earlobe as a ground. All electrode impedances were below 5 kΩ, the sampling rate was 256 Hz, the band-pass filtering was 0.1–50 Hz, and the notch filtering was 60 Hz.

Neurofeedback protocol

All participants' resting baseline EEG signals with eyes closed were measured for five minutes at pre-test and post-test. Then, both ALAY and Beta groups received 10 sessions neurofeedback, twice a week, for five weeks, and the BioGraph Infiniti was used to record and feedback EEG data (Thought Technology Ltd., Montreal, Quebec, Canada). During the neurofeedback training for the ALAY and Beta groups, five minutes resting EEG with eyes closed was measured at pre-training. Following this, a 30-sec resting EEG with eyes open was measured to calculate EEG thresholds for each training session, which included five trials of three minutes. The procedure, training screen, and manuals for the therapists and patients in both neurofeedback groups were the same, except for the target EEG parameters (Fig. 2).

Participants in the ALAY group were reinforced to increase the A1 score. This was done by using audio feedback (a ding sound) and visual feedback (green light and animation of a boat moving forward) when the A1 score exceeded the threshold (Fig. 2 Top). Participants were instructed to maintain a positive mental/emotional state that kept the A1 score increased when the green light shone and the boat moved forward. Based on prior protocols, the starting values (the A1 score) were set at 0 in the first session to develop a threshold in the ALAY group (Baehr et al., 1997; Choi et al., 2011; Hammond, 2000). In sessions two through ten, the starting values were based on a 30-sec resting EEG with eyes open. The success rate referred to the percentage of time in one minute that the A1 score was above the threshold. When participants achieved their treatment goals, they received visual and audio feedback. If the success rate was higher than 50% for more than one minute, the A1 score was increased by 0.5 μV. The feedback was inhibited if the ocular activity (43-59 Hz) exceeded $\pm$ 10 μV.

Participants in the Beta group were reinforced to decrease high-beta power. When the P3 and P4 high-beta powers were below the threshold, they received audio feedback (a ding sound) and visual feedback (green light and animation of a boat stopping) (Fig. 2 Bottom). When participants were instructed to concentrate and maintain a clear and calm mental state that kept high-beta decreased, the green light

shone and the boat stopped. Based on prior protocol, the starting values of high-beta power at P3 and P4 were set based on the average of 30-sec resting EEG with eyes open to developing a threshold in the Beta group (Schmidt & Martin, 2015). The success rate referred to the percentage of time in one minute that high-beta power was below the threshold. When participants achieved their treatment goals, they received visual and audio feedback. If the success rate was higher than 50% for more than one minute, the high-beta power was decreased by 0.5 μV. The feedback was inhibited if the ocular activity (43-59 Hz) exceeded $\pm$ 10 μV.

Participants in the control group did not receive any additional psychological treatment. All participants, including those in the control group, continued their usual medical treatments during pre-test and post-test.

Medication data were collected from medical records and were compared between the three groups. Among the medications used, participants used benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, other antidepressants, antipsychotics, atypical antipsychotics, and other sedative-hypnotics.

Fig. 2 here

Data reduction

The EEG raw signals were visually analyzed in a 20-sec window, with a 10-sec overlap by using BrainAvatar analysis (BraniMaster Technologies, Inc., Bedford, Ohio). After removing eye blink, muscle movement, and movement artifacts, the joint time-frequency analysis was used to analyze absolute EEG power into the following bands: total alpha (8–12Hz) at F3 and F4, and high-beta power (20-32 Hz) at P3 and P4 (Collura, 2014). The frontal alpha-asymmetry score (A1) was calculated by subtracting the log of left-alpha power from the log of right-alpha power (A1 = log [F4] - log [F3]) (Baehr et al., 1997).

Statistical analysis

All statistical analyses were performed using SPSS software version 20.0 (International Business Machines Corporation, Armonk, New York, USA). The one-way analysis of variance (ANOVA) was used to examine differences between group scores of psychological questionnaires and EEG parameters in the pre-test. This procedure confirmed that there was an equal group design employed in this study. Sphericity of variables was examined prior to the use of repeated-measure ANOVA. If violations of sphericity occurred, the Huynh-Feldt correction was used to correct a Type I error. All *p* values reported were Huynh-Feldt corrected, and the alpha values were corrected for multiple tests. The mixed-model ANOVA with a

between-subjects factor (three groups: ALAY, Beta, and control groups) and a within-subjects factor (two measurements: pre-test and post-test) was used to examine group differences in scores of psychological questionnaires and EEG parameters. The Bonferroni post-hoc comparison was used to examine group differences and test differences in data from the psychological questionnaires scores and EEG parameters.

The effect size was determined by partial eta-squared (η_p^2). The η_p^2 was considered to represent small, medium, and large effects are 0.01, 0.06, and 0.14, respectively (Cohen, 1988).

Results

Participants' characteristics

Results found no significant difference between the ALAY, Beta, and control groups in age, gender, years since diagnosis of MDD, number of readmissions, frequency of suicidal ideation, number of suicide attempts, total score of BDI-II, total score of BAI, A1 score, P3 high-beta, and P4 high-beta (Table 1).

Table 1 here

There were no significant differences found in medications used among the three groups at pre-test and post-test, including use of benzodiazepines ($\chi^2 = 0.465$, $p = 0.793$ and $\chi^2 = 3.343$, $p = 0.188$), SSRIs ($\chi^2 = 3.009$, $p = 0.222$ and $\chi^2 = 2.415$,

$p = 0.298$), SNRIs ($\chi^2 = 0.524$, $p = 0.769$ and $\chi^2 = 1.421$, $p = 0.491$), tricyclic antidepressants ($\chi^2 = 2.165$, $p = 0.339$ and $\chi^2 = 1.986$, $p = 0.371$), other antidepressants ($\chi^2 = 1.088$, $p = 0.580$ and $\chi^2 = 0.096$, $p = 0.953$), antipsychotics ($\chi^2 = 2.850$, $p = 0.241$ and $\chi^2 = 1.842$, $p = 0.398$), atypical antipsychotics ($\chi^2 = 0.566$, $p = 0.754$ and $\chi^2 = 2.016$, $p = 0.365$), and other sedative-hypnotics ($\chi^2 = 0.861$, $p = 0.650$ and $\chi^2 = 0.005$, $p = 0.998$).

The effects of neurofeedback on scores of psychological questionnaires

The significant Group × Time interaction effects were found in total BDI-II scores and total BAI scores. Bonferroni-corrected post-hoc comparisons revealed significantly lower BDI-II and BAI scores at post-test than at pre-test in both ALAY and Beta groups. There were no significant differences found between pre-test and post-test BDI-II and BAI scores in the control group. In addition, there were significantly lower BDI-II scores in the Beta group at post-test than those in the control group, and lower BAI scores in the ALAY and Beta groups at post-test than those in the control group. The improvements in symptoms of depression (BDI-II) and anxiety (BAI) were found in both neurofeedback groups; however, the efficacy did not differ between the two neurofeedback groups (Table 2 & Fig. 3).

Table 2 here

Fig. 3 here

The effects of neurofeedback on EEG parameters

There was no significant interaction effect for A1, F3, and F4 alpha power between the ALAY, Beta and control groups (Table 2). D*escriptive statistics* were used to identify the changes of the A1 score between three groups, in that participants increased their A1 score by 0.024 (an average from -0.010 to 0.014) in the ALAY group, and by 0.005 (average from 0.003 to 0.008) in the control group. Participants did not increase their A1 score in the Beta group.

There was a significant interaction effect on P3 high-beta power with medium effect size. Bonferroni-corrected post hoc comparisons revealed that there was lower P3 high-beta power at post-test than pre-test in the Beta group. In contrast, there was higher P3 high-beta power at post-test than pre-test in the control group and a slight decrease in P4 high-beta power at post-test than that at pre-test in the Beta group. Despite this, no statistically significant interaction effect was found between the three groups at pre-test and post-test (Table 2 & Fig. 4).

D*escriptive statistics* were used to identify the reduction of high-beta power between the three groups, in that participants decreased their P3 high-beta power by 0.113 μV^2 (an average of 2.939 μV^2 to 2.826 μV^2) and 0.253 μV^2 (an average of 2.807 μV^2 to 2.554 μV^2) in the ALAY and Beta group, respectively. In the control group, however, P3 high-beta power increased by 0.162 μV^2 (an average of

2.826 μV^2 to 2.988 μV^2). Moreover, participants in the ALAY and Beta groups decreased their P4 high-beta power by 0.077 μV^2 (an average of 2.882 μV^2 to 2.805 μV^2) and 0.149 μV^2 (average from 2.861 μV^2 to 2.712 μV^2) respectively, and the control group increased P3 high-beta power by 0.087 μV^2 (average from 2.889 μV^2 to 2.976 μV^2). Participants did not significantly decrease their high-beta power in the ALAY group at P3 and P4.

Fig. 4 here

Discussion

The most significant findings of the present study were the improvement in symptoms of depression and anxiety in both neurofeedback groups; and the equally effective treatment of depression and anxiety in both neurofeedback protocols. The efficacy of EEG changes between groups that when there was a slight increase in A1 scores in the ALAY group, there were no significant differences between the three groups. The EEG efficacy of neurofeedback was identified in the Beta group, that significantly decreased high-beta power at the parietal cortex among patients with comorbid MDD and anxiety symptoms. Results of the ALAY group in this study are mixed. In keeping consistent with previous studies, ALAY neurofeedback was found to reduce symptoms of depression without A1 change (Cheon et al., 2016; Peeters et al., 2014). Contrasting previous studies, however,

ALAY neurofeedback also correlated with increased A1 scores as well as a reduction of depressive symptoms (Baehr et al., 1997, 2001; Choi et al., 2011; Rosenfeld, 2000). Although A1 scores in the current study increased by 0.024, the level of increase was too small to determine statistical significance. One possible reason for inconsistent findings in this study is that the FAA is not a trait marker for patients with comorbid MDD and anxiety symptoms. Our primary study also found findings unsupportive of the claim that the FAA phenomenon existed in every MDD patient. Lin et al. (2018) found that 57.04% of patients with comorbid MDD and anxiety symptoms did not exhibit FAA (an A1 score higher than 0), and only 54.17% (13 of 24) patients exhibited FAA at pre-test. A second reason for inconsistent study results may be that the length of training sessions was insufficient to improve A1 scores. Adopting ten sessions of neurofeedback in the present study was based on Choi et al. (2011) and Dias et al. (2011); however, some previous studies used 30–36 neurofeedback sessions for patients with MDD (Baehr et al., 1997; Peeters, 2014). Ten sessions of neurofeedback in this study may not have been enough to change brain activity. Third, the mean A1 score was between +1 and -1, meaning the variances of A1 scores were too small to achieve statistical significance. The fourth reason for mixed study findings may be that the linked-ear reference, rather than Cz reference, was used in this study, and may not have been consistently able to

reference FAA in depression. Some early studies of ALAY neurofeedback used Cz as the reference (Baehr et al., 1997, 1998, 2001; Choi et al., 2011; Rosenfeld et al., 2000), where the linked-ear (A1/A2) was used as the reference in recent studies (Cheon et al., 2016; Peeters et al., 2014; Paquette et al., 2009). The linked-ear reference was used in this study due to the limitations of EEG sensors; because the pair of ear clips cannot place on Cz.

In previous studies, the A1 scores increased in the neurofeedback group and decreased in the control group, finding a significant interaction effect at pre-test and post-test between the two groups (Choi et al., 2011). The current study found an increase in both ALAY and control groups and no change in the Beta group from pre-test to post-test; therefore, no interaction effect was found in this study. The increased A1 score for both groups may be the result of a placebo effect for the second EEG measurement.

This study used high-beta down-training neurofeedback for patients with comorbid MDD and anxiety symptoms and examined the protocol's efficacy by comparing it with ALAY and control groups. Bruder et al. (1997) proposed that excessive EEG beta power is present in the posterior region in patients with comorbid MDD and anxiety symptoms. In addition, Lin et al. (2018) indicated that comorbid MDD with anxiety symptoms presented excessive high-beta power in

frontal, central, parietal, temporal, and occipital cortices in Taiwanese populations. Based on these studies, we developed the high-beta down-training neurofeedback protocol, which was confirmed to improve negative emotions and decrease hyperarousal of the parietal cortex. This study supported the three treatment components of neurofeedback: trainability (the neurofeedback protocol trained participants to increase or decrease the target EEG frequency bands, such as the A1 score and high-beta power), independence (neurofeedback increased A1 only in the ALAY group, not in the Beta group, while neurofeedback decreased high-beta power only in the Beta group, not in the ALAY group), and interpretation (neurofeedback decreased EEG frequency bands, which were related to neurophysiological mechanisms of MDD, and thus caused symptom improvement) (Zoefel et al., 2011).

Regarding the clinical implications, we suggest that a neurophysiological assessment using a 19-channel EEG should be the first step in clinical practices. Then, an analysis of the raw EEG and transformation of EEG data to different frequency bands be done in order to calculate the A1 score and high-beta power. Finally, clinical therapists should decide which protocols will be applied to patients with MDD based on their EEG data. If the A1 score is lower than 0, the ALAY neurofeedback would be suitable for patients. If high-beta power at P3 or P4 is

higher than one standard distribution from the mean (deriving z-scores), then high-beta down-training neurofeedback would be suitable for patients using z-score or quantitative EEG-based neurofeedback training (Koberda, 2015).

There were several limitations to this study. First, because the study adopted a case-control design by matching age and gender in the clinical settings, the potential sampling biases may not have been random by design. Nevertheless, we did not observe group differences in the participants' characteristics prior to the study. Second, 10 sessions of neurofeedback were chosen based on previous studies (Choi et al., 2011; Dias et al., 2011; Koberda, 2015), and as a result, the length of training might not have been enough to achieve treatment goals. Even though this study still achieved statistically significant effects in improving symptoms of depression and anxiety, as well as decreasing high-beta power in the parietal region, some patients with severe MDD may need more than 10 sessions of training to reach neurofeedback goals. Third, the P3 region may not be the most suitable location for electrode placement in the Beta group. The electrode placement at P3/P4 was based on hyperarousal of the right parietal-temporal cortex (Engels et al., 2010; Heller et a., 1995), and the electrode placement was considered to be comparable with the ALAY group that had electrodes placed at F3/F4. In previous research, White et al. (2017) found decreased high-beta power

or sensorimotor rhythm at the Pz in patients with symptoms of anxiety and depression, and Hung et al. (2016) found greater high-beta power at the Pz in a group with MDD compared to healthy control groups. Future research might apply high-beta down-training at the Pz to confirm the effect of neurofeedback changes in the EEG. Fourth, there was a lack of follow-up data for evaluating the treatment effectiveness after neurofeedback. Finally, though our results did not reveal a significant difference in categories of the medications used at pre-test and post-test between the three groups, the effects of medication may still interact with neurofeedback.

In summary, the findings suggest that non-invasive psychological interventions of both ALAY and high-beta down-training neurofeedback are effective in improving the symptoms of depression and anxiety. This study proposed a new protocol (high-beta down-training neurofeedback) that not only improved symptoms of depression and anxiety, but also decrease hyperarousal of the parietal cortex among patients with comorbid MDD and anxiety symptoms. Future research should consider using randomized controlled trials with multiple-center designs, increasing the number of training sessions for patients with severe MDD, and analyzing the EEG signals during each training session, to more comprehensively clarify the efficacy of ALAY and high-beta down-training neurofeedback. A follow-up study

will be completed to examine the effects of emotional symptoms on EEG data; it will tailor a treatment approach based on quantitative EEG data and patterns of symptoms before the neurofeedback protocol.

Author Statement

Contributors

I-Mei Lin designed the study, wrote the proposal, applied the research project, monitored study procedure, prepared the manuscript, and proof-reading. San-Yu Wang assisted data collection, statistical analysis, and wrote the first draft in Chinese. Sheng-Yu Fan participated and corrected the manuscript. Yu-Che Tsai assisted the EEG data analyses. Cheng-Fang Yen, Yi-Chun Yeh, Mei-Feng Huang, Yu Lee, Nien-Mu Chiu, Chi-Fa Hung, Peng-Wei Wang, Tai-Ling Liu, and Huang-Chi Lin were assisted psychiatric diagnostic and expertized in three hospitals. All authors contributed to and have approved the manuscript.

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Conflict of Interest

I-Mei Lin has received research grant from the Ministry of Science and Technology. All authors declare that they have no conflict of interest.

Human rights and Informed consent

All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation (intuitional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants for being included in the study.

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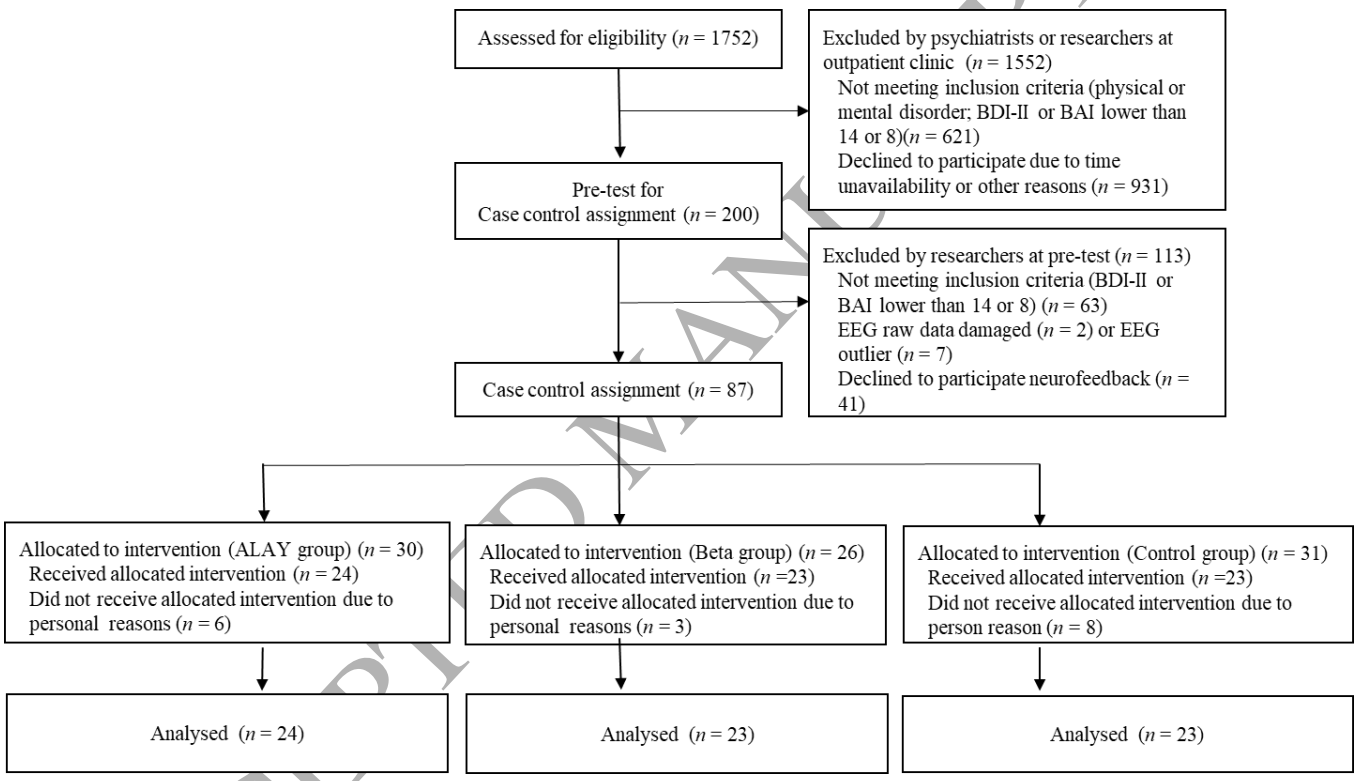
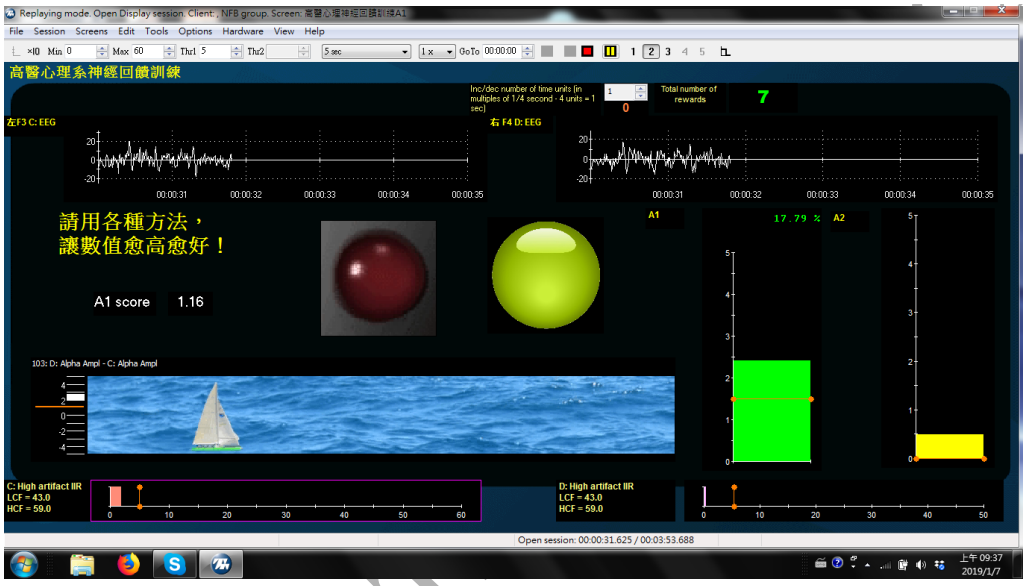


Fig.1. Study flow chart.



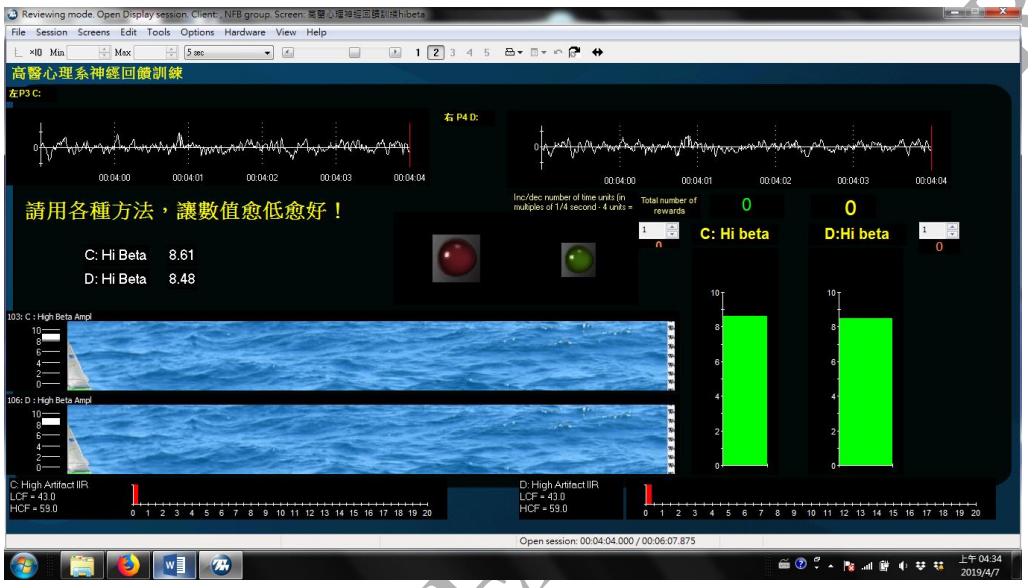


Fig. 2. The screens for neurofeedback training

(Top: ALAY group;「請用各種方法，讓數值愈低愈好」means that “Please increased the A1 score in various ways”

Bottom: Beta down-training group;「請用各種方法，讓數值愈低愈好」means that “Please decreased the high beta power in various ways”

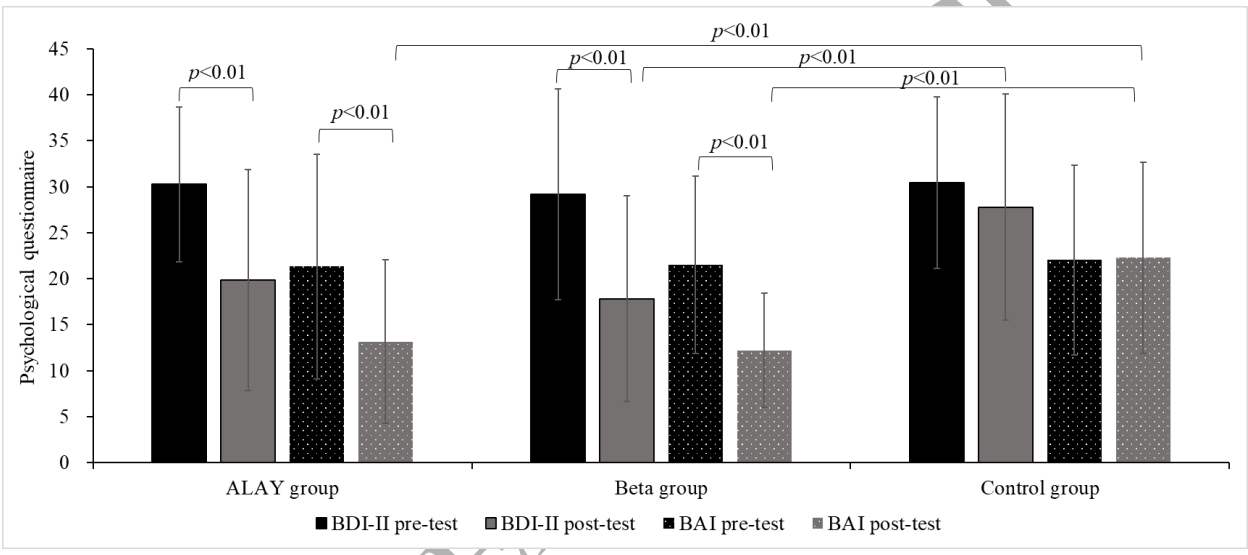


Fig. 3. The psychological questionnaires applied at pre-test and post-test to the ALAY, Beta, and control groups.

Note: The values of the error bars were 1 standard deviation.

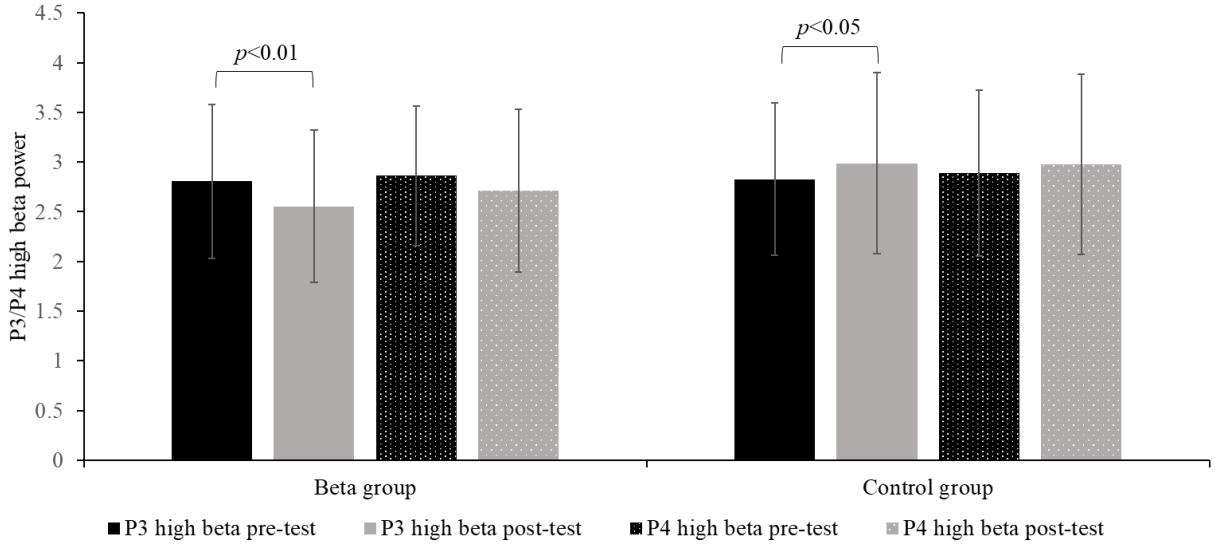


Fig. 4. P3/P4 high-beta power of EEG at pre-test to post-test for Beta and control groups.

Note: The values of the error bars were 1 standard deviation.

Table 1

The demographic characteristics for all participants.

Variables		ALAY group (n = 24)	Beta group (n = 23)	Control group (n = 23)	F / χ^2	p	ηp^2
Age (years)		40.330 (14.714)	42.830 (15.816)	42.610 (13.937)	0.205	0.815	0.06
Gender	Female	19	12	16	3.970	0.137	
	Male	5	11	7			
Years since diagnosis of MDD		3.783 (5.768)	4.522 (6.423)	5.826 (6.043)	0.665	0.518	0.020
Number of readmission		0.130 (0.626)	0.044 (0.209)	0.217 (0.518)	0.742	0.480	0.022
Frequency of suicidal ideation		1.957 (1.261)	2.130 (1.424)	2.565 (1.037)	1.446	0.243	0.042
Number of suicide attempts		0.565 (0.896)	0.391 (0.839)	0.783 (1.085)	0.988	0.378	0.029
Total score of BDI-II		30.250 (8.389)	29.174 (11.472)	30.435 (9.312)	0.112	0.894	0.003
Total score of BAI		21.333 (12.218)	21.522 (9.619)	22.044 (10.324)	0.027	0.973	0.001
A1		-0.010 (0.069)	0.006 (0.032)	0.003 (0.029)	0.697	0.502	0.020

P3_high beta (μV^2)	2.939 (0.697)	2.807 (0.774)	2.826 (0.767)	0.216	0.806	0.006
P4_high beta (μV^2)	2.882 (0.680)	2.861 (0.706)	2.889(0.835)	0.009	0.991	<0.001

Note: A1 = frontal alpha asymmetry score; ALAY group = alpha asymmetry neurofeedback group; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; Beta group = high beta down-train neurofeedback group; MDD = major depressive disorder; P3 = parietal 3; P4 = parietal 4.

Table 2

The psychological questionnaires and EEG at pre-test and post-test between the ALAY, Beta, and control groups.

Variables	ALAY group (A) (*n* = 24)		Beta group (B) (*n* = 23)		Control group (C) (*n* = 23)		*F*			ηp^2	Bonferroni-corrected post hoc comparison
	Pre-test (1)	Post-test (2)	Pre-test (3)	Post-test (4)	Pre-test (5)	Post-test (6)	Group (*p*)	Time (*p*)	Group×Time (*p*)		
BDI-II	30.250 (8.389)	19.833 (12.017)	29.174 (11.472)	17.826 (11.195)	30.435 (9.312)	27.783 (12.303)	2.167 (0.123)	**40.173***** (< 0.001)	**4.566*** (0.014)	0.120	Time: 2 < 1; 4 < 3 Group: B < C at post-test
Cognitive depression	21.417 (7.126)	14.000 (9.278)	20.565 (9.322)	12.522 (9.322)	22.870 (7.671)	20.391 (10.152)	2.732 (0.072)	**33.534***** (< 0.001)	2.878 (0.063**)**	0.079	
Somatic depression	8.833 (5.983)	5.833 (3.345)	8.609 (2.776)	5.304 (2.324)	7.565 (2.293)	7.391 (4.500)	0.203 (0.817)	**13.231**** (0.001)	2.793 (0.068**)**	0.077	

BAI	21.333 (12.218)	13.167 (8.874)	21.522 (9.619)	12.217 (6.186)	22.044 (10.324)	22.261 (10.385)	2.737 (0.072)	**25.767*** (< 0.001)**	**6.956** (0.002)**	0.172 Time: 2 < 1;4 < 3 Group: A,B < C at post-test
A1 score	-0.010 (0.069)	0.014 (0.023)	0.006 (0.032)	0.006 (0.029)	0.003 (0.029)	0.008 (0.026)	0.118 (0.889)	3.159 (0.080)	1.316 (0.275)	0.038
F3_total alpha (μV^2)	4.186 (2.110)	4.195 (2.144)	4.537 (2.272)	4.470 (2.375)	4.155 (1.765)	4.177 (1.831)	0.200 (0.819)	0.009 (0.926)	0.046 (0.955)	0.001
F4_total alpha (μV^2)	4.112 (2.171)	4.317 (2.200)	4.599 (2.273)	4.543 (2.461)	4.065 (1.806)	4.220 (1.948)	0.277 (0.759)	0.558 (0.458)	0.352 (0.705)	0.011
P3_high beta (μV^2)	2.939 (0.697)	2.826 (0.798)	2.807 (0.774)	2.554 (0.767)	2.826 (0.767)	2.988 (0.914)	0.626 (0.538)	1.655 (0.203)	**5.303**** (0.007)	0.137 Time:3 > 4; 5 < 6
P4_high beta (μV^2)	2.882 (0.680)	2.805 (0.851)	2.861 (0.706)	2.712 (0.816)	2.889 (0.835)	2.976 (0.905)	0.216 (0.806)	0.547 (0.462)	1.225 (0.300)	0.035

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Note: BAI = Beck Anxiety Inventory; ALAY group = alpha asymmetry neurofeedback group; BDI-II = Beck Depression Inventory-II; Beta group = high beta down-train neurofeedback group.