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Brainwaves Oscillations as a Potential Biomarker for Major Depression Disorder Risk

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Abstract

Major depressive disorder (MDD) is a multidimensional disorder that is characterized by the presence of alterations in mood, cognitive capacity, sensorimotor, and homeostatic functions. Given that about half of the patients diagnosed with MDD do not respond to the various current treatments, new techniques are being sought to predict not only the course of the disease but also the characteristics that differentiate responders from non-responders. Using the electroencephalogram, a noninvasive and inexpensive tool, most studies have proposed that patients with MDD have some lateralization in brain electrical activity, with alterations in alpha and theta rhythms being observed, which would be related to dysfunctions in emotional capacity such as the absence or presence of responses to the different existing treatments. These alterations help in the identification of subjects at high risk of suffering from depression, in the differentiation into responders and nonresponders to various therapies (pharmacological, electroconvulsive therapy, and so on), as well as to establish in which period of the disease the treatment will be more effective. Although the data are still inconclusive and more research is needed, these alpha and theta neurophysiological markers could support future clinical practice when it comes to establishing an early diagnosis and treating state disorders more successfully and accurately of mood disorders.

Keywords

major depressive disorder, brainwaves, EEG, alpha oscillation, theta oscillation

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Introduction

Major depressive disorder (MDD) is a multidimensional disorder, in which alterations in mood (excessive sadness), cognitive abilities (difficulty concentrating), sensomotor functions and homeostatic functions (those that control sleep, appetite and libido) are observed.[1-3] Nowadays, we find several different lines of treatment, such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), or deep brain stimulation (DBS),[4,5] although the use of antidepressants remains the first of them. However, about 40% to 50% of patients with MDD do not respond to current treatments despite the wide variety of drugs.[6] For this reason, research is being carried out to discover new neurobiological mechanisms and particular characteristics of patients who respond to treatment in order to predict the course of the disease, increase the therapeutic response and be able to detect previously those patients who will be resistant to the different therapies.[7,8]

Since Hans Berger recorded electrical brain rhythms in humans in 1924 by electroencephalogram (EEG),[9] this technique has been widely used in the clinical setting to record both normal and abnormal patterns in the electrical brain activity of healthy patients with various pathologies (sleep disorders, epilepsies, and headaches).[10] However, its use in MDD is mainly confined to the field of research, as the outputs obtained so far are very mixed results, making it difficult to define a specific pattern for this disorder (Jaworska et al. 2012; Price et al. 2008).[11,12] The objectives guiding these lines of research focus on finding possible neurophysiological markers that can predict the development and progression of the disease in subjects

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at high risk[13-16] and to understand the properties of electrical brain activity associated with responders and nonresponders, which would increase treatment response and, therefore, treatment efficacy.[17-22]

For this reason, a detailed analysis is needed, covering the latest developments in this field and allowing the results, so far, presented to be grouped together in order to be able to direct future lines of research. The aim of this review is to examine the different scientific articles that link the different electroencephalographic measures with the risk of suffering MDD. Also, we want to compare how they would be related to an increase in the response to different therapies and treatments, emphasizing the possible value that the changes registered in the cerebral electrical activity related to symptoms and even to remission could have in clinical practice. It is, also, intended to establish guidelines for future research based on the limitations of previous studies to avoid heterogeneity of results

Methodology

We searched for articles in PubMed and Scopus including the following concepts: "MDD" or "major depressive disorder" and "EEG," "electroencephalography," or "brainwaves," covering aspects such as alpha, alpha asymmetry, frontal alpha asymmetry, and theta oscillations. These searches resulted in a total of 92 articles. Of all of them, only 41 articles were included in this review. Articles that focused on other psychiatric disorders (such as schizophrenia and attention deficit hyperactivity disorder) or articles focused mainly in biological approaches (NMDA receptors, AMPA) were excluded.

The inclusion criteria were (*a*) diagnostic criteria of depression; (*b*) comorbidity (anxiety, melancholy, hypersomnia); (*c*) different variables studied (sex, age, education, manual dominance); (*d*) medication consumption; (*e*) EEG recording both during the performance of tasks and at rest; and (*f*) control group or comparison with other types of disorders.

Alpha Oscillations

Alpha waves (α) are electromagnetic oscillations with a frequency range between 8 and 13 Hz. They are predominantly recorded in posterior regions and with eyes closed during wakefulness.[23] These waves are related to states of relaxation and their activity is one of the most studied in MDD, since it is inversely related to cortical activity,[24,25] which is altered in this disorder, that is, in difficulty concentrating, attention and memory tasks.[26]

Using electroencephalographic records, most studies proposed that subjects with MDD tend to show left frontal cortical hypoactivation, that is, greater left frontal activation α.[11,27-38] This lateralization in cortical activity would be associated with the "model of anterior asymmetry and emotion",[39] more specifically with the system of approximation and processing of positive emotions, which is affected in MDD,[34,40,41] indicating a tendency to more negative emotional states,[42] anhedonia, avoidance behaviors with social difficulties and alterations in the ability to adapt to the problems of daily life.[41]

Frontal asymmetry would also be linked to deficits in reward processing, which would be a key element in predicting the onset of depression.[43] It has been observed that, during the performance of reward-threat tasks, subjects with depression show a lower sensitivity to reward, manifesting a more "symmetrical" frontal pattern than control subjects (higher left frontal activation) when they have to predict rewarding stimuli.[44] Therefore, several authors have proposed the measurement of "Frontal Asymmetry α" (FAα) as a prognostic marker to identify subjects at higher risk of depression.[11,33,45-50] These authors consider their activation, whether reduced or increased, as a dimension that encompasses both risk and resistance to the disorder,[51,52] presenting an anomalous pattern when compared with healthy subjects.

This left frontal cortical hypoactivation is also observed in studies that record encephalographically the descendants (children and adolescents) of mothers with depression, which compare these results with those found in research with depressive versus non-depressive adults[53-57] suggesting that if there are environmental changes in this association between familial FAα and risk of depression, it may provide key clues to the pathogenesis of depressive disorders, guiding the periods in which therapeutic intervention may be most effective.[16] These findings would propose FAα as a possible biomarker of vulnerability in person with high risk for this disorder, presenting it as evidence of the first depressive episode.[45,46,49,58]

If this hypothesis is valid, the appearance of the disease in high-risk subjects could be predicted at an early stage, its course could be established and even the periods of action in which the response to the treatments was greater could be determined, its effects increased and the remission of the disorder favored. Although these results are promising, several studies have failed to find these differences in FAα between MDD patients and control subjects,[12-15,28,31,42,59-64] making it difficult to generalize a defining pattern for this disorder.

Other studies have found gender differences in this asymmetric pattern FAα. While the results are inconclusive, they do propose possible differences between men and women in establishing respondents and nonresponders.[18,19,59,65-69] Some of these suggest that FAα would be associated with treatment response only in women with depression, with an increase observed in right frontal α (decreased right frontal cortical activity) associated with SSRI responders and in remission.[19,69] This relationship between FAα and response to treatment in women would also be found in anterior, central, and posterior regions[18,67] posit the existence of an FAα pattern in severely depressed women contrary to that traditionally established and unobservable in men. On the other hand, it is proposed that men with depression show a greater left FAα[65,68] compared to women with MDD (> right FAα), indicating that decreased connectivity α could be used as a biomarker of treatment response only in them.[66] These results require further research

to help clarify whether patterns in the electrical brain activity of men and women play an important role in differentiating them in both disease development and treatment response.

FAα has also been proposed as a possible biomarker that predicts response to treatment with various antidepressants. Different activation patterns are observed depending on whether or not subjects respond to medication[42,65,69-74] reported lower potencies of α in parieto-occipital and frontal regions in subjects not responding to antidepressants, while other studies related an increase in α later with a higher probability of response to various antidepressants.[19,69] Thus, along with other neurophysiological indices such as activity θ in anterior cingulate cortex subgenual (ACCsg), α could be considered a robust biomarker for discriminating responders and nonresponders.[20,22,75] However, although the effects of drugs on different brain rhythms are known, several studies have not found evidence that antidepressants influence asymmetry α.[19,34,59,76,77] A comprehensive research is very important to discover the possible predictive value of such asymmetry in the response to multiple treatments.

Theta Oscillations

Another of the most studied brain rhythms observed electrophysiologically altered in MDD, both during the course of the disease and before and after therapeutic intervention, is theta activity (θ). This activity is composed of waves of different morphology (regular or irregular), with a frequency of 4 to 8 Hz.[23] It is observed in temporal regions and has been related to various memory processes (working memory, episodic), spatial navigation,[78-80] attention and learning, which are affected in depressive disorder.[81,82]

The frontal rhythm θ has been located in the ACC,[83] an important brain area in emotional and behavioral control.[84] Rostral ACC (ACCr) represents a fundamental region in the neurobiology of depressive disorders.[85] The anomalies found in the band θ in MDD are disparate. Most studies indicate that this disorder would be associated with increased activity θ in ACCsg.[11,36,64,84,86-91] Since activity in this region is involved in the resolution of emotional conflicts, it has been considered that its hyperactivity in MDD could reflect a compensatory activity of fronto-cingulate neural networks that mediate and regulate emotional aspects.[84] However, studies have also been found in which MDD seems to be more associated with a decrease in activity θ,[21,41,86,92-94] suggesting that this alteration would evidence a functional disconnection in such networks altering the emotional processing capacity.[95]

Several investigations suggest that θ activity in the rostral and subgenual areas of the CCA could be used as a response index to treatment with antidepressants, with rTMS, and with DBS, which would allow predicting and differentiating between responders and nonresponders.[11,20,76,85,93,96-99] Many of them, suggest that a pretreatment increase in θ activity in CCAr,[20-22,50,99,100,101] in CCAsg,[20,22,50,75] in the mid-frontal orbital cortex (COFm),[21] or in frontomedial regions[96] or frontoparietal regions[102], could predict an increase in the response to different therapies, different antidepressants, ECT or rTMS, allowing a possible differentiation between responders and non-responders to different therapies.[76,85,96,100,101,103]

This increase in θ activity could enhance the effects of all these treatments by altering areas that are dysfunctional in MDD[85] and exhibiting a possible compensatory response that increases the likelihood that a patient will improve the response to treatment.[22,100,101] Thus, since θ frontomedio would be a reflection on the scalp of increased activity in ACCr, it could be useful as a measure to predict both cognitive and affective improvement, helping as an early biomarker of response to antidepressants[104] and other treatments,[96,97] as well as being used as a possible specific biotype of responders.[76]

These approaches contrast with previous studies suggesting that reductions in cordance (a measure of the EEG signal that integrates information on absolute and relative potencies for each frequency band and for each topographic region from the application of fast Fourier transform to the EEG signal)[105] from prefrontal θ after starting treatment could predict response to antidepressants and rTMS.[106,107] Therefore, it is important to confirm which values from θ would be relevant in determining the exact time at which treatment may be most effective.

Limitations

These studies have several methodological problems that make it difficult to generalize the data. Some of them, suggest that the main problem lies in the small sample size and even in the wide age range of the groups,[16,76,85,98] which makes subsequent statistical analysis difficult and diminishes the significance of the results,[16] also, proposes longitudinal studies covering different life stages of those at risk of depression, allowing more frequent recording of electrophysiological measures that seem to be relevant in this disorder. In addition, to considering paternal depression as an aspect that may also influence the development of the disease.

Another of the most relevant problems affecting the results is the assembly of the EEG, which varies according to the number of electrodes placed and how this information is processed once collected, and its low spatial resolution, since this hinders the reliable knowledge of the neuroanatomical source of the different rhythms, as well as the normalization of the different measures in the general population and their extrapolation to subjects with disorders.[8,11,59] It is also important to consider the different variables that can influence both the registry and the disease such as sex, age or severity of the disease, and that can reduce possible inconsistencies.[8,16,59] In this sense, it is also essential to know the basic activity of the participants, since this could indicate differences between groups during the performance of tasks that may or may not be due to the disorder to be studied[11,93] and that in some cases they cannot be generalized to the entire depressive group.[76]

It is also essential to consider the clinical history of each participant and their treatment during the study such as dose, duration, quantity, and types of antidepressants. Many of these aspects are not always taken into account,[20,93,99] and which

could cause the results on responders and nonresponders to vary (nonresponders could respond depending on the dose and duration of treatment). These inconsistencies limit outcomes when applied in clinical practice and highlight the need for further research.

Conclusions

Although the results are not conclusive, research so far on EEG in MDD patients indicates some lateralization of brain electrical activity, associating MDD with a decrease in left frontal cortical activation, which influences both mood and cognitive status of patients. The key to future research will be to confirm whether by altering and reducing this asymmetry patients will experience an improvement (partial or total) in their symptoms,[108] thus establishing a guideline in the responses to the different treatments that allows predicting and increasing their effects. Special attention should be paid to the bands α and θ,[109,110] as they are the most promising rhythms to become neurophysiological markers that allow early identification of subjects at risk of depression, as well as to differentiate between responders and nonresponders, even considering them as 2 different subgroups within depression, rather than as part of a depressive continuum.[76]

It is also important the identification and study of the different sub-bands of α waves, since the cognitive processes associated with them are altered in MDD[111] and could help to focus different lines of therapy that increase their therapeutic efficacy. In addition, the hypotheses raised about the possible predictive value of θ oscillation in the responses to different treatments for depressive disorder are promising, as its clear activity in the ACC would allow acting in the areas most closely related to the disorder, altering communications between regions and disseminating its effects. It is for this reason that the EEG constitutes a cheap and noninvasive technique that allows the study of electrophysiological alterations associated with the different mood disorders, providing promising neurophysiological indices for the selection of treatments and for predicting the response to them,[17] helping clinical practice in the future.

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Author Contributions

PFP, TRB, DRA, SFG, MCVC, MAA, ML, CRJ, JLB, EH and CSC reviewed the bibliography and discussed the papers. PFP, JMO and CSC wrote the manuscript.

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