CLINICAL SCIENCE

MEASURING THE EFFICACY OF TREATMENT WITH NEUROFEEDBACK METHOD IN PATIENTS WITH AFFECTIVE DISORDERS

Aleksandar Risteski[1], Slavica Arsova[1], Elizabet Miceva-Velichkoska[1], Ana Filipce[1], Stefanija Mitrovska[1]

[1] *University Clinic for Psychiatry; Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia*

Citation: Risterski A, Arsova S, Miceva-Velickovska E, Filipce A, Mitrovska S. Measuring the efficacy of treatment with neurofeedback method in patients with affective disorders Arch Pub Health 2025; 17 (1). 51-62.

doi.org/10.3889/aph.2025.6134

Key words: affective disorders, antidepressants, neurofeedback

***Correspondence:** Aleksandar Risteski, University Clinic for psychiatry; Faculty of Medicine, Ss Cyril and Methodius University in Skopje, Republic of North Macedonia.

E-mail: risteskialeksandar@gmail.com

Received: 6-Dec-2024; **Revised:** 25-Jan-2025; **Accepted:** 30-Jan-2025; **Published: 2**7-Jun-2025

Copyright:© 2025. Aleksandar Risteski, Slavica Arsova, Elizabet Miceva-Velichkoska, Ana Filipce, Stefanija Mitrovska. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

Competing Interests: The author have declared that no competing interests

Abstract

Depression affects approximately 280 million people globally, with about 5% of adults experiencing an episode each year, making it a major public health concern. The high prevalence of treatment-resistant depression and the limitations of standard therapies highlight an urgent need for alternative treatments, such as neurofeedback, which has shown promising results in improving depressive symptoms when used alongside conventional pharmacological approaches. Aim of the study: To assess the efficacy of combining neurofeedback training with standard antidepressant therapy in adult patients with affective disorders. Materials and methods: This prospective, randomized study was conducted at the University Clinic for Psychiatry in Skopje, in a 2 month period. It involved a total of 100 outpatients diagnosed with affective disorders (ICD-10 codes F32, F33, F34). Participants were randomized into two groups: the study group (SG) that received both neurofeedback and antidepressant therapy, and the control group (CG) that received antidepressant monotherapy. The HAM-D and HAM-A scales, alongside with a structured psychiatric interview and sociodemographic questionnaire at baseline, were used to assess depressive and anxiety symptoms at baseline, 2 weeks, and 1 month. Data were analyzed with SPSS v23.0, using parametric and non-parametric tests, with significance set at $p<0.05$. The study received ethics approval, and all participants provided informed consent. Results: At baseline, both groups showed similar levels of depression and anxiety symptoms, with comparable average scores on the HAM-D (SG: 17.98 ± 5.7, CG: 18.42 ± 6.1) and HAMA (SG: 17.98 ± 6.8, CG: 21.36 ± 8.3) scales. At the two-week follow-up, the study group (SG) exhibited significant reductions in both HAM-D and HAMA scores compared to the control group (CG), with a decrease of 2.42 points in HAM-D (or 13.46% vs 0.65%) ($p<0.0001$) and 2.86 points in HAMA (13.72%, $p<0.0001$) for the SG, while the CG showed minimal change by 3.78%. At one-month follow-up, the SG continued to demonstrate marked improvement, with HAM-D scores at 14.50 ± 5.5 versus 17.56 ± 6.2 in the CG ($p=0.0064$) and HAMA scores at 16.82 ± 6.7 in the SG compared to 20.14 ± 8.3 in the CG. Conclusion: The results from the study suggest that neurofeedback, when combined with medication, may enhance both early and sustained symptom improvement of depression and anxiety.

КЛИНИЧКИ ИСТРАЖУВАЊА

МЕРЕЊЕ НА ЕФИКАСНОСТ НА МЕТОДАТА NEUROFEEDBACK ПРИ ТРЕТМАН НА ПАЦИЕНТИ СО АФЕКТИВНИ РАСТРОЈСТВА

Александар Ристески[1], Славица Арсова[1], Елизабет Мицева-Величкоска[1], Ана Филипче[1], Стефанија Митровска[1]

[1] *Универзитетска клиника за психијатрија; Медицински факултет, Универзитет "Св. Кирил и Методиј" во Скопје, Северна Македонија*

Цитирање: Ристески А., Арсова С., Мицева-Величковска Е, Филипче А, Митровска С. Мерење на ефикасност на методата neurofeedback при третман на пациенти со афективни растројства Арх Ј Здравје 2025;17 (1) 51-62.

doi.org/10.3889/aph.2025.6134

Клучни зборови: афективни растројства, антидепресиви, неврофидбек

***Кореспонденција:** Александар Ристески, Универзитетска клиника за психијатрија; Медицински факултет, Универзитет "Св. Кирил и Методиј" во Скопје, Северна Македонија.

E-mail: risteskialeksandar@gmail.com

Примено: 6-дек-2024; **Ревидирано:**25-јан-2025; **Прифатено:** 30-јан-2025; **Објавено:** 27-јун-2025

Печатарски права: ©2025 Александар Ристески, Славица Арсова, Елизабет Мицева-Величковска, Ана Филипче, Стефанија Митровска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Депресијата погодува приближно 280 милиони луѓе на глобално ниво, при што околу 5% од возрасните доживуваат епизода секоја година, што ја прави голем товар за јавното здравје. Високата преваленција на депресија резистентна на третман и ограничувањата на стандардните терапии ја нагласуваат итната потреба за алтернативни третмани, како што е неврофидбекот, кој покажува ветувачки резултати за подобрување на депресивните симптоми кога се користи заедно со конвенционалните фармаколошки пристапи. Цел на студијата: Да се процени ефикасноста на комбинирањето на неврофидбек тренинг со стандардна антидепресивна терапија кај возрасни пациенти. Материјали и методи: Оваа проспективна, рандомизирана студија беше спроведена на Универзитетската клиника за психијатрија во Скопје во текот на 2 месеци, во која беа вклучени 100 пациенти дијагностицирани со афективни растројства (МКБ-10 кодови F32, F33, F34). Учесниците беа поделени во две групи: испитувана група (ИГ) доби и неврофидбек и антидепресивна терапија, додека контролната група (КГ) беше лекувана со антидепресивна монотерапија Скалите HAMD и HAMA, заедно со структурирано психијатриско интервју и социодемографски прашалник, беа користени за проценка на симптомите на депресија и анксиозност на почетокот, 2 недели и 1 месец од почетокот на третманот. Податоците беа анализирани со SPSS v23.0, користејќи параметарски и непараметриски тестови, со статистичка значајност поставена на $p<0.05$. Студијата беше одобрена од етичката комисија и сите учесници дадоа информирана согласност за учество. Резултати: На почетокот, двете групи покажаа слични нивоа на симптоми на депресија и анксиозност, со споредливи просечни резултати на HAMD (ИГ: 17,98 ± 5,7, КГ: 18,42 ± 6,1) и HAMA (ИГ: 17,98 ± 6,8, КГ: 21. ± 8.3) скалите. На двонеделното следење, испитуваната група (ИГ) покажа значителни намалувања и во резултатите на HAMD и HAMA споредено со контролната група (КГ), со намалување од 2,42 поени во HAMD (или 13,46% наспроти 0,65%) ($p<0,0001$) и 2,86 поени во HAMA (13,72%, $p<0,0001$) за ИГ, додека КГ покажа минимална промена од 3,78%. До едномесечното следење, ИГ продолжи да демонстрира значително подобрување, со HAMD резултати од 14,50 ± 5,5 наспроти 17,56 ± 6,2 во КГ ($p=0,0064$) и HAMA резултати од 16,82 ± 6,7 во ИГ во споредба со 20,14 ± 8,3 во КГ. Заклучок: Резултатите од студијата сугерираат дека неврофидбек третманот комбиниран со лекови може да го забрза и одржи подобрувањето на депресивните и симптомите на анксиозност.

Introduction

Depression affects approximately 280 million individuals worldwide, representing a major global health issue that is often neglected despite its significant impact[1]. Each year, around 5% of adults experience an episode of depression, with prevalence rates varying across different regions and demographic groups[2]. The highest prevalence is observed in North America (4.4% for women and 2.5% for men) and the lowest in the Western Pacific[3]. Women are disproportionately affected, experiencing depression nearly twice as often as men, with hormonal changes during puberty, menstruation, pregnancy, and perimenopause, as well as different psychosocial stressors between genders, different learnt models of behavior and socio-economic inequities contributing to this disparity [4,5]. While retrospective reports suggest a 10.6% average lifetime prevalence, prospective studies estimate a higher range of 30-40%, underscoring the pervasive nature of the condition and the need for effective treatment strategies [3,6]. Moreover, depression is projected to be the leading cause of disease burden by 2030, particularly impacting women[1,7]. Furthermore, the risk factors associated with the COVID-19 pandemic such as greater exposure to stressors, lower social, healthcare and economic resources, employment loss, isolation and fear, contributed to a dramatic increase in the prevalence of depression worldwide reaching 25%, which is seven times higher than the pre pandemic estimates[4]. This alarming trend highlights the urgency for comprehensive research and interventions to mitigate its widespread consequences, which beyond significant subjective suffering, accompanying disability and high risk of suicide in affected individuals, contribute to broader social impacts and economic burden due to the high rates of recurrence and relapse[4,7].

In spite of evidence supporting the efficacy of conventional antidepressants, psychotherapeutic interventions, and additional modalities, the majority of individuals with major depressive disorder (MDD) show inadequate responsiveness to first-line treatments while a significant proportion fail multiple antidepressant interventions, leading to treatment-resistant depression (TRD). TRD is characterized by the inadequate response to conventional antidepressant treatments, despite adherence to appropriate dosage and duration. According to the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), TRD is defined as the failure to respond to at least two different antidepressant regimens under these conditions[8,9]. This condition is significant as it affects approximately 30% of individuals with MDD, and accounting for nearly 50% of the total annual burden estimated $43.8 billion in recent studies from the U.S.[4,10,11]. The high prevalence and treatment challenges associated with TRD emphasizes the need for exploring alternative and adjunctive therapeutic options.

Neurofeedback training, a non-invasive intervention, has emerged as a promising supplementary treatment for major depressive disorder, showing significant improvements in depressive symptoms and neurophysiological outcomes, even in patients who do not achieve sufficient remission of symptoms with standard

pharmacological treatments[12,13]. Systematic reviews and meta-analyses support its potential efficacy as an adjunction in enhancing the outcomes of conventional therapies, underscoring its low risk of side effects and beneficial impact on neuropsychological function [12].

The aim of this study was to assess the efficacy of combining neurofeedback training with standard antidepressant therapy in adult patients with affective disorders, and to determine if this combined approach could enhance symptom reduction in comparison to antidepressant monotherapy.

Materials and methods

This prospective, randomized, controlled study was conducted at the University Clinic for Psychiatry, Skopje, North Macedonia, over the course of 2 months. The study aimed to evaluate the efficacy of combining neurofeedback training with standard antidepressant therapy in patients diagnosed with affective disorders. The study included 100 outpatients aged 18 to 65 years, diagnosed with affective disorders per ICD-10 codes F32 (depressive episode), F33 (recurrent depressive disorder), and F34 (persistent affective disorder). Participants were randomized into two groups of 50: the study group (SG) receiving combined antidepressant and neurofeedback treatment, and the control group (CG) treated solely with antidepressant as monotherapy. The SG received neurofeedback sessions in addition to antidepressants (SSRIs, SNRIs, NASsA). The neurofeedback utilized the "Encephalan-EEGR-19/26" device with "Rehacor" software for alpha/theta training, applied in 10 sessions of 25 minutes each. The CG was treated with monotherapy, including SSRIs (e.g., Escitalopram 10 mg), SNRIs (e.g., Duloxetine 60 mg), or NASsA (e.g., Mirtazapine 30 mg).

Participants in this study were assessed at three time points: baseline, 2 weeks, and 1 month after the start of treatment. Baseline data collection included a structured psychiatric interview, a sociodemographic questionnaire, and psychodiagnostic assessments using the HAMD and HAMA scales to measure affective symptoms. The HAMD and HAMA scales were also administered at the second (2 weeks) and third (1 month) assessment point to evaluate changes in depressive and anxiety symptoms over the course of the treatment.

The HAMD17 scale was utilized to assess depressive symptomatology, encompassing a range of clinical features associated with major depressive disorder, including affective symptoms, insomnia, hypochondriasis, and weight loss. The HAMD is a widely used clinician-rated scale for evaluating the severity of depression and treatment response in patients diagnosed with depressive disorders [14-18].

To compare the study and control groups regarding demographic and clinical characteristics and the total scores on the HAMA scale and HAMD scale, non-parametric tests (Pearson Chi-square and Fisher's exact test) and a parametric test (t-test for independent samples) were used. Testing the differences in the total scores on the HAMA scale and HAMD scale between the three assessment points (baseline, two weeks and 1 month

after treatment initiation) within the groups was performed using the parametric t-test for dependent samples. Statistical significance was defined at a level of $p<0.05$.

Results

Comparative analysis in terms of demographic and clinical characteristics Patients from both groups, study and control, were homogenous in terms of sex, and there was a statistically insignificant difference regarding sex (p=0.84). Female patients were predominant in both groups (52% and 54% in the study and in the control group, respectively) (Table 1).

Forty percent from the SG and 14% of patients from the CG were aged between 18 and 34 years; 30% from the SG and 22% from the CG were aged between 35 and 44 years; 26% from the SG and 60% from the CG were aged between 45 and 64 years; 4% from each group were 65 years of age or older (Table 1).

Table 1. Demographic distribution of patients

Sex	Groups			p-level
	n	SG n=50	CG n=50	
Male	47	24 (48%)	23 (46%)	X2=0.04
Female	53	26 (52%)	27 (54%)	p=0.84
Age	**n**	**SG** n=50	**CG n=50**	
18 – 34	27	20 (40%)	7 (14%)	X2=13.56
35 – 44	26	15 (30%)	11 (22%)	**p=0.0035
45 – 64	43	13 (26%)	30 (60%)	
≥65	4	2 (4%)	2 (4%)	

X^2 (Pearson Chi-square)

Comparative analysis by HAMA (Hamilton Anxiety Rating Scale)

Scores on the Hamilton Anxiety Rating Scale calculated for both groups at baseline and during the first follow up are given in Table 2.

Table 2. HAMA scale on baseline examination and first follow up assessment

HAMA 0 and HAMA 1		Groups		p-level
		SG n=50	CG n=50	
HAMA 0	mean ±SD	20.84 ± 7.0	22.20 ± 8.2	t=0.89
HAMA 0	min- max	8 – 41	6 – 46	p=0.375
HAMA 1	mean ±SD	17.98 ± 6.8	21.36 ± 8.3	t=2.23
HAMA 1	min- max	6 – 39	5 – 46	*p=0.028

t (Student t-test)

Quantitative analysis made by HAMA scores at baseline, that is, at the beginning of antidepressant treatment showed an average score of 20.84 ± 7.0 in the SG, and 22.20 ± 8.2 in the CG, with no statistically significant difference between the groups (p=0.375). In accordance with the

total HAMA result, at baseline both groups of patients most often suffered from mild to moderate anxiety (42% *vs.* 50%), followed by mild anxiety (34% *vs.* 22%). There was a statistically non-significant difference in the distribution of patients with mild, mild to moderate, moderate to severe and severe anxiety between patients from both groups (p=0.597).

The average HAMA score was 17.98 ± 6.8 in the SG, and 21.36 ± 8.3 in the CG on the first follow-up assessment, two weeks after treatment initiation. The difference of an average 3.38 scores was statistically significant (p=0.028). Patients treated with antidepressants in combination with neurofeedback (SG) showed a significantly lower score on the anxiety scale than patients treated with antidepressant medications alone (CG).

Table 3 illustrates the distribution of patients from both groups and the different severity of anxiety symptoms presented in number and percentage. During the first follow-up assessment, in accordance with the interpretation of the total HAMA score, mild anxiety was more often registered in patients from the study group compared to the control group (48% *vs.* 30), and mild to moderate anxiety was rarely encountered (36% *vs.* 44%), followed by moderate to severe anxiety (14% *vs.* 16%), and severe anxiety was rarely seen (2% *vs.* 10%, respectively). These differences between the groups were not statistically significant (p=0.16).

Table 3. Distribution of patients by HAMA categories at the first follow-up assessment

HAMA 1	Groups			p-level
	N	SG n=50	CG n=50	
Mild anxiety	39	24 (48%)	15 (30%)	X2=5.2 p=0.16
Mild to moderate anxiety	40	18 (36%)	22 (44%)	
Moderate to severe anxiety	15	7 (14%)	8 (16%)	
Severe anxiety	6	1 (2%)	5 (10%)	

X^2 (Pearson Chi-square)

Comparison of HAMA scores for assessment of anxiety is given in Table 4. It helps in estimating the speed of onset by which the effects of antidepressant treatment can be seen, that is, it enables to see the difference in the onset of the treatment efficacy in SG patients *versus* CG patients. This correlation was made in order to determine eventual difference in the efficacy of neurofeedback method as complementation to the pharmacological treatment in the study group against the effect of the drugs administered in the control group as monotherapy. The scores are shown as numerical values and percentages.

During the first follow-up assessment, a significant decrease in the HAMA scores was registered in the SG compared to the CG. The average HAMA score shows a significant decrease, by 2.86 points in the SG (p<0.0001), and by 0.84 points in the CG (p=0.0017). Percentage decrease in the HAMA score was by 13.72% points in the SG, and by 3.78% points in the CG.

Table 4. Total score on HAMA scale baseline/first follow-up assessment

HAMA score	SG n=50		CG n=50	
	Baseline	First follow-up assessment	Baseline	First follow-up assessment
mean ±SD	20.84 ± 7.0	17.98 ± 6.8	22.20 ± 8.2	21.36 ± 8.3
difference	2.86		0.84	
p-level	t=11.96 p=0.00000		t=3.32 **p=0.0017	
% of change	13.72%		3.78%	

**sig p<0.01, ***sig p<0.0001

The result of the HAMA scale at the second follow-up assessment was significantly lower in the study group treated with antidepressants in combination with the neurofeedback method compared to the control group treated only with antidepressants (p=0.029, difference=3.32). In the study group (SG), the average score on this scale was 16.82 ± 6.7, while in the control group (CG) 20.14 ± 8.3 (Table 5)

Table 5. HAMA scale scores at second follow-up assessment

HAMA - 2	groups		p-level
	SG n=50	CG n=50	
mean ±SD	16.82 ± 6.7	20.14 ± 8.3	t=2.21 *p=0.029
min- max	4 – 36	5 – 45	

t(Student t-test)
*sig p<0.05

Comparative analysis by HAMD (Hamilton Depression Rating Scale)

The average HAMD score was 17.98 ± 5.7 in the SG and 18.42 ± 6.1 in the CG at baseline; there was no statistically significant difference between both groups (p=0.1) (Table 6).

Table 6. Total score on HAMD at baseline and first follow up assessment

HAMD 0 and HAMD 1	groups		p-level
	SG n=50	CG n=50	
HAMD 0 mean ±SD	17.98 ± 5.7	18.42 ± 6.1	t=0.37 p=0.71 t=2.32 *p=0.022
HAMD 0 min- max	7 – 34	7 – 32	
HAMD 1 mean ±SD	15.56 ± 5.4	18.30 ± 6.3	
HAMD 1 min- max	6 – 30	7 – 32	

t(Student t-test)
*sig p<0.05

Analyzing the HAMD scores tallied at baseline and during the first follow-up assessment (2 weeks after the initiation of treatment), the following results were obtained. At baseline, patients from the study group mostly had severe depression, followed by moderate depression (32% and 28%, respectively). Patients from the control group mostly had moderate depression followed by very severe depression (34% and 28%, respectively).

No significant difference was found in the distribution of patients without depression, with mild, moderate, severe and very severe depression between both groups (p=0.44). Patients treated with antidepressants in combination with neurofeedback (SG) had significantly higher scores than patients treated only with antidepressants.

Table 6 illustrates scores measured during the first follow-up assessment. The average HAMD score was 15.56 ± 5.4 in the SG and 18.30 ± 6.3 in the CG; the difference of an average 2.74 scores was statistically significant for p=0.022.

Results obtained during the first assessment, in numerical and percentage values, are presented in Table 7.

Table 7. Distribution of patients by HAMD categories at first follow-up assessment

HAMA 1	Groups			p-level
	N	SG n=50	CG n=50	
No depression	3	2 (4%)	1 (2%)	X^2=7.9 p=0.096
Mild depression	25	15 (30%)	10 (20%)	
Moderate depression	35	21 (42%)	14 (28%)	
Severe depression	15	6 (12%)	9 (18%)	
Very severe depression	22	6 (12%)	16 (32%)	

X^2 (Pearson Chi-square)

Table 8 presents the correlation of HAMD scores obtained at baseline and during the first follow-up assessment in order to determine probable difference in the onset of antidepressant effect. The initial results demonstrated that scores measured in the SG were lower than those in the CG, suggesting that SG patients achieved faster onset of antidepressant effect compared to that in CG patients. Scores on the HAMD scale showed a significant decrease in the SG compared to the CG at the first follow-up assessment. The average HAMD score was significantly reduced by 2.42 points in the SG (p<0.0001), and non-significantly by 0.12 points in the CG (p=0.63). Percentage decrease in the HAMD score was by 13.46% in the SG, and by 0.65% in the CG.

Table 8. Total score on HAMD scale at baseline/first follow-up assessment – SG and CG

HAMA score	SG n=50		CG n=50	
	First examination	Second examination	First examination	Second examination
mean ±SD	17.98 ± 5.7	15.56 ± 5.4	18.42 ± 6.1	18.30 ± 6.3
difference	2.42		0.12	
p-level	t=15.44 ***p=0.000000		t=0.48 p=0.63	
% of change	13.46%		0.65%	

**sig p<0.01, ***sig p<0.0001

The result of the HAMD scale for depression on the second assessment was significantly lower in the group treated with antidepressants and the neurofeedback method compared to the group treated with antidepressants alone (p=0.0064, difference=3.06). In the SG, the average score on this scale was 14.50 ± 5.5, while in the CG it was 17.56 ± 6.2 (Table 9).

Table 9. Total score of HAMD scale at second follow-up assessment

HAMA - 2	groups		p-level
	SG n=50	CG n=50	
mean ±SD	14.50 ± 5.5	17.56 ± 6.2	t=2.8 **p=0.0064
min- max	4 – 28	6 – 31	

t(Student t-test)
*sig p<0.05

Discussion

Several clinical trials have been conducted in our country and in the region aimed at evaluating the efficacy of antidepressant drug therapy in the treatment of affective disorders[19]. This study is the first one in our country that has assessed the comparative efficacy between monotherapy with antidepressant drugs and a combined treatment with neurofeedback contributing to the growing body of research on alternative and adjunctive treatments for depression, particularly for those who do not achieve sufficient remission from standard pharmacological interventions. Given the high global prevalence of depression, its profound social and economic impact, and the substantial portion of patients experiencing treatment-resistant depression (TRD), exploring effective supplementary treatments like neurofeedback is essential.

This prospective randomized controlled study evaluated the efficacy of combined neurofeedback and pharmacological treatment *versus* antidepressant monotherapy in patients with affective disorders, focusing on depressive and anxiety symptoms. Our sample was demographically balanced, with a slight female predominance in both the study group (SG) and control group (CG), 52% and 54% in the study and in the control group respectively, consistent with findings in affective disorder epidemiology indicating a higher prevalence in women due to biological and psychosocial factors.

At baseline, both groups displayed comparable levels of depressive and anxiety symptoms on the HAMD and HAMA scales, with average total scores ranging 17.98 ± 5.7 in the SG and 18.42 ± 6.1 in the CG for HAMD, and 20.84 ± 7.0 in the SG, and 22.20 ± 8.2 in the CG for HAMA, indicating homogeneity before intervention. At the first follow-up assessment – two weeks after treatment initiation, the SG showed a significant reduction in both depression and anxiety scores compared to the CG, demonstrated by a statistically significant reduction in the total HAMD score by 2.42 points in the SG (p<0.0001), and non-significant 0.12 points reduction in the CG (p=0.63). As for the HAMA scale, the average score was

significantly reduced by 2.86 points or 13,72% in the SG ($p<0.0001$), and by 0.84 points or 3,78% in the CG ($p=0.0017$). This early improvement in the SG may highlight the potential of neurofeedback to accelerate therapeutic responses when used alongside medication. By the first follow-up, the average HAMD score in the SG dropped significantly, with more patients shifting from severe to moderate or mild depression, aligning with findings reported by Lee *et al*. (2019). They registered a significant decrease in the HAMD and CGI scores in the neurofeedback augmentation group when compared to those in the medication-only group, indicating that objective depressive symptoms and depression severity were further improved using neurofeedback when compared to medication-only[20].

At the second follow-up assessment, one month after the initiation of treatment, the SG continued to show marked improvements, with statistically lower HAMD and HAMA scores than the CG. The result of the HAMD scale for depression on the second assessment was significantly lower in the group treated with medication and the neurofeedback method compared to the group treated with antidepressants alone ($p=0.0064$, difference=3.06), with total average scores average score of 14.50 ± 5.5 in the SG, and 17.56 ± 6.2 in the CG. The efficacy of the combined treatment in the reduction of anxiety symptoms was further confirmed by the results from the HAMA scale on the second follow-up assessment, with statistically significant lower scores in the SG *vs*. the CG, 16.82 ± 6.7 for SG, and 20.14 ± 8.3 in the CG. This sustained effect supports the hypothesis that neurofeedback may enhance long-term outcomes in the treatment of depression by reinforcing neural regulation, as evidenced in a substantial body of literature incorporated in the recent meta-analysis by Xia *et al.* (2024) and the systematic review by Patil *et al.* (2023) that report neurophysiological improvements alongside the reduction in affective symptomatology[12,13]. This is in line with previous studies that demonstrate neurofeedback value in lowering symptom intensity in depressive patients who are not fully responsive to medication alone[20].

The results of our study align with the findings presented by Liu *et al.* and Patil *et al*., which demonstrated that neurofeedback contributed to significant symptom improvement in patients with depression[13,21]. Due to its non-invasive nature, minimal side effects, and relatively low cost, neurofeedback has emerged as a valuable adjunct of pharmacological treatments for affective disorders. Similarly, our findings are consistent with the conclusions of Dobbins *et al.* , who conducted a systematic review and noted that neurofeedback has recently gained prominence as an effective intervention for recurrent depressive disorder[22]. Many studies in their review emphasized neurofeedback's role in reducing depressive symptoms, reinforcing its potential as a promising non-pharmacological option. Collectively, these conclusions support the efficacy of neurofeedback observed in our study, highlighting its therapeutic value as an adjunctive treatment for individuals with treatment-resistant or recurrent depression.

Conclusion

The neurofeedback method is a well-established approach in treating patients with anxiety disorders as well as those with ADHD (Attention Deficit Hyperactivity Disorder). In recent years, it has increasingly emerged as a preferred method in treating patients with affective disorders. Additional research is needed to measure the efficacy of the neurofeedback method in treating patients with affective disorders, although initial results from our study are encouraging and motivate the inclusion of new patients. From the data we have processed so far, we can conclude that patients in the study group who were treated with medication therapy supplemented by the neurofeedback method showed lower scores on all scales used to quantify depressive and anxiety symptoms during the second assessment, compared to scores of participants in the control group who were treated with antidepressant monotherapy.

References

1. World Health Organization. Depressive disorder (depression). WHO. Available from: https://www.who.int/news-room/fact-sheets/detail/depression. Accessed 2024 Nov 10.
2. Shelton RC, Tollefson GD, Tohen M, Stahl S, Gannon KS, Jacobs TG, *et al.* A novel augmentation strategy for treating resistant major depression. Am J Psychiatry. 2001 Jan;158(1):131-4. doi: 10.1176/appi.ajp.158.1.131.
3. Herrman H, Patel V, Kieling C, Berk M, Buchweitz C, Cuijpers P, *et al.* Time for united action on depression: A Lancet-World Psychiatric Association Commission. Lancet. 2022;399(10328):957-1022. doi: 10.1016/S0140-6736(21)02141-3.
4. Ettman CK, Abdalla SM, Cohen GH, Sampson L, Vivier PM, Galea S. Prevalence of depression symptoms in US adults before and during the COVID-19 pandemic. JAMA Netw Open. 2020;3(9):e2019686. doi: 10.1001/jamanetworkopen.2020.19686.
5. Albert P. Why is depression more prevalent in women? J Psychiatry Neurosci. 2015;40(4):219-21. doi: 10.1503/jpn.150205.
6. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, *et al.* Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl. 2004;420:21-7. doi: 10.1111/j.1600-0047.2004.00327.x.
7. Heo M, Murphy CF, Fontaine KR, Bruce ML, Alexopoulos GS. Population projection of US adults with lifetime experience of depressive disorder by age and sex from year 2005 to 2050. Int J Geriatr Psychiatry. 2008 Dec;23(12):1266-70. doi: 10.1002/gps.2061. PMID: 18500691; PMCID: PMC3207493.
8. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Major depressive disorder: Developing drugs for treatment. Silver Spring: U.S. Food and Drug Administration; 2018.
9. European Medicines Agency. Clinical investigation of medici-

nal products in the treatment of depression – Scientific guideline. Amsterdam: European Medicines Agency; 2018.

10. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, *et al.* Treatment-resistant depression: Definition, prevalence, detection, management, and investigational interventions. World Psychiatry. 2023;22(3):394-412. doi: 10.1002/wps.21120.
11. Zhdanava M, Pilon D, Ghelerter I, Chow W, Joshi K, Lefebvre P, *et al.* The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. J Clin Psychiatry. 2021;82(2):20m13699. doi: 10.4088/JCP.20m13699.
12. Xia Z, Yang PY, Chen SL, Zhou HY, Yan C. Uncovering the power of neurofeedback: a meta-analysis of its effectiveness in treating major depressive disorders. Cereb Cortex. 2024;34(6):bhae252. doi: 10.1093/cercor/bhae252.
13. Patil AU, Lin C, Lee SH, Huang HW, Wu SC, Madathil D, Huang CM. Review of EEG-based neurofeedback as a therapeutic intervention to treat depression. Psychiatry Res Neuroimaging. 2023;329:111591. doi: 10.1016/j.pscychresns.2023.111591.
14. Boessen R, van den Brink W, de Boer D, Gijsman HJ. Comparing HAMD17 and HAMD subscales on their ability to differentiate active treatment from placebo in randomized controlled trials. J Affect Disord. 2013;145(3):363-9. doi: 10.1016/j.jad.2012.08.026.
15. Carrozzino D, Bech P, Patrascu E, Moeller SB, Hofmann B, Tomba E. The Hamilton rating scales for depression: A critical review of clinimetric properties of different versions. Psychother Psychosom. 2020;89(3):133-50. doi: 10.1159/000506879.
16. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959 Mar;32(1):50-5. doi: 10.1111/j.2044-8341.1959.tb00467.x.
17. Jeong H, Lee B. Psychometric properties and factor structure of the Hamilton anxiety rating scale among Korean university students during COVID-19. Open Psychol J. 2024;17(1). doi: 10.2174/0118743501268244231108104216.
18. Asghar J, Arain SM, Hussain J, Bashir H, Iqbal R. A randomized clinical trial comparing two treatment strategies, evaluating the meaningfulness of HAMD rating scale in patients with major depressive disorder. Front Psychiatry. 2022;13:873693. doi: 10.3389/fpsyt.2022.873693.
19. Latas M, Stefanovski B, Mihaljević-Peleš A, Memić Serdarević A, Pajević I, Radulović NZ, *et al.* Diagnostic psychiatric and somatic comorbidity in patients with depression in the Western Balkan countries. PLoS ONE. 2024;19(1):e0295754. doi: 10.1371/journal.pone.0295754.
20. Lee YJ, Kim S, Lee WK, Choi J. Neurofeedback treatment on depressive symptoms and functional recovery in treatment-resistant patients with major depressive disorder: An open-label

pilot study. J Korean Med Sci. 2019;34(42):e287. doi: 10.3346/jkms.2019.34.e287.

21. Liu H. Neurofeedback training intervention for persons with major depression disorder: Reducing depressive symptoms. NeuroQuantology. 2017 Sep 7;15(3). doi: 10.14704/nq.2017.15.3.1091.

22. Dobbins ICS, Bastos M, Ratis RC, Silva WCFND, Bonini JS. Effects of neurofeedback on major depressive disorder: a systematic review. Einstein (Sao Paulo). 2023 Jul 21;21:eRW0253. doi: 10.31744/einstein_journal/2023RW0253.