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Review on EEG and ERP predictive biomarkers for major depressive disorder

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ABSTRACT

The selection of suitable antidepressants for Major Depressive Disorder (MDD) has been challenging and is mainly based on subjective assessments that include minimal scientific evidence. Objective measures that are extracted from neuroimaging modalities such as electroencephalograms (EEGs) could be a potential solution to this problem. This approach is achieved by the successful prediction of antidepressant treatment efficacy early in the patient's care. EEG-based relevant research studies have shown promising results. These studies are based on derived measures from EEG and event-related potentials (ERPs), which are called neurophysiological predictive biomarkers for MDD. This paper seeks to provide a detailed review on such research studies along with their possible limitations. In addition, this paper provides a comparison of these methods based on EEG/ERP common datasets from MDD and healthy controls. This paper also proposes recommendations to improve these methods, e.g., EEG integration with other modalities such as functional magnetic resonance imaging (fMRI) and magnetoencephalograms (MEG), to achieve better evidence of the efficacy than EEG alone, to eventually improve the treatment selection process.

Contents

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1. Introduction

Major Depressive Disorder (MDD) is characterized by persistent low mood and hampered functional disability and is often associated with higher treatment costs. MDD, which is commonly called depression, is chronic, recurrent and comorbid in nature. It has been reported to be a leading cause of disease burden, especially in women, in many countries [1]. Patients who receive adequate pharmacotherapy achieve remission with no symptoms or symptoms that are almost absent [2]. Less scientific evidence of the treatment selection and incomplete pathophysiological understanding have restricted MDD treatment as a subjective assessment process. High medical costs arise from non-response to the treatment because the initial treatments do not usually lead to recovery [3].

Various theories have been presented to elucidate the underlying associated pathophysiological implications, and further details on the theories are reviewed by [4–7]. According to one such theory, abnormalities in the inter-neuronal signalling pathway can increase the vulnerability to environmental stresses and result in neuronal atrophy. This process significantly reduces the brain's volume, e.g., the hippocampus was consistently recorded as shrunken in MDD patients [8]. However, complete manifestations of the situation described in such theories could not be observed in every MDD patient.

Treatment with antidepressants has been associated with low efficacy. A study called Sequenced Treatment Alternative to Relieve Depression (STAR*D), which involved patient treatment with various antidepressants in a sequential manner, revealed only modest rates of remission (20 to 30%) in the first attempt. Moreover, the response rates were even less (47%) in the study participants [2]. Multiple factors could cause low treatment efficacy. First, MDD is heterogeneous; one antidepressant might not be as efficient for a patient as it could be for another. Second, in the event of failure, re-selection or augmentation is subjective and also leads to multiple trial-and-error steps in sequential iterations until suitable antidepressants are identified. To improve the situation, objective assessment techniques are needed based on strong scientific evidence, for early disease diagnosis and prognosis.

Objective techniques based on neuroimaging modalities are being incorporated during the treatment selection process with improved efficacy. Such techniques generate sufficient evidence to predict the treatment outcome prior to its onset, and therefore, these factors are characterized as predictive biomarkers. The modalities such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) have shown promising results towards being diagnostic in MDD treatment; however, there are pros and cons. Among these, EEG offers higher temporal resolution than fMRI, has a low cost and is suitable for small clinical environments. It is also more feasible for patients with claustrophobia [9], in addition to being easier to obtain hands-on training. The issue on its low spatial resolution can be partially resolved by the increasing number of electrodes/sensors, with up to as many as 1024. However, a smaller number of electrodes is easier to manage and is desirable for patient care. In contrast, fMRI provides a higher spatial resolution. However, it is not feasible in small setups for quick assessments. In short, EEG provides a stronger base for the development of predictive biomarkers. Therefore, in this paper, we restricted our discussion to methods that involve EEG/ERP only. The current review paper addresses two main application areas in which EEG/ERP can be utilized: (1) MDD diagnosis based on EEG/ERP abnormalities, and (2) prediction of treatment outcomes based on quantities/features extracted from EEG/ERP. The first part will include a review on the EEG and ERP abnormalities found during MDD that can help to discriminate MDD patients and healthy controls. The second part provides a brief account of features that are extracted from EEG and ERP that have shown a relationship to clinical responders (R) and nonresponders (NR) to treatments with antidepressants. The limitations associated with each type are also highlighted.

The EEG signals recorded from the human scalp could have different neuronal sources deeper inside the brain. Estimating these deep sources from the EEG signals is an inverse problem that can be ill-conditioned, which can lead to the existence of multiple solutions for the deep sources. These solutions are based on assumptions about the hypothetical neuronal sources inside the brain and could result in false localizations. EEG-based techniques for brain source localization (BSL) such as Low Resolution Electromagnetic Tomography (LORETA) have been proposed to estimate or localize neuronal electrical activities inside the brain based on multichannel surface EEG recordings [10]. However, over the past decade, various extensions of LORETA were developed, for example, the standard LORETA (sLORETA) [11] and standardized shrinking LORETA-FOCUS (ssLOFO) [12]. A substitute to the inverse modelling approach is beam-forming technology [13]. Recently, a method based on a local spatial Fourier transformation of EEG measurements was offered [14,15]. Yet another technique, 2q-Exo-MUSIC (2q-th ordered extended multiple signal classification), has been developed to localize distributed sources that have a large number of dipoles with highly synchronized activities [16]. Details of the different techniques that involve discussing the BSL problem have also been reviewed [17,18].

Electrophysiological signals contain information about neural activities inside the brain at different frequencies, which range from delta (0.4–5 Hz), theta (5–8 Hz), alpha (8–12 Hz), low beta (12–18 Hz), high beta (19–30 Hz) and gamma (30–70 Hz). Electrophysiological signals can be helpful during the diagnosis or quantification of physiological states. For example, the automatic diagnosis of epileptic seizures [19,20], assessment of depth of anaesthesia [21] and quantification of sleep stages known as polysomnography studies are well established [22]. In addition, EEG data are helpful in studying the elevated states of the resting brain [23]. Furthermore, EEG data that are saved and processed digitally are called quantitative EEG (QEEG). At the same time, event-related potential (ERP) studies include the analysis of neuronal data acquired during the performance of an experimental activity to observe aberrant cognitive processes inside the brain. An ERP signal is acquired by grand averaging the various epochs of similar types, including either visual or auditory stimuli. Averaging suppresses the background noise in the signal and effectively improves the signal-to-noise ratio (SNR). The grand averages result

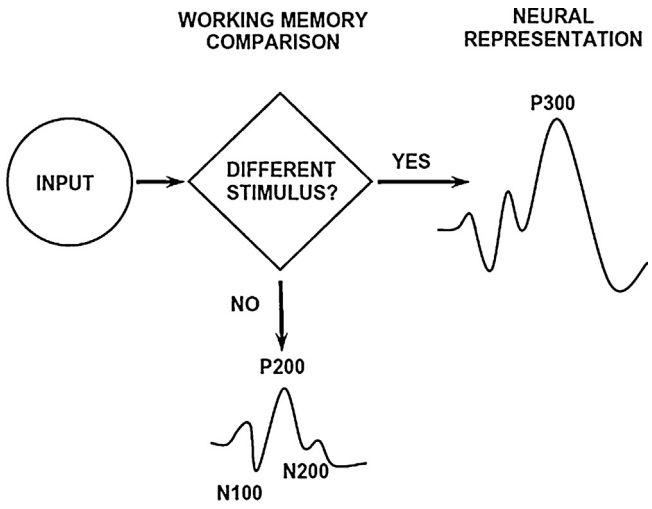

Fig. 1. Schematic illustration of the P300 context updating model [25].

in various prominent positive and negative peaks that occur at the time points of 100, 200 and 300 milli-seconds (ms), called N100/P100, N200/P200 and P300, respectively [24]. A schematic diagram of a P300 context updating model has been illustrated [25]. P300 is generated if the stimulus is different from the previous ones; otherwise, components such as N100/P200 can be observed (Fig. 1).

2. EEG/ERP abnormalities due to MDD

Depressive disorders are associated with changes in normal electrophysiology and neurocognitive processes. These changes include frequency abnormalities, differences in the activation of the left and right hemispheres (known as asymmetry), aberrant cognitive brain behaviours and hypothalamic–pituitary–adrenal (HPA) axis dysfunction. These factors are discussed in the following subsections.

2.1. Aberrant activations including EEG frequency bands

Abnormalities in the EEG/ERP activations in different frequency bands have been studied during the discrimination of MDD versus healthy controls and for the prediction of treatment outcomes. The power computations from individual frequency bands have shown relevance to the pathophysiology of depression. For example, elevated EEG alpha activity during resting has been commonly observed [26]. Similarly, elevated absolute alpha power has been reported in the literature [27–30], while other studies have described increases in the relative power [31,32]. This increase in the EEG activity was commonly observed in frontal, parietal [28,33] and occipital areas [34]. In addition, early stages of depression were characterized by the presence of elevated alpha activity [35]. However, some of the studies could not find alpha power differences between the MDD patients and healthy subjects [36,37]. Moreover, an increased beta band activation in depressed patients has also been reported [38,39]. Regarding the prediction of treatment outcomes, excessive alpha values were associated with a response to antidepressant treatment [40]. Similarly, excessive theta values were found to be correlated with treatment nonresponse within the MDD group [41–43].

Although an extensive discussion on these activation abnormalities including the different frequency bands is beyond the scope of this review, a brief viewpoint is that the absence of consistent findings could be due to methodological differences across studies and inherent heterogeneity of the populations under investigation. The non-specificities of these findings have made clinical applications almost impossible.

2.2. EEG alpha asymmetry

During MDD, alterations that are associated with EEG alpha asymmetry were studied extensively as a vulnerability measure. Furthermore, it was hypothesized that MDD manifested hyperactive right prefrontal cortex and hypoactive left prefrontal cortex. Davidson et al. [50] investigated alpha asymmetry during depression and reported a relative hyper-activation of the right prefrontal cortex. Later, they considered 'approach' and 'withdrawal' as being fundamental to the EEG asymmetry [44], where both the withdrawal and approach systems were orthogonal. In addition, the approach system facilitated appetitive behaviour and resulted in positive effects, whereas the withdrawal system motivated negative emotions and aversive stimulation [45]. The decreased left-sided frontal EEG activation was considered to be related to a deficit in the approach system. Based on these observations, it was concluded that the study subjects who have such symptoms were considered to be at risk of negative emotional states and depression in response to environmental stress. In contrast, EEG activation of the right-side frontal cortex was related to withdrawal of related emotions and the pathophysiology of depression [44]. In a recent study, alpha EEG asymmetry was found to be significantly higher in MDD patients compared to healthy controls [46]. A number of studies reported a decrease in the right frontal area relative to the left side [47–50].

However, EEG asymmetry was considered to be an unreliable indicator for discriminating MDD and healthy subjects. This consideration has been based on the finding that increased right frontal activity in postmenopausal depressed women could not be replicated [51]. Many other studies failed to reproduce the observations of EEG asymmetry during MDD [52,53] [54–56].

2.3. EEG coherence

EEG coherence is a measure that can suitably examine synchrony across brain regions. In addition, it represents the coupling of activity between two nodes that are functionally linked, but not time-locked to a specific event [57,58]. EEG coherence has been successfully used to examine spatial integration both at short- and long-distances in the brain [59,60]. It was first examined in clinical populations with depression or dementia [61]. However, it has not been extensively studied with MDD patients compared to controls. In a study, Fingelkurts and colleagues [62] examined 12 medication-free depressed outpatients and used the structural synchrony to analyse nine categories of functional connectivity. Furthermore, Leuchter and colleagues [63] have extended the study conducted by Fingelkurts and colleagues. Specifically, they have concluded an increased neurophysiological connectivity in depression compared with a normal condition. In a recent study [64], MDD is characterized by increased EEG functional connectivity within frontal brain areas. Hence, EEG coherence has been suggested as a potential marker of distributed neuronal communication for MDD.

However, the EEG coherence like any metric derived from EEG does not directly measure brain activity. Connectivity of brain region is inferred from the EEG recorded at surface sites overlying the various cortical regions. Moreover, there is no single technique that has proven to be ideal to measure the interaction between two brain regions. Coherence measures are susceptible to both electrode reference effect and volume conduction [65–67].

2.4. The ERP component: P300

The ERP component P300 that is achieved by grand averaging various auditory stimuli of a single type is known as an auditory evoked potential (AEP). AEPs have been shown to have a positive correlation with the cognitive abilities and auditory processes of the brain [68,69]. In addition, depression has been associated with a delay in the P300 component [70]. Similar findings were found in some other studies in which a delay in P300 was only found in MDD patients compared with the control [71–73]. A decrease in the P300 intensity in the right hemisphere during LORETA analysis has also been reported [74]. Longer P300 latencies were observed in depressed patients compared to healthy controls for visually evoked stimuli [75]. The relationship between the P300 response and responses under antidepressants was reported as the normalization of P300 latency after 4 weeks of antidepressant intake [76]. Moreover, the normal P300 amplitude predicted the response to electro-convulsive therapy [77]. However, no significant differences were found in the P300 amplitude among the treatment responders, non-responders and controls [78].

2.5. EEG/ERP abnormalities during HPA axis dysfunction

Hyperactivity of the HPA axis during MDD is one of the main findings in psychoneuroendocrinology [79]. The HPA axis is a major endocrine stress response system that helps during challenging situations and thereby maintains mental health and stability [80]. The HPA axis triggers a stress response by releasing certain chemicals, such as adrenocorticotropic hormone (ACTH) and cortisol, which are generated from the hypothalamus, pituitary and adrenal glands. In addition, cortisol has been consistently found during depression [6]. This finding warrants highlighting the EEG and ERP and their relationship with HPA axis dysfunction.

EEG and ERP studies have revealed neurobiological changes due to cortisol administration in healthy subjects. It was concluded that both exogenous and endogenous cortisol administration have specific effects on episodic memory processing [81]. Studies that focused on EEG correlations with episodic memory resulted in greater activation of the frontal and parietal lobes at 800 ms to 1100 ms post-stimulus for healthy subjects compared to the depressed subjects. In addition, a correlation between the cortisol levels and EEG laterality was observed during an episodic memory task. EEG and ERP studies of cortisol administered to healthy subjects depicted qualitative changes in the ERP waveforms associated with episodic memory over the frontal scalp region [82,83]. Moreover, altered ERP components were related to an error processing task [84]. However, these associations could not be replicated. For example, a single dose of cortisol could not alter the ERPs in a face recognition memory task. However, a short-term memory task could easily modulate the related ERP components [85]. Hence, we can infer the complexity of the cortisol as being impacted by multiple factors, for example, the types of stimuli, dosage levels and time-dependence on the EEG.

2.6. Machine learning (ML) approaches for MDD diagnosis

Recently, the automated classification algorithms that involve neuroimaging techniques are gaining importance in diagnosing different types of mental ailments [86]. Specifically speaking, EEG data in combination with machine learning (ML) techniques have been utilized for the identification of MDD [87–89]. These techniques have utilized non-linear EEG-based quantities. Ref. [87] utilized Katz's and Higuchi's fractal dimensions (HFD) as a measure of nonlinearity and complexity in the EEG data. Another study reported a combination of spectral asymmetry and HFD features for discriminating the depression conditions [90]. In addition to EEG-based studies, ERP features such as the P600 component were utilized for the same purpose [91].

The advantages of incorporating ML methods when compared with conventional techniques include the automatic identification of EEG/ERP patterns that are specific to diseased and control conditions. The ML techniques allow identification of such patterns for individual subjects and are therefore superior to the conventional methods, which are discriminative at the group level only. The evidence-based treatment management for individual MDD patients is possible by incorporating ML techniques during the diagnosis and treatment selection. Moreover, the high accuracies shown by ML techniques motivate their clinical utility as well. However, generalizations of these findings require further validation with larger populations.

2.7. Summary

We have discussed EEG/ERP-based abnormalities, which have revealed significant differences between depressed patients and healthy controls. Key findings of the studies discussed in this section are summarized in Table 1.

3. EEG-based predictive biomarkers

The MDD treatment could be improved by reducing the ineffective treatment trials. This result is anticipated by having an accurate prediction of the treatment outcomes using predictive biomarkers. According to the definition, the predictive biomarkers should be sufficiently sensitive to changes in disease conditions [92,93]. In addition, these should cater to clinical applications, including accurate treatment predictions for individual patients. This section will highlight the identification of EEG/ERP biomarkers for predicting treatment outcomes that involve MDD. We will describe the quantities extracted from the EEG and ERP that have shown significant correlations with either the R or NR subgroups. Some of the examples include the alpha and theta activations, asymmetries, antidepressant treatment response (ATR) index and EEG theta cordance.

3.1. Alpha power and alpha asymmetry

The alpha power and asymmetry have been studied extensively due to the relative ease of computation. In the case of alpha power, the treatment response and non-response were categorized based on changes in the absolute and relative powers. For example, Ulrich and colleagues treated 40 MDD patients with tricyclic antidepressants (TCA) and claimed that the subjects who had lateralization in the alpha power at the baseline were responders (R) with 4 weeks of treatment. In addition, the R also exhibited a decrease in the absolute alpha power at the baseline [94]. Further studies [95,96] reported early changes in the alpha band that were shown in R only. A similar study [97] reported that less alpha current source density was associated with non-responders (NR) compared with both R and controls. The study patients were treated with selective serotonin reuptake inhibitor (SSRI), serotonin–norepinephrine reuptake inhibitor (SNRI) and a combined therapy with an SSRI and norepinephrine–dopamine reuptake inhibitor (NDRI). In contrast, a study reported increased alpha power associated with R with 29 MDD patients who were treated with imipramine for 6 weeks [42]; however, the study did not provide any statistical support. In addition, an increase in the alpha power accompanied with a decrease in the theta power among R compared with NR was reported, including paroxetine administration for 50 MDD patients for 6 weeks [98].

Alpha asymmetry refers to the alpha power differences between the left and right hemispheres. Their associations were reported

Table 1
Summary of the changes in EEG/ERP associated with the pathophysiology of depression that can be useful in discriminating MDD patients from healthy controls.

Brain dynamics	Associated measures	Main findings	Critical analysis
Changes associated with EEG activations, including different frequency bands	Activations in alpha and beta bands	• Elevated EEG alpha activity manifested depressive pathophysiology • Excess alpha was found to be associated with the response to antidepressant treatment	Frequency changes have shown their promises. However, they were not specific to either the patient or control groups. The inconsistency in the findings resulted in low specificities. The inter-study comparisons were necessary to improve the future research directions and to standardize the methodological procedures
EEG alpha asymmetry	Changes in the Alpha activation between the left and right hemispheres	• Hyperactive right frontal cortex and hypoactive left frontal cortex manifested during depression • Decreased left sided frontal activations can be a vulnerability indicator for depression	Alpha asymmetry was observed to be inconsistent among different studies and, therefore, was considered to be unreliable to discriminate the normal and MDD subjects. Low specificity of the findings can be improved by increasing the sample sizes and balancing the gender distributions. The results should have common evaluation criteria. The sensitivity and specificity of the findings should be reported
EEG coherence	Difference of functional connectivity between MDD patients and normal controls	Increased neurophysiologic connectivity is observed in MDD patients when compared with normal controls	EEG coherence is affected by volume conduction in the brain. Research is still going on to improve the reliability to be used clinically
ERP component	AEP P300 intensities and latencies	Depressed subjects have shown greater P300 latency and smaller P300 amplitudes than healthy controls	The ERP component P300 has been considered to be an index of cognition. From antidepressant intake, improvement in the amplitudes and latencies are not exhibited for all patients. In addition, the P300 could not explain the brain under medication with antidepressants
HPA axis dysfunctions	ERP waveforms and EEG laterality associated with memory experiments	Healthy participants have shown greater activation compared with depressed subjects	HPA axis was found to be consistent in describing stress-related abnormalities. However, it exhibited contradictory findings in the case of depression
Non-linear EEG/ERP quantities	Katz's and HFD, Spectral asymmetry	Aberrant patterns are identified automatically based on ML concepts	The findings cannot be generalized due to small sample sizes

with respect to the antidepressant treatment outcomes. For example, Bruder and colleagues observed alpha asymmetry among 52 MDD patients who were treated with fluoxetine for 12 weeks [99]. They highlighted the presence of EEG alpha asymmetry, which could differentiate responders (R) and nonresponders (NR). Greater activation in the left hemisphere at the baseline compared to the NR was also reported. Moreover, the alpha asymmetry showed significant differences between the female R and female NR; however, the male participants did not show this behaviour. In addition, the same medication (fluoxetine) was used by Bruder and colleagues with 36 participants (18 controls and 18 MDD patients) [34]. The study resulted in 11 R with a greater baseline EEG alpha power in the occipital region compared to that with the NR. In the left hemisphere, the R showed higher alpha power when compared with the NR.

The alpha power and asymmetry were not standardized to a specific medication because the studies discussed thus far have utilized different medications for different patients. Consequently, the treatment efficacy could not be identified as either medication-specific or individual-specific. Moreover, the studies did not provide any quantitative analysis on the sensitivity and specificity of the data. Moreover, contradictions among the studies rendered them insignificant clinically and warrant further research effort.

3.2. Theta band activations

An increase in the EEG theta band power (also called theta band activation) was found to be correlated with the antidepressant treatment outcome. The MDD patients with greater theta and lower beta band activities were R compared to NR [98]. Furthermore, an increase in the left frontal theta activity compared to baseline was reported after electroconvulsive therapy (ECT) [100]. Further follow-up after the 4th ECT treatment resulted in a response that was correlated with the theta activity.

In addition to the theta band power, the frontal theta relative power was also observed [101]. This study indicated that there was a significant correlation in the EEG relative power values at baseline and after 1 week with treatment outcome. In addition, a positive association in the increased absolute theta band power at baseline with changes in the Hamilton depressive rating scale (HAM-D) scores over 8 weeks of treatment was also reported [102].

Few studies analysed the effects of randomization on either the treatments or study participants, e.g., the absence of placebo effects. Due to such discrepancies, the ability to discriminate medication-specific and nonspecific effects could not be formalized. Moreover, some earlier studies did not report any efficiency results in terms of their sensitivities, specificities and accuracies. Therefore, within-studies comparisons could not be performed. For clinical applications, further validation of the findings is needed.

3.3. Antidepressant treatment response (ATR) index

Various studies have identified the suitability of ATR as a predictive marker for the treatment response and remission based on EEG data acquisition twice, i.e., (a) at baseline and (b) after one week. The ATR was defined to be a nonlinear combination of the three frontal

QEEG parameters described in Eq. (1) [101]. Its value can vary from 0 (low probability) to 100 (high probability of a response).

$$\mathrm{ATR} = \max(0, \min(100, A \times (\mathrm{Alpha}B - \mathrm{Alpha}A) + B \times \mathrm{RelativeThetaPlusAlpha} + C)) \quad (1)$$

where Alpha$B$ is the absolute power in the frequency band (9–11.5 Hz) at week 1, Alpha$A$ is the absolute power in the frequency band (8.5–12 Hz) at baseline, and RelativethetaPlusAlpha is the relative combined theta and alpha power (3–12 Hz/2–20 Hz) at week 1. However, the exact values of the constants A, B and C were not reported.

The ATR index resulted in 70% correct predictions, including 82 MDD patients treated with SSRIs [101]. A further replication with 220 MDD patients resulted in 74% correct treatment predictions [101,103]. However, the clinical indicators could not predict either R or NR. Initially, the patients were treated with escitalopram for 1 week and then divided into three subgroups. The first group continued with escitalopram, the second with bupropion and the third with both escitalopram and bupropion. The ability of the ATR index to predict the differential response to escitalopram, bupropion and their combination has previously been reported [103]. When the value of the index was higher than a threshold (ATR index = 52), the prediction was accurate for escitalopram R. An ATR index of <52 showed the prediction to be accurate for bupropion R. However, this method could not predict the differential response to both escitalopram and bupropion. The placebo effect for the ATR index was studied for 23 MDD patients, of which 12 were treated with fluoxetine and 11 with placebo for 8 weeks [104]. Furthermore, the threshold (ATR index = 47.3) resulted in a 100% sensitivity, 66.6% specificity, 75% positive predictive value and 100% negative predictive value.

The studies that involved the ATR index utilized larger sample sizes. However, they utilized different thresholds of treatment response or non-response, which were mainly based on empirical findings. Due to the simplified EEG montages and the differences in the number of electrodes, the studies could not be compared with a traditional approach. In addition, the ATR formula was less clear, e.g., the relative combined theta and alpha powers in the formula could not be clearly explained.

3.4. Theta QEEG cordance

The QEEG theta cordance is a measure that is computed mathematically based on Eqs. (2)–(6) [105]. It utilizes the EEG absolute and relative power at different scalp locations and frequencies.

$$\mathrm{CORDANCE}_{(s,f)} = \pm\left(\left|a_{\mathrm{NORM}(s,f)} - 0.5\right| + \left|r_{\mathrm{NORM}(s,f)} - 0.5\right|\right) \quad (2)$$

$$T_s = \sum_f a_{s,f} \quad (3)$$

$$r_{s,f} = \frac{a_{s,f}}{T_s} \quad (4)$$

$$a_{\mathrm{NORM}(s,f)} = \frac{a_{s,f}}{\mathrm{AMAX}_f} \quad (5)$$

$$r_{\mathrm{NORM}(s,f)} = \frac{r_{s,f}}{\mathrm{RMAX}_f} \quad (6)$$

where $a_{s,f}$ is the absolute power at the recording site s in the frequency band f; T_s is the total power summed at the recording site s; $r_{s,f}$ is the relative power at site s with the frequency band f; AMAX_f is the maximum absolute value in the frequency band f; RMAX_f is the maximum relative value in the frequency band f.

A number of studies have reported that a decreased prefrontal QEEG theta cordance is correlated with treatment response [106–111]. For example, a prefrontal decrease in the theta cordance after 48 h of intake was found to be correlated with the treatment response [106,107]. This response was observed after 8 weeks of treatment with SSRIs and SNRIs. A decrease in the prefrontal theta cordance after 1 week of treatment (fluoxetine/venlafaxine versus placebo) was observed to be correlated only with treatment R [108]. Changes in the prefrontal theta cordance at week 1 significantly distinguished medication R from all of the other groups (medication NR, placebo R and NR). A prediction accuracy of 72% was achieved [112]. Moreover, the accuracy was improved to 75% with the other treatment of SSRIs for 8 to 10 weeks [109].

Several independent studies were conducted to observe the predictive ability of the theta cordance. A decrease in the theta cordance observed at week 1 predicted the treatment response with an 88% accuracy [110]. A separate study with 25 MDD subjects treated with venlafaxine reported a much larger decrease in the theta cordance in treatment R than in NR [111,113]. Unfortunately, these studies were based on small sample sizes, and consequently, a true generalization was not possible. Hence, there is a need to replicate these findings in large populations. Moreover, similar to the ATR index, the cordance formula did not reflect the neural mechanism for MDD [114].

3.5. Referenced EEG (rEEG)

Referenced EEG (rEEG) was based on a well-organized database that included records of EEG patterns that corresponded to various disease symptoms based on the patients' medical and EEG records (1700 patients with 18,000 antidepressant treatments) after treatment with specific antidepressants [115]. During the treatment selection process, rEEG could help by performing a comparison between the patient's EEG patterns and the database patterns. Based on the most suitable comparison, appropriate medicines were selected. The database has been validated with different research studies [116]. For example, an rEEG-based research study with two groups of patients was conducted [115]. The 1st group (7 patients) was treated with rEEG-guided treatment, and the 2nd group (6 patients) received a normal treatment such as STAR*D [117]. The study resulted in higher rates of response (6 out of 7) for the rEEG-guided group compared to the 2nd group (1 out of 6). A replicated study with 114 patients endorsed these findings [117].

The rEEG has been used as a guidance tool for treatment selection. However, the studies did not provide any performance metrics such as the sensitivity and specificity of the prediction. The clinical applicability and generalization of the findings require further investigation by utilizing patients from other geographical areas. Other geographical locations provide diversity in the population under investigation and increase the generalizability of the proposed method. In addition, the incorporation of variables other than the QEEG in such demographical and clinical data could further improve its predictive ability.

3.6. Rostral anterior cingulate cortex (rACC) activations for MDD

The surface EEG signals recorded from the scalp provide information to perform source localization deep inside the brain, which could reveal the activation that is specific to a certain brain region. Studies based on QEEG biomarkers that utilized LORETA performed localizations by constructing 3D maps of the whole brain. Activation in the rostral anterior cingulate cortex (rACC) was consistently found to be associated with treatment outcomes during MDD. For example, a resting rACC activity in the theta band was found to be correlated with the treatment response [118], where 18 MDD patients were treated with nortriptyline for 16 weeks. In addition, a re-analysis was performed by introducing threshold levels for the response and nonresponse, called 'high responders' and 'low responders', respectively [119]. Pretreatment rACC activity

Fig. 2. A Generalized ML Strategy.

correctly classified high responders (88.9%) and low responders (89.9%). Furthermore, Mulert and colleagues recruited 20 MDD patients who were treated with citalopram or reboxetine and reported a treatment response association with increased resting state rACC theta activity [120]. In another study, higher theta rACC and orbitofrontal cortex activations were correlated with the medication response [121].

However, the threshold selection was based on empirical findings and could not explain the neurobiology of MDD. Due to the potential problem with LORETA, i.e., the assumptions on which it is based, the results might not be accepted confidently by clinicians. Moreover, the small sample sizes in the studies above require future validation in larger populations.

3.7. ML techniques for the prediction of treatment outcomes

ML techniques inherently involve feature extraction, selection and classification sub-processes (Fig. 2). They provide identification of the most relevant variables or patterns specific to a disease condition. These relevant variables were derived from EEG and ERP during the feature extraction sub-process. The ML techniques were commonly applied for biomedical research [122,123]. For example, the 'Psychiatrist in the Machine', an ML-based system, was developed to automate the treatment selection process for mental patients [124]. The system could assist MDD patients in choosing suitable treatment according to the EEG data acquired. Furthermore, treatment outcome prediction for the MDD patients, divided into R and NR based on the ML techniques, has shown promise (sensitivity = 94.9%, specificity = 80.9%, accuracy = 87.9%) [125,126]. A similar study was conducted by applying an ML technique to schizophrenia, which achieved a classification accuracy of 85% [127].

However, the studies based on ML techniques used a small number of patients, and further investigation into this promising area is required with a larger number of recruited patients in addition to different antidepressant treatments. A summary that includes the EEG biomarkers is described in Table 2.

4. ERP-based predictive biomarkers

The ERP components, P300 intensities and latencies were found to be correlated with the treatment outcome for MDD patients [128–132]. The ERP type called the Loudness Dependence Auditory Evoked Potential (LDAEP) describes how one EPR component (N100/P200) changes with increasing loudness of the auditory stimulus. It is believed to quantify the magnitude of the serotonergic neurotransmission in primary auditory cortex. Lower values of LDAEP indicated higher levels of chemical (serotonin) inside the brain and vice versa. Related studies are described in the following subsections.

4.1. ERP component P300

P300-based morphological quantities, e.g., P300 amplitudes, latencies and P200 slopes, were found to be associated with the treatment outcome. The P300 peak amplitudes at the occipital electrodes were found to be correlated with the treatment response during a dichotic listening task [128]. Another study [129] revealed that patients with a larger P300 latency at baseline failed to remit after 6 weeks, while the patients who remitted along with the

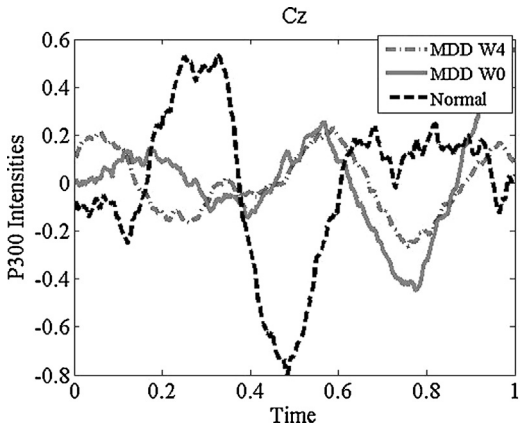

Fig. 3. Observations of differences, including P300 intensities and latencies, between MDD patients (before treatment and after the 4th week of treatment) and controls.

controls showed normal latencies. Moreover, 23 out of 24 remitted MDD patients were identified by the P300, with a specificity of 65.9% and a sensitivity of 95.8%. In an observational study [130], higher P200 slopes were found to be correlated with the treatment response at baseline compared with the non-response. P300 latencies were observed while 28 MDD patients were treated with sertraline for 12 weeks. As a result, longer latencies were discovered in NR (10) compared with both R (18) and controls (28) [78]. However, no correlations were observed between the P300 intensities and treatment response. In an early study [130], 17 MDD patients (11 R, 6 NR) were recruited for 4 to 8 weeks and treated with fluoxetine, bupropion, or desipramine. Larger slopes of P200 at baseline were found in R only when compared with NR.

Fig. 3 is plotted based on the EEG/ERP data acquired from the experiment design described in Section 5.2. The figure describes grand averaged P300 components at a central region (Cz), which could significantly discriminate the groups: controls (normal) and MDD patients. The controls had shown higher ERP intensities with a 300-ms latency. However, the patients showed low amplitudes and longer latencies than the control group.

4.2. LDAEP

Studies based on LDAEP have shown an association with treatment outcome. For example, higher LDAEP slopes were found to be correlated with R [133]. In addition, lower LDAEP slopes at baseline were associated with treatment response to reboxetine [131]. Furthermore, higher values of LDAEP in R were observed compared to NR [132]. LDAEP could be a differential marker for two types of medications with different mechanisms of action (MOA): serotonergic and non-serotonergic. In [134], 20 of the MDD patients were treated with citalopram (an SSRI) and 15 others with reboxetine (a norepinephrine reuptake inhibitor (NRI)). The former showed a higher LDAEP slope at baseline in contrast to the reboxetine R, and similar results were reported by [135]. In [136], a low LDAEP at baseline was found in an MDD patient (only 1 patient) with severe side effects to the SSRI treatment. In that case, a medication with a different neurochemical profile called tianeptine was found to be useful instead.

However, the above-mentioned studies based on P300 utilized different features, e.g., the P300 amplitude or latency. Because

Table 2
Summary of the findings related to EEG-based predictive biomarkers for MDD.

Predictive biomarkers	EEG parameters	Common findings	Critical analysis & limitations
Alpha power and asymmetry	• Alpha power and alpha asymmetry • Lateralization of alpha power	• Decreased lateralization and alpha power was associated with the treatment response • Less current source density was associated with a non-response • Increased alpha power was associated with the treatment response	EEG power measurements were considered to be reliable. However, few studies have shown contradictory findings. In addition, changes that are associated with alpha asymmetry could not discriminate R and NR
Theta band activations	Theta band powers	Treatment response was associated with increased theta activations	Studies that investigated pre-treatment and early changes in the theta band have reported conflicting results. For example, decreased activity was associated with the treatment response [93,101]. In contrast, others have reported a response association with increased theta band activity [98]
ATR index	Relative theta and alpha power	• Classifications based on the ATR index values were conducted. A higher accuracy means better predictions involving the ATR index • The ATR index can be a differential indicator for more than one antidepressant treatment outcome	The ATR index utilizes empirically adjusted threshold values. These adjustments were based on experimental observations and could need further validation to be accepted confidently for clinical applications
QEEG theta cordance	Absolute and relative power in theta bands	Decreased QEEG theta cordance was consistently found to be correlated with treatment R	The decreased QEEG theta cordance was found to be consistent as a predictive biomarker. However, due to their low specificity values, the measure cannot be confidently applied in clinical applications
Referenced EEG (rEEG)	Pattern matching based on the QEEG database	The rEEG-guided treatment proved to be efficient in the STAR*D study. It depicted the importance of evidence-based therapy over a sequential treatment strategy	The rEEG performed better than STAR*D. However, the database was specific to the geographical area. For generalization, patterns from other geographical areas should be included
rACC activations	EEG power computations and their LORETA-based source localization	Activation in rACC was correlated with the treatment response	The rACC activations were found to be consistent during MDD. However, the empirically adjusted thresholds require further validation
Algorithmic approach based on machine learning and data mining	EEG-derived quantities were used as feature vectors. Their significance was found based on discriminating the treatment response and non-response	ML techniques have proven to be promising and reliable predictors of treatment outcomes because of their stronger classification abilities	Incorporating data mining and algorithmic concepts achieved higher discriminating efficiency. However, the studies were based on small sample sizes and un-even gender distributions

of these differences, it is impossible to compare them with one another. Moreover, studies reported only statistical associations between QEEG biomarkers and outcomes; i.e., the studies failed to report sensitivity and specificity values. LDAEP showed a link with serotonergic activity, but it was not fully demonstrated that LDAEP might differentiate the response to serotonergic versus non-serotonergic antidepressants. The clinical utility of LDAEP requires further validation. Table 3 summarizes the comments about ERP biomarkers discussed in this section. In the previous sections, various EEG- and ERP-based studies have been discussed. These studies

Table 3
Summary of the findings related to ERP-based predictive biomarkers for MDD.

Brain dynamics	Associated measures	Main findings	Critical analysis and limitations
ERP component: P300	P300 peak amplitude, latencies, P200 slopes	• Treatment response was associated with higher P300 peak amplitudes and higher P200 slopes • Patients with larger P300 latencies were observed as NR	The association between the ERP and antidepressants were less studied. The studies discussed here have focused on different ERP parameters. Therefore, a comparison with multiple studies was not possible
LDAEP	ERP component (N100/P200) changes with increasing loudness of the auditory stimulus	• A higher LDAEP slope was exhibited in R • A differential prediction including two different types of drugs could be possible	Studies based on LDAEP have utilized optimal threshold values, which were empirically selected

have shown EEG and ERP abnormalities that are specific to patient conditions used for MDD diagnosis and for generating predictions about treatment outcomes.

5. Comparison based on a common dataset

In this section, we have reanalysed the quantities/features derived from EEG/ERP data discussed so far in the previous sections. The EEG and ERP datasets were acquired and pre-processed in our laboratory. The objective was to classify the study participants into respective subgroups based on these features. The significance of these features is directly proportional to their classification abilities. Theoretically, classification could involve different statistical tools that can model the relationships between the features and the participant's target groups. In this study, two different types of classifications were performed: (1) discrimination between the MDD patients and controls, and (2) treatment responders (R) and treatment non-responders (NR).

5.1. Participant recruitment and data acquisition

The recruitment involved two groups of participants from Hospital Universiti Sain Malaysia (HUSM): (1) 33 MDD patients (16 males and 17 females, mean age = 40.33 ± 12.861), and (2) 19 age-matched healthy control subjects (9 males and 10 females, mean age = 38.277 ± 15.64). The study design was approved by the human ethics committee, HUSM. The MDD patients met the international diagnostic criteria for depression, as described in the Diagnostic and Statistical Manual-IV (DSM-IV) [137]. MDD patients went through a 2-week medication washout time period before the EEG data acquisition. After the 1st EEG recording, the MDD patients started taking antidepressants under the general category of selective serotonin reuptake inhibitors (SSRIs). To access the disease severity, clinical questionnaires such as the Beck Depression Inventory-II (BDI-II) and Hospital Anxiety and Depression Scale (HADS) were administered twice: (a) during week 1 at the start of treatment, and (b) during week 4. The questionnaires were designed to rate the disease severity by assigning a number. A higher number reflected a more severe disease condition. The healthy control subjects were examined for many psychiatric conditions and were found to be normal.

EEG/ERP data acquisition hardware included a 19-channel electro-gel cap interfaced with a Brain Master Discovery amplifier. The 19 recording sensors were placed over the scalp and were named as Fp1, F3, C3, P3, O1, F7, T3, T5, Fz, Fp2, F4, C4, P4, O2, F8, T4, T6, Cz and Pz. In addition, the amplifier was attached to the computer system through a universal serial bus (usb) port. The EEG cap with 19 sensors covered the whole scalp according to 10–20 electrode placements, which were standard with a link-ear (LE) reference. In practice, the EEG data recorded with the LE reference can be re-referenced as the average reference (AR). Our data analysis was based on AR-referenced EEG/ERP data. Moreover, the data were band-pass filtered from 0.5 Hz to 70 Hz with an additional notch filter (50 Hz) to filter out the main power supply line noise. The analogue EEG data were digitized at 256 samples per second and saved in a database.

5.2. Experimental design and data preprocessing

The experimental design for EEG and ERP data acquisition involved different physiological conditions. For example, EEG recordings were conducted during eyes closed (EC) and eyes open (EO) conditions for 5 min each. During EO, the participants were instructed to sit relaxed with minimum eye movement. In the case of drowsiness, the study participants were interrupted by a beep sound. On the other hand, the ERP recordings involved an experiment called the 3-stimulus visual oddball task [138]. During this task, individual responses were recorded for three different types of stimuli: the target (a blue-coloured circle with a radius of 5 cm), the distractor (a checker board of similar size as the target), and the standard (a blue-coloured circle with a radius of 2.5 cm). ERP component P300 was achieved by taking a grand average of the epochs of a similar type. Before performing data analysis, both the EEG and ERP datasets were preprocessed to remove artefacts due to eye blinks, movement and muscular activity using brain source localization software (BESA) [139].

5.3. Data analysis

EEG/ERP data analysis inherently involves feature extraction, selection, classification, and validation. During feature extraction, the power of alpha and theta frequency bands, alpha asymmetry, P300 intensities, ATR index, coherence and theta cordance were computed. The total number of participants was (33 + 19) 52, and each participant underwent 3 physiological states, i.e., EC and EO and ERP. Furthermore, these features were arranged in a matrix, called as the data matrix. In the matrix, the rows correspond to the number of study subjects and the features were arranged column-wise. For example, the number of rows for 33 MDD patients was 33 that correspond to either EC or EO conditions. Similarly, in the data matrix of 19 control subjects, the number of rows was 19. In case of ERP features, the rows of the data matrices for the MDD patients and controls were 33 and 19, respectively. Moreover, the features were combined by concatenating column-wise with equal number of rows, i.e., combination of the resting-state features and the ERP features as described in Table 4.

The feature extraction was followed by feature selection as described in the following paragraph. Feature selection is indispensable because many features in a data matrix could be redundant or even irrelevant [140]. In this study, a nested feature selection was performed including the training and testing of the classifier models. Mainly, the feature selection included 2 steps.

First, the computed features were ranked according to a criterion, called the receiver operating characteristics (ROC) [141]. According to the criterion, the area between the empirical ROC curve and the random classifier slope was computed for the individual features and assigned a weight value (z-value), accordingly. The z-value could vary from 0 to 0.5, which indicates a bad to good classification ability to discriminate the target groups, i.e., the MDD patients and controls or R and NR. Moreover, the features were listed in descending order according to their computed z-values such as a feature with highest z-value was listed at the top. Finally, a grouping was performed such as top-ranked 5, 10, 15, and 19 features were sub-grouped. For classification purposes, the logistic regression (LR) classification was employed. The LR is a statistical tool to model the functional relationship between the EEG/ERP features and the target groups [142].

Second, the classifier accuracy was computed for each feature sub-group and was validated with 100 iterations of 10-fold cross-validation, termed as Monte Carlo Cross-Validation (MCCV). The MCCV was adopted to avoid the possibility of misleading classification results [143]. A supervised learning model, such as the LR, requires training and testing processes. According to the MCCV procedure, the data samples are randomly permutated between the training and test subsets in an iterative manner. In our experiments, 100 iterations are used. In each iteration, performance is evaluated using a 10-fold cross-validation procedure. As a result, 100 values of the accuracies, sensitivities, and specificities were achieved. Moreover, a median of the 100 values was computed. Finally, the feature subsets that provided highest values of the accuracies were selected and reported in Tables 5 and 6.

Table 4
Dimensions of data matrices (before feature selection) for the EEG and ERP features.

Sr.	EEG/ERP features	MDD patients (EC/EO) × features	Healthy controls (EC/EO) × features
1	Asymmetry	33 × 64	19 × 64
2	Coherence	33 × 1920	19 × 1920
3	Power alpha	33 × 19	19 × 19
4	Power theta	33 × 19	19 × 19
5	Combination of asymmetry, coherence, power alpha, power theta	33 × 2022	19 × 2022
6	P300 intensities	33 × 9000	19 × 9000
7	Combination of asymmetry, coherence, power alpha, power theta and P300 intensities	33 × 11,022	19 × 11,022

Table 5
Discriminating MDD patients and Healthy controls based on the EEG and ERP features.

EEG/ERP feature	Accuracy (%)	Sensitivity (%)	Specificity (%)	No. of features
Alpha power	74.9	63.57	81.6	19
Theta power	74.20	61.07	80.49	15
Asymmetry	87.51	76.4	93.8	10
Coherence	91.38	82.5	96.92	5
ERP features (P300 intensities)	90.5	80.5	96.66	5
Combined resting-state features (alpha power, theta power, asymmetry, coherence)	98	95	100	5
Combined resting-state and ERP features	99	98	100	5

Table 6
Discriminating R and NR during MDD. Higher accuracies indicate more significance.

EEG/ERP feature	Accuracy (%)	Sensitivity (%)	Specificity (%)	No. of features
Alpha power	53.56	47.14	61.42	5
Theta power	56.23	62.85	50	5
Asymmetry	64.89	69.04	59.76	5
Coherence	69.52	79.04	60	5
ERP features (P300 intensities)	82.24	85	80	5
Theta cordance	75.09	76	74.66	5
ATR index	55.45	43	66	10
Combined resting-state features (alpha power, theta power, asymmetry, coherence)	82.24	79.52	84.28	10
Combined resting-state and ERP features	91.66	90	95	5

The outcome of classification was evaluated using confusion matrices. The performance metrics computed from the confusion matrix are presented by Eqs. (7)–(9). According to the definition, the sensitivity of a classification model corresponds to the percentage of true cases (TP) which are correctly classified as cases defined by Eq. (7). Moreover, the specificity of a classification model refers to the percentage of true non-cases (TN) which are correctly classified as non-cases as described by Eq. (8). In addition, the accuracy of a classification model illustrates the percentage of correctly classified cases and non-case among all the example points as depicted in Eq. (9). Finally, the false positive (FP) and negatives (FN) are defined as misclassified cases and non-cases, respectively.

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}} \tag{7}$$

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}} \tag{8}$$

$$\text{Accuracy} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{TN} + \text{FP} + \text{FN}} \tag{9}$$

5.4. Results

This paragraph addresses the issue of diagnosis (discrimination between MDD patients and healthy controls). The features that provide the highest classification accuracies reflected the discriminating ability of the individual EEG/ERP features. Table 5 shows a significant increase in accuracy (98%) while combining all of the EEG features compared with the maximum accuracy computed for the individual EEG features. Among the individually computed features, EEG coherence has shown the highest accuracy values, i.e., 91.38%. In addition, alpha and theta band powers have also provided higher specificities. Moreover, the P300 intensities required only 5 features and achieved 90.5% accuracy in discriminating the MDD patients and healthy controls (Table 5). The asymmetry required 10 features and achieved 87.51% accuracy. The alpha and theta power require 19 features each to achieve approximately equal accuracies of ∼74%. Finally, the integration of EEG and ERP features has resulted as the maximum accuracy (accuracy = 99%).

This paragraph addresses the issue of prediction of treatment efficacy (discrimination between treatment responders and non-responders). The classification results for the discriminating responders and nonresponders based on common feature variables are described in Table 6. The theta cordance and the ATR index were added because they were specific to the MDD patients. The theta cordance has also provided better results (accuracy = 75.09%) than the other EEG features. The combined EEG features provided an improved accuracy (82.24%) when compared with the individual EEG features (max accuracy achieved = 69.52%). On the other hand, the ERP features such as P300 intensities were found to be highly significant, by achieving accuracies of 82.24%. Finally, the theta cordance achieved a higher accuracy (75.09%) than the ATR Index (accuracy = 55.45%), which indicated that the theta cordance could prove to be better than ATR during predictions of treatment outcomes. Finally, the integration of EEG and ERP features has resulted as the maximum accuracy (accuracy = 91.66%).

6. Discussion and conclusions

This study addresses the problem of identifying predictive EEG- and ERP-based biomarkers for the treatment of MDD. MDD is a serious mental illness and is highly prevalent. Unfortunately, the treatment for MDD is still based on subjective assessments with trial-and-error treatment approaches for identifying suitable medication. There has been considerable effort by the mental health care

community to develop personalized approaches for the treatment of MDD. These approaches are based on identifying biomarkers that could predict an effective medication for a specific MDD patient. However, the methods developed in this respect are either ineffective due to having low prediction accuracies or their findings cannot be generalized due to having a small number of subjects used in the respective studies. In this review, all of these methods are reviewed comprehensively. During this process, the limitations are identified and suggestions are provided to improve the situation.

For the studies reviewed here combined with previous studies [144,145], several features derived from EEG and ERP have been associated with treatment response. EEG/ERP has certain advantages over other neuroimaging modalities in terms of its cost effectiveness and temporal resolution. Additionally, there is portability and adaptability of the modality, i.e., using EEGs for clinical purposes makes it possible to have quick acquisition of neuronal data. A psychiatrist/practitioner can use this approach with little hands-on training. In addition, wireless EEG caps are more feasible for data acquisition than caps that have cables. Despite all of the benefits, EEGs have less spatial resolution than fMRI. LORETA and the latest techniques (sLORETA, ssLOFO, 2q-Exo-MUSIC) provide solutions to this problem. However, these techniques might not be suitable in the context of clinical utility. For example, the original LORETA method is very sensitive to the assumed underlying mathematical model, a fact which can lead to erroneous results when the model contains errors. However, recent techniques are robust in cases when more than single neuronal sources inside the brain are to be estimated, or under low SNR conditions.

To answer the question posed by the clinical utility of EEG/ERP-based biomarkers, the techniques discussed in this paper have provided promising research results. However, more solid evidence, such as treatment outcome prediction, is required to translate them into clinical practice. This could be achieved through generalizing the findings discussed in this paper. Existing QEEG biomarkers have shown responses to different antidepressants, but none of them can explain the neurobiology of MDD development [114]. In addition, some of the biomarkers (theta cordance, ATR index, LDAEP) have defined thresholds and cut-offs to discriminate between treatment response and nonresponse.

The classification ability provided by the EEG cordance and ATR index make them potential candidates for clinical use. The ATR (with a threshold value) could be a differential indicator of treatment response for two different types of antidepressants. The theta cordance could be a 'quick check' of the treatment efficacy, e.g., as early as after one week. Based on a threshold, an inefficient treatment could be augmented or changed entirely. A QEEG biomarker, for example, rEEG, achieved better results than in the STAR*D study, i.e., the selection of the treatment based on individual disease conditions. However, only a few studies have reported the efficiency of the QEEG biomarkers. Further investigation to prove their utility is required. Similarly, ML techniques have proven their efficacy but only with a small sample size, and thus further replication of the results with a large sample size is required.

Future studies should focus on validation for clinical purposes based on the following key points:

(i) ML techniques

Exploratory techniques such as data mining could be suitable to mine offline data for the identification of specific patterns that are common to either R or NR. Data mining can be employed on large databases such as those used in the case of rEEG. The data will provide a unique opportunity to learn statistical tools such as support vector machine (SVM), which can be used clinically for choosing prescriptions and predicting treatment outcomes for a new patient.

(ii) Fusion of modalities

A multimodal approach would be a better choice to acquire neuronal data; such an approach would involve a combination of EEG, fMRI and MEG [146] or fMRI and MEG [147]. EEG-fMRI fusion involves a higher level of temporal detail and can be achieved through EEG and fMRI spatial resolution. Data acquired from multimodalities can be analysed based on newly developed techniques, for example, EEG and fMRI [148]. Unfortunately, the fusion creates artefacts in the recorded data and hence hampers the data analysis, e.g., simultaneous acquisition of EEG and fMRI causes production of an artefact in the EEG data called the ballistocardiographic effect [149], which must be addressed.

(iii) Fusion of methods

Various QEEG biomarkers discussed, such as the theta cordance and ATR index, can be combined and fused in multiple ways to improve the efficiency of training a classifier, for example, the use of available off-line data provided by the rEEG database.

(iv) Metric measures

The majority of the MDD prediction studies do not report the accuracy, sensitivity and specificity. It is important to have these measures for validation of the predictive methods shown in this paper. The validation must be performed with larger datasets.

In conclusion, several EEG/ERP technologies, especially from the resting EEG, have the potential to provide treatment outcome predictions. Although it is premature to judge whether EEG/ERP-based quantities would predict treatment outcome with their promises, the research results thus far have provided positive results. Further studies are necessary to generalize and validate the current findings for the purpose of clinical practice.

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