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Biomedical informatics: AI models for predicting treatment response in Major Depressive Disorder using neuroimaging and genetic data

Kimberly Morton Cuthrell
American University of Anguilla, School of Medicine United States, Anguilla
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Abstract
Major Depressive Disorder (MDD) is a psychiatric disorder diagnosed globally and is a contributor of disability due to its complex nature and varied treatment response. Current complexities to treating MDD (e.g., pharmacological or psychotherapy) encompass delayed or ineffective treatments, resulting in the development of treatment-resistant MDD. Advancements in Emerging Technologies (e.g., neuroimaging, genomic research, and artificial intelligence) enhance treatment approaches of MDD through predictive modeling to optimize treatments. Neuroimaging and genetic-based biomarkers combined with AI-driven biomedical analytical frameworks are promising predictive treatment responses to optimize psychiatry. Neuroimaging tools such as fMRI, PET and EEG may pinpoint depression pathology and neurobiological components as well as structural-and functionally-related deficits across different brain systems (e.g., prefrontal, amygdala, and hippocampus). Genetic variants and data have the propensity to identify polygenic risk factors, pharmacogenomic markers, and epigenetic mechanisms that underlie the unique susceptibility for MDD, including the possibility of distinguishing psychosis from depression by analyzing early structural brain changes with neuroimaging. While integrating biomarkers with AI machine learning and deep learning techniques produce multimodal data from neuroimaging, genetics, and clinical assessments, there remain obstacles with limited datasets, interpretability, privacy of information, and algorithm bias. Translating AI-based predictive models into clinical work ultimately may yield grounded treatment effectiveness, reduce treatment trial-and-error, and revolutionize biological, neurological, and psychological biometrics to forecast treatment responses and ameliorate MDD.

Keywords: Major Depressive disorder, neuroimaging, Artificial Intelligence, genetic data, biometrics, neuropsychiatry

Introduction

Data-driven biometrics aimed at predicting early risk-factors of Major Depressive Disorder (MDD) exemplify future possibilities of neuroimaging combined with AI predictive models to forecast treatment preventions, interventions, and outcomes. Incorporating a patient-focused care (patient-centered care) approach with biomarkers is paramount to fully understand the biological, neurological, and psychological manifestation of MDD, including other psychiatric conditions. MDD is a debilitating psychiatric disorder that affects millions of individuals globally, making MDD one of the most common causes of disability internationally [1]. MDD consists of an multitude of clinical symptomologies involving sadness, declined self-worth, reduced quality of life, fluctuated appetite, lack of interest to engage in activities, and other mental and emotional factors. Among many clinical factors associated with MDD, suicidal ideation presents great concerns making suicide prevention and MDD treatment approaches top priorities for global awareness to prevent formation of a world-wide health crisis. According to the World Health Organization (WHO), over 264 million people are affected and the world has a high degradation to the society [2]. Although MDD is among the most prevalent disorders and it has become a significant burden for individuals trying to manage their condition and on the health care systems, the diagnosis and treatment have been a complicated issue [3].

Overview of Major Depressive Disorder (MDD)

MDD requires clinical an evaluation and analysis of signs and symptoms experienced by an individual that must align with the MDD criteria, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [4]. Although MDD symptoms may vary with severity, including the frequency of depressive episodes may fluctuate, the causes of MDD has no single origin though it highly associated with hereditary, neurobiological stressors, environmental stressors, or a broad scope of unknown sources. The heterogeneity of the disorder in which the symptoms and the severity of the disorder can vary greatly in individuals complicates the effective diagnosis and treatment of the disorder [5]. The current approaches and management of MDD consists of pharmacological (e.g., selective serotonin reuptake inhibitors [SSRI], serotonin-norepinephrine reuptake inhibitors [SNRIs]), lifestyle healthy choices, self-care practices, and psychotherapeutic (e.g., Cognitive Behavioral Therapy [CBT], behavioral therapy, etc.). There are individuals who fail to respond to such traditional therapies, in which it is termed as treatment-resistant depression (TRD) which is approximately 30-40% [6]. The process of undergoing treatment trial and error (the time experienced until the right treatment is found) can be limited by the time-consuming delays which can bring about discomfort for individuals with diagnosed with MDD. The rate of high treatment failure pressures the urgency for to have more precise and customized treatment plans that are better at determining which treatment would be effective with a given patient [7]. One of the prevailing concerns with MDD treatment responses is that some individuals usually react differently to similar treatment plan which supports the need for individualized treatment. Non-compliance with treatment recommendations or delayed treatment responses

contribute to prolonged uncertainty of treatment possibilities, longer trial-and-error processes, exacerbated MDD progression, and higher expenses related to treatment approaches, including possibly increased cost for short or long duration of stay in a psychiatric inpatient hospital. Furthermore, prolonged treatment responses may enhance the chances of advanced depression level (mild, moderate, severe with or without psychotic features) which increase the likelihood of suicide ideation or attempt, functional disability, internal stressors, and impaired social determinants.

Individualized treatment is essential to align individuals to the best intervention strategies in terms of their peculiar features, including the biological processes that could have led to their depression [8-10]. Personalized medicine is currently evolving by predicting a response to the treatment with consideration of trial-and-error. Individualized treatment plans also consider personal factors concerning the individual, including genetic composition, brain functioning, and reactions to medications given currently and in the past. Individualized treatment plans also help prevent senseless treatment, minimize the trial-and-error approach, and offer more specific interventions by predicting the response of a particular patient to a specific treatment in the most accurate possible way that not only enhance patient outcomes but also reduces the emotional as well as the financial cost of ineffective treatments [11-13].

Predicting the response to treatment prior to initiating a regimen may strategically lower healthcare expenditures with treating MDD. Early prediction can result in effective utilization of healthcare resources by averting treatment failure and the costs of side effects management or medication, while transforming the quality of life of individuals as it would provide more efficiency and faster treatment [14, 16].

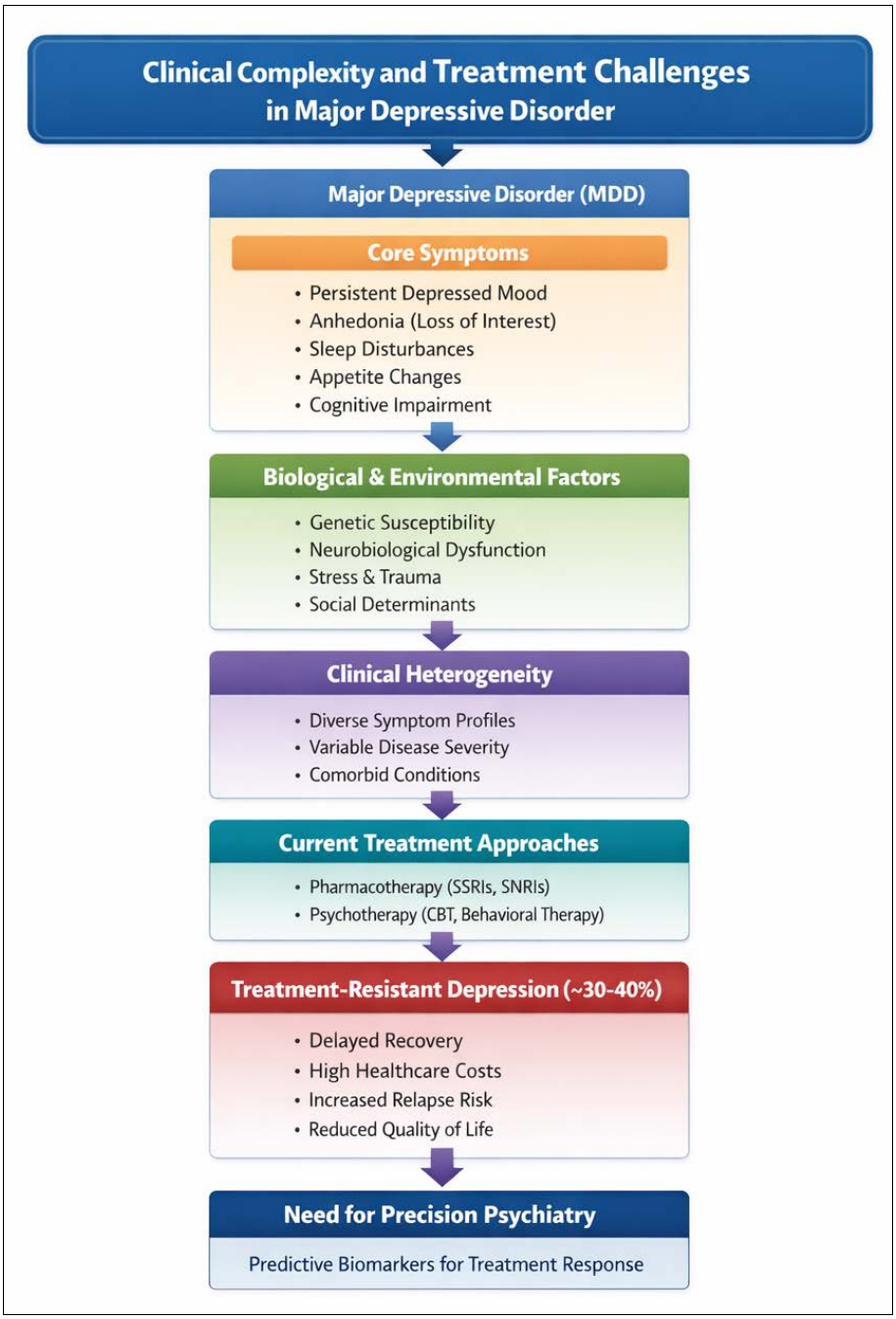

Fig 1: Clinical complexity and treatment challenges in Major Depressive Disorder (MDD)

Role of Artificial Intellignce (Ai) Models in Psychiatry

Artificial Intelligence (AI) has demonstrated tremendous potential in transforming the healthcare sector, especially in the psychiatry sector. Machine learning (ML), deep learning (DL), and neural networks are AI methods that provide an effective resource to analyze complex, high-dimensional data that otherwise would be challenging to analyze. The application of AI usage with MDD is the process of combining several forms of data, including neuroimaging (brain scans) and genetic data with the goal of determining how an individual may react to various treatments [17, 18].

The integration of AI to examine and analyze extensive datasets of neuroimaging (including fMRI, PET scans, EEG) and genetic studies are beneficial methods to identify biomarkers that are predictive of MDD and treatment responses. Neuroimaging attributes to information about the structure and functioning of the brain, revealing abnormalities in certain parts of the brain such as the prefrontal cortex, amygdala, and hippocampus [19]. Likewise, genetic information, including single variation or polygenic risk score, offers an insight into the genetic vulnerability of an individual diagnosed with MDD. The combination of neuroimaging and genetic datasets with AI models not only identify underlying biological processes of MDD but also may predict what types of treatments may have the highest likelihood of being most effective. Advanced generalized treatment regimens to pinpoint individualized care has a potential to enhance the accuracy and the effects of MDD therapy [20]. The possibilities of predicting treatment with the help of AI models based on a set of neuroimaging (fMRI, PET, and EEG) and genetic data is likely to identify depression biomarker patterns and how to utilize predictive treatment outcome.

Future personalized medicine designed to treat MDD by incorporating data, namely neuroimaging and genetics informatics, may expand treatment options and simplify the complex pattern analysis capabilities of AI. Extrapolated data may contribute to insight into the narrowing obstacles, enhance recent developments, and revolutionize AI models in precision psychiatry as well as generate a new horizon on enhancing the diagnosis, treatment, and management of the MDD. Despite advancements in neuroimaging and genomics, the combination of different types of data from both areas with AI models for determining how individuals with MDD will respond to a particular treatment is still limited due to some studies may analyze either neuroimaging or genetic factors instead of a combined viewpoint to maximize diagnosing and treatment possibilities . Limitations in diagnosing, treatment, and management of MDD has prevented the full understanding of characterizing the multitude of biological reasons of MDD and the different responses to treatment. Therefore, a comprehensive synthesis of AI-based prediction models that combine neuroimaging and genetic data is essential to achieve optimal treatment stratification and effectiveness. .

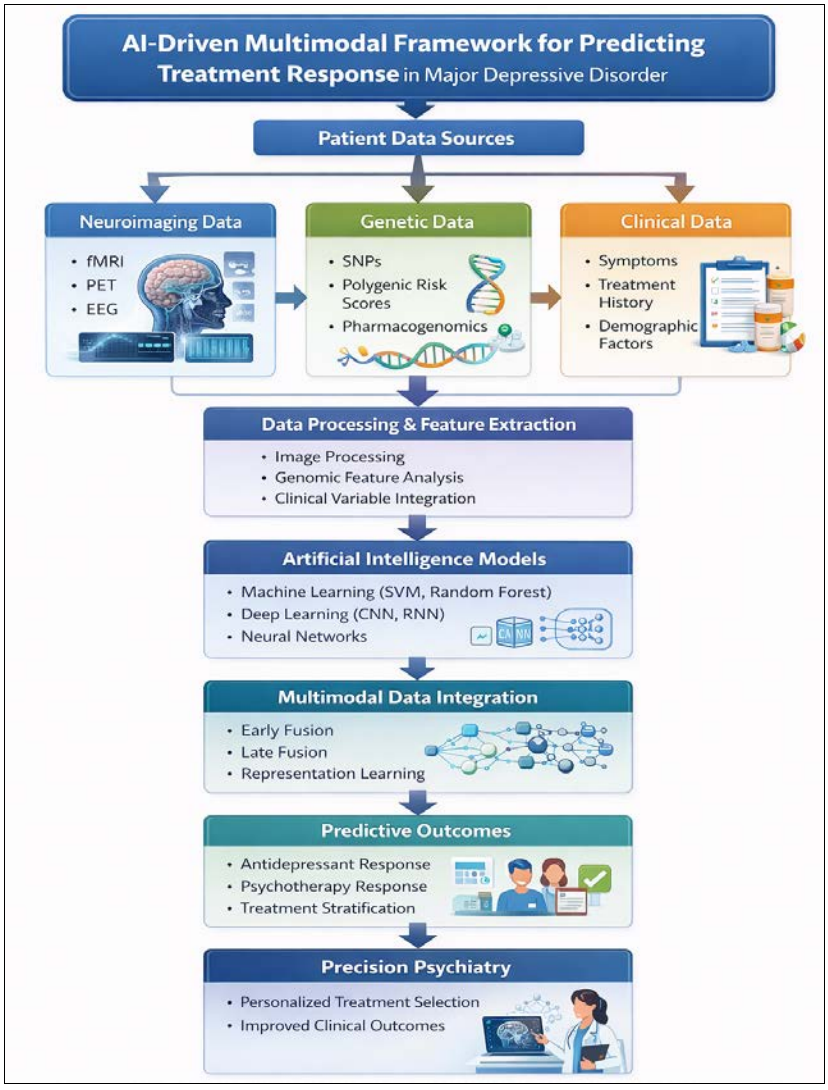

Fig 2: AI-driven multimodal framework for predicting treatment response in Major Depressive Disorder (MDD)

Neuroimaging in MDD

Neuroimaging is now a critical instrument in the study of neurobiological basis of Major Depressive Disorder [21]. Neuroimaging methods is used to describe abnormalities in brain structure, functions, and activity, which makes it possible to detect such abnormalities in the brain and determine whether they are the cause and the maintenance of the state of depression [22]. Neuroimaging methods allow visualizing the brain areas that are engaged in the regulation of emotions, response to stress, and cognitive processes, areas that tend to be activated in MDD. Neuroimaging is instrumental in the way the brain reacts to different treatments and as such, it is a major contributor to the ability to predict the outcome of patients who undergo different treatments [23].

1. The Sections of the Brain Involved In MDD.

Pathophysiology of MDD is related to the operation of a number of brain areas, especially those related to emotion processing, memory, and cognitive control. Neuroimaging is beneficial to understand the functionality and interaction of parts of the brain in depressive persons [24].

Prefrontal Cortex (PFC): The PFC controls executive functions, impulse control, and emotional control, while the lowered activities of the dorsolateral prefrontal cortex (DLPFC) are frequently seen in MDD patients which is believed that this hypoactivity in the PFC is one of the causes of the difficulties in the regulation of negative emotions, as well as in cognitive processes such as concentration and decision-making, resulting in the impairment of the PFC that may lead to rumination and negative thought processes that are typical of MDD [25].

Amygdala: The amygdala is a major component that takes part in the processing of emotions particularly fear and anxiety. The amygdala may possibly become hyperactive in individuals with MDD, especially when negative emotional stimuli are used whereby the hyperactivity could be one of the factors that increase the emotional reactivity and the inability of negative feelings management that characterize MDD. The prefrontal cortex may also fail to regulate the emotions and this is further worsened by the overactivation of the amygdala, which also contributes to the emotional dysregulation in depression [26].

Hippocampus: Hippocampus is important in memory consolidation, stress regulation, and emotions processing. The hippocampal volume and activity have been found to be reduced in MDD and this atrophy has been attributed to chronic stress exposure and the long-term release of cortisol in which this contraction of the hippocampus is believed to increase the brain inability to control emotions and memory, results in problems in coping with stress and increases the risk of experiencing depressive episodes [27].

Table 1: Major Brain Regions Involved in Major Depressive Disorder

Brain Region	Primary Function	Neurobiological Changes in MDD	Clinical Implications
Prefrontal Cortex (PFC)	Executive function, decision making, emotional regulation	Reduced activity in dorsolateral PFC and impaired connectivity with limbic structures	Difficulty regulating emotions, impaired concentration, increased rumination
Amygdala	Emotional processing, fear response, threat detection	Hyperactivity in response to negative emotional stimuli	Heightened emotional reactivity, negative emotional bias
Hippocampus	Memory formation, stress regulation	Reduced hippocampal volume and impaired neurogenesis due to chronic stress	Memory impairment, increased vulnerability to depressive episodes
Anterior Cingulate Cortex (ACC)	Emotional regulation, cognitive control, error monitoring	Altered functional connectivity with PFC and limbic regions	Poor emotional regulation and impaired decision-making
Insula	Interception, emotional awareness, salience detection	Abnormal activation patterns and connectivity changes	Altered perception of emotional and bodily states
Basal Ganglia	Reward processing, motivation, motor control	Reduced activity in reward-related circuits	Anhedonia and decreased motivation

PFC, amygdala, and hippocampus are the brain areas that are interrelated, creating a network, which affects the mood control, emotional processing, and cognitive control. The changes may affect the connections and functionality of these areas by MDD through the symptoms of the condition which include emotional dysregulation, cognitive deficits as well as the negative pervasively of thoughts that characterize depression [28].

2. Neuroimaging Techniques MDD Research

Complex neuroimaging methods are used in the research of the brain structure and functioning of people with MDD, and these methods give distinct information on the mechanisms in the brain that give rise to depression [29].

Functional MRI (fMMRI): fMMRI is a popular technique used to determine how the brain works that involves the measurement of blood flow which is an indication of neuronal activity. In particular, resting-state fMRI provides opportunities to study the connection of the brain and determine patterns of activity that can be impaired in MDD [30]. Altered connection within the default mode network (DMN) or a network that is involved in self-referential thoughts and rumination is an important findings of resting-state fMRI studies of depression. Network disorder in the PFC-amygdala connectivity and DMN connectivity has been reported among the MDD patients and such alterations are believed to be associated with negative emotional biases and cognitive impairments commonly experienced during depression [31].

Positron Emission Tomography (PET): PET scans provides data regarding neurochemical activity of the brain by tracing the association of radiolabeled substances with receptors or proteins. PET imaging has been used in investigating serotonin and dopamine systems which form the core of mood regulation. PET usage in MDD studies have depicted changes in serotonin receptor binding and dopamine transporter activity which could assist in explaining the mood disturbances in depression, and these neurochemical biomarkers have the potential of becoming biomarkers to predict treatment response of antidepressant drugs [32].

Electroencephalography (EEG): EEG is the electrical activity of the brain measures using electrodes that are placed on an individual's head. EEG can be applied to analyze brain wave patterns, which are linked with various types of cognition and emotion. Abnormal EEG activity has been noted in MDD, including high levels of slow-wave activity (e.g., in theta waves) and low levels of fast-wave activity (e.g., in alpha waves), especially at rest, or in reaction to negative emotional provocations, and these brain wave activity alterations might indicate dysregulation in the neural activity related to depression and may be applicable in determining the response to treatment [33].

3. Biomarkers of Depression Using Neuroimaging

Neuroimaging biomarkers are defined as certain brain features or patterns that may be quantified to offer objective depression and response to depression treatment. The biomarkers are essential in the development of individualized treatment of MDD since they may be helpful in providing information on treatments that are likely to be effective among individual patients [34].

Resting-State Connectivity: Resting-state fMRI has revealed that there are a few patterns of connectivity which are disrupted in individuals diagnosed with MDD such as losing connectivity between the prefrontal cortex and the amygdala that is linked to uncontrolled emotions and negative emotional prejudice, whereas abnormal DMN connectivity is associated with rumination, self-referential thought, in depression in which such connectivity anomalies can be used as depression biomarkers, and could be utilized in anticipating the type of treatments beneficial in restoring normal brain functions [30]. PET imaging allows an opportunity to examine neurotransmitter systems of the brain, and this enables the possibility of learning vital information about neurochemical changes involved in depression. The low levels of serotonin receptors and the distorted activity of dopamine transporters is typical of patients with MDD. Not only can these neurochemical markers be useful in the underlying biology of depression but also in predicting which patients are likely to respond to particular pharmacological therapy [30].

4. Neuroimaging and Forecasting Treatment Response

Among the most encouraging applications of neuroimaging in the MDD is the possibility of determining the patient who is likely to respond to certain therapy. Tailored treatment plans and preventive trial-and-error method of finding an effective treatment approach are beneficial to determine brain activity patterns or neurochemical indicators of treatment response that may result in a delay to effective care [35, 36].

Forecasting Response to Antidepressants: fMRI and PET scans are useful to identify biomarkers that can predict an individual's response to antidepressant drugs, e.g. SSRIs or SNRI. The closer the relationship between the prefrontal cortex and amygdala or certain neurochemical patterns, may reveal the likely that pharmacological interventions may be helpful, while individuals with lower hippocampal volumes may react to more psychotherapy or other forms of non-pharmacological intervention [36, 37].

Response to Psychotherapy: Neuroimaging has the capability to predict how likely an individual may respond to psychotherapies, including cognitive-behavioral therapy (CBT). Individual patients with specific patterns of brain connectivity, especially those in the prefrontal cortex can respond better to CBT, and results of a study indicate that neuroimaging can be utilized to determine the best therapeutic interventions depending on the activity pattern of the brain [38].

Genetic Factors in MDD

Genetics have a significant contribution to the MDD) which is in a distributed, probabilistic manner, not by having a single, so-called depression gene. Twin and family designs imply that there is a heritable factor but the majority of the correlation is due to many effective DNA variants (single-nucleotide polymorphisms, SNP), with each impact being very small, with consideration of polygenic architecture that causes genome-wide association studies (GWAS) to discover many loci and why genetic risk is thought of as a continuum [38, 39]. The polygenic risk score (PRS) is a practical summary of polygenic liability, effectively a summary of thousands of SNP effects into one statistic. PRS has the ability to stratify vulnerability at the population level, and in studies, it can be identified as being associated with intermediary phenotypes, including stress sensitivity, disrupted reward learning, sleep disturbance or inflammation-related biology. PRS is not diagnostic by itself and is sporadically reliably used to predictive factors in individuals, as the context and environment of development are powerful determinants of clinical manifestation, and the focus of MDD is on gene environment interaction inherited vulnerability can be enhanced or compensated by adversity, chronic stress, and social determinants [40, 41].

Risk factors of MDD is vast, and predisposition of genetics is associated with a multitude of possible treatment response. Changes in monoaminergic (serotonin and dopamine pathways) and neurotrophic (e.g., BDNF) signaling, circadian regulation and hypothalamic pituitary adrenal (HPA) axis genes are possible predictors of antidepressant response, adverse effect, or relapse. Simultaneously, drug metabolism pharmacogenomic variation (particularly, CYP450 enzymes CYP2D6 and CYP2C19) can influence drug exposure, tolerability, and dose requirements, which is important when a nominal prescription results in extremely different blood levels in patients [42, 43].

Single variants may pose challenges with accounting for much variance in outcome, varying with current times, pathway-level signals, and polygenic predictors of response, rather than risk, are being prioritized. Stratification of single variants may be enhanced through the combination of PRS and pharmacokinetic genes and clinical moderators an observations. Observations may encourage the inclusion to neuroimaging endophenotypes, in which genetic influences can be more commonly observed [44].

Table 2: Genetic and Epigenetic Factors Associated with Major Depressive Disorder

Genetic Factor	Key Genes / Markers	Biological Function	Evidence in MDD	Clinical Implications
Polygenic Risk Scores (PRS)	Multiple SNPs across genome	Aggregate genetic susceptibility to depression	GWAS studies show cumulative genetic variants increase MDD risk	Risk stratification and prediction of disease vulnerability
Serotonin Transporter Gene	SLC6A4 (5-HTTLPR polymorphism)	Regulates serotonin reuptake in synaptic transmission	Variants associated with stress sensitivity and antidepressant response variability	May influence SSRI treatment response
Brain-Derived Neurotrophic Factor	BDNF (Val66Met polymorphism)	Neuroplasticity, neuronal survival, synaptic plasticity	Altered BDNF expression linked to depression severity and treatment outcomes	Potential biomarker for antidepressant response
Dopamine System Genes	DRD2, DRD4, COMT	Dopamine signaling and reward processing	Variants associated with anhedonia and motivational deficits	May influence response to dopaminergic antidepressants
Stress Response Genes	FKBP5, NR3C1	Regulation of hypothalamic–pituitary–adrenal (HPA) axis	Genetic variants linked to stress reactivity and trauma-related depression	Important for understanding stress-related depression
Pharmacogenomic Genes	CYP2D6, CYP2C19	Drug metabolism enzymes	Variability affects antidepressant metabolism and plasma drug levels	Used in personalized antidepressant dosing
Circadian Rhythm Genes	CLOCK, PER2	Regulation of circadian rhythm and sleep cycles	Dysregulation associated with sleep disturbance and mood disorders	May influence response to chronotherapy
Epigenetic Modifications	DNA methylation, histone modification	Regulation of gene expression without DNA sequence changes	Stress and environmental factors alter gene expression in depression	Potential dynamic biomarkers for treatment monitoring
Inflammation-Related Genes	IL-6, TNF-α	Immune system regulation and inflammatory response	Increased inflammatory markers observed in MDD patients	May guide anti-inflammatory treatment approaches

Another layer of mechanistic explanation is epigenetics in that experience can modify gene regulation without modifying the DNA sequence in the context of MDD. Transcriptional processes may be altered in response to early adversity, persistent stress, inflammation, loss of sleep, and substance use by DNA methylation, histone modifications, and regulatory non-coding RNAs. Epigenetic variations linked to MDD may encompass glucocorticoid signaling, immune signaling, and synaptic plasticity and certain marks that vary in response to symptomatic recovery, treatment experience, or relapse, and thus are likely dynamic biomarkers but not fixed risk factors. Genomic datasets may have limitation of ancestry imbalance that limits generalizability, as well as tissue specificity, which is difficult due to the potential lack of biological reflection on the blood-based measures of the brain in which genetics is, therefore, most effective as a single layer of multi-modal models incorporating genomic properties with neuroimaging, clinical variables, and longitudinal course information [45-47].

Ai in Psychiatry: Methods and Approaches

Artificial intelligence (AI) is a collection of computational techniques that develop patterns based on data to assist in the process of diagnosing, predicting, and prognosticating response to treatment [48]. Neuropsychiatry integrated with AI is a promising approach to detect MDD and to analyze neurons involved in MDD. AI is especially appropriate to psychiatry since clinical phenotypes (including MDD) are heterogeneous and due to multiple interacting biological and psychosocial factors. The high-dimensional neuroimaging and genetic/omic data include subtle signals that are challenging to understand by the traditional statistics. AI provides a structure to recover multivariate signatures which may represent distributed brain-network modification and polygenic effects and possibly allow more personalized choice of therapy (e.g., medication vs psychotherapy vs neuromodulation) [49].

Artificial Intelligence (AI) has tremendous potential in transforming healthcare, especially in the psychiatry sector. Machine learning (ML), deep learning (DL), and neural networks are AI methods that provide an effective resource to analyze complex data. The application of AI to MDD allows combining several forms of data, including neuroimaging (brain scans) and genetic data, with the goal of determining reaction to various treatments [50]. The capacity of AI to examine and analyze extensive datasets of neuroimaging (including fMRI, PET scans, and EEG) and genetic studies has resulted in the identification of biomarkers that are predictive of MDD and its response to treatment. Neuroimaging provides information about brain structures and functions, and genetic information, including single variation or polygenic risk score, offers an insight into the genetic vulnerability of an individual to MDD [51].

Generalized treatment regimens has the potential to enhance the accuracy of MDD therapy [52]. Deep learning (DL) involves multi-layer neural networks which learn representations directly on the complex inputs. Convolutional neural networks (CNNs) can work either on 3D structural MRI or 2D brain slices, whereas graph neural networks (GNNs) can also take the form of a brain graph. Longitudinal symptom trajectories or multi-visit imaging can be applied to recurrent neural networks (RNNs) or transformer-like models. DL has the ability to minimize the use of manual feature engineering, and can represent nonlinear interactions between distributed circuits, but large datasets and strong regularization are normally needed to prevent overfitting [53].

The focus of multimodal integration is in prediction of treatment since imaging can be used to capture the physiology of the current brain-state, whereas genetics can capture biological background and pharmacokinetic

variability. Different modalities can be integrated with the help of AI:

a. Early fusion
b. Late fusion, or
c. Intermediate/representation fusion (learn latent embeddings of each modality, and merge them).

Different modalities enable models to acquire joint patterns, such as whether a polygenic profile varies for individual connectivity signatures that are associated with SSRI responses.

Ai Models for Predicting Treatment Response in Mdd

Artificial intelligence (AI) models are becoming an effective predictive instrument in the treatment response of MDD. AI presents high-caliber capabilities improve precision medicine by combining the information provided by various sources, which may include neuroimaging and genetic profiles, to help determine the most efficient treatment according to personalized features. Artificial intelligence uses in psychiatry, especially in MDD, is aimed at enhancing prediction accuracy, minimizing trial-and-error treatment, and individualized treatment to achieve improved results [54]. Antidepressants and other pharmacological treatments of MDD have been used as the initial treatment, though not every individuals is responsive to pharmacology. Traditional antidepressants such as the selective serotonin reuptake inhibitors (SSRI) or the serotonin-norepinephrine reuptake inhibitors (SNRIs) can take a couple of weeks before having a therapeutic effect, and approximately 30-40 percent of patients fail to improve significantly [55]. AI models have the potential to forecast individuals wo may respond to pharmacology and enable clinicians to make more decisions and not to have to undergo the trial-and-error process that is long and exhausting [56].

Neuroimaging biomarkers and genetic data may yield promising treatment innovative when combined with AI modalities in which data modalities can be used to enhance treatment prediction. Imaging type, such as functional magnetic resonance imaging (fMMRI), are resourceful to detect brain activity patterns that are associated with response to treatment. In a study conducted on fMRI, patients whose prefrontal cortex-amygdala connectivity patterns revealed certain specific patterns were more likely to respond to SSRIs as these patterns were found to be linked to emotional regulation, which is the target of the medication in which the neural activity-based identification of the most effective antidepressant with the help of AI models incorporated such patterns would contribute to the increased success of treatment and the low likelihood of non-response [57].

Besides neuroimaging, genes information and neuropsychiatry components, are also being incorporated into AI models to predict antidepressant efficacy. The genetic differences like the serotonin transporter gene (5-HTTLPR) can influence the way an individual metabolizes and responds to medication. Neural networks that are a combination of the genetic risk scores, neuroimaging, and clinical history findings can be used to predict the type of medication that is more likely to benefit an individual. With the help of various modalities, it is possible to find the most appropriate dose and predict side effects and treatment effectiveness, and this may be key to produce an individualized approach to antidepressant treatment [58]. Although pharmacological therapy is very common, psychotherapy, including cognitive-behavioral therapy (CBT), can also be applied to treat MDD. Similar to medications, psychotherapy is ineffective for some patients, making it challenging to choose an initial appropriate treatment method. Incorporating artificial intelligence will be useful in determining which of the patients will respond better to psychotherapy, enabling the clinician to tailor treatment plan strategies [59].

The implementation of AI models in predicting the response to psychotherapy is mainly based on neuroimaging, genetics, biomarkers, patient feedback, and neurotransmitters to analyze the pattern of brain activity that is linked to positive therapeutic results. Research revealed that the more a patient is connected in the prefrontal lobe and the less activation of the amygdala, the better the therapy, such as CBT, is likely to work, and neuroimaging features can be combined with clinical data (severity of symptoms and response to previous interventions) by AI to create individual predictions about the appropriate form of psychotherapy to use with a particular person [60].

Genetic information is a contributing source to help predict psychotherapy response, creating a plethora of treatment potentials. Stress-related response genetic factors, including the body response affected by stress, can lead to a different reaction to neurobiological stress factors endured by an individual diagnosed with MDD. Such genetic elements may be used together with neuroimaging information to enable AI models to forecast whether a patient is capable of responding to psychotherapy or may require extra measures, including medical treatment [61].

The combination of neuroimaging and genetic information with the AI models is a novel trend that transforms the way of predicting treatment. Using the combination of these two data sources, AI models can take into consideration the current condition of the brain (neuroimaging) and genetic predispositions of a particular person (genetic profile). The combination of this prevailing information is capable of providing a more in-depth insight into the biological processes of depression and how they respond to various treatments [62]. Neuroimaging can show how brain circuits in charge of emotion regulation or intellectual functioning are disrupted whereas genetic data can be used to identify the predisposition of the patient to depression as well as his or her reaction to certain medication in which when coupled with data, AI models can generate personalized prediction model, considering both the structure and the functioning of the brain, and genetic risk [63].

Prediction of multimodal treatment response is one of the most promising AI models in the combination of neuroimaging and genetic data. Patients diagnosed with MDD may need a combination of pharmacological and psychological treatment, depending on the neurobiological and genetic characteristics of a particular patient. Patients whose brain responds appropriately to activity may be treated with a combination of medicine and psychotherapy and others can be treated only with either of them [64].

Table 3: Key Challenges and Limitations of AI-Based Prediction Models in Major Depressive Disorder

Limitation Category	Description	Impact on AI Models	Potential Solutions
Limited Dataset Size	Many neuroimaging and genetic datasets include relatively small sample sizes	Risk of overfitting and reduced model reliability	Multi-center data sharing and larger cohort studies
Data Heterogeneity	Variability in imaging protocols, clinical assessments, and genetic datasets	Difficulty in model generalization across different populations	Standardization of data acquisition and preprocessing
Model Interpretability	Deep learning models often function as "black boxes," making predictions difficult to interpret	Reduced clinical trust and limited adoption in healthcare settings	Development of explainable AI (XAI) techniques
Population Bias	Training datasets may lack demographic diversity	AI models may perform poorly in underrepresented populations	Use of diverse and representative datasets
Generalizability Issues	Models trained in one clinical setting may not perform well in another	Reduced applicability in real-world clinical environments	External validation across multiple institutions
Integration of Multimodal Data	Combining neuroimaging, genetic, and clinical data is technically complex	Challenges in feature extraction and data harmonization	Advanced multimodal machine learning frameworks
Ethical and Privacy Concerns	Use of sensitive data such as genetic profiles and brain imaging	Risk of data misuse and patient privacy violations	Strong regulatory frameworks and data protection policies
Clinical Implementation Barriers	Lack of standardized AI tools for routine psychiatric practice	Slow translation from research to clinical settings	Development of clinical decision-support systems
Computational Complexity	High computational cost for training deep learning models	Limited accessibility for smaller healthcare facilities	Efficient algorithms and cloud-based AI platforms

Future Directions and Potential of Ai in Precision Psychiatry

The technology of AI integrated with psychiatry has been changing at an incredible pace and the future is very promising with regards to advancement. A particular focus is the explainable AI (XAI) field of development that focuses on enhancing the visibility and comprehensibility of machine learning models. Although AI models, such as deep learning may be accurate in prediction, they tend to operate as a black box, and it is challenging to determine how a specific model came to a certain conclusion [65]. XAI) approaches are being introduced to produce more understandable models that can be used to explain how predictions are made which may enhance the confidence of AI models within the healthcare to make it possible to make time-sensitive clinical decisions. Moreover, even greater developments in the field of reinforcement learning and transfer learning may enable AI models to evolve to the unique profiles of individual patients and keep learning to make better predictions for treatment [66].

The future of AI in psychiatry may expand to seamless adoption of other medical technologies, including electronic health records (EHR) data analyses with minimal errors, mobile health applications, neurobiological trackers, stress modulations monitors, and wearable devices. Technologies may advance to offer a real-time tracking of symptoms, side effect preventions, and patient's propensity for adherence medication compliance through continuous feeding information into AI systems. Through a combination of real-time data inputs with neuroimaging and genetic data, AI models may be able to monitor the mental and physical health of a patient in real-time and modify treatment recommendations which would allow flexible, unique treatment regimens that are continually optimized to achieve the best patient presentation and optimal care. Telemedicine platforms can also be integrated into AI models and enable remote monitoring and intervention of a patient [67, 68].

The combination of AI and genetics as well as neuroimaging and clinical data is introducing the future of precision psychiatry. The AI models can offer individualized approaches to treatment, offering a custom intervention on the basis of the neurobiological and genetic profile of a patient that may minimize the trial-and-error method and lead to more effective treatment while reducing side effects. Though precision psychiatry can be promising with MDD, it can be applied to various psychiatric disorders, such as anxiety, schizophrenic, bipolar disorder, and other conditions [69].

Lastly, the future of AI in psychiatry will be in the AI systems and clinicians working together. Although AI can be used to improve predictivity, human supervision is essential to decipher the outcomes and clinically make subtle decisions. Through its collaboration with clinicians, AI can develop a more comprehensive and successful way of treating mental health disorders.

Conclusion

Neuroimaging, genetic information, and artificial intelligence expands the possibility of predicting treatment response in Major Depressive Disorder (MDD). MDD is a heterogeneous disorder and the management of the disorder is a complicated challenge because treatment non-response for some individuals. The pursuit of more personalized methods is essential to adapt an evolving patient-focused care approach which can maximize the therapeutic results and decrease the trial-and-error methods while reducing risk of pharmacology/medication and psychotherapy non-compliance. AI modalities can analyze complex datasets of neuroimaging and genetic information which is key to determining how biomarkers are utilized to forecast how a particular individual may react to a particular treatment. Brain imaging methods including fMRI, PET, and EEG have offered great information on the parts of the brain and neural pathways that are involved in MDD that makes it possible to predict some treatment responses with the help of identifying functional and structural abnormalities of the brain as well as neurochemical imbalances. Genetic data is also critical since it helps to demonstrate polygenic risk factors, epigenetic alterations, and pharmacogenomic variations that may influence the tendency of an individual to develop MDD and reveal the individual's reaction to antidepressant drugs or psychotherapy. The combination of neurobiological and genetic data into AI models have demonstrated positive outcomes in improving prediction

accuracy, and the vast possibilities of AI (especially machine learning and deep learning) may reveal patterns in the dataset that are unrecognized by human intelligence. AI is promising to provide precise psychiatry, though there are current limitations surrounding understanding the large datasets and interpretability of model output, including identifying certain bias in the datasets. The next evolution stage of psychiatry should focus on the ability to refine AI models to enhance the quality of psychiatric-related data and overcome ethical issues and legal stipulations, including the privacy and bias, to foster treatment outcomes that result in effective approaches with elimination or reduced trial-and-error. With the integration of AI, neuroimaging, and genetic information, clinical availabilities may reach optimal levels with delivering personalized and effective treatment to patients diagnosed with MDD, which may eventually transform into preventive measures to eliminate or reduce the prevalence of MDD globally. Revolutionized strategies may branch into the creation of MDD-related clinical approaches to enhance patient care outcomes, AI-generated components embedded in psychiatric telemedicine (inpatient and outpatient settings), and psychoeducation modules for patients and healthcare professionals to readily utilize to increase the understanding of MDD.

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