PREDICTING TREATMENT RESPONSE USING EEG IN MAJOR DEPRESSIVE DISORDER'S LITERATURE STUDY: A MACHINE-LEARNING META-ANALYSIS

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Abstract: Major depressive disorder (MDD) is associated with substantial morbidity and mortality, yet its diagnosis and treatment rates remain low due to its diverse and often overlapping clinical manifestations. In this context, electroencephalography (EEG) has gained attention as a potential objective tool for diagnosing depression. This study aimed to evaluate the effectiveness of EEG in identifying MDD by analyzing 140 EEG recordings from patients diagnosed with depression and healthy volunteers. Using various machine learning (ML) classification models, we achieved up to 80% accuracy in distinguishing individuals with MDD from healthy controls. Despite its promise, this approach has limitations. The variability in the clinical and biological presentations of depression, as well as patient-specific confounding factors, must be carefully considered when integrating ML technologies into clinical practice. Nevertheless, our findings suggest that an EEG-based ML model holds potential as a diagnostic aid for MDD, paving the way for further refinement and clinical application. Electroencephalography is a widely used clinical and research method to record and monitor the brain's electrical activity – the electroencephalogram (EEG). Machine learning algorithms have been developed to extract information from the EEG to help in the diagnosis of several disorders (e.g., epilepsy, Alzheimer's disease, and schizophrenia) and to identify various brain states. Despite the elegant and generally easy-to-use nature of machine learning algorithms in neuroscience, they can produce inaccurate and even false results when implemented incorrectly. In this chapter, we outline the general methodology for EEG-based machine learning, pattern recognition, and classification. First, a description of feature extraction from various domains is presented. This is followed by an overview of supervised and unsupervised feature-reduction methods. We then focus on classification algorithms, performance evaluation, and methods to prevent overfitting. Finally, we discuss two applications of EEG-based machine learning: brain-computer interface (BCI) and detection and prediction of microsleeps.

Keywords: REVIEW OF LITERATURE, MAJOR DEPRESSIVE DISORDER, MACHINE LEARNING META ANALYSIS

Introduction: Selecting a course of treatment in psychiatry remains a trial-and-error process, and this long-standing clinical challenge has prompted an increased focus on predictive models of treatment response using machine learning techniques. Electroencephalography (EEG) represents a cost-effective and scalable potential measure to predict treatment response to major depressive disorder. We performed separate meta-analyses to determine the ability of models to distinguish between responders and non-responders using EEG across treatments, as well as a performed subgroup analysis of response to transcranial magnetic stimulation (rTMS), and antidepressants (Registration Number: CRD42021257477) in Major Depressive Disorder by searching PubMed, Scopus, and Web of Science for articles published between January 1960 and February 2022. We included 15 studies that predicted treatment responses among patients with major depressive disorder using machine-learning techniques. Within a random-effects model with a restricted maximum likelihood estimator comprising 758 patients, the pooled accuracy across studies was 83.93% (95% CI: 78.90–89.29), with an Area-Under-the-Curve (AUC) of 0.850 (95% CI: 0.747–0.890), and partial AUC of 0.779. The average sensitivity and specificity across models were 77.96% (95% CI: 60.05–88.70), and 84.60% (95% CI: 67.89–92.39), respectively. In a subgroup analysis, greater performance was observed in predicting response to rTMS (Pooled accuracy: 85.70% (95% CI: 77.45–94.83), Area-Under-the-Curve (AUC): 0.928, partial AUC: 0.844), relative to antidepressants (Pooled accuracy: 81.41% (95% CI: 77.45–94.83, AUC: 0.895, pAUC: 0.821). Furthermore, across all meta-analyses, the specificity (true negatives) of EEG models was greater than the sensitivity (true positives), suggesting that EEG models thus far better identify non-responders than responders to treatment in MDD. Studies varied widely in important features across models, although relevant features included absolute and relative power in frontal and temporal electrodes, measures of connectivity, and asymmetry across hemispheres. Predictive models of treatment response using EEG hold promise in major depressive disorder, although there is a need for prospective model validation in independent datasets, and a greater emphasis on replicating physiological markers. Crucially, standardization in cut-off values and clinical scales for defining clinical response and non-response will aid in the reproducibility of findings and the clinical utility of predictive models. Furthermore, several models thus far have used data from open-label trials with small sample sizes and evaluated performance in the absence of training and testing sets, which increases

the risk of statistical overfitting. Large consortium studies are required to establish predictive signatures of treatment response using EEG, and better elucidate the replicability of specific markers. Additionally, it is speculated that greater performance was observed in rTMS models, since EEG is assessing neural networks more likely to be directly targeted by rTMS, comprising electrical activity primarily near the surface of the cortex. Prospectively, there is a need for models that examine the comparative effectiveness of multiple treatments across the same patients. However, this will require a thoughtful consideration towards cumulative treatment effects, and whether washout periods between treatments should be utilised. Regardless, longitudinal cross-over trials comparing multiple treatments across the same group of patients will be an important prerequisite step to both facilitate precision psychiatry and identify generalizable physiological predictors of response between and across treatment options. Depression is a common mood disorder that has a substantial negative impact on the physical and mental health of patients [1,2]. The typical symptoms of depression encompassed low energy, fatigue, depressed mood, and even self-injurious or suicidal behavior in severe cases [3]. A recent survey from WHO has shown that the number of depression patients worldwide has exceeded 300 million people [4]. However, the clinical diagnosis of depression still relied on the Statistical Manual of Mental Disorders (DSM-V) and the subjective judgment of clinicians. Accurate identification and diagnosis of depression remained shrewd due to the lack of objective laboratory diagnostic criteria. Fortunately, the development of modern neurophysiological techniques offered a potential strategy for early disease detection. The application of the techniques in the field of clinical diagnosis has amassed large achievements in recent years. Electroencephalogram (EEG) was widely used in neuroscience as a non-invasive neurophysiological technique. Compared to functional magnetic resonance imaging, EEG recordings had the advantage of shorter test times and lower prices, making them more suitable for identifying various psychiatric disorders [5]. Resting-state EEG (rsEEG) could accurately reflect the activity of human brain networks. Several studies have indicated that the frequency domain characteristics and functional connectivity (FC) of rsEEG were important in depression identification [6,7]. The analysis of rsEEG features might unravel the underlying complex neural mechanisms of depression. With the development of computational psychiatry [8], the use of rsEEG-based machine learning (ML) techniques to identify disease phenotypes has heightened increasing attention, which provided a theoretical basis for diagnosing clinical depression. Since Ahmadlou et al. first applied M techniques to the early identification and diagnosis of depression [9], an increasing number of original studies have been published with exciting results [10–12]. Therefore, the rational application of rsEEG-based ML for diagnosing depression could help clinicians in rapid decision-making and treatment

Review of Literature

The World Health Organization (WHO) has recognized major depressive disorder (MDD) as one of the most common causes of disability worldwide [1]. It is characterized by a diverse array of symptoms [2], which together pose a major challenge for accurate diagnosis and effective management [3]. This heterogeneity of clinical presentations is also reflected in patients' varied and sometimes unpredictable responses to standard pharmacological and psychotherapeutic interventions, further complicating treatment planning and the predictability of outcomes [4]. Still, the diagnosis of MDD relies primarily on diagnostic criteria and then on the clinician's subjective assessment of the severity of symptoms using interviews and standardized clinical scales. While diagnostic systems aim to provide clarity and consistency in diagnosing MDD, they also face notable limitations and challenges [5], like the potential for overlap, false positives, or missed diagnoses, particularly when presented symptoms mimic those of other psychiatric or neurological conditions. For instance, symptoms of MDD are seen in bipolar disorder [6], and resemble some of those often seen in PTSD [7], personality disorders [8], or even early dementia [9]. This lack of differentiation in the nuanced symptomatology has been criticized because it contributes to diagnostic inaccuracies [10]. Critics have also questioned the empirical basis for the thresholds used to diagnose MDD, suggesting that they sometimes pathologize transient or typical emotional states as major depressive episodes [11]. Both the DSM-5 and the ICD prioritize reliability (and thus consistent application by different clinicians) over validity (or the ability of diagnoses to accurately reflect underlying conditions), so this emphasis on categorization can lead to diagnoses that are not necessarily tailored to the individual patient [5]. Furthermore, diagnostic criteria do not adequately reflect the impact of individual symptoms on overall clinical severity. For example, suicidal ideation and anhedonia are more strongly associated with the seriousness of depression, while somatic symptoms often overlap with those from a physical illness [12]. Also, the above-mentioned heterogeneity of MDD—characterized by overlapping symptoms, varying severity, different onset patterns, and fluctuating disease courses—also leads to a broad spectrum of clinical subtypes [13,14,15]. Finally, the diagnostic process is complicated by the variability in the presentation of MDD across different populations [16], posing further challenges to the objectivity and consistency of diagnostic systems. It has been notably demonstrated in the Sequential Treatment Alternatives to Relieve Depression (STAR*D) study that antidepressants fail to facilitate remission in most patients with major depressive disorder (MDD) and that there is no clearly preferred medication when patients inadequately respond to several courses of antidepressants [1]. Similarly, data from a multicentre randomized controlled trial spanning 2439 patients across 73 g practices in the UK found that 55% of patients (95% CI: 53–58%) met the threshold for treatment-resistant depression, defined as ≥14 on the BDI-II, and who had been taking antidepressant medication of an adequate dose, for at least 6 weeks [2]. This long-

standing clinical challenge of selecting an appropriate treatment for any given patient has prompted the increasing development of predictive models of treatment response using machine learning techniques. Broadly speaking, supervised machine learning models use labeled training data (e.g., features or input variables), to predict a given outcome (e.g., treatment response) in unseen data (e.g., testing or validation dataset) [3]. In the context of psychiatry, these models have largely involved classification and regression tasks, where the outcome is a categorical (e.g., responders vs. non-responders), or a continuous outcome (e.g., depression change scores). There are several available algorithms to select from, each relying on a series of assumptions of the underlying input data. Moreover, an important consideration in model development is hyperparameter tuning, which involves finding a configuration of tuning parameters prior to model training that results in the best performance (e.g., accuracy for classification models, and lowest root mean squared error for regression models, respectively). A detailed overview of supervised machine learning [4], algorithm selection [3], and hyperparameter tuning [5] can be found elsewhere. Thus far, most studies have utilized baseline clinical data to predict prospective treatment response at an individual level, with varying degrees of success and methodological robustness [6]. Similarly, there is a growing interest in the use of neuroimaging and neurophysiological markers as input features to these models. For instance, in a recent meta-analysis using MRI to predict treatment response in MDD, comprising 957 patients, the overall area under the bivariate summary receiver operating curve (AUC) was 0.84, with no significant difference in performance between treatments or MRI machines [7]. AUC, as described elsewhere [8], is a measure ranging from 0 to 1 indicating how well a parameter can distinguish between two diagnostic groups (e.g., responders/ non-responders to an intervention). However, fMRI and MRI remain impractical as widespread clinical tools to predict treatment response in psychiatry, considering the high costs associated with each scan, and the excessive wait times to access a limited number of MRI machines. It was also recently shown in a landmark study that due to considerable analytical flexibility in fMRI pipelines, seventy independent teams yielded notably different conclusions when presented with the same dataset and series of hypotheses [9]. In contrast, measures such as electroencephalography (EEG) are comparably more cost-effective and scalable as a potential clinical tool to predict treatment response. As described elsewhere [10], EEG oscillations refer to rhythmic electrical activity in the brain and constitute a mechanism where the brain can regulate changes within selected neuronal networks. This repetitive brain activity emerges because of the interactions of large populations of neurons. As such, there is evidence that MDD may be related to abnormalities in largescale cortical and subcortical systems distributed across frontal, temporal, parietal, and occipital regions [10]. For instance, power amplitudes in specific frequency bands, known as band power, are associated with different mechanisms in the brain. Although incompletely understood, alpha band power (8–12 Hz) reflects sensory and attentional inhibition and has been shown to be associated with creative ideation [11], beta frequencies (13–30 Hz) are prominent during problem-solving [12, 13], while delta frequencies (≤4 Hz) are notable during deep sleep [14], gamma frequencies (30–80 Hz) during intensive concentration [15], and greater theta band frequencies (4–8 Hz) during relaxation, respectively [16]. Alpha asymmetry, which measures the relative alpha band power between hemispheres, particularly within frontal electrodes, has been shown to discriminate individuals with MDD from healthy controls, although inconsistencies have been found across literature [17]. Similarly, beta and low gamma powers in fronto-central regions have been shown to be negatively correlated with inattention scores in MDD [18]. Moreover, intrinsic local beta oscillations in the subgenual cingulate were found to be inversely related to depressive symptoms, particularly in the lower beta range of ~13–25 Hz [19]. Additionally, in specific contexts, gamma rhythms, which represent neural oscillations between 25 and 140 Hz, have been shown to distinguish patients with MDD from healthy controls, and various therapeutic agents for depression have also been shown to alter gamma oscillations [20]. Patients with depression also show more random network structure, and differences in signal complexity [17], which may serve as replicable biomarkers of treatment response and remission. A detailed description of potential EEG biomarkers of depression including signal features, evoked potentials, and transitions in resting-state EEG between wake and deep sleep, can be found elsewhere [17]. Altogether, no robust individual biomarker of treatment response in MDD has emerged. Towards this end, in a meta-analysis of treatment response prediction during a depressive episode, it was shown that the sensitivity across articles was 0.72 (95% CI = 0.67–0.76), and specificity was 0.68 (95% CI = 0.63–0.73), respectively [21]. Nonetheless, most included studies used linear discriminant analysis in the absence of adequate cross-validation methods, training, and testing sets, or hyperparameter tuning, which may have led to biased performance metrics and a greater likelihood of statistical overfitting. Therefore, in the present study, we aimed to meta-analyze and systematically review studies that used machine learning techniques to predict treatment response in MDD.

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