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REVIEW

Advances and Challenges in Depression Marker Research

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Abstract: Depressive disorders diagnosis relies on subjective clinical assessment due to the lack of validated biomarkers. This review synthesizes recent advances in depression biomarkers across genetic, epigenetic, neuroendocrine, neuroimaging, immune/inflammatory, and gut microbiota domains. Literature was systematically searched via PubMed/Web of Science.We analyze mechanisms, highlight challenges (eg, clinical heterogeneity, inadequate animal models), and propose future directions: multidimensional bioinformatics, AI-driven models, RDoC framework implementation, and interdisciplinary collaboration. Critically, our analysis reveals that multimodal integration of biomarkers—rather than single-domain approaches—holds the greatest promise for overcoming diagnostic heterogeneity and guiding personalized interventions. These strategies may revolutionize MDD management through early detection and tailored therapeutics.

Keywords: depressive disorders, biomarkers

Introduction

Epidemiological Overview of Depression

Depression is a common mental illness that causes ongoing low mood and difficulties in thinking and concentration. Recent studies have shown that the global prevalence of depressive disorder is about 4.36%.[1] In addition, the lifetime prevalence of depression varies across countries and regions, but is generally estimated to be between 12% and 20%.[2] In recent years, epidemiological studies of depression have shown that the disorder not only affects the mental health of patients, but is also strongly associated with a variety of somatic diseases (eg, cardiovascular disease, diabetes), further increasing the burden of the disease.[3] In addition, the recurrence rate and chronicity trend of depression poses a major challenge to public health.Research indicates that around half of individuals who have their initial bout of depression will have another episode in the future, and the likelihood of recurrence rises with each subsequent episode.[4]

Current Status of Depression Diagnosis

Presently, the identification of depression primarily depends on the evaluation of mental health professionals, along with the guidelines outlined in the DSM-5 or ICD-10.The diagnosis of depression lacks objective biomarkers.[5] The current subjective assessment of the diagnosis, which is not only susceptible to patient self-report, but may also be biased by the subjective judgement of the physician.[6] Second, the heterogeneity of depression symptoms complicates diagnosis. Different patients may exhibit different combinations of symptoms, and even the same patient may have different symptoms at different stages.In addition, depression is often co-morbid with other psychiatric disorders (eg, anxiety disorders, bipolar disorders), further increasing the difficulty of diagnosis.[7]

To address the above issues, future research needs to make breakthroughs in several areas.First, finding and validating biomarkers for depression is one of the hotspots of current research.Finding biomarkers that can objectively reflect the state of depression through blood, brain imaging, genomics and other means is expected to improve the accuracy and reliability of diagnosis.Secondly, individualised treatment is the future direction of development.By understanding the

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patient's genes, neurobiological characteristics and medical history, a personalised treatment plan can be formulated, which can improve the effectiveness of treatment and reduce side effects.[8]

Importance and Significance of Studying Markers of Depression

The development of reliable biomarkers is important for understanding the pathophysiological mechanisms of depression, improving diagnostic accuracy, optimising therapeutic regimens, and predicting therapeutic response.[9,10] Biomarker research may also guide more effective treatments. Knowing which biomarkers are activated or inhibited in depression can help physicians choose treatment regimens that are more appropriate for a patient's specific pathology. For example, if a particular biomarker is strongly correlated with the effects of an antidepressant drug, then that drug may be more appropriate for those patients with higher activity of that biomarker.[11] In addition, biomarker research can help reduce the social stigma attached to depression. By identifying objective biological correlates of depression (eg, neuroimaging alterations, immune dysregulation), research counters the harmful misconception that depression stems solely from personal weakness. This evidence, integrated with psychosocial insights, legitimizes depression as a medical condition requiring professional intervention.[12,13] This study analysed depression markers in a multidimensional way that can be used by clinicians and researchers. Compared to previous reviews, this paper not only systematically reviews the latest evidence and mechanisms of action of depression biomarkers across a wide range of fields, including genetics, epigenetics, neuroendocrinology, neuroimaging, immune inflammation, and the gut microbiome, but also focuses on in-depth analysis of the core challenges currently facing this field (such as clinical and biological heterogeneity, limitations of animal models, and multifactorial complexity). Based on this analysis, the paper proposes key future directions, including the integration of multi-omics technologies, artificial intelligence, large-scale clinical trials, the RDoC framework, and interdisciplinary collaboration, with the aim of providing more comprehensive insights and more translational strategies for the precise diagnosis, personalised treatment, and effective management of depression.Based on this, this review will systematically explore the latest research progress and mechanisms of depression biomarkers across the following key dimensions: genetic markers (eg, gene polymorphisms, GWAS findings), epigenetic markers (eg, DNA methylation, miRNA), neuroendocrine markers (eg, BDNF, HPA axis hormones, neurotransmitter precursors), neuroimaging markers (structural MRI, functional MRI, PET/SPECT), immunological and inflammatory markers (eg, cytokines, immune cells), and emerging gut microbiota markers, See Table 1. By integrating the latest evidence across these fields and conducting an in-depth exploration of existing challenges, this review aims to provide directional guidance for future research.

Survey Methodology

A literature review of biomarkers for depression was conducted using databases such as PubMed and Web of Science. Irrelevant literature was excluded through group review. The final included literature was comprehensively analysed.

Classification and Mechanism of Action of Markers of Depression

Genetic Markers

Association of Gene Polymorphisms with Depression

Studies of genetic markers of depression have revealed the important role of genetic polymorphisms in depression. Specifically, variations in the promoter area of the serotonin transporter gene have been discovered to influence how stressful life events impact depression.[14] Different variations of the 5-HTTLPR gene also play a significant role in how stress and depression are connected, particularly the s allele which increases the likelihood of developing depression when exposed to stress.[15] This indicates that the 5-HTTLPR gene variant could impact how stressful life events affect depression by altering an individual's response to environmental stress.While certain research has indicated a correlation between 5-HTTLPR, stress, and depression, other studies have suggested that this correlation could vary depending on gender.For example, one study of adolescents found that adolescents with lower serotonin transcription efficiency genotypes exhibited more anxiety/depression symptoms when their mothers reported more stressful events and had greater increases in developing anxiety and depression symptoms, especially at ages 16 and 17.[16] Another study found

Table 1 Classification and Diagnostic Potential of Depression Biomarkers

Category	**Mechanisms**	**Diagnostic Potential**
1. Genetic markers	– **5-HTTLPR polymorphism**: s-allele increases stress sensitivity - **Familial aggregation**: Higher heritability in females - **GWAS loci**: 190 loci (eg, PCLO) associated with depression	Requires environmental interaction;
2. Epigenetic markers	- **DNA methylation alterations**: Childhood trauma-induced BDNF/SLC6A4 hyper/hypomethylation affecting HPA axis - **miRNA dysregulation**: miR-1237-5p dysregulation impairs neuroplasticity (TGF-β/MAPK pathways)	Methylation patterns predict treatment response; miRNA levels correlate with symptom severity
3. Neuroendocrine markers	- ↓**BDNF**: Reduced neuroplasticity - **Amino acid dysmetabolism**: Tryptophan/tyrosine pathway disruption - **HPA axis hyperactivity**: Elevated morning cortisol (especially with childhood trauma) - **Thyroid dysfunction**: Positive TSH-PHQ-9 correlation	Serum BDNF/cortisol/amino acid profiles supplement diagnosis; dynamic monitoring of treatment efficacy
4. Neuroimaging markers	**Structural**: - Hippocampal atrophy (reduction in glial cell count) - Prefrontal cortex volume reduction **Functional**: - Default mode network (DMN) hyperactivity - ↓Prefrontal-parietal network connectivity **Molecular**: - TSPO-PET detects microglial activation	Hippocampal atrophy shows high specificity; DMN connectivity patterns enable subtyping; TSPO-PET aids neuroinflammation research
5.Immune/inflammatory markers	- ↑**Pro-inflammatory cytokines**: IL-6, TNF-α, CRP - **Th17/Treg imbalance** **- "Leaky gut" effect**: Microbial translocation triggers systemic inflammation	CRP/IL-6 easily measurable but low specificity; combinatorial panels improve diagnostic value
6. Gut flora markers	- **Microbiota dysbiosis**: ↑Bacteroidetes, ↓Firmicutes - ↓**SCFAs**: Attenuated anti-inflammatory effects - **Metabolite dysregulation**: Altered gut-brain axis signaling	Microbiota composition correlates with symptom severity; fecal microbiome analysis shows non-invasive diagnostic potential
7. Multi-omics integration	- **Cross-omics integration**: Combines neuroimaging (sMRI/dMRI features), proteomics (WGCNA-identified protein clusters), and clinical data - **Pathway analysis**: Links inflammatory/metabolic pathways to symptoms	Enhances subtyping precision (eg, 3 depression subtypes); outperforms single-omics models in diagnostic efficacy
8. AI/Machine Learning	- **Algorithmic screening**: SVM/Random Forests identify biomarker panels from big data (eg, erythrocyte distribution width + serum glucose in NHANES) - **Diagnostic models**: Blood transcriptome-derived SVM classifiers (6-gene panels)	Efficient biomarker discovery; model accuracy >90% (eg, SVM classifiers)
9. Event-related Potential	- **ERN (Error-Related Negativity)**: Cognitive monitoring deficits - **RewP (Reward Positivity)**: Aberrant reward processing - **Autonomic indices**: ↓Skin conductance (EDA), ↓Heart rate variability (HRV)	Real-time monitoring of cognitive-emotional deficits; ERN/RewP predict treatment response
10. Markers of Aging	- **Telomere attrition**: Leukocyte telomere shortening correlates with illness chronicity - **Mitochondrial dysfunction**: Energy metabolism failure → neural network dysregulation - **Brain Age Gap Estimation (BrainAGE)**: Accelerated brain aging via MRI	Telomere length assesses chronicity risk; BrainAGE quantitatively assesses neurodegeneration; guides age-specific interventions

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that during childhood, children carrying the short allele were more likely to develop depressive symptoms under high stress life event exposure and showed fewer depressive symptoms under low stress life event exposure.[17] This indicates that the 5-HTTLPR gene variant could offer flexibility in reacting to external factors that could change depending on age, surroundings, and results.Some other studies have indicated that while there is evidence supporting a link between 5-HTTLPR and stress and depression, there are also studies that have not found a connection between the 5-HTTLPR genotype and depression.Furthermore, a connection has been discovered between the 5-HTTLPR genotype and obsessive-compulsive disorder, indicating that this genotype is linked not only to depression but also to other mental health issues.[18] The impact of stressful life events on depression is affected by functional variations in the promoter region of the 5-HTTLPR gene, which alter an individual's reactivity and adaptation to environmental stress.[19] This effect may vary according to gender, age, and the specific environmental conditions in which the individual is exposed.

Findings from Family Genetic Studies

Familial genetic studies have shown that there is a significant familial aggregation of depression, which is largely or exclusively attributable to genetic influences.[20] Twin studies have indicated variations in depression rates among identical and fraternal twins, primarily stemming from unique genetic and environmental influences.Genetic factors are more important in females and relatively less so in males,[21–23] which supports a higher genetic susceptibility to depression.Specific genetic variants associated with the development of depression include several aspects.Genes located in the HLA region have been proposed as a potential factor in determining vulnerability to affective disorders, especially in cases of monophasic depression.Furthermore, brain imaging research has shown the impact on brain structure and function of serotonin genes (for example, SLC6A4, HTR1A, MAOA, TPH2) and BDNF, which are linked to neural characteristics of depression, like amygdala response, amygdala-anterior cingulate cortex interaction, anterior cingulate size, hippocampal size, and 5-HT1A receptor binding potential.[24] Additionally, a study explored the phenotypic effects between TAAR6 and HSP-70 gene variants and found that specific interactions of these gene variants may constitute a risk profile for major mood disorders.[25] This study, using a multifactorial downscaling (MDR) approach and controlling for covariates associated with diagnosis, showed that interactions between specific genotypes had significant predictive value.[26] Depression presents in various forms and is influenced by factors such as age, other health conditions, and environment.[27] These factors add complexity to genetic studies of depression.Genomic association studies (GWAS) have made significant progress in understanding the genetic architecture of depression.Researchers have discovered various genetic regions linked to depression by examining numerous GWAS datasets, leading to a more comprehensive understanding of the genetic underpinnings of depression.In the Dutch GAIN-MDD cohort, a genome-wide association study revealed that the non-synonymous coding SNP rs2522833 in the PCLO gene showed only nominal significance when combined with the Australian cohort in further analyses.Furthermore, through additional examination of two single nucleotide polymorphisms (SNPs), rs2715147 and rs2715148, within the PCLO gene along with the non-synonymous coding SNP rs2522833, the P-value decreased to 9.9E-7. While this finding did not meet the threshold for genome-wide significance, it indicates that the potential causal variant could be situated in these SNPs within areas of strong linkage disequilibrium (LD).[28] Furthermore, a multi-ancestry study using GWAS found 190 loci that were significantly associated, with 53 of them being newly discovered, in a diverse sample that included individuals of African, East and South Asian descent, as well as Hispanic/Latino background.This study not only adds to the assessment of transferability of previously reported GWAS loci of European origin, but also improves fine-tuning by increasing sample diversity, thus providing important information on target genes and underlying mechanisms of depression.[29] The findings from these GWAS studies enhance our comprehension of the genetic makeup of depression through the identification of genetic regions linked to the condition.For example, through GWAS and gene set analysis (eg, MAGMA), researchers have been able to identify sets of genes associated with depression and explore how these genes interact with each other through biological networks to influence the development of the disease.[30,31] Furthermore, utilizing the Multi-Trait GWAS (MTAG) method has improved the capacity to identify genetic links for individual traits through the collective analysis of GWAS findings for various related traits, resulting in the discovery of extra loci linked to depressive symptoms, neuroticism, and subjective well-being.[32] Studies of genetic markers of depression have revealed the important role of genetic polymorphisms in depression.Specifically, variations in the promoter area of the serotonin transporter gene have

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been discovered to influence how stressful life events impact depression.[14] Different variations of the 5-HTTLPR gene also play a significant role in how stress and depression are connected, particularly the s allele which increases the likelihood of developing depression when exposed to stress.[15] This indicates that the 5-HTTLPR gene variant could impact how stressful life events affect depression by altering an individual's response to environmental stress.While certain research has indicated a correlation between 5-HTTLPR, stress, and depression, other studies have suggested that this correlation could vary depending on gender.For example, one study of adolescents found that adolescents with lower serotonin transcription efficiency genotypes exhibited more anxiety/depression symptoms when their mothers reported more stressful events and had greater increases in developing anxiety and depression symptoms, especially at ages 16 and 17.[16] Another study found that during childhood, children carrying the short allele were more likely to develop depressive symptoms under high stress life event exposure and showed fewer depressive symptoms under low stress life event exposure.[17] This indicates that the 5-HTTLPR gene variant could offer flexibility in reacting to external factors that could change depending on age, surroundings, and results.Some other studies have indicated that while there is evidence supporting a link between 5-HTTLPR and stress and depression, there are also studies that have not found a connection between the 5-HTTLPR genotype and depression.Furthermore, a connection has been discovered between the 5-HTTLPR genotype and obsessive-compulsive disorder, indicating that this genotype is linked not only to depression but also to other mental health issues.[18] The impact of stressful life events on depression is affected by functional variations in the promoter region of the 5-HTTLPR gene, which alter an individual's reactivity and adaptation to environmental stress.[19] This effect may vary according to gender, age, and the specific environmental conditions in which the individual is exposed.

However, there is significant controversy regarding the central role of the 5-HTTLPR genotype in the onset of depression. Key large-scale meta-analyses have failed to consistently replicate the strength of its interaction with stress, suggesting that the effects observed in earlier studies may have been overestimated or strongly influenced by study design, stress measurement methods, and population heterogeneity. This inconsistency highlights the limitations of single-gene markers in complex diseases such as depression.

Epigenetic Markers

DNA Methylation

DNA methylation is a type of epigenetic change that impacts gene activity through modifications to the chemical makeup of DNA.Depression is linked to changes in methylation levels of certain genes like BDNF, SLC6A4, and NR3C1, which are connected to the onset of depression.[33] The methylation of these genes has the ability to control the production and distribution of neurotransmitters, impacting mood and behavior.Environmental challenges in early stages can alter gene expression in the brain through DNA methylation, particularly impacting the 5-HT system and the Hypothalamic-Pituitary-Adrenal Axis (HPA) axis.The interaction between genes and the environment could be crucial in the onset of depression.[34] Additionally, DNA methylation patterns have been utilized as indicators to forecast how depressed individuals will react to various therapies.[35] Certain specific CpG loci have been linked to the therapeutic effects of antidepressant medications, while the methylation status of certain genes may be strongly associated with the development of depressive disorders.[36] In addition, there are also alterations in DNA methylation modifications between childhood trauma and depression, and early life adversity, through alterations in DNA methylation, may lead to long-term effects on behaviour and mental health.[37] This suggests that alterations in DNA methylation modifications may be implicated in the development of childhood trauma and depression.[38] Some genes linked to stress response include NR3C1 (glucocorticoid receptor), FKBP5 (which encodes FK506-binding protein 51), and BDNF (brain-derived neurotrophic factor).The methylation status of these genes has been linked to the development of depression.It has been found that methylation levels of these genes change after childhood trauma, which may partly explain the increased risk of depression.[39,40] Gender may differ in the expression of DNA methylation, which may have an impact on the risk of PTSD and depression.A study suggests that alterations in DNA methylation under environmental stress may occur in a gender-specific manner, which may be a way to understand gender differences in risk for mental illness.[41]

Role of miRNAs

miRNAs, which are short non-coding RNA molecules approximately 22 bases in length, play a role in controlling gene expression by interacting with mRNAs to suppress translation or support certain genes.[42] Researchers are increasingly focusing on miRNAs for their involvement in central nervous system function and associated neuropsychiatric conditions.miRNAs, crucial in controlling epigenetic processes, are key players in the advancement of depression by regulating protein expression, impacting neuroplasticity, synaptic structure and function, and neurogenesis, ultimately influencing the development and progression of depression.[43] These alterations consist of dysregulation of monoamines, abnormalities in neuroplasticity and neurogenesis, hyperactivity of the HPA axis, and dysregulation of the immune-inflammatory response.[44] miRNAs can also affect depression-related gene expression through interactions with multiple signalling pathways, such as the TGF-β and MAPK pathways.For example, miR-1237-5p has been associated with the efficacy of therapeutic antidepressant medications (eg, mirtazapine and selective 5-hydroxytryptamine reuptake inhibitors), with changes in its levels negatively correlating with therapeutic remission.[45] miRNAs not only have the potential to have an impact on the diagnosis of depression, but also serve as a therapeutic target for the treatment of depression. They may become new therapeutic approaches by modulating specific signalling pathways and gene expression.[46]

Researchers have discovered a mutual control mechanism involving miRNAs and DNA methylation.On the one hand, certain miRNAs can directly target DNA methyltransferases or proteins associated with methylation, thus regulating the level of DNA methylation.[47] Conversely, changes in DNA methylation can impact the expression and operation of miRNA as well.DNA methylation has the ability to suppress miRNA production through the methylation of CpG islands.[48]

Existing DNA methylation and miRNA studies have primarily focused on specific candidate genes or pathways, lacking systematic exploration at the genome-wide/transcriptome-wide level. A fundamental challenge is the unclear correlation between epigenetic markers in peripheral blood (easily accessible) and the brain (the site of disease onset), which severely limits their clinical utility.

Genetic risk scores (PRS) and epigenetic markers (such as specific gene methylation levels) hold long-term promise for predicting disease risk or treatment response, particularly for personalised medicine. However, the predictive accuracy of current PRS remains low, and there are significant differences in performance across different racial/ethnic groups. The tissue specificity and dynamic nature of epigenetic markers (influenced by environment and treatment) are key obstacles to their stable application in clinical decision-making.

Neuroendocrine Markers

Neuroendocrine markers are an important part of depression research.BDNF is an important neurotrophic factor involved in neuronal growth, differentiation and survival. It has been shown that serum levels of BDNF are significantly reduced in depressed patients, suggesting an important role in the pathogenesis of depression. Reduced BDNF levels may be associated with decreased neuroplasticity and cognitive dysfunction.[49–51] The relationship between plasma amino acid levels and major depressive disorder has also received considerable attention.Lu et al found that patients with major depressive disorder had significantly lower plasma levels of Asp, Gly, and GABA and significantly higher levels of NO, and that these changes persisted even after 2 months of fluoxetine treatment.[52] Another study examined the relationship between dietary intake of branched-chain amino acids and psychological disorders: a high intake of branched-chain amino acids was associated with reduced odds of depression and anxiety. This may be related to the competition between branched-chain amino acids and aromatic amino acids for transport across the blood-brain barrier, thereby affecting neurotransmitter synthesis in the brain.[53] In exploring the role of plasma amino acids in the pathology and pharmacology of major depressive disorder, a study by Gammoh et al suggests that disturbances in the metabolism of tryptophan, phenylalanine, and tyrosine may be a key factor in MDD, and that further studies are needed to reveal their specific roles in MDD.[54] A study by Islam et al assessed the effect of unmedicated MDD patients' serum amino acid and non-enzymatic antioxidant levels. It was found that serum levels of methionine, phenylalanine, tryptophan, and tyrosine as well as vitamins A, E, and C were significantly lower in patients with MDD compared to healthy controls. These findings suggest that reductions in these parameters may be related to the pathogenesis of MDD and may be potential biomarkers of MDD.[55] High levels of serum copper ions are associated with depression and other psychiatric disorders. Copper ions play a key role in the regulation of neurotransmitter and receptor function.Chan's study indicated that abnormal serum copper ion levels may affect the normal functioning of the nervous system and thus correlate with the symptoms of depression.[56] Antioxidant enzymes show a trend towards reduced activity in depressed patients along with increased oxidative stress markers. This suggests that oxidative stress may play an important role in the pathogenesis of depression.[57,58] Abnormal lipid metabolism is also one of the important features of depression, and abnormal cholesterol levels have been observed in the serum of depressed patients.[59,60] The relationship between serum levels of 5-HT and disease severity and duration of illness in depressed patients can be quantified in a number of ways, and in a study by Wonsuk Choi it was shown that there was a significant correlation between serotonin levels at baseline and short- and long-term treatment outcomes.[61] Cortisol is an important hormone in the stress response and is mainly secreted by the adrenal cortex. Depressed patients often exhibit dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in abnormal cortisol levels. It has been found that childhood trauma may be associated with elevated cortisol levels in the morning upon awakening in patients with MDD that are not apparent in patients without a history of childhood trauma. In addition, gender differences and variability in stress responses have been associated with the severity of MDD, especially in women.[62,63]

Depressive disorders are associated with attenuated dopamine signaling. This attenuation may be due to reduced dopamine release or impaired signal transduction, including changes in receptor number or function and abnormal intracellular signal processing. This is supported by animal models and autopsy studies showing reduced concentrations of dopamine metabolites in the cerebrospinal fluid of severely depressed patients.[64] Abnormal thyroid function is more common in depressed patients. For example, one study showed that a higher percentage of women with depressive symptoms showed signs of hypothyroidism.[65] Another cohort study found that severely depressed patients were more likely to have higher TSH levels and that TSH was positively correlated with PHQ-9 scores.[66] In addition, abnormal thyroid hormone levels have been associated with the severity of depressive symptoms.[67]

Measurements such as serum BDNF, cortisol rhythms, and specific amino acid profiles are relatively convenient and have the potential to be translated into auxiliary diagnostic or subtype stratification tools. However, their sensitivity and specificity are currently insufficient, and the high cost of individualised monitoring of dynamic patterns (eg, circadian rhythms, stress responses) limits their widespread clinical application. Inflammation-related markers (eg, CRP) are easy to detect but lack specificity.

Neuroimaging Markers

Structural Imaging Markers (MRI)

Hippocampal atrophy: the specific manifestations and mechanisms of hippocampal atrophy in depression can be analysed from several perspectives. Firstly, the hippocampus is one of the regions of the brain that is particularly sensitive to stress, and it is not only affected by glucocorticoids, but also responds to changes in gonadal, thyroid, and adrenal hormones, which regulate synaptic formation and dendritic structural changes, as well as modulating dentate gyrus volume during development and adult life. This suggests that structural plasticity in the hippocampus is influenced by a variety of factors, including stress and hormone levels.[68,69] Repetitive stress causes dendritic atrophy in the CA3 region, while acute and chronic stress inhibits the neogenesis of dentate gyrus granule neurons. This structural change is associated with selective atrophy of the human hippocampus, which is accompanied by deficits in declarative, spatial and contextual memory performance. Impairment of these memory functions is one of the common symptoms in depressed patients.[68] It has also been shown that individuals with a history of depression have significantly reduced left and right hippocampal volumes compared to normal controls.[70,71] This atrophy may be related to the neurotoxic effects of glucocorticoids, which may be due to a prolonged stress response. In addition, hippocampal atrophy in depressed patients may also be related to a decrease in the number of glial cells. Glial cells play a key role in maintaining normal neural activity, including the regulation of extracellular potassium ions, glucose storage and metabolism, and glutamate uptake. In patients with familial major depressive disorder and bipolar disorder, the number of glial cells in the subgenual prefrontal cortex is significantly reduced, especially in the subgroups with a clear family history. This reduction in the number of glial cells may be an important factor contributing to hippocampal atrophy, as it directly affects neuronal function and survival.[72]

Changes in the prefrontal cortex: Structural and functional abnormalities of the prefrontal cortex, particularly the anterior cingulate cortex, dorsolateral prefrontal cortex, and orbital frontal cortex, have been widely reported in depressed patients.[73] Atrophy or hypofunction of these regions has been associated with impairments in emotion regulation and cognitive control. The function of the prefrontal cortex may be affected in depressed patients, leading to reduced emotion regulation. This functional abnormality may be associated with genetic factors.[74]

Functional Imaging Markers

Changes in functional connectivity: depressed patients differ in the functional connectivity of the default mode network and the prefrontal-parietal network, which may affect cognitive functioning.[75] In addition, depressed patients have enhanced activity in the default mode network and diminished activity in prefrontal regions associated with emotion regulation.[76] In depressed patients, connectivity within the default mode network is altered. Specifically, connectivity between posterior, ventral, and core default mode network subsystems increased, while interactions from prefrontal to ventral default mode network subsystems decreased.[77] This suggests that the functional connectivity of the default mode network in depressed patients is not only affected overall, but also differs significantly between subsystems; although there is less evidence directly regarding the difference in functional connectivity between the prefrontal-parietal network and the default mode network in depressed patients, some connections can be inferred from related studies. For example, it has been shown that lateral prefrontal regions show significant negative correlation connectivity with the PCC when performing tasks.[78] For the dopamine system, Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography(SPECT)imaging techniques can be used to assess dopamine receptor activity in the brain. For example, dopaminergic activity in striatal regions can be assessed using specific radiopharmaceuticals such as 6-[^{18}F] fluoro-L-DOPA and iodoaniline.[79] In addition, by measuring the availability of the dopamine transporter (DAT), further insights into the metabolic processes of dopamine and their relationship with depression can be gained.[80] For the serotonin system, SPECT imaging techniques can be used to assess 5-hydroxytryptamine (5-HT) receptor activity. For example, the use of radiopharmaceuticals at the 5-hydroxytryptamine 2A receptor can help to understand the mechanism of action of serotonin in depression.[81] The use of these imaging techniques not only helps to diagnose depression, but can also provide important information for studying its pathophysiology. For example, studies have shown that dysfunction of the dopamine and serotonin systems in the brains of depressed patients may be associated with symptoms such as mood regulation, sleep disturbances, and cognitive dysfunction.[79] In addition, the development of these techniques has facilitated the development of novel antidepressant drugs because they can help scientists better understand the mechanism of action of these drugs.[82]

PET imaging techniques using TSPO radioligands can detect microinflammatory changes in the brains of depressed patients, which provides new insights into understanding the pathophysiological mechanisms of depression.[83] Using specific TSPO radioligands (eg [18F]FEBMP), neuroinflammation can be visualised non-invasively in vivo by PET imaging. For example, in a rat model, [18F]FEBMP showed increased radioactivity accumulation in regions of ischaemia-induced brain damage (eg, striatum), reflecting TSPO-specific binding.[84] Furthermore, this increased radioactivity accumulation can be displaced by specific TSPO ligands, thus validating its specificity. In clinical studies, several TSPO PET tracers have been developed that are capable of assessing neuroinflammation in the Alzheimer's disease spectrum. The development of these techniques has provided new tools for the study of other neurodegenerative diseases, such as depression, allowing a more precise monitoring and understanding of the inflammatory state in the brain.[85]

Although hippocampal volume reduction is a relatively consistent finding, the underlying pathological mechanisms remain controversial. The mainstream hypothesis emphasises the neurotoxic effects of elevated glucocorticoids under chronic stress. However, autopsy studies revealing significant glial cell reduction offer an alternative explanatory pathway, suggesting that the collapse of the neurosupportive system may play a more direct role. These differing findings (structural atrophy on imaging vs cellular pathology on autopsy) have not yet been fully integrated, and the mechanisms remain incompletely elucidated.

fMRI functional connectivity patterns (eg, excessive DMN connectivity) may provide unique pathophysiological insights and objective brain function assessment metrics, offering significant potential. However, the high cost of equipment, insufficient standardisation of scanning and analysis processes, issues with intra-individual stability (reproducibility), and high costs are major barriers to its adoption as a routine clinical diagnostic tool. PET imaging (eg, TSPO tracers) is highly attractive for detecting neuroinflammation, but the availability, cost, and radiation exposure associated with radioactive tracers limit its widespread application.

Immune and Inflammatory Markers

Research has linked the onset of depression to irregular functioning of different immune cells and substances. Numerous studies have indicated that individuals with depression frequently display increased levels of inflammatory indicators like C-reactive protein, interleukin 6, and tumor necrosis factor α.Abnormal expression of certain cytokines and chemokines like IL-8 and CCL2 has been observed in individuals with depression, and these molecules are crucial in the crosstalk between the immune and nervous systems.[56,86,87] Depression can not only trigger the immune system, but also an irregular immune system activity may elevate the likelihood of depression.[88] Various particular components of the immune system, like natural killer cells, CD4 and CD8 cells, and associated cytokines, exhibit irregularities in individuals with depression.[89,90] Th17 cells,[91] regulatory T cells,[92] pro-inflammatory cytokines,[93,94] and other immune system elements[95,96] play a role in the pathological aspects of depression through various mechanisms, including the control of the inflammatory response.processes, including the regulation of inflammatory responses, neurotransmitter synthesis and release, and neuronal protection.Given the role of inflammation in depression, several studies have raised the possibility of using inflammatory markers as new therapeutic targets.This provides new ideas for developing new antidepressant treatments.[97,98]

Although multiple studies have observed elevated levels of pro-inflammatory cytokines (such as IL-6, TNF-α), this inflammatory activation state is not present in all depressed patients, and its extent and pattern exhibit high individual variability. More importantly, similar inflammatory profile changes are also commonly observed in various other somatic diseases (eg, autoimmune diseases, infections) and mental disorders (eg, schizophrenia), significantly undermining their potential as depression-specific diagnostic markers.

Gut Flora Markers

The idea that gut flora serves as a marker for depression has gained much attention and validation in recent studies. Several studies have identified the presence of multiple deficits or changes in gut flora in depressed patients compared to healthy controls.[99,100] These changes include increased or decreased abundance of specific bacterial species, as well as changes in metabolites associated with depression. For example, the abundance of the genus Bacteroides was increased in patients with MDD, whereas the abundance of the genera Blautia and Eubacterium was decreased,[101] and at the phylum level, the proportions of the phyla Anaplasma, Aspergillus, and Actinobacteria were significantly higher, and the proportions of the phyla Thick-walled Bacteria were significantly lower.[102] In addition, several other studies have found that alterations in gut flora are associated with clinical features, inflammatory markers, metabolic indicators, and response to medication in depressed patients.[103–105]

Dysbiosis of the intestinal flora is thought to be one of the important factors contributing to this systemic inflammation. For example, changes in the gut microbiota lead to a decrease in the production of short-chain fatty acids, which normally have anti-inflammatory effects. In addition, increased intestinal permeability allows intestinal microbial components to enter the circulation, further triggering a systemic inflammatory response.[106]

Although changes in microbiota composition have been observed, key questions remain unresolved: Are these changes the cause, consequence, or concomitant phenomenon of depression? The powerful influence of confounding factors such as diet and medications (especially antidepressants themselves) has not been sufficiently excluded, making it extremely difficult to establish causal relationships and identify core pathogenic bacterial species.

Non-invasive sampling is its greatest advantage, with significant potential as a diagnostic aid or prognostic marker. Treatment strategies based on microbiota intervention (probiotics/prebiotics/diet) are an attractive translational direction. However, the complexity of microbiota-host interactions, substantial interindividual variability, lack of standardised detection and analysis protocols, and most importantly—the ambiguity of causality—are fundamental challenges to its clinical translation.

The pathophysiological process of depression is essentially the result of Multi-pathway dynamic interactions, with the primary evidence manifested in three core axes

On the gene-environment-epigenetic axis, early life stress events (such as childhood trauma) induce abnormal methylation modifications of key genes (such as NR3C1), leading to dysfunction of the glucocorticoid receptor and subsequent sustained activation of the hypothalamic-pituitary-adrenal (HPA) axis; Genetic susceptibility factors (such as the 5-HTTLPR risk genotype) can significantly amplify the regulatory effects of environmental stress on epigenetic modifications, jointly shaping an individual's predisposition to depression.

On the neuroendocrine-immune-microbiota axis, elevated cortisol levels driven by HPA axis overactivation directly increase intestinal epithelial permeability, promoting the translocation of microbial products such as lipopolysaccharides into the circulatory system and triggering systemic inflammatory responses (manifested by elevated pro-inflammatory factors such as IL-6 and TNF-α); These inflammatory factors further feedback-inhibit the expression of brain-derived neurotrophic factor in the hippocampus, impairing neural plasticity and accelerating hippocampal structural damage, ultimately amplifying emotional and cognitive dysfunction.

Along the microbiota-metabolism-neuroaxis, gut microbiota dysbiosis (such as reduced levels of the Blautia genus) leads to insufficient short-chain fatty acid synthesis, weakening its anti-inflammatory regulatory effects on immune cells and indirectly exacerbating neuroinflammation; simultaneously, peripheral tryptophan metabolism disorders (significantly reduced plasma levels) directly limit the biosynthesis of serotonin in the central nervous system, with the extent of this reduction showing a significant negative correlation with the severity of depressive symptoms.

New Perspectives in Marker Research

Multi-Omics Integration Analysis

The case for integrated multi-omics analysis in depression marker studies mainly involves the combined analysis of neuroimaging, proteomics and clinical data to reveal biomarkers and pathological mechanisms of depression. Neuroimaging studies utilized various imaging methods (such as diffusion MRI and structural MRI) to pinpoint indicators of major depressive disorder (MDD).By using modelling techniques such as penalised logistic regression, random forests and support vector machines (SVMs), the study identified four image-based features that may be useful for future research.[107] Another study used proteomics data to calculate protein clusters by weighted correlation network analysis (WGCNA) and identified six protein clusters associated with MDD that are linked to inflammatory and metabolic pathways and have been linked to multiple depressive symptoms.[108] Earlier studies have pointed out that classification and diagnosis of depression need to take into account multiaxial features, as demonstrated by the extended application of the DSM-III, which shows that depressed patients vary significantly across axes, which is useful for developing comprehensive treatment plans.[109] Recent studies have developed a new hierarchical framework to systematically deconstruct clinical and neurobiological heterogeneity using data from the UK Biobank.This approach not only revealed the neurobiological features associated with specific clinical subgroups, but also further explored the neurobiological heterogeneity within each subgroup through data-driven cluster analysis.[110]

Although multi-omics integration (neuroimaging + proteomics + clinical data) shows promise, there are still significant methodological challenges in effectively integrating data from different dimensions, scales, and noise levels and extracting robust, interpretable biomarker combinations from them.

Artificial Intelligence and Machine Learning

Artificial Intelligence (AI) and Machine Learning (ML) play an important role in improving the efficiency of depression biomarker identification and validation. By analysing large-scale datasets, these techniques can effectively identify biomarkers associated with depression and provide support in the diagnosis and treatment of depression. Firstly, key biomarkers associated with depression can be efficiently identified from large epidemiological studies by combining data mining, machine learning algorithms and traditional statistical methods. For example, one study utilised a hybrid approach of multiple interpolations, machine learning augmented regression algorithms and logistic regression to successfully identify three biomarkers associated with depression from the National Health and Nutrition

Examination Study: erythrocyte distribution width, serum glucose and total bilirubin.[111] Second, machine learning algorithms play a key role in the diagnosis of mental illness. A study of different machine learning algorithms has revealed that algorithms such as Support Vector Machines (SVM), Gradient Boosting Machines (GBM), Random Forests, Plain Bayes, and K Nearest Neighbours (KNN) have been widely used in the field of mental health.[112] These algorithms are able to process large datasets and identify biomarkers associated with depression, thus improving the accuracy of diagnosis. In addition, machine learning methods have been used to construct predictive models for the diagnosis of major depressive disorder (MDD). By analysing peripheral blood transcriptome data, researchers successfully identified six differentially expressed genes and modelled them using support vector machine (SVM), random forest (RF), k-nearest neighbours (kNN), and plain Bayes (NB) tools, ultimately constructing an SVM classifier with high diagnostic power.[113] Machine learning also shows great potential in biosignal processing, which is important for the diagnosis and treatment of depression. By detecting and analysing different biosignals, machine learning algorithms are able to differentiate between typical and atypical functional states, enabling personalised mental health care.[114] Finally, the application of machine learning to numerical phenotypic measures also provides new perspectives in the study of depression. By analysing social media behaviours, machine learning algorithms are able to effectively identify depressed patients, providing a basis for selecting the most appropriate numerical phenotype variables for clinical trials.[115]

The efficiency of identifying and confirming biomarkers for depression has been greatly enhanced by artificial intelligence and machine learning by analyzing extensive datasets, building predictive models, and processing biosignals using various methods.

While artificial intelligence and machine learning have demonstrated potential in enhancing the efficiency of identifying biomarkers for depression, the diagnostic accuracy of these algorithms remains in the exploratory stage, and their generalisability in independent cohorts requires rigorous validation. Potential risks include: the risk of overfitting in high-dimensional, limited clinical samples; poor reproducibility when applied to datasets with demographic/technical differences; and the lack of biological interpretability due to "black box" decision-making processes. Future research and development must prioritise the use of explainable artificial intelligence frameworks to establish associations between predictive features and neurobiological mechanisms.

Event-Related Potential

Event-related potentials (ERPs) serve as a neurophysiological tool that can provide important information about brain activity. For example, error-related negativity (ERN) and reward positivity (RewP) in ERPs are considered biomarkers of depressive symptoms and risk.[116] Patients with depressive disorders often show abnormal skin conductance activity; in one study, it was shown that EDA in depressed patients was lower than that of normal controls across all tasks and conditions.[117] In another study, it was found that, in the untreated state of depressed patients, the skin conductance levels, skin conductance response amplitude, skin conductance response rate, and non-response index were significantly lower than in healthy controls.[118] Heart rate variability in depressed patients also differed significantly from the healthy group, with Sarlon J et al demonstrating that depressed patients had lower heart rate variability at rest and that there was no significant correlation with symptom severity.[119] Another study of patients showed significantly increased heart rate and lower HRV, which was associated with an increased risk of future cardiovascular disease.[120]

Although ERPs provide highly time-resolved neurophysiological indicators for depression research, their clinical application still faces significant challenges: ERPs are highly sensitive to participants' alertness, task engagement, and acute emotional states (eg, transient increases in anxiety can distort ERN amplitude), leading to insufficient inter-trial measurement stability (test-retest reliability) and making it difficult to distinguish between depressive trait deficits and state fluctuations. The extraction of ERP components is highly dependent on experimental paradigms, electrode placement protocols (variants), and preprocessing workflows. Methodological differences significantly reduce inter-study comparability, hindering the establishment of biomarker consensus. Mapping a single ERP component to multi-brain region network interactions cannot precisely locate pathological nodes; moreover, similar abnormalities are observed in comorbid disorders such as anxiety and ADHD, weakening the diagnostic specificity of depression.

Marker of Aging

Recent studies have shown significant evidence for a link between biological abnormalities in depression and biological changes common to the aging process.[121]

Telomere Attrition

Telomeres are protective structures at the ends of chromosomes, and shortening of their length is commonly associated with cellular senescence and apoptosis and may also affect genetic stability. In patients with depression, studies have found that leukocytes generally have shorter telomere lengths, which may reflect a state of cellular aging and dysfunction.[122] Further studies have found that shortened telomere lengths in patients with depression correlate with the severity and duration of the illness.[123] This implies that the prolonged presence and severity of depression may lead to more pronounced telomere shortening, which may exacerbate the process of cellular aging.

Mitochondrial Dysfunction

Dysfunctional brain networks in patients with depressive disorders are mainly characterized by hyperactivation and enhanced connectivity in the default mode network (DMN),[124,125] and diminished connectivity in the prefrontal network (FPN) and the dorsal attention network (DAN).[126] Abnormal functioning of these networks may be associated with the generation of depressive symptoms, such as decreased attention to cognitive tasks and impaired emotion regulation. Dysfunction of mitochondria, the energy factories of the cell, may lead to abnormalities in brain energy metabolism, which in turn affects the function of neural networks. Although current evidence focuses on brain network dysfunction, it can be speculated that mitochondrial dysfunction may indirectly lead to abnormalities in the function of these networks by affecting the energy supply to the brain. For example, mitochondrial dysfunction may lead to reduced neuronal activity, which in turn affects communication and coordination between neural networks.[127] In addition, several studies have shown that certain brain regions, such as the amygdala and the anterior cingulate cortex, in patients with depressive disorders show functional connectivity patterns that are different from those in normal controls.[128,129] Abnormal connectivity in these regions may be related to mitochondrial dysfunction, as these regions have higher energy demands, and decreased mitochondrial function may directly affect the function of these regions.

In studies of depressive disorders, some studies have found increased levels of CCF-mtDNA in patients with untreated depression and recent suicide attempts, whereas other studies have found unchanged or decreased levels of CCF-mtDNA. This suggests that ccf-mtDNA may play different roles in different types of depressive disorders or that changes in its levels may be influenced by a variety of factors, such as co-morbidity, medication status, etc.[130] Second, the potential role of mitochondrial DNA as a neuroinflammatory biomarker in major depressive disorder (MDD) has also been supported. Mitochondrial DNA may act as a trigger for chronic stress-related neuroinflammation with its release from dysfunctional mitochondria in the central nervous system into the peripheral circulation. This provides a theoretical basis for the use of mitochondrial DNA as a biomarker for the diagnosis and treatment of MDD.[131]

Brain Age and Depressive Disorder

It has been shown that patients with depressive disorders experience more rapid brain aging, which is associated with multiple dysfunctions and an increased risk of death.[132] Second, the development of depressive disorders is age-related, with patients with depressive disorders of different ages exhibiting different clinical characteristics and course.[133] For example, patients with early-onset depressive disorders are associated with more residual depressive symptoms, whereas patients with late-onset depressive disorders are associated with more cognitive decline.[134] This suggests that the biological basis of depressive disorders may change with age.

Although aging-related markers such as telomere attrition, mitochondrial dysfunction, and accelerated brain aging provide important insights into the chronic pathological process of depression, their clinical application still faces multiple fundamental constraints: First, these markers exhibit significant interindividual heterogeneity and difficulties in dynamic monitoring—telomere length is not only influenced by the course of depression but is also strongly intertwined with genetic background, lifestyle, and comorbid physical diseases, leading to insufficient discriminatory validity as depression-specific biomarkers; Second, mitochondrial-related indicators exhibit contradictory changes across different depression subtypes or disease stages. This inconsistency may stem from methodological differences or uncontrolled confounding factors, rendering interpretation highly context-dependent; Finally, while brain age prediction models can quantify neurobiological aging shifts in depression patients, their spatial resolution limitations prevent the localization of specific brain region damage, and the training data for these algorithms primarily originate from healthy populations, with their generalizability to psychiatric populations yet to be validated in large-scale studies.

Challenges and Perspectives of Depression Marker Research

Major Depressive Disorder (MDD) is a complex illness with diverse causes, including genetic predisposition and harmful environmental factors. The varied clinical presentation of MDD and limited understanding of its biological processes make accurate diagnosis and treatment challenging. The complexity of studying MDD is exacerbated by the absence of appropriate animal models, the barriers posed by clinical and biological diversity, and the presence of distinct subtypes. Individual biomarkers are not sufficiently significant to be used alone for the diagnosis of MDD due to the lack of significant differences between depression (MDD) and normal populations.[135,136] For example, a study by Professor Eun Young Kim found that the composite effect of a group of a total of six biomarkers had a diagnostic accuracy of 68% for MDD, suggesting that a combination of multiple biomarkers is needed to improve diagnostic accuracy.[137] The etiology and symptoms of depression show a high degree of heterogeneity, which poses great challenges for clinical diagnosis and treatment.For example, Zhao's study revealed a longitudinal brain structure developmental trajectory of depression and defined three distinct subtypes of depression, each with different clinical symptoms and genetic expression differences.[138] Studies examining the entire genome for associations with major depressive disorder have shown a complex genetic makeup with multiple variants contributing to a slightly higher risk, potentially influenced by the diverse symptoms and causes of the disorder.Research has demonstrated that enhanced lineage and worldwide variety in genetic research could be crucial in identifying key genes and guiding the applicability of results.[139] As a result, it is important to consider this diversity when utilizing biomarkers for the identification and management of depression in order to enhance accuracy in diagnosis and effectiveness in treatment.

The Research Domain Criteria (RDoC) project, initiated by the National Institute of Mental Health (NIMH), aims to facilitate the shift from descriptive phenomenology to a research approach that integrates neuroscience and psychopathology by reclassifying mental disorders on the basis of dimensions that are based on observable behavioral and neurobiological measurements.[140] The study of depression as a psychiatric disorder receives special attention. Firstly, the RDoC framework seeks to explain the etiology and pathophysiology of mental disorders by identifying brain mechanisms that provide earlier and more accurate diagnoses and predict treatment response and outcomes.[141] This approach provides a more comprehensive understanding of mental disorders, particularly in complex disorders such as depression, than the traditional symptom-based classification of the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders). The introduction of the RDoC framework has provided new perspectives for understanding the biological context of depression and the effects of treatment.[142] For example, by exploring the relationship between specific RDoC constructs (eg, the negative value system, the positive value system, and the cognitive system) and the depressive phenotype and the effects of antidepressant medications, researchers have been able to gain a deeper understanding of the pathophysiological mechanisms of depression. In addition, the RDoC framework highlights the important role of psychophysiological models in reconceptualizing depression susceptibility, which helps to advance our understanding of the pathophysiological mechanisms of depression susceptibility.[143]

Conclusions

This review systematically integrates key advances in six major biomarker areas for depression: genetic markers provide evidence for the genetic basis of the disease, but require functional validation; epigenetic modifications dynamically reflect gene-environment interactions; neuroendocrine dysregulation is associated with symptom severity and treatment resistance; neuroimaging features provide direct evidence of structural and functional brain changes; immune-inflammatory markers highlight immune-neural system interactions; and gut microbiota dysbiosis has emerged as a new target for dietary/probiotic interventions. These findings hold clear clinical translation potential: in diagnosis,

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multimodal combinations can complement subjective assessments to enable early identification; in personalised treatment, inflammatory markers can screen for suitable candidates for anti-cytokine therapy, while microbiota profiles can guide probiotic interventions; in prognostic monitoring, telomere attrition and mitochondrial dysfunction can serve as indicators of accelerated biological ageing in depression. Future research should prioritise three key directions: 1) validating biomarker-guided treatment algorithms through large-scale clinical trials; 2) establishing standardised testing protocols for key biomarkers; 3) leveraging the RDoC framework to link biomarkers with neurobehavioural dimensions, thereby reconceptualising depression subtypes based on biological mechanisms.

Future directions in depression marker research will emphasize the combined use of various bioinformatics methods, including genomics, transcriptomics, proteomics, and metabolomics, to fully understand the intricate pathological processes of depression.Large-scale clinical studies will validate the accuracy, specificity and reproducibility of these potential biomarkers to ensure their effectiveness in clinical applications.Further studies will aim to identify biomarkers that can predict the risk of depression at an early stage to enable early diagnosis and intervention, thereby improving the timeliness and effectiveness of treatment.In addition, the achievement of individualised healthcare will rely on in-depth research into biomarkers that can guide personalised treatment regimens to meet the specific medical needs of different patients.At the same time, dynamic monitoring of disease progression and treatment efficacy will be achieved by studying the changing patterns of biomarkers during the course of depression.Interdisciplinary collaboration is also crucial, as experts in the fields of psychology, neuroscience, and immunology will work together to fully understand the multifactorial pathogenic mechanisms of depression.Through the study of these markers, it is expected that more precise and personalised medical services can be provided to patients with depression.

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