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The Efficacy of Neurofeedback in Patients with Major Depressive Disorder: An Open Labeled Prospective Study

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Abstract The purpose of this study was to evaluate the effect of neurofeedback on depressive symptoms and electrophysiological disturbances in patients with major depressive disorder. We recruited participants suffering from depression to evaluate efficacy of left prefrontal beta with alpha/theta training. An 8-week, prospective, open-label study was undertaken. Twenty participants were recruited. The treatment protocol was twice or three times a week training of beta at F3 with alpha/theta at Pz for 8 weeks. When every visit, patients were received beta training for 30 min, and then alpha/theta training for 30 min. Baseline, 4 and 8 week scores of; the Hamilton rating scale for Depression (HAM-D), the Hamilton rating scale for Anxiety (HAM-A), the Beck Depression Inventory (BDI)-II, the Beck Anxiety Inventory (BAI), Clinical global impression-severity (CGI-S), and pre- and post-treatment resting state EEGs were compared. Interhemispheric alpha power asymmetry (A score) was computed for homologous sites F3–F4. Pre- and post-training clinical assessments revealed significant improvements in HAM–D, HAM-A, BDI, and CGI-S scores. Cumulative response rates by HAM-D were 35.0 and 75.0 % at 4 and 8 weeks, respectively, corresponding cumulative remission rates by HAM-D were 15.0 and 55.0 %, respectively. No significant differences were found between pre- and post-treatment A score. Neurofeedback treatment could improve depressive symptoms significantly. In addition, anxiety symptoms and clinical illness severity decreased significantly after neurofeedback treatment. Despite its several limitations, such as, small sample size and lack of a control group, this study suggested neurofeedback has significant effects in patients with major depressive disorder.

Keywords Neurofeedback · Beta training · Depression · Asymmetry score

Introduction

Antidepressant medications, when used as monotherapies in placebo-controlled registration trials, typically result in remission rates of 30–35 % (Rush et al. 2011; United States, Depression Guideline Panel and United States, Agency for Health Care Policy and Research 1993). To enhance treatment effectiveness and address the limitations of conventional methods, many complementary treatments have been proposed, and neurofeedback is one of the most sophisticated of these methods. Neurofeedback provides an alternative approach that aims to help individuals alter brain activation spontaneously (Niv 2013). Neurofeedback is an encouraging development that holds promise as a method for modifying biological brain patterns associated with a variety of mental health and medical (e.g., stroke, head injury, effects of aging) disorders—particularly because unlike drugs, electroconvulsive therapy, and intense transcranial magnetic stimulation, it is non-invasive and seldom associated with even mild side effects (Hammond 2005).

The region most frequently found to be dysfunctional in major depressive disorder (MDD) is the prefrontal cortex

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(PFC) (Brody et al. 2001; Davidson and Henriques 2000). Many studies have found prefrontal cortical hypoactivity at baseline improved after treatment (Mayberg 2003). In EEG studies of depression, an abnormal pattern of asymmetric activity in frontal regions resulting from relative hyperactivity over the right frontal regions and/or relative hypoactivity over the left frontal regions has frequently been observed (Henriques and Davidson 1990). A neurofeedback protocol for modifying this frontal asymmetry has been proposed (Rosenfeld 2000; Rosenfeld et al. 1995). Baehr and Baehr (1997) have used alpha asymmetry training for depressive patients. 3 of 6 patients improved both immediately after training and at 1 and 5 years after neurofeedback treatment. Hammond (2000) had similar results using the Roshi procedure. According to the recent paper (Dias and van Deusen 2011), 21 clinical studies reported on neurofeedback treatment in patients with depressive disorders, and there have been only six original articles. These studies were not controlled and included fewer than 15 patients (Baehr and Baehr 1997; Baehr et al. 2001; Earnest 1999; Hammond 2000; Rosenfeld 1997), and all reported positive results (Baehr and Baehr 1997; Baehr et al. 2001; Earnest 1999; Hammond 2000; Rosenfeld 1997). The most commonly used protocol focuses on alpha inter-hemispheric asymmetry and the theta-beta ratio for the left prefrontal cortex (Dias and van Deusen 2011). Choi et al. (2011) were the first to conduct a RCT alpha symmetry approach study. In ten sessions, clinically significant changes in depression, and average depression symptoms were found to fall significantly as compared with a ''placebo psychotherapy'' group that underwent assessment and psychoeducation (Niv 2013).

Recently, Walker and Lawson (2013) reported FPO2 (the right fronto-polar orbital location) beta training reduced depression and maintenance of the reductions in the majority of the patients. Since the neurobiological studies of depression indicate that left frontal activation is important in being happy rather than depressed, it would seem that training beta (15–18 Hz) activity would be a more direct way to train the relevant area than would training to normalize symmetry between right and left frontal alpha, which might or might not be associated with an increase in left frontal activation in the 15–18 Hz range. This might account for failures in alpha asymmetry training for long-term prevention of depression in some cases (Walker et al. 2007).

The purpose of this study was to evaluate the effect of neurofeedback treatment on depressive symptoms and electrophysiological disturbances in patients with major depressive disorder. We recruited participants suffering from clinical depression to evaluate efficacy of left prefrontal beta with alpha/theta training.

Materials and Methods

Participants

All included patients met DSM-IV-TR criteria for major depressive disorder (American Psychiatric Association 2000) and were 18 years or older. Diagnoses were made on the basis of clinical assessments conducted by experienced, board certified psychiatrists. All patients were able to communicate with the evaluator and consented to participate. Patients with low tolerability to medications or with an unsatisfactory treatment response were regarded suitable candidates. However, patients with dementia, mental retardation, head trauma, epilepsy, and other organic mental disorders were excluded. The patients were evaluated during weekly neurofeedback team meetings with three psychiatrists and a neurofeedback therapist. All authors were obliged to participate weekly neurofeedback meeting and diagnosis and inclusion of the patients were confirmed in this meeting.

Experimental Procedure

This is an 8 week, prospective, open-label study of neurofeedback treatment in patients with major depressive disorder. Treatment protocol was twice or three times a week training of left hemisphere beta at F3 with alpha/theta training at Pz for 8 weeks. Baseline, 4 and 8 week Hamilton rating scale for Depression (HAM-D), Hamilton rating scale for Anxiety (HAM-A), Beck Depression Inventory (BDI)-II, Beck Anxiety Inventory (BAI), and Clinical global impression (CGI) scores were compared as were before and after treatment resting state EEGs. Medications were maintained at the same dosage during the study period, but adding a new antidepressant or an atypical antipsychotic was prohibited. Written informed consents were obtained and the study was approved by our hospital ethics committee. Demographic data, psychiatric histories, and the neurofeedback treatment protocol were recorded.

Measures

The primary outcome measure was determined a priori to be a change in HAM-D score, and the secondary measures of treatment effectiveness were remission and response rate as determined by the HAM-D, and a change in HAM-A, BDI, BAI, and CGI score.

The Hamilton Rating Scale for Depression (HRSD), also called the Hamilton Depression Rating Scale (HDRS) and abbreviated to HAM-D, is a multiple item questionnaire used to provide an indication of depression and as a guide

for the evaluation of recovery. HAM-D is the most commonly used symptom severity scale used to evaluate the efficacy of antidepressant treatment. The questionnaire is designed for adults and is used to rate the severity of depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss, and somatic symptoms. Based on the findings of a large study of psychiatric outpatients with major depressive disorder, the following severity ranges for HAM-D were recommended: no depression (0–7); mild depression (8–16); moderate depression (17–23); and severe depression. Remission was defined as an exit score of ≤ 7 by HAM-D. Response was defined as a reduction of ≥ 50 % in baseline HAM-D (Zimmerman et al. 2004). A recent study reported internal consistency coefficients of 0.83 for HAM-D-17 (Bagby et al. 2006) and recent review article showed that the majority of HAM-D items have adequate reliability (Rush et al. 2003). Raters of the HAM-D in this study had trained until they had reached above 0.80 at interrater reliability using kappa index before the study and we found significant inter-rater correlation ($\kappa > 0.90$).

The Hamilton Anxiety Rating Scale (HAM-A) is a widely used 14-item clinician-administered rating tool in the public domain that is used to measure the severity of anxiety symptoms among individuals with a previously diagnosed anxiety disorder. The 14 items reflect 13 categories of anxiety-related symptoms, that is, anxious mood, tension, fear, insomnia, intellectual/cognitive symptoms, depressed mood, general somatic (muscular and memory symptoms), cardiovascular, respiratory, genitourinary, and gastrointestinal symptoms, with one item capturing rater assessment of behavioral symptoms. Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where <17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe (Hamilton 1959). HAM-A is the primary outcome measure most often used in treatment studies of Generalized Anxiety Disorder, and it is also used to rate severities of anxiety symptoms in other disorders. In some studies it has demonstrated sensitivity to change and can be useful outcome measure in the clinical setting (Shear et al. 2001).

The Beck Depression Inventory-second edition (BDI-II) (Beck et al. 1996) is composed of 21 groupings of four statements that assess the severity of various depression symptoms (e.g., sadness, anhedonia, appetite changes) during the preceding 2 weeks. Items are summed to obtain a total score, which ranges from 0 to 84, where higher scores indicating more severe depression. Total score of 0–13 is considered minimal range, 14–19 is mild, 20–28 is moderate, and 29–63 is severe. The BDI-II's reliability and validity have been well established (Kung et al. 2013).

The Beck Anxiety Inventory (BAI) consists of 21 items related to signs and symptoms of anxiety. Responses range from none, slight, moderate, and severe, which are graded 0–3, respectively. The recommended rating for level of anxiety is minimal (0–7), mild (8–15), moderate (16–25), and severe (26–63) (Beck and Steer 1990). The BAI is psychometrically sound. Internal consistency (Cronbach's alpha) ranges from 0.92 to 0.94 for adults and test–retest (1 week interval) reliability is 0.75 (Osman et al. 1993; Leyfer et al. 2006).

The Clinical Global Impression-Severity (CGI-S) scale is a widely used tool for the objective rating of treatment effectiveness, and is rated using the following seven-point scale: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = extremely ill. The CGI can track clinical progress longitudinally and has been shown to be correlated with longer, more tedious, time consuming rating instruments across a wide range of psychiatric diagnoses. In addition, it has shown good inter-rater reliability and validity, and recently published guidelines have improved the precision of CGI scoring. The standard CGI is used in virtually all FDA-regulated and most other CNS trials, and is regarded effective if certain medication or treatment methods decrease its score by more than one point. CGI ratings were determined during weekly neurofeedback team meetings with attending psychiatrists from outpatient clinic and by psychiatrists in charge of the initial planning and supervising of neurofeedback treatment; furthermore, a significant inter-rater correlation was found ($\kappa > 0.90$) (Busner and Targum 2007; Busner et al. 2009). Raters of the CGI-S in this study had trained until they had reached above 0.80 at interrater reliability using kappa index before the study. Interrater reliability of CGI in this study was 0.86.

Neurofeedback Apparatus and Neurofeedback Protocol

When every visit, patients were received beta training at F3 for 30 min, and then alpha/theta training at Pz for 30 min. Brain's electrical activity was displayed on a monitor in the form of an audiovisual exercise. During the beta training protocol, patients were introduced to a computer game: reward feedback took the form of achievement scores and graphs during and after training. During the alpha-theta training protocol at the Pz area, a patient sat in a chair with eyes closed and only audio feedback was provided. During beta training, the reward band ranged from 15 to 18 Hz, and during alpha-theta training, patients were trained simultaneously to reduce alpha and increase theta to the point at which they 'crossed over', which was defined as the point at which the alpha amplitude dropped below the level of theta (Rostami and Nadali 2013). Reward bands for theta and alpha were 5–8 and 8–12 Hz, respectively.

Before and during training, participants were instructed to develop the most successful mental strategy to obtain as much reward feedback as possible.

EEG Recording and Analysis

EEG was recorded at eight scalp locations (C3, C4, F3, F4, T3, T4, O1, O2) as described by the international 10/20 system, and all placements were referenced to A1 or A2. EEG were analyzed using complexity version 2 of LAXTHA. Interhemispheric alpha power asymmetry, called A score, was computed for homologous sites F3–F4 as described by Tomarken et al. (1992). An asymmetry metric (A score) was computed for each epoch by subtracting the log-transformed alpha power of the left midfrontal site from that of the right site (log R–log L). A negative A score means a more depressed state.

Statistics

Subjects' demographic characteristics and clinical patterns were examined by frequency and descriptive analysis. The effects of neuro-feedback on subjects were analyzed by repeated measure ANOVA using HAM-D, HAM-A and CGI-S as objective indicator and BDI and BAI as subjective indicators: these measures were applied at baseline and 4 and 8 weeks later. In addition, in order to find out the difference between before and after treatment of Asymmetry scores, paired t test was carried out. The statistical analysis was performed using PASW Version 18.0 for Windows (Chicago, IL), and the level of significance for each analysis was set at 0.005 with a Bonferroni correction procedure.

Results

Demographic Data

Participants were enrolled from a population of patients undergoing neurofeedback treatment at an outpatient clinic of the psychiatric department of a university hospital between July 2009 and July 2012 according to the above-mentioned inclusion and exclusion criteria. A total of 20 patients were recruited. Table 1 summarizes demographic data and clinical characteristics. Of the 20 study subjects, 16(80 %) were female, and overall mean age was 43.25 years. Twelve patients (60 %) were taking medications (see Table 1).

Table 1 Demographic and clinical characteristics of the subjects

Variables	Mean	SD
Age	43.25	14.29
Education (year)	13.60	3.56
	N	%
Sex		
Female	16	80.0
Male	4	20.0
Marriage		
Single	13	65.0
Married	6	30.0
Divorce	1	5.0
Occupation		
Office worker	1	5.0
Self-employed	1	5.0
Profession	1	5.0
Housewife	12	60.0
Student	5	25.0
Presence of medication		
Pt without medication	8	40.0
Pt with medication	12	60.0
Medical history		
Hypertension	2	10.0
Diabetes mellitus	1	5.0
Cerebrovascular diseases	1	5.0
Etc	3	15.0

SD standard deviation

Neurofeedback Effectiveness

Figure 1 and Table 2 surmmarize pre- and post-treatment HAM-D, HAM-A, BDI, BAI and CGI scores. Mean HAM-D ($p < 0.0001$), HAM-A ($p < 0.0001$), BDI ($p = 0.002$) and CGI-S ($p = 0.0001$) scores improved significantly. Cumulative response rates by HAM-D were 35.0 and 75.0 % at 4 and 8 weeks, respectively ($p = 0.002$) (see Table 3), and cumulative remission rates by HAM-D were 15.0 and 55.0 % at 4 and 8 weeks ($p = 0.002$) (see Table 3).

Discontinuation and Tolerability

Discontinuation rates were 5 and 25 % at 4 and 8 weeks, respectively. Reasons for discontinuation were adverse events of medication (1, 5 %), adverse events of neurofeedback (1, 5 %), difficulties associated with visiting hospital weekly (1, 5 %), and lost to follow up (2, 10 %). The adverse event of neurofeedback leading to early discontinuation was 'feeling tired after treatment'. No serious adverse events were reported during the study.

Pre- and Post-training Comparisons of Asymmetry Scores (A scores)

No significant differences were found between pre- and post-treatment Asymmetry scores (A score).

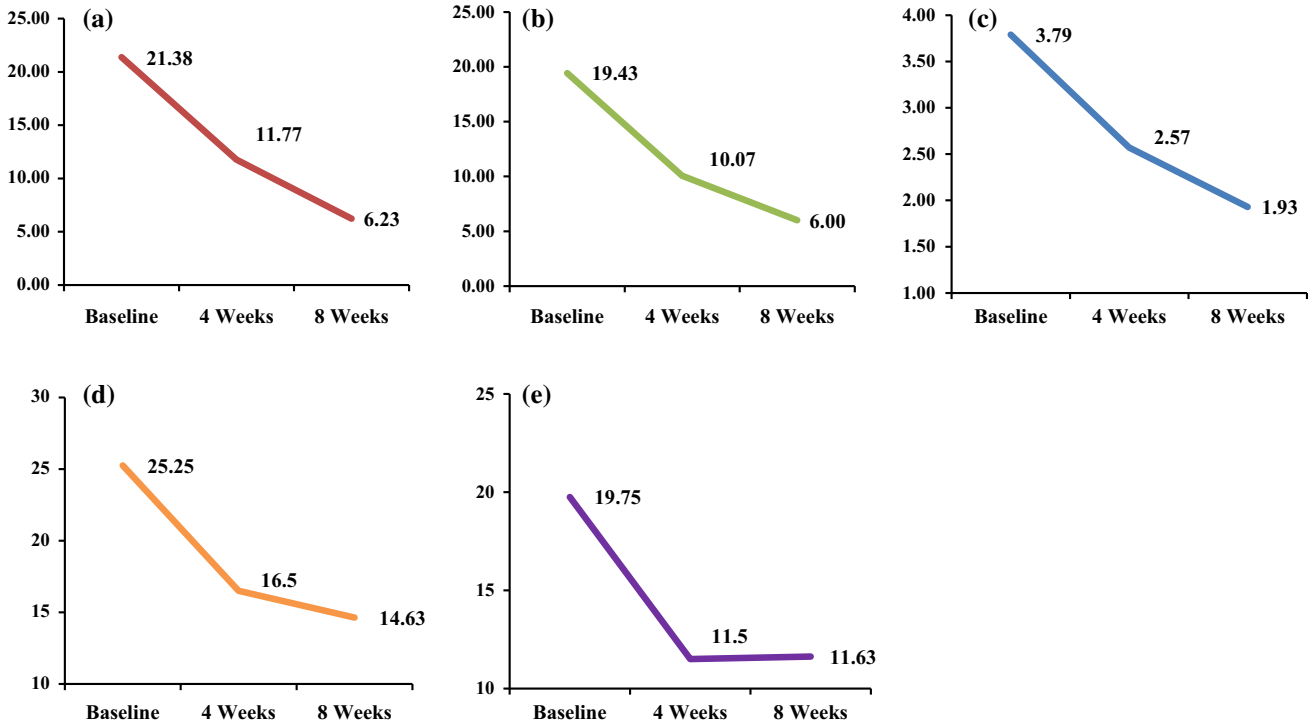

Fig. 1 Neurofeedback effectiveness. **a** HAM-D, **b** HAM-A, **c** CGI, **d** BDI, **e** BAI

Table 2 Neurofeedback effectiveness

Rating scales	Baseline	4 weeks	8 weeks	*df*	*F*	*p* value
HAM-D	21.38 ± 5.82	11.77 ± 6.00	6.23 ± 3.60	2	82.14	<0.0001*
HAM-A	19.43 ± 8.70	10.07 ± 8.42	6.00 ± 5.80	2	59.13	<0.0001*
BDI	25.25 ± 7.91	16.50 ± 9.75	14.63 ± 10.98	2	10.10	0.002*
BAI	19.75 ± 12.76	11.50 ± 11.45	11.63 ± 11.16	2	12.01	0.01
CGI	3.79 ± 1.30	2.57 ± 0.65	1.93 ± 0.92	2	14.90	0.001*

Significant *p* value <0.05

HAM-D Hamilton depression rating scale, *HAM-A* Hamilton anxiety rating scale, *BDI* Beck depression inventory, *BAI* Beck anxiety inventory, *CGI* clinical global impression

Table 3 Responders and remitters in each visit by Hamilton depression scale

	Responders (n = 20)		Remitters (n = 20)		*p* value*	*p* value^{+}
	N	%	N	%		
Baseline	–	–	–	–	0.002*	0.002*
4 weeks	7	35.0	3	15.0		
8 weeks	15	75.0	11	55.0		

Significant *p* value <0.05

Discussion

Depressive disorders belong to the areas where evidence of neurofeedback efficacy is insufficient. This lower rating of efficacy is due to the insufficient number of studies or the minimal sample sizes used in reported studies despite findings of positive outcomes (Larsen and Sherlin 2013). Our results suggested the effectiveness of neurofeedback in patients with major depressive disorder. Beta at F3 and alpha/theta at Pz training improved depression significantly according to both objective and subjective rating scales. Remission and response rates were also increased

significantly after neurofeedback treatment, and also, anxiety symptoms and clinical illness severities decreased.

We used left frontal beta training as main treatment protocol for depressed patient. It was suggested that beta training could be a more direct way to treat the relevant area than asymmetry training (Walker et al. 2007). Beta rhythm has been shown to increase with attention (Murthy and Fetz 1992), arousal (Bonnet and Arand 2001), vigilance (Bouyer et al. 1987), and more recently directly through cortical stimulation via transcranial magnetic stimulation (Paus et al. 2001). Specific symptoms of depression may be accompanied by different dysfunctional patterns of activation. Psychomotor retardation, anhedonia, and flat affect, for example, have been associated with decreased left (but not right) dorsolateral prefrontal cortex (DLPFC) activation (Bench et al. 1993; Galynker et al. 1998). We have recently carried out a retrospective study of the effects of neurofeedback in adult patients with psychiatric disorders in naturalistic setting. In our study, the treatment protocol of depressed patients was not uniform but individualized. Patient's most agonizing symptoms were considered that needed preferential treatment. Depressed patients with severe anxiety symptoms were treated with SMR at T4 and alpha-theta at Pz. After their serious anxiety symptoms were addressed, treatment goals and protocols were revised to alleviate depression by beta training at F3. On the other hand, depressed patients whose chief complaints were energy loss and concentration difficulties were provided with neurofeedback training starting with beta training at either T3 or F3. The most commonly used protocol for depressive patients was beta at F3 and/or alpha/theta at Pz (Cheon et al. 2015).

Relatively higher right than left prefrontal activity relates to depressive symptoms (Davidson 1998) and asymmetric findings concur with Positron Emission Tomography (PET)/Single-Photon Emission Computed Tomography (SPECT) results of increased right activation (Reischies et al. 1989; Brody et al. 2001) as well as decreased left frontal activation (e.g., Bench et al. 1992, 1993; Drevets et al. 1997; Martinot et al. 1990). Depression severity has been associated with reduced left (e.g., Baxter et al. 1989; Bench et al. 1993; Drevets et al. 1992; Kato et al. 1995) or increased right (Galynker et al. 1998; Osuch et al. 2000) frontal metabolism and blood flow. Remission from depression has been associated with increased DLPFC activation (Baxter et al. 1989; Martinot et al. 1990; Mayberg 2003). Previous studies have reported that repetitive transcranial magnetic stimulation (rTMS) at high frequency to the left dorsolateral perfrontal cortex facilitated left prefrontal cortex activity and improved mood symptoms (Conca et al. 1996; George et al. 1995; Pascual-Leone et al. 1996), which suggests facilitation of left frontal lobe function by beta neurofeedback training offers a potential means of improving depressive symptoms in major depressive disorder. Asymmetry score increased after training, however, this increase was not statistically significant. We believe this was due to the small sample size, and because the duration of neurfeedback treatment was not enough to produce a significant change. Treatment protocol was not the asymmetry training therefore it was possible that Asymmetry score was not a proper index of treatment outcome. Further research is needed to elucidate the mechanism underlying the effectiveness of neurofeedback treatement in depressive patients.

The previous study by Scott et al. (2005) have used 2 phases of neurofeedback treatment. In Phase I, mixed substance abusing inpatient underwent 10–20 sessions of beta or SMR treatment to address attentional problems. In Phase II, subjects underwent 30 sessions of alpha-theta training. In the current study, depressed patients were received both beta and alpha/theta training, at every visit. Alpha/theta training have been reported to produce relief from depression in other studies although these were not controlled, thus, this might be a worthwhile avenue for future research (Niv 2013). Alpha/theta neurofeedback reduced depression and anxiety in alcoholism and resolved post-traumatic stress disorder (Peniston and Kulkosky 1989; Saxby and Peniston 1995). The efficacy of alpha-theta neurofeedback may lie in its ability to allow participants to deal with anxiety and anxiety-eliciting situations (Peniston and Kulkosky 1989). It has also been suggested that neurofeedback targeting lower frequencies such as alpha/theta may directly affect core neurocognitive networks, and thereby produce widespread symptom improvements (Niv 2013). Neuroanatomical circuitry involves the ascending mescencephalic-cortical arousal system, and limbic circuits subserving cognitive as well as affective/motivational functions, and including coupling between frontal and posterior cortices, exemplifying a role for theta and alpha waves in mediating the interaction between distal and widely distributed connections (Gruzelier 2009).

The present study is limited by its small sample size, lack of control group, and the non-blinding of subjects. Furthermore, the majority of patients were already receiving pharmacological treatment, although changes in dosage and the addition of new medication were prohibited during the study period. Double blinded large controlled studies are needed to determine the efficacy and safety of neurofeedback treatment in patients with major depressive disorder. We also recommend evaluations be conducted to investigate long-term effectiveness and safety, relapse prevention, cost effectiveness and identifying an optimum treatment protocol.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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