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A Review on Classification of Major Depressive Disorder from Brain fMRI Data using Machine Learning Techniques

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A B S T R A C T

Major Depressive Disorder is one of the leading causes of disability worldwide. Impacting individuals across diverse age groups with far-reaching social, economic, and health-related implications. Clinicians confront substantial challenges in accurately diagnosing and promptly treating depression. Consequently, the emergence of various machine learning approaches seeks to classify this disorder utilizing brain fMRI data. This survey paper aims to achieve three primary objectives: (1) to present a comprehensive background on Major Depressive Disorder, brain fMRI scans, and the classification of depression using machine learning methodologies; (2) to delve into the methodologies employed in prior studies that leverage imaging and machine learning to explore depression; and (3) to formulate proposals for future depression-related studies.

Keywords: Major Depressive Disorder, Diagnosis, Machine Learning, Brain fMRI Data, Classification, Imaging

1. Introduction

Depressive disorder, commonly referred to as depression, constitutes a prevalent mental health condition characterized by persistent feelings of a depressed mood, along with a notable loss of pleasure or interest in activities endured for prolonged periods. The global impact of depression is substantial, affecting an estimated 5% of adults worldwide. A comprehensive breakdown reveals that 3.8% of the global population, comprising 5% of adults (with a gender-specific distribution of 4% among men and 6% among women), and 5.7% of adults aged 60 years and older experience depression.[1] The Global Burden of Diseases, Injuries, and Risk Factors Study 2016 identified it as a major contributor, causing 34.1 million years lived with disability (YLDs) and ranking as the fifth largest cause of YLD.[2]

The diagnosis of Major Depressive Disorder (MDD) relies on criteria provided by the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM).[3] Within clinical settings, the evaluation of depression often employs the Hamilton Rating Scale for Depression (HAM- D), a clinician administered tool meticulously crafted to assess the severity of depressive symptoms.[4] The original HAM-D uses 21 items about symptoms of depression, but the scoring is based only on the first 17 items.[5] In primary care settings, the Patient Health Questionnaire-9 (PHQ-9) serves as a valuable self-report, standardized rating scale for depression. The PHQ-9 uses 9 items corresponding to the DSM-5 criteria for MDD and also assesses for psychosocial impairment. The PHQ-9 scores 0 to 27, with scores of equal to or more than 10, indicate a possible diagnosis of MDD.[6]

While these diagnostic tools are essential for assessing MDD across healthcare settings, they emphasize the complexity in accurately characterizing this mental health condition.

In a global context, medical institutions and training institutes prioritize teaching dominant classification systems like the DSM and ICD, which primarily reflect Western illness presentations.[7] The inconsistency in defining MDD is apparent, with common rating scales covering over 50 diverse depressive symptoms, exhibiting limited content overlap with DSM-5 MDD criteria. Moreover, MDD itself is marked by high heterogeneity, where two patients with a DSM-5 diagnosis may share no symptoms.[8] Additionally, the notion that a single sum-score can adequately proxy for the severity of depression contradicts decades of psychometric literature, emphasizing that depression rating scales are not unidimensional.[9] These diagnostic challenges further manifest in the absence of treatment specificity, a lack of clear clinical presentation, imprecise diagnostic boundaries, high comorbidity rates, and very low interrater reliability associated with MDD diagnosis.[8] Addressing these complex challenges is crucial for advancing our understanding and developing effective classification strategies for mental health disorders.

Functional Magnetic Resonance Imaging (fMRI) stands out as a powerful tool for delving into the pathophysiology of MDD.[10] Unlike traditional diagnostic methods which rely on subjective reports, fMRI unveils objective patterns of brain activity associated with MDD, potentially paving the way for a more precise and nuanced understanding of the disorder. As a class of imaging methods designed to showcase regional, time-varying changes in brain metabolism [11], fMRI provides a non-invasive means to measure brain activity in vivo during both resting and task-related states.[12] Blood oxygenation level-dependent (BOLD) fMRI, commonly applied in these studies, discerns brain activation by monitoring heightened oxygen consumption, resulting in an elevation of BOLD signals. The distinctive activation patterns produced by patients during rest and task-related activities contribute valuable insights into the neural signatures of MDD. [13]

Identifying biomarkers with fMRI is crucial for diagnosing MDD, providing unique neurobiological insights that improve diagnostic accuracy and deepen our understanding of the disorder's underlying neural mechanisms. A biomarker is defined as an objectively measurable image feature serving as indicators of MDD diagnosis.[14] Various brain regions have been scrutinized as potential key biomarkers associated with MDD using fMRI. Among these, the amygdala exhibits heightened reactivity to negative stimuli, a consistent observation in MDD studies.[15], [16], [17] Conversely, the orbitofrontal cortex (OFC) demonstrates dampened responses to negative emotions, with the exception of disgust, underscoring the intricate nature of depression's emotional circuitry.[15] Alterations in the activation patterns of the ventral-rostral/sgACC and dorsal ACC during emotive processing have been observed. In the basal ganglia and thalamus, MDD patients tend to display increased activation in response to negative stimuli and decreased activation to positive stimuli compared to their healthy counterparts.[17] These findings exhibit the potential of fMRI to unveil neurobiological markers associated with MDD, paving the way for more precise diagnostics.

The utilization of machine learning in the diagnosis of Major Depressive Disorder holds immense potential for advancing the field of computational psychiatry. Machine learning, recognized for its proficiency in deciphering intricate patterns from expansive datasets, plays an instrumental role in analyzing the complexities of neuroimaging and biomarker data associated with MDD. The primary goal of ML in this context is to develop classification models for accurate assessments of new data, allowing a deep exploration of the relationship between observed brain changes and depression symptoms. The classification of MDD studies has unfolded along two predominant streams: traditional machine learning methodologies and deep learning techniques. This survey paper aims to consolidate and evaluate various methodologies to offer a comprehensive insight into how machine learning enhances early diagnosis and intervention strategies for Major Depressive Disorder.

2. Past Studies

The compilation of studies investigating the classification of major depressive disorder based on resting state fMRI through machine learning techniques provides a comprehensive overview of methodologies and findings. (Table 1) This review highlights features derived from resting-state data, notably functional connectivity and graph theory.

Table 1 - Past Studies Observations

AUTHOR	PATIENT SAMPLE	CROSS-VALIDATION METHOD	MACHINE LEARNING METHOD	ACCURACY
Zhu et al. (2023) [18]	830 MDD, 771 HC	10-fold CV	DGCNN	72.10%
Zhongwan Liu et al. (2022) [19]	41 MDD, 20 HC	5000 iterations bootstrap	DNN	53%
hi et al. (2021) [20]	1021 MDD, 1100 HC	10-fold CV	XGBoost	72.80%
Baoyu Yan et al. (2020) [21]	43 MDD, 56 HC	10-fold CV	SVM	95.96%
Chun et al. (2020) [22]	262 MDD, 277 HC	10-fold CV	SVM	SVM: 60.63%
			RF	RF: 58.58%
			XGBoost	XGBoost: 60.62%
			CNN	CNN: 70.98%
Sen et al. (2020) [23]	49 MDD, 33 HC	LOOCV	SVM	82%
Bhaumik et al. (2017) [24]	38 MDD, 29 HC	LOOCV	SVM	76.1%
Sundermann et al. (2017) [25]	180 MDD, 180 HC	10-fold CV	SVM	45.0%~56.1%
Wang et al. (2017) [26]	MDD = 31, HC = 29	LOOCV	SVM	95%
Zhong et al (2017) [27]	1st : 29 MDD, 33 HC;	LOOCV	SVM	91.9%,
	2nd : 46 MDD,57 HC			86.4%
Drysdale et al. (2016) [28]	333 MDD, 378 HC	LOOCV	SVM	89.20%

Ramasubbu et al. (2016) [29]	45 MDD, 19 HC	5-fold CV	SVM	Mild-moderate MDD: 5 Severe MDD: 52% Very severe MDD: 66%

3. Discussions

3.1 SAMPLE SIZE

The observed sample sizes across the surveyed studies demonstrate a wide range of participant numbers, emphasizing the challenges inherent in assembling comprehensive datasets for MDD classification using fMRI data. Studies such as Baoyu Yan et al. (2020) and Shi et al. (2021) featured large cohorts, each comprising over a thousand participants, while others, like Zhongwan Liu et al. (2022), reported smaller sample sizes with fewer than a hundred subjects in total. Larger sample sizes, as seen in Baoyu Yan et al. (2020) and Shi et al. (2021), offer the potential to enhance the generalizability and robustness of findings by providing more representative population coverage and statistical power. Conversely, studies with smaller sample sizes, exemplified by Zhongwan Liu et al. (2022), may offer more nuanced insights but may also be prone to increased variability and reduced statistical power, necessitating careful interpretation of results.

3.2 FEATURES

Features used by past studies are focused on functional connectivity and graph theory which are derived from the resting state fMRI.Functional connectivity analysis explores temporal correlations between brain regions, revealing disrupted communication patterns associated with MDD. Graph theory quantifies network properties, highlighting structural and functional abnormalities in MDD. Leveraging these features, machine learning models effectively distinguish between MDD patients and healthy controls, aiding in diagnostic and treatment advancements.

3.3 CROSS VALIDATION

Cross-validation is crucial for assessing the performance and generalization capability of machine learning models. The surveyed studies employed various cross-validation techniques, including k-fold cross-validation, leave-one-out cross-validation (LOOCV), and bootstrap resampling. Studies like Sen et al. (2021) opted for LOOCV, a method that iteratively trains the model on all but one sample, using the left-out sample for validation. This technique is particularly useful for small datasets, as it maximizes the use of available data for both training and validation.

On the other hand, studies like Chun et al. (2020) utilized k-fold cross-validation, where the dataset is divided into k subsets, with each subset serving as the validation set while the remaining data are used for training. This method provides a balance between computational efficiency and robustness in estimating model performance. Additionally, bootstrap resampling, as employed by Zhongwan Liu et al. (2022), involves repeatedly sampling from the dataset with replacement to generate multiple bootstrap samples. Each bootstrap sample is then used for model training and validation, allowing for the estimation of variability in model performance. This technique is particularly useful for assessing the stability and reliability of the classification model. Overall, the choice of cross-validation technique should be guided by factors such as dataset size, computational resources, and the desired balance between bias and variance in model estimation.

3.4 MACHINE LEARNING METHODS

The selection of machine learning algorithms varied across the surveyed studies, reflecting the diversity of approaches in MDD classification using fMRI data. Support Vector Machine (SVM) emerged as a popular choice due to its ability to handle high-dimensional data and nonlinear relationships effectively. Several studies, including Sen et al. (2021), Baoyu Yan et al. (2020), and Bhaumik et al. (2017), leveraged SVM for its robust performance in distinguishing between MDD patients and healthy controls. Deep Neural Networks (DNNs) have garnered attention for their capability to automatically learn hierarchical representations from raw fMRI data. Zhongwan Liu et al. (2022) exemplified this trend by employing DNNs, which can capture intricate patterns and complex relationships within the data, potentially enhancing the discriminative power of the classification model.

Ensemble methods such as Random Forest (RF) and XGBoost have also gained popularity for their ability to combine multiple weak learners to improve classification performance. Chun et al. (2020) demonstrated the effectiveness of ensemble techniques by integrating SVM, RF, XGBoost, and even Convolutional Neural Networks (CNN) in their classification pipeline. By leveraging the strengths of different algorithms, ensemble methods can mitigate the limitations of individual classifiers, leading to enhanced generalization and robustness against overfitting. The selection of the machine learning method should consider various factors, including data complexity, interpretability, and computational resources available. While SVM offers simplicity and interpretability, deep learning methods like DNNs excel at automatically learning intricate patterns but require substantial computational resources and expertise in hyperparameter tuning. Ensemble methods strike a balance between simplicity and complexity, offering improved performance without sacrificing interpretability.

4. Challenges and Future Directions

4.1 SMALL SAMPLE SIZE

A common challenge in previous studies is the small sample size, which falls short of what's optimal for ma- chine learning methods to improve accuracy, sensitivity, and specificity, especially in predicting depression treatment responses. Recruiting enough patients for such studies is tough, leading to understandable limitations. However, variations in imaging parameters among contributing sites may introduce biases.[14] As we move forward, standardizing acquisition and processing methods in neuroimaging research will enhance data pooling. Furthermore, the training of deep learning networks typically necessitates an extensive collection of annotated data.

However, acquiring such data in medical imaging poses significant challenges, as it is often costly and subject to strict privacy regulations, making it difficult to obtain. A scarcity of data can lead to overfitting issues, where the algorithm becomes entrenched in local minimum values, resulting in suboptimal classification performance. To address this challenge, transfer learning offers a viable solution. In transfer learning, the network's initial weights are not randomly assigned but rather transferred from a pre-trained network that has been fine-tuned on a more extensive dataset[30]. This approach leverages the knowledge encoded in the pre-trained network to enhance the performance of the model on the limited dataset at hand. [31]

4.2 FEATURE REDUCTION

Training classifiers on fMRI data poses a significant challenge due to the high-dimensional nature of the data. fMRI data consists of a multitude of voxels (3D pixels), resulting in a large number of potential features for each subject. However, this abundance of features leads to high computational complexity and prolonged processing times, making it impractical for real-world applications. Moreover, the sheer volume of features can contribute to overfitting issues and complicates the interpretation of results, adding further complexity to the task of analyzing fMRI data for detecting MDD. Furthermore, in the classification of brain disorders, such as Major Depressive Disorder, utilizing functional connectivity data may introduce redundant information. Employing all connections as features without addressing this redundancy could undermine classification accuracy. Therefore, integrating effective feature reduction strategies becomes crucial for identifying pertinent functional connectivity features.

4.3 VARIATION IN BIOMARKERS

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4.4 CLINICAL APPLICATIONS

Focusing on the classification of MDD using fMRI scans stems from the need for advancements in mental health diagnostics. Our idea for the application involves utilizing the patient's fMRI scan as input to our model, which then provides insights on whether the patient likely has MDD. Additionally, based on the model's output, appropriate medications can be prescribed, and doctors can provide their valuable input to finalize the treatment approach. In a clinical setting, this application serves as a valuable asset for early detection, personalized treatment planning, and advancing research in neuroscience. [34] The utilization of fMRI-based classification of MDD in healthcare systems presents a significant opportunity to revolutionize mental health diagnostics. As advancements in machine learning continue to unfold, the implications for psychiatry as a whole are substantial. Therefore, the integration of fMRI-based classification methods into clinical practice holds immense promise for the future of mental health diagnostics and treatment.

5. Conclusion

The reviewed studies illuminate the complexities of classifying Major Depressive Disorder using functional Magnetic Resonance Imaging (fMRI) data. Variation in sample sizes, cross-validation techniques, and machine learning methods reflects the diverse landscape of this research field. While larger samples offer statistical robustness, smaller cohorts provide focused insights. The choice of cross-validation methods is crucial for balancing computational efficiency and validation rigor. Furthermore, the array of machine learning algorithms, from traditional SVM to advanced DNN, demonstrates the versatility in approach. Moving forward, interdisciplinary collaboration and methodological refinement are vital for advancing MDD classification with fMRI data. Such efforts hold promise for developing more accurate diagnostic and prognostic tools, ultimately improving our understanding and management of MDD. As research evolves, maintaining methodological robustness and embracing diverse perspectives will be crucial for unlocking the full potential of fMRI-based classification in MDD diagnosis and treatment.

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