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ORIGINAL ARTICLE/ARTIGO ORIGINAL

tDCS em Casa na Depressão *Major*: Análise do Valor Preditivo dos Biomarcadores de EEG

Home-Administered tDCS for Major Depressive Disorder: Exploring the Predictive Value of EEG Biomarkers

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RESUMO

Introdução: A depressão *major* é uma condição altamente prevalente, com uma população significativa resistente ao tratamento. A estimulação transcraniana por corrente contínua (tDCS) emergiu como um tratamento promissor e não invasivo, mas são necessários biomarcadores para prever a sua eficácia.
Este estudo teve como objetivo avaliar a viabilidade e a eficácia da tDCS auto-administrada em casa no tratamento da depressão major e investigar a assimetria alfa frontal como preditor da resposta ao tratamento.
Métodos: Um total de 35 doentes diagnosticados com depressão major foram submetidos a um tratamento de quatro semanas de tDCS. A gravidade da depressão foi medida utilizando a escala *Patient Health Questionnaire* - 9 e a assimetria alfa frontal foi calculada a partir de registos de EEG. Foram utilizados testes t emparelhados e a correlação de Pearson para analisar as alterações nas pontuações da depressão e na assimetria alfa frontal, enquanto a regressão logística avaliou o valor preditivo da assimetria alfa frontal para a resposta ao tratamento.
Resultados: Sessenta por cento dos doentes mostraram melhorias nos sintomas de depressão após o tratamento, com 63% classificados como respondedores. Foram observadas alterações significativas na assimetria alfa frontal nos respondedores (p<0,05) e foi encontrada uma forte correlação positiva entre as alterações na assimetria alfa frontal e a redução dos sintomas depressivos (r= 0,63). A assimetria alfa frontal pré-tratamento foi um preditor significativo da resposta ao tratamento (p<0,05), com valores mais elevados de assimetria alfa frontal associados a uma menor probabilidade de resposta.
Conclusão: A tDCS auto-administrada em casa é uma intervenção eficaz para a depressão major, com a assimetria alfa frontal a emergir como um biomarcador valioso para prever a resposta ao tratamento. Estes resultados apoiam a utilização da assimetria alfa frontal na personalização do tratamento com tDCS para a depressão major.

Palavras-chave: Biomarcadores; Eletroencefalografia; Estimulação Magnética Transcraniana; Perturbação Depressiva Major/tratamento

ABSTRACT

Introduction: Major depressive disorder (MDD) is a highly prevalent condition with a significant treatment-resistant population. Transcranial direct current stimulation (tDCS) has emerged as a promising non-invasive treatment, but biomarkers to predict its efficacy are needed.
This study aimed to evaluate the feasibility and effectiveness of home-administered tDCS in treating MDD and investigate frontal alpha asymmetry (FAA) as a predictor of treatment response.

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Methods: A total of 35 patients diagnosed with MDD underwent a four-week tDCS treatment. Depression severity was measured using the PHQ-9 scale, and FAA was calculated from EEG recordings. Paired t-tests and Pearson correlation were used to analyze changes in depression scores and FAA, while logistic regression assessed FAA's predictive value for treatment response.
Results: Sixty percent of patients showed improvement in depression symptoms post-treatment, with 63% classified as responders. Significant changes in FAA were observed in responders ($p<0.05$), and a strong positive correlation was found between FAA changes and reductions in depressive symptoms (r= 0.63). Pre-treatment FAA was a significant predictor of treatment response ($p<0.05$), with higher FAA values associated with a lower probability of response.
Conclusion: Home-administered tDCS is an effective intervention for MDD, with FAA emerging as a valuable biomarker for predicting treatment response. These findings support the use of FAA in personalizing tDCS treatment for MDD.

Keywords: Biomarkers; Depressive Disorder, Major/therapy; Electroencephalography; Transcranial Magnetic Stimulation

INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent and debilitating condition, affecting approximately 300 million people worldwide.[1] Over the past decade, the incidence of MDD has increased by 18%, making it the fourth leading cause of disability globally.[2] The prevalence of MDD varies significantly across age groups and genders.[3] Despite the availability of pharmacological and psychotherapeutic treatments, a substantial proportion of patients do not achieve adequate relief from symptoms, or they experience adverse effects that limit treatment efficacy. This condition highlights the urgent need for alternative therapeutic strategies and predictive tools to guide treatment selection.

Although transcranial direct current stimulation (tDCS) has shown promising results in multiple studies, it is important to note that this technique is not yet formally approved as a treatment for depression by major regulatory agencies, such as the Food and Drug Administration (FDA) in the United States or the European Medicines Agency (EMA) in Europe. Additionally, tDCS is not included as a first-line recommendation in international medical guidelines for the treatment of depression. However, the investigation of subgroups of patients who may have a higher likelihood of responding to this intervention emerges as a relevant and promising area. This study contributes to this effort by identifying, through neurophysiological markers (EEG), potential responder subgroups to tDCS, advancing the understanding of which populations may specifically benefit most from this treatment.

Transcranial direct current stimulation (tDCS) has emerged as a promising non-invasive neuromodulation technique for treating MDD. This approach involves delivering a low-intensity electrical current to specific brain regions, modulating cortical excitability and potentially promoting neural plasticity, which may alleviate depressive symptoms. Several studies have reported positive outcomes with tDCS in MDD patients.[4-7] However, individual responses to tDCS vary widely, necessitating the identification of biomarkers that can predict which patients are most likely to benefit from this intervention.

Electroencephalography (EEG) offers a non-invasive method of capturing brain electrical activity, providing insights into the neurophysiological mechanisms underlying MDD. One biomarker of particular interest is frontal alpha asymmetry (FAA), which reflects the difference in alpha power between the right and left frontal regions of the brain. Alpha activity, inversely related to cortical activity, has been linked to emotional processing, with lower relative left frontal activity associated with depressive symptoms.[8] Research has shown that individuals with MDD often exhibit greater right frontal activity,[9] which may contribute to the emotional dysregulation central to the disorder.[10] Traditional EEG montages capture alpha power from multiple brain regions, including the occipital cortex, which may reduce the sensitivity of FAA as a biomarker. In contrast, reference-free montages, such as Laplacian transformations, enhance the detection of localized activity by reducing the influence of distant sources.[11,12] These techniques may provide more precise measures of frontal asymmetry, potentially improving the predictive value of FAA in MDD.

Given the involvement of the dorsolateral prefrontal cortex (DLPFC) in emotional regulation, the standard tDCS montage for treating MDD involves stimulating the left DLPFC (anode) and inhibiting the right DLPFC (cathode), corresponding to the F3 and F4 EEG sites, respectively. This configuration aims to normalize the pathological FAA seen in depressed individuals by increasing cortical excitability in the left frontal region.[13] The current study aims to: (1) evaluate the feasibility, tolerability, and clinical effectiveness of home-administered tDCS for the acute treatment of MDD, and (2) investigate the use of FAA as a predictor of tDCS treatment response. By focusing on EEG recordings from the F3 and F4 sites, we seek to determine whether baseline FAA can predict the degree of clinical improvement following tDCS treatment. Additionally, we will explore whether targeted stimulation of the left DLPFC and inhibition of the right DLPFC leads to measurable changes in FAA and whether these changes correlate with improvements in depressive symptoms.

MATERIAL AND METHODS

a. Procedure

For this study, the records of 60 patients from an outpatient neuropsychiatry clinic were assessed. Out of these,

19 patients were excluded for not meeting the inclusion criteria (5 because they did not meet the PHQ-9 scoring criteria — 5 or more points —, and fourteen because they changed their medication during the treatment), and 6 patients discontinued the treatment. Ultimately, 35 patients were included in the final analysis (Fig. 1).

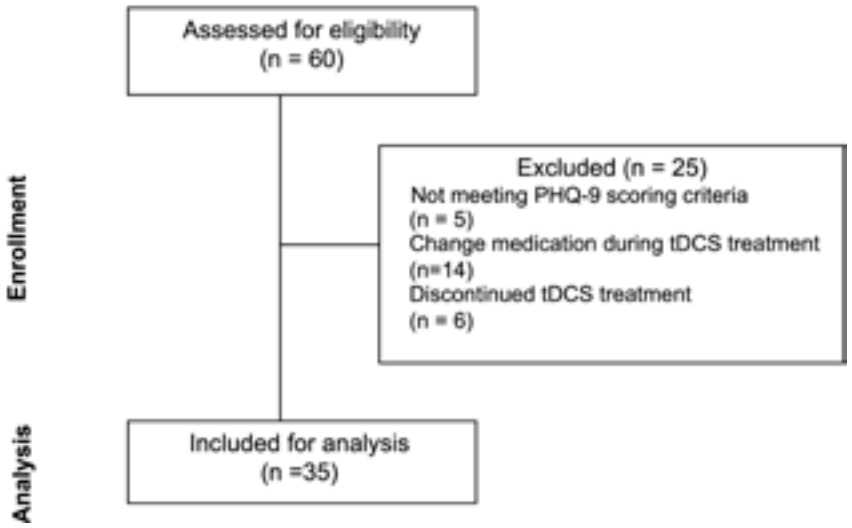

Figure 1. Patient selection procedure

This study analyzed the records of 60 patients from an outpatient neuropsychiatry clinic diagnosed with a depressive episode according to DSM-IV criteria assessed using the Mini-International Neuropsychiatric Interview (MINI). Diagnosis and treatment were conducted by clinic psychiatrists following routine clinical practices used in the Clinic, which included qEEG recording, pharmacological interventions when indicated and tDCS, in addition to provide written informed consent whether for qEEG recording, tDCS treatment, or the anonymous dissemination of data in a scientific context. Eligibility criteria included received tDCS treatment at home, a Patient Health Questionnaire-9 (PHQ-9) score of 5 or higher and no changes in medication during the four-week tDCS treatment. Forty-one patients met these criteria and were included in the study, none of the patients had a depressive episode in the context of bipolar disorder, and none met the criteria for treatment--resistant depression.

Patients received their first tDCS session at the clinic, where they were trained to use the device correctly. The clinicians involved in the study had completed Certified tDCS Practitioner training, in line with the International Federation of Clinical Neurophysiology guidelines,[14] covering neurophysiology, safety, and clinical applications of tDCS. Patient training included a demonstration of the correct application of the tDCS headset and instructions on reporting side effects. The first eight home sessions were monitored via video call to ensure proper technique, with weekly telephone follow-ups conducted thereafter. At the end of the treatment, patients returned to the clinic for a psychiatric evaluation and completion of the PHQ-9. One-month post-treatment, a follow-up quantitative EEG (qEEG) was recorded.

The device used was the Sooma® portable tDCS device, featuring a pre-configured head cap for fixed electrode placement. The stimulation targeted the left DLPFC at the F3 position, with the return electrode at the F4 position, according to the International 10/20 system. Each session delivered a direct current of 2 mA for 30 minutes, five times per week.

b. Sample

Of the 41 patients enrolled, 35 (85%) completed the study, with 15 (43%) being male. The main reason for exclusion (n=6) was discontinuation of treatment. At baseline, 7 patients had mild depression (20%), 8 had moderate depression (23%), 9 had moderately severe depression (26%), and 11 had severe depression (31%), based on PHQ-9 scores (Mild depression – 5-9; Moderate depression – 10-14; Moderately severe – 15-19; Severe depression – 20-27) (Table 1).

Table 1. Demographic and baseline characteristics of the study participants

Characteristic	Full sample (n=35)	Subgroup 1: Mild/Moderate (n = 15)	Subgroup 2: Moderately Severe/Severe (n = 20)
Age (mean± SD)	48.9 (13.7)	50.6 (14,3)	47.7 (13.4)
Gender (Male, %)	15 (43%)	5 (33.3%)	10 (50%)
Baseline PHQ-9 (mean± SD)	15.9 (5.7)	10.3 (2.9)	20.1 (2.9)
Depression severity	Mild: 20% (7); Moderate: 23% (8); Moderately Severe: 26% (9); Severe: 31% (11)	Mild: 47% (7); Moderate: 53% (8);	Moderately Severe: 45% (9); Severe: 55% (11)
Medication status (%)	On medication: 74% (26); No medication: 26% (9)	On medication: 67% (10); No medication: 33% (5)	On medication: 80% (16); No medication: 20% (4)

Table 1 presents the demographic and baseline characteristics of the study participants, including age, gender, baseline PHQ-9 scores, depression severity at the start of the study and medication status.

For analytical purposes, patients were categorized into two subgroups based on depression severity: Subgroup 1: Mild or moderate depression (n = 15, 42%); Subgroup 2: Moderately severe or severe depression (n = 20, 56%)

Patients were further classified as responders or non-responders based on their PHQ-9 scores before and after treatment. Responders were defined as those achieving a complete clinical response (CCR), characterized by a 50% reduction from their baseline depression score. A 50% reduction in PHQ-9 scores is commonly used in clinical trials and practice to define a clinically significant improvement in depression severity. This threshold has been validated as a meaningful indicator of treatment response in various studies.[15,16] Remission was defined as a PHQ-9 score of less than 5 points.

Additionally, we included another indicator, the Minimal Clinically Important Difference (MCID), which aims to identify the smallest changes in depressive symptoms that are meaningful to patients. For the PHQ-9, some authors[16,17] have suggested that a change of 5 points may represent a minimal clinically important difference. However, this indicator was not included as a primary study outcome and was instead added to provide an objective perspective on patients' perceived improvements following treatment.

c. EEG Data Acquisition

EEG data were acquired using a Brain Quick Micromed system (version NS FLXI EEG with SystemPLUS Evolution software). Participants were seated in a slightly dim room and instructed to remain relaxed but awake. EEG was recorded for 5 minutes with eyes closed and 5 minutes with eyes open. Nineteen Ag/AgCl electrodes were placed according to the international 10–20 system, with electrode impedance kept below 5 kΩ. Data were sampled at 1000 Hz and filtered with a 0.1–100 Hz bandpass filter. Ground and reference electrodes were placed on the forehead and at Cz, respectively.

d. EEG Preprocessing

Raw EEG data were preprocessed using Neuroguide® software (Applied Neurosciences Inc., USA). A Laplacian reference was applied to the data, which reduces the influence of distant sources and emphasizes local cortical activity. Data were filtered using a Butterworth bandpass filter (1–50 Hz), and artifacts caused by muscle or eye movements were automatically rejected. EEG segments of 150 seconds were selected for analysis. For each segment, absolute power values were obtained across five frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–25 Hz), and high beta (25–30 Hz).

e. Feature Extraction

FAA was calculated by subtracting the log-transformed alpha power (8–12 Hz) at the right frontal electrode (F4) from the left frontal electrode (F3). Given that alpha power is inversely related to cortical activity, higher FAA values indicate greater left frontal activity, while lower FAA values indicate greater right frontal activity. This approach has been widely used in studies exploring hemispheric asymmetry in affective disorders.[10,18] Fig. 2 shows the flowchart of overall EEG analysis procedure.

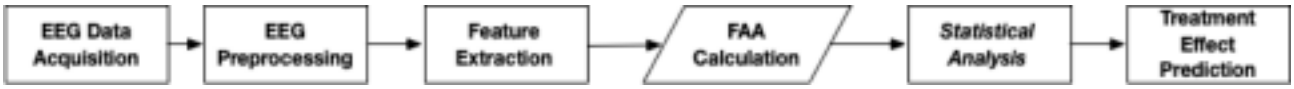

Figure 2. The flowchart of the overall EEG analysis procedure

f. Statistical Analysis

The primary outcomes of this study were to assess the effectiveness of tDCS in reducing depressive symptoms, measured by changes in PHQ-9 scores, and to evaluate FAA as a predictor of treatment response. Criteria for responders and cut-off points were already defined for statistical analysis purposes. The effectiveness was assessed by complete clinical response.

Paired t-tests were used to compare pre- and post-treatment PHQ-9 scores and FAA values across all participants, as well as within the two subgroups (mild/moderate depression and moderately severe/severe depression). To explore the relationship between changes in FAA and changes in PHQ-9 scores, a Pearson correlation was conducted. A logistic regression model was used to evaluate whether pre-treatment FAA (FAA_Pr) could predict the likelihood of being a responder to tDCS treatment. Odds ratios were calculated to quantify the strength of the association between FAA_Pr and treatment response. A receiver operating characteristic (ROC) curve was also generated to assess the model's discriminative ability, and the area under the curve (AUC) was calculated to quantify this ability.

RESULTS

a. Change in Depression Scores After tDCS Treatment

The feasibility of home-administered tDCS was evaluated by examining patient compliance with the treatment protocol. Of the 35 patients included in the study, 25 completed all 20 at-home tDCS sessions, while 7 completed between 15–19 sessions. Two patients completed 11–14 sessions, and 1 patient completed 10 sessions.

The safety of the treatment was assessed through side effects reported by the patients. A total of 10 patients reported no side effects. Of the side effects reported, the most frequent were temporary tingling sensation reported by 18 patients, redness or skin irritation reported by 8 patients, and mild headaches reported by 5 patients. No severe adverse effects were observed.

Table 2 summarizes patient compliance with the tDCS treatment protocol, and the incidence of side effects reported during the study.

Table 2. Compliance and side effects

Compliance and Side Effects	Number of patientes (n=35)	Percentage (%)
Compliance (No. of sessions completed)		
20 sessions (Full compliance)	25	71%
15-19 sessions	7	20%
11-14 sessions	2	6%
10 sessions	1	3%
Side Effects reported		
Temporary tingling sensation	18	51%
Redness or skin irritation	8	23%
Mild headache	5	14%
No reported side effects	10	20%

After the completion of tDCS treatment, 51.4% of all patients (n = 18) had improvement in depression scores. The proportion of patients in remission was 11.4% (n = 4), in the total study population, all of whom belonged to subgroup 1 (mild or moderate depression). In the total sample, CCR was achieved by 28.6% (n=10) of the patients, and MCID was achieved by 22.8% (n=8) of the patients.

In subgroup 1, 8 patients (53.3%) did not experience any improvement in PHQ-9 scores, while 6 patients (40%) achieved a CCR, with 4 patients experiencing a full remission, and 1 patient (6.7%) achieved an MCDI. In subgroup 2 (moderately severe or severe depression), 9 patients (45%) did not experience a decrease in their PHQ-9 scores, while 4 patients (20%) achieved a CCR, and 7 patients (35%) achieved an MCDI.

The mean PHQ-9 scores in the total sample at baseline (before the intervention) were 16.22 (SD=5.65), and post-intervention, the mean was 12.19 (SD=6.17). This difference was statistically significant (t=4.52; p=0.00005).

A statistically significant difference in the change of depression scores was observed between responders and non-responders in the full sample. The mean change in PHQ-9 scores for responders was 9.11, while for non-responders, the mean change was 2.35 (t=4.0009; p=0.0003). Significant differences were also found between the two subgroups as can be seen in Figure 3.

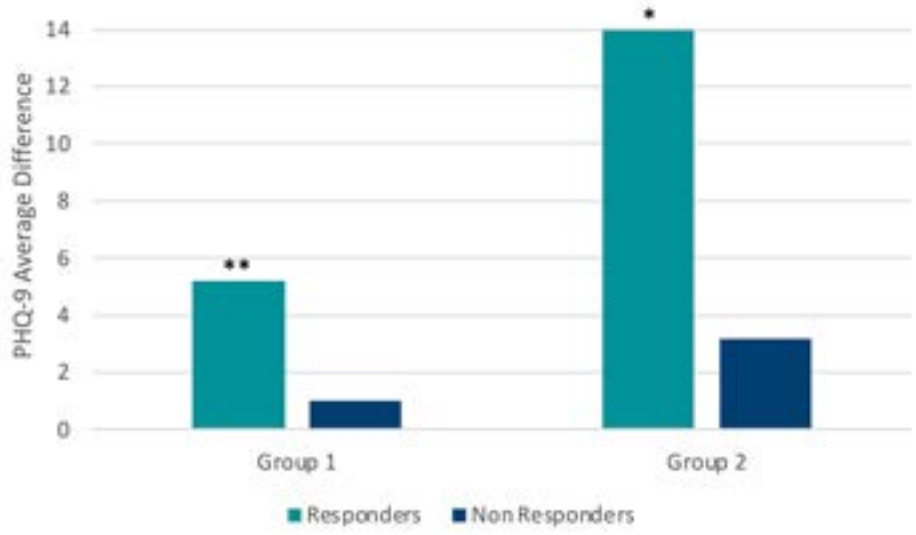

Figure 3. Change in PHQ-9 scores after tDCS treatment (*-p<0.01; ** - p<0.001)

Fig. 3 illustrates the average change in PHQ-9 scores before and after tDCS treatment, categorized by responders and non-responders in both depression severity subgroups. The y-axis represents the average difference in PHQ-9 scores (pre-treatment minus post-treatment), with positive values indicating an improvement (reduction in depressive symptoms).

Group 1 (Mild/Moderate depression responders) showed a significant reduction in PHQ-9 scores, with an average decrease of approximately 5 points, compared to the non-responders group with an average difference of 1 point (p<0.001).

Group 2 (Moderately Severe/Severe depression responders) exhibited the most substantial improvement, with an average decrease of 14 points in PHQ-9 scores, compared to the non-responders group with an average decrease of approximately 3 points (p<0.01).

b. Analysis of EEG Metrics

The analysis of frontal alpha asymmetry (FAA) before and after tDCS treatment revealed a significant change in the overall sample (FAA before treatment = -0.099; FAA after treatment = 0.052, t = 2.199, p=0.043). However, a detailed analysis by respondents and by depression severity groups reveals distinct patterns based on depression severity and treatment response.

Among non-responders with mild to moderate depression, the mean FAA values were -0.05 before treatment and -0.04 after treatment, indicating no significant change (t= 1.04, p=0.32). Non-responders with moderately severe to severe depression had mean FAA values of -0.024 before treatment and -0.026 after treatment, again showing no significant change (t=0.026, p=0.98).

In contrast, responders demonstrated significant changes in FAA. Among responders with mild to moderate depression, the FAA shifted from -0.2 before treatment to 0.22 after treatment, a statistically significant change (t = -9.98, p=0.0002). Responders with moderately severe to severe depression showed a similar trend, with FAA changing from -0.473 before treatment to 2.243 after treatment, also yielding a significant difference (t= -4.885, p=0.016). These findings suggest that FAA changes are more pronounced in patients who respond to tDCS.

c. Correlation Between FAA Changes and Depression Score Changes

A significant positive correlation (r= 0.63, p<0.01) was observed between changes in FAA and changes in PHQ-9 scores, indicating that greater shifts in FAA (i.e., a left-lateralized activity) were associated with greater reductions in depressive symptoms.

Fig. 4 presents a scatterplot illustrating the correlation between changes in FAA and changes in PHQ-9 scores.

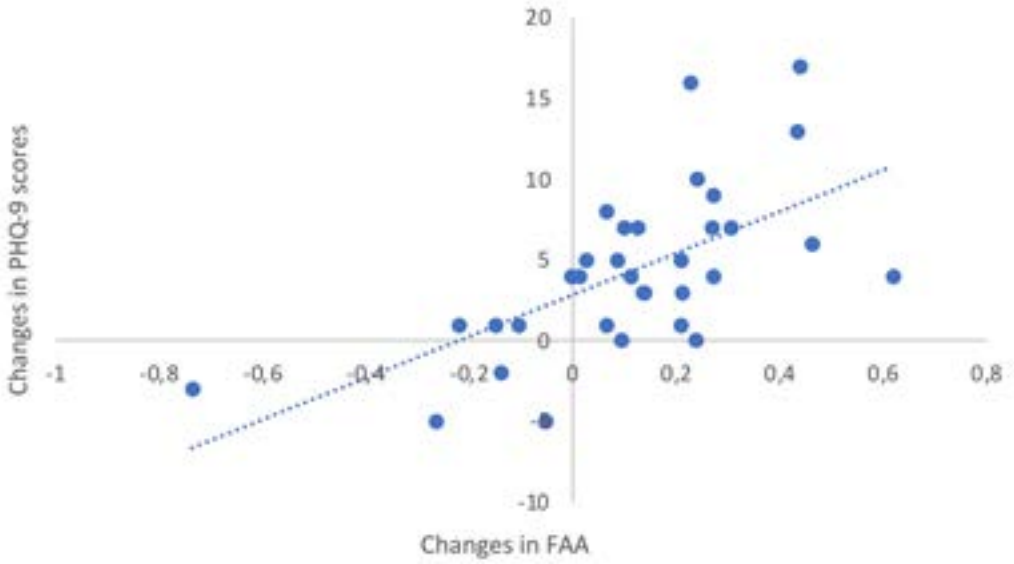

Figure 4. Correlation between changes in FAA and changes in PHQ-9 scores.

In Fig. 4 each point represents an individual patient, with the x-axis showing the change in FAA and the y-axis showing the change in PHQ-9 scores. The regression line shows a positive association between the two variables, with the equation y = 12.874x + 2.821, indicating that greater shifts in FAA towards left-lateralized activity are associated with larger improvements in depressive symptoms. The R^2 value of 0.3941 suggests that FAA changes account for approximately 39.4% of the variance in PHQ-9 score improvements, demonstrating a moderate correlation.

This result supports the idea that FAA could serve as a useful biomarker for assessing the effectiveness of tDCS in reducing depressive symptoms.

d. Predictive Value of FAA

Logistic regression analysis was conducted to evaluate whether pre-treatment FAA could predict treatment response. The regression model revealed that FAA_Pr was a significant predictor of response to tDCS (β= -7.9346, p=0.014), indicating that higher pre-treatment FAA values were associated with a lower likelihood of responding to treatment. The intercept of the model (β= -0.6311, p=0.198) was not statistically significant, meaning that the model's predictive power was largely driven by FAA_Pr.

A ROC curve was generated to assess the discriminative ability of FAA_Pr in predicting responders.

Fig. 5 shows the ROC curve generated from the logistic regression model. The AUC is 0.76, indicating that FAA has a good ability to discriminate between responders and non-responders. An AUC closer to 1 indicates better discrimination, and the AUC of 0.76 suggests that FAA is a moderately effective predictor of treatment response.

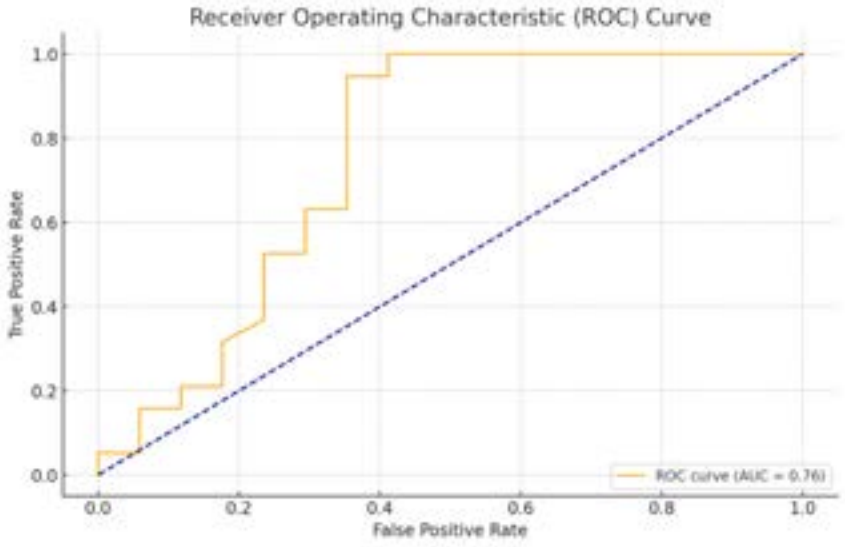

Figure 5. Receiver Operating Characteristic (ROC) Curve for FAA Predicting Treatment Response.

DISCUSSION

This study aimed to evaluate the effectiveness of home-administered tDCS in patients with major depressive disorder (MDD) and to explore the role of frontal alpha asymmetry (FAA) as a predictive biomarker for treatment response. Our results demonstrate that at-home tDCS is a viable treatment option, with nearly 29% of patients achieving a complete clinical response (CCR), including 11% who achieved full remission. To assess the clinical relevance of changes in depression scores, we also employed the Minimal Clinically Important Difference (MCID) metric, which represents the smallest change in a treatment outcome perceived as beneficial by patients. In addition to those achieving a CCR, approximately 23% of patients achieved an MCID.

Furthermore, we found that FAA, measured via EEG, was a significant predictor of treatment response, with changes in FAA strongly correlating with reductions in depressive symptoms. These findings have important implications for the use of neuromodulation in depression treatment, particularly regarding the potential of FAA as a biomarker for personalizing tDCS interventions.

The results of this study align with previous research on the efficacy of tDCS in treating MDD. For example, Brunoni *et al*[5] conducted a meta-analysis of individual patient data and reported that 34% of patients achieved a CCR following tDCS. Our study contributes to this growing body of evidence by demonstrating that home-administered tDCS is not only feasible but also effective, with about one-third of patients showing a complete clinical response and more than 23% showing a minimal clinically important difference. This is a critical advancement, as most prior tDCS studies have been conducted in clinical settings, which limits the generalizability of the findings to real-world applications. The ability to administer tDCS at home provides a more accessible and cost-effective treatment option, particularly for patients with limited access to in-clinic treatments or those in underserved areas.

Additionally, several studies[4,5] have shown that repeated tDCS sessions can lead to sustained improvements in depressive symptoms. In our study, the most significant improvements were observed in patients with moderately severe to severe depression, with an average reduction of 14 points in PHQ-9 scores. This finding is consistent with existing literature, which often shows that higher baseline severity is associated with greater absolute reductions in depression scores following treatment.[4]A major contribution of this study is the finding that changes in frontal alpha asymmetry (FAA) were predictive of treatment response, with greater shifts towards left-lateralized FAA associated with greater reductions in depressive symptoms. This aligns with earlier studies suggesting that left-lateralized prefrontal cortical activity is associated with positive affect and approach-related behaviors, while right-lateralized activity is linked to negative affect and withdrawal tendencies.[9,10] Previous research has indicated that individuals with MDD often exhibit greater right-sided prefrontal activity,[8] contributing to the emotional dysregulation characteristic of depression. By targeting the left dorsolateral prefrontal cortex with tDCS, we aimed to normalize this asymmetry, promoting a shift towards left-sided activity associated with improved emotional regulation and mood.

Our findings build on this body of research by demonstrating that FAA is not only a marker of depressive symptomatology but also a predictor of treatment response. Specifically, patients who exhibited greater shifts in FAA following tDCS treatment were more likely to experience reductions in depressive symptoms. This observation is consistent with recent studies exploring EEG-based biomarkers to predict neuromodulation outcomes. For instance, Keeser *et al*[19] found that tDCS modulates resting-state cortical activity, particularly in prefrontal regions, closely related to FAA changes. However, our study advances this understanding by demonstrating that FAA can be utilized pre-treatment to predict which patients are most likely to respond to tDCS, offering clinicians a proactive tool for tailoring interventions.

While prior studies (e.g.,[13]) have examined the relationship between FAA and emotional processing, our study is among the first to rigorously test FAA as a predictor of clinical outcomes following tDCS treatment. This positions FAA as a practical screening tool to identify patients who are most likely to benefit from tDCS, paving the way for personalized treatment strategies and improved clinical outcomes. This could significantly enhance clinical practice, where not all patients respond to neuromodulation therapies, and early identification of responders could reduce unnecessary treatments, patient burden, and associated costs.

Additionally, FAA's accessibility as an EEG-based biomarker highlights its potential for widespread clinical use. Unlike neuroimaging techniques such as fMRI, which provide high-resolution brain function images but are costly and impractical for routine clinical application, EEG is non-invasive, cost-effective, and feasible in outpatient and remote settings. This makes FAA a highly practical and scalable biomarker for real-world clinical practice.

Our findings contribute significantly to the advancement of frontal alpha asymmetry (FAA) research by bridging the gap between theoretical neuroscience and practical clinical applications. Although FAA has been extensively investigated in the context of emotional processing and depression, its potential as a predictor of treatment outcomes has received relatively little attention. By emphasizing FAA as an EEG-based biomarker, our study highlights its simplicity of measurement, clarity of interpretation, and reliability as a predictor of therapeutic response. The moderate R^2 value of 0.3941 in our correlation analysis demonstrates that FAA, while not the sole determinant, plays a substantial role in predicting clinical outcomes. This underscores its potential value within multi-modal predictive models that incorporate additional biomarkers, such as genetic, neurochemical, or functional connectivity markers.

The clinical implications of these findings are profound. By establishing FAA as a robust predictor of tDCS treatment response, our study underscores its utility for integration into routine clinical assessments. Including FAA in diagnostic processes could enable clinicians to identify

patients most likely to benefit from neuromodulation therapies, thereby enhancing resource allocation and optimizing treatment effectiveness. Beyond depression, FAA's predictive utility could extend to other neuropsychiatric conditions involving prefrontal dysregulation, such as anxiety, PTSD, and cognitive disorders, further expanding its clinical relevance.

In addition to its predictive capabilities, these findings provide valuable insights into the neurobiological mechanisms underpinning major depressive disorder (MDD), particularly the role of prefrontal-limbic circuit dysregulation. By demonstrating that FAA normalization through targeted neuromodulation improves emotional regulation, our study deepens the understanding of the physiological basis of depressive symptoms. This concrete link between neural activity and clinical outcomes underscores FAA's importance in elucidating the complex interplay between brain function and behavior.

a. Limitations and Future Directions

This study provides compelling evidence supporting tDCS as an effective treatment for depressive episodes and highlights the role of FAA in predicting tDCS response. However, several limitations should be acknowledged. The sample size, while adequate for preliminary analysis, restricts the generalizability of the findings. Validation through larger and more diverse populations is critical to strengthen the conclusions. Additionally, the open-label design may have introduced potential bias in the reporting of depressive symptoms. Future randomized controlled trials with blinded assessments are essential to confirm these results. Furthermore, the durability of FAA shifts and their relationship to long-term remission or the prevention of relapse remains an open question.

To fully harness FAA's potential in advancing depression treatment, future research should focus on several key areas. Expanding population diversity is crucial, particularly by including individuals with treatment-resistant depression and comorbid conditions, to ensure findings are applicable across varied demographic and clinical profiles. Long-term efficacy should also be investigated by examining whether sustained FAA changes are associated with enduring remission or reduced relapse rates. Additionally, the feasibility and effectiveness of home-administered tDCS protocols, including the potential need for booster sessions, warrant further exploration. Finally, integrating FAA with other biomarkers, such as genetic, neurochemical, or functional connectivity markers, is necessary to enhance predictive accuracy and support more personalized treatment strategies.

CONCLUSION

This study demonstrates that home-administered tDCS is a feasible and effective treatment for major depressive disorder, with about 29% of patients showing complete symptom improvement, and more 23% showing a minimal clinically important difference. Frontal alpha asymmetry (FAA) emerged as a robust predictor of tDCS response, with shifts towards left-lateralized FAA correlating with significant reductions in depressive symptoms.

Despite its limitations, the study underscores the transformative potential of FAA in personalizing mental health care. By serving as a practical and accessible biomarker, FAA offers a pathway to optimize treatment outcomes, streamline clinical workflows, and deepen our understanding of depression physiology. These findings pave the way for innovation in neuropsychiatric treatment, making mental health care more effective, targeted, and grounded in cutting-edge science. Future research building on this foundation will help bring personalized, biomarker-driven therapies into everyday clinical practice, improving the lives of individuals affected by depression and related disorders.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.
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ETHICAL DISCLOSURES

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).
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DECLARAÇÃO DE CONTRIBUIÇÃO

JEMT: Conceção do estudo, análise dos dados, análise estatística e escrita.
JC: Aplicação do tratamento e recolha de dados.
Os autores aprovaram a versão final a ser publicada.

CONTRIBUTORSHIP STATEMENT

JEMT: Study design, data analysis, statistical analysis and writing up.
JC: Implementation of data processing and collection
The authors approved the final version to be published

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