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Recent developments in omics studies and artificial intelligence in depression and suicide

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Major depressive disorder (MDD) is the most prevalent and severe form of mental illness and is significantly linked to suicide. At present, addressing the treatment and prevention of depression and suicide poses significant challenges, largely due to the remaining uncertainties surrounding their pathogenesis. Thus, there is an urgent need to find new molecular pathways, as well as effective biomarkers and drug targets, to provide effective diagnosis, prognosis, and treatments for depression and suicide. Recent advancements in high-throughput sequencing technology and whole-genome analysis have enabled the collection of extensive omics data from blood samples, human autopsy brain tissue, and various animal models. This data captures significant molecular-level changes, including alterations in gene transcripts, epigenomes, and proteins, effectively reflecting the biological state of the disease. This review provides a systematic overview of advancements in transcriptomics, non-coding RNA, and AI related to depression and suicide. It discusses new research approaches, such as spatial transcriptomics, addresses challenges connected to various research materials and methodologies, and proposes avenues for future studies.

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INTRODUCTION

Major depressive disorder (MDD) is the most common but severe mental illness, affecting approximately 15–17% of the population [1–3]. Its main symptoms include low self-esteem, a depressed mood, and anhedonia, accompanied by cognitive, sleep, and eating disorders [4, 5]. Suicidal behavior is often reported during depressive episodes, and the suicide risk is approximately 15% in depressed individuals [6–8]. A recent meta-analysis showed that the prevalence of suicidal ideation and suicide attempts in MDD patients was approximately 53 and 31%, respectively [9, 10]. At present, treating and preventing depression and suicide pose significant challenges, largely due to the unclear pathogenesis and the absence of objective clinical diagnostic criteria [11]. Additionally, substance use disorder and disease severity are significant predictors of non-adherence. Moreover, in the treatment of depression, non-adherence to treatment is a critical reason for the gap in efficacy and effectiveness of the disease. For example, one study evaluated patients at various time points and identified several predictors of non-adherence in individuals with mood disorders. These predictors included younger age, co-occurrence of substance use and personality disorders, patient beliefs, poor insight, severity of illness, treatment-related side effects, specific characteristics of the disease, and a weak treatment alliance [12]. From the perspective of neurobiology and pathogenesis, not only is there a need to identify novel molecular pathways, but also effective biological markers and drug targets, which can provide effective diagnosis and treatment of MDD and suicide [13].

In recent years, whole-genome data obtained from blood samples, human autopsy brain tissue, and animal models through high-throughput sequencing technology have allowed for the collection of extensive omics data that captures the biological state of diseases. This includes alterations at the molecular level, such as gene transcripts, epigenomes, and proteins [14, 15]. With the emergence of patients' omics data and the use of advanced bioinformatics analysis and artificial intelligence (AI) methods to integrate the genomic, transcriptomic, and epitranscriptomic data, combined with imaging, phenotype, and other multi-level clinical data to carry out systematic research, is expected to provide new methods and approaches for systematically explaining the mechanism of MDD development and suicidal behavior. This approach aims to maximize the discovery of potential drug targets and effective molecular markers [16–18]. Transcriptomics can not only measure approximately 25,000 coding transcripts but also evaluate the expression of gene isoforms and the use of differential exons. The application of AI–transcriptome in depression and suicide behavior is provided in Fig. 1. Microarray technology, based on the hybridization of fluorescently labeled complementary DNA with hundreds of thousands of oligonucleotide probes generated from the genomic sequence library and the subsequent bulk mRNA sequence, can not only quantify the annotated transcripts but also discover new genes [19]. The recent single-cell sequencing can provide the gene expression profile of a single cell and phenotype-related cell type information [20]. The current omics research mainly relies on two types of tissues: (1) brain tissue, which is biologically meaningful for the occurrence of MDD and suicide, and (2) peripheral blood or saliva samples, which are easier to obtain and study for biomarkers. From the perspective of research use, transcriptomics research in animal models and human cadaveric brain tissue can not only enhance understanding of the molecular characteristics of gene expression

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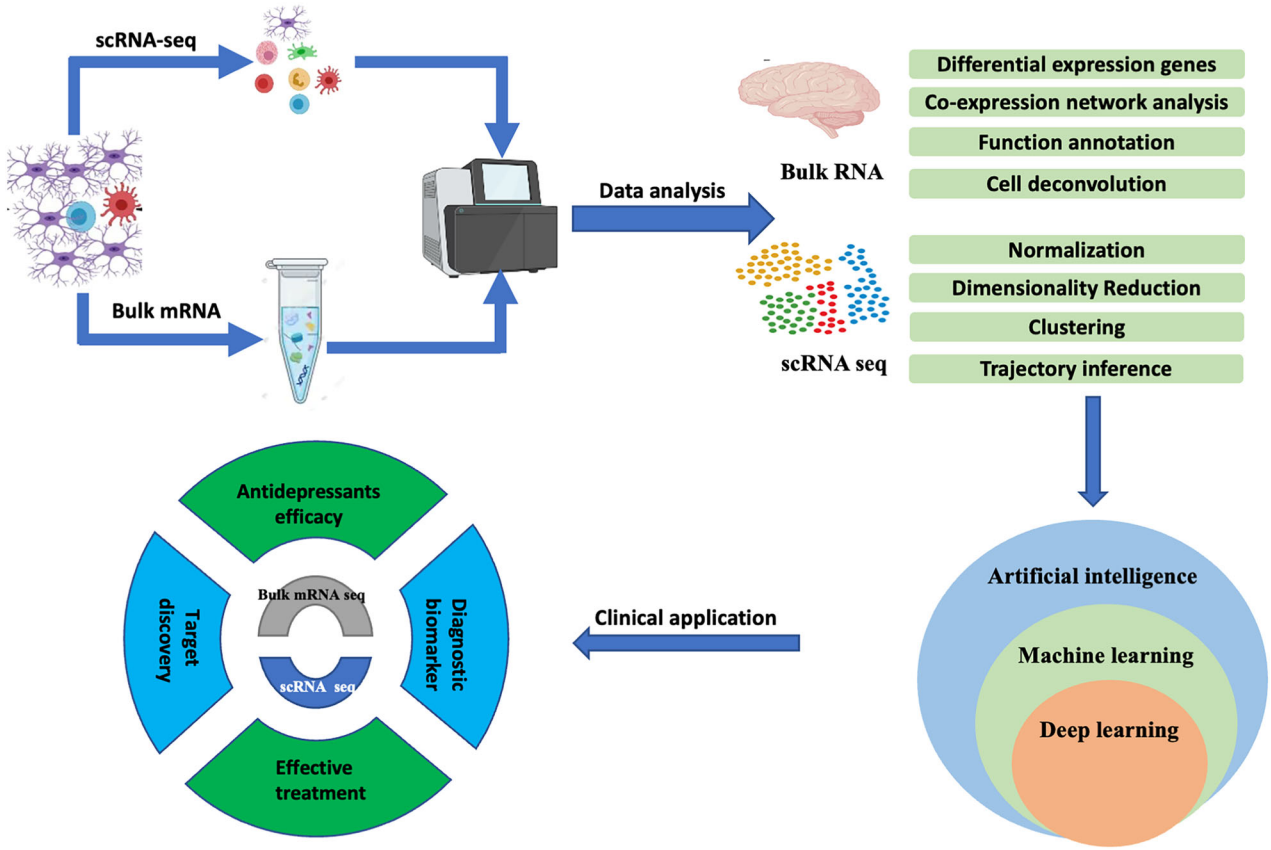

Fig. 1 The application of AI–transcriptome in depression and suicide behavior. Transcriptomics technology has become a powerful tool for analyzing depression-related neurobiology at the bulk tissue and single-cell levels. Currently, artificial intelligence (AI) methods play a key role in utilizing the big data generated by transcriptome analysis. In particular, the application of machine learning and deep learning in the field of transcriptomics research is growing rapidly. AI-assisted transcriptomics is often used to study the heterogeneity of neuronal cells, new target discovery, and key molecular biomarkers.

under environmental and stress exposure but also verify the key functions of perturbed genes. This review offers a comprehensive overview of advancements in transcriptomics and non-coding RNAs related to depression and suicide. It also discusses new research approaches, such as spatial transcriptomics, while addressing the challenges associated with various research materials and methods. Additionally, it presents recommendations for future investigations.

BULK RNA-SEQUENCING APPROACH IN DEPRESSION AND SUICIDE

RNA transcript profiling in depression and suicide

High-throughput technologies such as DNA microarrays and RNA sequencing can explore the expression levels of transcripts across the entire genome and identify changes in gene expression using hypothesis-free methods [21]. In the past decade, many studies have used postmortem brain tissue, peripheral blood cells, and tissue samples from animal models to conduct transcriptomic studies to identify molecular expression profiles associated with MDD and suicide. The following is a summary of bulk mRNA-seq studies on the above three materials:

i. Human postmortem brain studies

Early transcriptomic studies primarily used DNA microarray and mRNA sequencing to conduct relevant transcriptomics studies in different brain regions, including the amygdala [22], anterior cingulate cortex [23–25], prefrontal and orbitofrontal cortex regions [26–28], and hippocampus and hypothalamus [29, 30]. These studies showed large-scale differences in transcriptional molecular profiles in depressed individuals. Overall, the consistent results between different studies showed abnormalities in glutamatergic and gamma-aminobutyric acid-related (GABA) signaling pathways [31]. We have recently summarized the transcriptomics data from different human tissues in MDD reported previously and identified tissue-specific functional modules and their mediated biological pathways based on weighted gene co-expression network analysis (WGCNA), robust rank aggregation with transcriptional profiling, and genome-wide association studies [32]. We identified tissue-specific modules [31], which were distributed across the four different brain areas in MDD. Recently, a group of researchers has conducted a large-scale transcriptomics study on six different brain areas to explore the issue of sex differences in MDD [33]. They found that there were almost no overlapping differentially expressed genes in men and women with MDD. Using a network-based approach to identify potentially relevant gene targets, the research team found that different brain regions in MDD had varying levels of network homology between males and females across brain regions. However, the associations between these structures and the expression of MDD remained highly sex-specific [34]. Similarly, another study conducted the transcriptomic analysis with the help of RNA-sequencing using different types of postmortem brain tissues obtained from MDD with or without suicide. The study discovered several differentially expressed genes (DEGs), such as

MTRNRL8 and IL8, and ATPase-mediated signaling pathways [26]. We integrated the above two transcriptomic datasets from MDD and suicide individuals and screened the overall differentially expressed genes with the help of multiple comparison analysis methods [34]. We identified the crucial target genes and signaling pathways that differentiated suicidality in patients with MDD, such as PRS26, ARNT, and SYN3 [34]. Recently, using RNA-sequencing data from postmortem brain samples, a study explored the gene modules related to suicidal ideation. These gene expression modules were related to microbial infection, inflammation, and immune response, and the presence of suicidal ideation was related to inflammatory characteristics in the blood and brain [35].

Overall, data derived from postmortem brain tissue can provide direct insights into the modifications in molecules, cells, and circuits linked to mental illness. However, numerous challenges exist in these studies, including comorbid diagnoses, varying symptom characteristics, heterogeneity, and confounding effects that must be addressed [36].

ii. Human blood studies

Peripheral blood can be used as a surrogate marker for disease processes such as MDD, which can characterize disease states [31, 37]. Compared with other tissues, peripheral blood has several advantages. For example, peripheral blood can be collected in large volumes, RNA can be rapidly stabilized, and specific cell subtypes, such as peripheral blood mononuclear cells (PBMCs) or white blood cells, can be isolated and monitored for the health status of patients [38]. A transcriptome analysis conducted in peripheral blood samples from remitters and non-responders MDD patients at admission and after 2 and 5 weeks of antidepressant treatment identified 127 transcripts significantly associated with treatment response. Validation with independent samples further confirmed that decreased expression of retinoid-related orphan receptor α (RORα), germinal center expressed transcript 2 (GCET2), and chitinase 3-like protein 2 (CHI3L2) at admission was associated with drug efficacy. In addition, it was found that leukocyte-specific protein 1 (LSP1) was significantly reduced after 5 weeks of drug treatment [39]. A recent study performed a genome-wide gene expression analysis of peripheral blood from patients with MDD, and the samples of the patients were divided into those who responded to or did not respond to 8 weeks of escitalopram treatment. In the ineffective group, the mRNA expression levels of two genes, CHN2 and JAK2, were found to be increased. Specifically, CHN2 can alter hippocampal neurogenesis, whereas JAK2 can activate innate and adaptive immunity, suggesting that these genes may be candidate predictors of treatment response [40]. Simultaneously, a thorough convergent functional genomics (CFG) strategy, combining genetic and functional genomics data within a Bayesian framework, identified and prioritized potential biomarkers linked to mood disorders and suicidal behavior in the blood of patients suffering from various mental illnesses [41, 42]. A different study focused on microarray-based transcriptomic data from peripheral blood. The gene expression of 38 MDD patients and 14 healthy controls was analyzed to identify DEGs and biological mechanisms in MDD. Seven DEGs were identified in these subjects and found to be involved in immune and inflammatory responses. Further, antidepressant responders and non-responders were analyzed after 6 weeks of treatment, which led to the identification of additional DEGs and biological mechanisms associated with treatment response in MDD [43].

In terms of suicide research, a recent study conducted RNA sequencing in participants with and without suicidal ideation and found that 19 co-expression modules were significantly associated with the presence of suicidal ideation [35]. We also conducted transcriptomic studies using peripheral blood samples from patients with severe and mild depression and found some key genes that were significantly related to the severity of depression [44]. In summary, transcriptomic research utilizing peripheral blood samples can assist in clinically identifying potential biochemical and molecular markers associated with drug effectiveness and disease severity.

iii. Animal models of depression studies

Animal models of depression-like behavior have several advantages over human studies, where various drug modalities and gene editing can be introduced to detect changes in neural circuitry and molecular cell signaling pathways. In previous reviews, we have comprehensively assessed relevant animal models of depression-like behavior, potential drug targets, and possible drugs that can be used to treat depression [45–47]. In recent years, relevant omics experiments have been carried out around topics such as stress, depression and resilience, sex differences, and antidepressant treatment with the help of animal models such as learned helplessness [48, 49], chronic unpredictable mild stress [50], and social defeat stress [51]. A recent study proposed a two-hit model to study whether stress in a specific postnatal period would increase sensitivity to social defeat stress in adulthood [52]. This model applied maternal separation in the early postnatal period (PND2-12) and the late postnatal period (PND10-20) as early life stress, and social defeat stress in adulthood (PND60-70). The results showed that postnatal stress occurring within 10–20 days after birth increased sensitivity to social stress in later life [52, 53]. With the help of transcriptomic analysis of the ventral tegmental area (VTA) and nucleus accumbens (NAc) brain areas, it was found that the gene Otx2 encoding orthodentine homeobox 2 is a differentially expressed gene in the VTA that is significantly related to depressive behavior. Promoting the function of an upstream regulator of depressive transcriptional signatures, transient overexpression of Otx2 in the ventral tegmental area of young male mice reduced susceptibility to social defeat in adulthood and reversed the downregulation of Otx2-regulated target genes in this brain region [52].

Our laboratory conducted transcriptomic and WGCNA in the learned helplessness animal model and found that genes involved in olfactory signal transduction mediated the occurrence of depressive-like behaviors [54]. At the same time, we also established the unpredictable chronic mild stress depressive-like behavior model and treated it with hypericin as an antidepressant. Then, we investigated genome-wide transcript level and m^6A modification changes in the hippocampus before and after treatment with hypericin. The results showed that hypericin could ameliorate the depressive-like behavior in UCMS mice, upregulate the two important m^6A-modifying enzymes METTL3 and WTAP, and further mediate downstream neurotrophic factor signaling pathway [55].

A recent study employed multi-point in vivo neurophysiology to measure EEG network activity previously identified as indicative of a potential stress-vulnerable brain state [56]. They combined this with single-cell RNA sequencing of the prefrontal cortex to identify distinct transcriptomic differences between groups of mice with inherently high and low-stress vulnerability. The results revealed that GABAergic (γ-aminobutyric acid) neuron gene expression had the most significant contribution to network activity in stress-vulnerable brain states. Additionally, genes differentially regulated with vulnerability network activity significantly

overlapped with genes identified by genome-wide association studies as having single-nucleotide polymorphisms strongly associated with depression, as well as with genes that were expressed at higher levels in the prefrontal cortex of patients who had major depression.

MicroRNA (miRNA) studies in depression and suicide

Among various non-coding RNAs, microRNAs (miRNAs) are the most studied and wellcharacterized ncRNAs [57]. miRNA is a fragment of approximately 22 nucleotides that can directly modify the cellular stability of messenger RNA (mRNA) after transcription, thereby regulating the protein translation process. Each miRNA can regulate hundreds of mRNA target genes with different functions [58]. In the cell nucleus, after transcription, primary miRNA (pri-miRNA) is cleaved into precursor miRNA (pre-miRNA) by Drosha ribonuclease III (DROSHA) and microprocessor complex subunit DGCR8. Then, under the action of export protein 5, the pre-miRNA is transferred to the cytoplasm, where they are converted into mature miRNA by endoribonuclease Dicer and TAR RNA binding protein (TRBP). Argonaute proteins and mature miRNAs are combined to form the RNA-induced silencing complex (RISC). The nucleotide sequence of mature miRNA is complementary to at least one mRNA, usually binding to the 3′ untranslated region of the target mRNA [59]. MiRNAs typically prevent mRNA translation into protein through an inhibitory process that involves deadenylation of the target mRNA. Alternatively, when the miRNA sequence is highly complementary to its target mRNA, it can cleave the mRNA and cause its degradation [60].

MiRNAs mediate and participate in various physiological processes such as neurogenesis, synaptic development, and neural plasticity (Rashidi, 2023 #152). Increasing clinical and preclinical evidence suggests that significant changes in miRNA expression occur in the MDD brain, and miRNAs mediate epigenetic regulation at the gene expression level. Our laboratory has long focused on miRNA research in MDD and suicidal behavior. We have carried out extensive research using postmortem brain tissue and animal models of depression, laying a foundation for the identification of the etiological mechanisms and molecular markers of depression and suicide. In terms of postmortem brain tissue, earlier, we conducted PCR arrays to detect a large number of miRNAs in the prefrontal cortex of MDD and suicide subjects and found that the expression of miRNA was generally downregulated. At the same time, we demonstrated a co-expression network composed of 29 miRNAs, whose target genes mediated splicing, apoptosis, DNA methylation, and axonal growth [61]. We also reported specific miRNA co-regulated networks that were distinct in healthy and suicide subjects. Subsequently, we found that a specific set of miRNAs was related to suicide, irrespective of psychiatric diagnosis [62]. Our research group further used miRNA PCR arrays to explore the expression changes of miRNA in the locus coeruleus of suicide subjects and identified significantly altered miRNAs and potential target genes forming specific networks, providing a basis for explaining suicidal behavior [63]. We also explored genome-wide miRNA expression in the synaptic fraction of the prefrontal cortex with the help of miRNA sequencing technology. In the purified synaptosomes of the prefrontal cortex, 351 differentially expressed miRNAs were found. Further cell culture and bioinformatics analyses revealed their role in synaptic plasticity, nervous system development, and neurogenesis, and provided a basis for specific synaptic miRNA libraries and local regulatory patterns [64]. Similarly, we explored the molecular expression characteristics of miRNAs in the anterior cingulate cortex with the help of miRNA sequencing. We found alterations in a distinct set of miRNAs in depressed suicide individuals [65]. In another study, we reported increased expression of miR-124-3p in the postmortem brains and blood of patients with depression, which mediated the expression of genes related to the glutamatergic system [66]. At the same time, we studied the potential mechanism of abnormal regulation of the expression of cytokine gene tumor necrosis factor-α (TNF-α) via miR-19a-3p in the brains of MDD subjects who died by suicide or causes other than suicide [67]. We reported that miR-19a-3p was unable to interact with TNF-α and competed with RNA-binding protein HUR, which led to the continuous production of this cytokine in suicidal subjects.

In terms of animal models of depression, our research team used the LH animal model and miRNA PCR array to explore the role of miRNAs in the development or resilience of depressive behavior. The results have shown that a larger number of miRNAs (miR-96, 141, 182, 183, 183*, 298, 200a, 200a*, 200b, 200b*, 200c and 429) were significantly down-regulated in the learned helpless rats. These microRNAtargeted transcripts were mainly enriched in the synaptic-associated functions [68].

In recent years, our research group has explored sex-specific differences in miRNAs in early-life and acute stress. The results showed that in male rats, separated from their mothers, the expression of miRs-29, −124, −132, −144, and −504 were significantly altered in the frontal cortex. However, environmental enrichment was able to reverse the downregulation of miR-29b-1–5p and miR-301b-3p in animals separated from their mothers [69, 70]. At the same time, we found that specific miRNAs increased susceptibility to depression-related reward deficits through genes that regulate the serotonin pathway [71]. In addition to our research group, the Turecki group has reported altered expression in miRNAs, including miR-1202 [72], miR-139-5p, miR-320c, miR-34c-5p, miR-425-3p, miR-24-3p, and miR-146a in the depressed brains [73, 74]. At the same time, with the help of blood materials, it was also found that some miRNAs, such as miR-1202, miR-135a, and miR-16 were significantly differentially expressed in depressed patients [75]. Overall, at the miRNome level, relevant clinical and preclinical studies support changes in the expression of miRNAs in MDD and suicide brains and that gene expression levels are highly epigenetically regulated via miRNAs.

lncRNA studies in depression and suicide

LncRNAs are transcripts with a length of more than 200 nucleotides. They cannot encode proteins. However, they play an important role in transcriptional regulation by modulating enhancer activity, chromatin looping, and epigenetic modifications [76]. Post-transcriptionally, lncRNAs influence alternative splicing, mRNA localization, and cytoplasmic granule assembly [77]. They are important regulatory molecules for interacting with genes and the environment [78]. Studies have found that lncRNA and mRNA have similar structures and lncRNA have lower expression levels compared with mRNAs [77]. About 40% of lncRNAs are specifically expressed in the brain [79]. Therefore, lncRNAs show tissue-specific and cell-specific expression characteristics and have important physiological functions as scaffolds, guides, or decoys [80]. There have been a few studies that demonstrate abnormal expression and functions of lncRNAs in depression and suicide. For example, it has been reported that a large number of lncRNAs were downregulated in the anterior cingulate cortex of cadaveric brain tissue [81] and blood PBMCs [82] of patients with depression and suicide, and there was not much overlap in the downregulation in the two disorders. In terms of candidate lncRNAs, LINC00473 was found to be a sex-specific target, which was only downregulated in the prefrontal cortex (PFC) of depressed women. The specific expression of LINC00473 can promote behavioral resilience, especially in women [81]. The lncRNA FEDORA is upregulated in the PFC of depressed women and is enriched in oligodendrocytes and neurons. Additionally, blood levels of FEDORA are related to the diagnosis of depression in women and ketamine treatment [83]. A recent study examined the role of long intergenic non-coding

RNAs (lincRNAs) LINC01268 to understand the interplay between genetics, brain function, and behavior in the context of aggressive behavior and suicide. The study found a significantly higher expression of LINC01268 in the PFC of individuals who died by violent suicide compared to non-suicides and suicides by non-violent means [84]. Carriers of the minor allele of this SNP, linked to increased LINC01268 expression in the brain, exhibited higher scores on a lifetime aggression questionnaire and showed diminished engagement of the PFC during fMRI tasks involving the processing of angry faces [84].

In animal models of depressive-like behavior, our research group discovered that specific types of lncRNAs mediate lncRNAs related to depression, resilience, and fluoxetine treatment. From the global view, using multiple comparison analyses, we identified some differentially expressed mRNAs and lncRNAs with each phenotype. By means of a machine learning approach and multi-omics analysis, we observed that Spp2, Olr25, Mboat7, Lmod1, Il18, and Rfx5 genes contributed to depression-like behavior, and Adam6 and Tpra1 in antidepressant response. Our study shows novel roles for lncRNAs in the development of specific depression phenotypes [85].

CircularRNA (circRNA) studies in depression and suicide

Circular RNAs, or circRNAs, have increasingly gained attention as promising biomarker targets to inform disease diagnosis and prognosis. CircRNAs are long, non-coding RNAs that are closed in a circular formation due to the covalent joining of back-spliced exons from a single pre-mRNA [86, 87]. CircRNAs are involved in various biological functions, including regulation of cell proliferation, direct and indirect regulation of gene transcription, regulation of protein function, and sequestration of miRNAs [88]. Emerging evidence has implicated potential roles for circRNAs in psychiatric diseases, including schizophrenia, bipolar disorder, and MDD [89]. At present, research on circRNA in depression is mainly reported in the peripheral blood of patients. It has been reported that there are significant differences in a few circRNAs, such as hsa_circRNA_103636 [90], circFKBP8 [91], and circMBNL1 circDYM in MDD patients [91]. As for biomarkers, the research on circRNA is still in its infancy, and there is a lack of omics research related to cadaver brain tissue as a material and the biological mechanisms that mediate the occurrence of depression and suicidal behavior.

Other novel ncRNAs (snoRNAs and pwiRNAs) in depression and suicide

In addition to non-coding RNAs, there are also non-coding RNAs composed of other functional RNA molecules, such as small nucleolar RNAs, snRNAs, and piwiRNAs. Although the number of these RNA molecules is small, they play an important role in regulating genes and are involved in a variety of complex mental and neurological diseases. Small nucleolar RNAs (snoRNAs) primarily exist in the nucleolus of eukaryotic cells and play an important role in rRNA modification [92]. Additionally, they are involved in a variety of biological mechanisms, including the regulation of alternative splicing, precursors of smaller miRNA-like RNA fragments, and cellular pathways [93]. Recent studies have found that antidepressant drugs can significantly increase the content of snoRNA (SNORD90), thereby changing the modification and expression level of its target gene NRG3. SNORD90 downregulates the expression of NRG3 and increases glutamate content, thereby producing antidepressant drug activity [94]. We have also reported significant alterations in snoRNAs in synaptosomes from the PFC of schizophrenia subjects [62]. SNORD85 was the most prominent one, which was found to be decreased by ~50%. This snoRNA belongs to a novel class of small non-coding RNAs highly expressed in humans, especially in synaptosomes.

PIWI-interacting RNAs (piRNAs) are small noncoding regulatory RNAs that form complexes with PIWI proteins and are found in both vertebrates and invertebrates [95, 96]. They belong to the same biological class as microRNAs (miRNAs) and small interfering RNAs (siRNAs). However, piRNAs differ from miRNAs in several ways, first in size (piRNAs are typically 24 to 32 nucleotides long rather than 21 nucleotides), second in the lack of sequence conservation, and third in their biogenesis, being independent of Dicer [97, 98]. Overall, piRNAs are the most diverse class of regulatory RNAs, originating from RNA transcripts at transposons, protein-coding genes, and specific intergenic sites [95, 96]. Animal research has shown that piRNAs in neurons play an important role in cognition and memory [99]. Animal models also show that Miwi/Piwil1 knockout mice exhibit hyperactivity and anxiety-like behaviors, and the reduction of Miwi/Piwil2 can increase fear memory [100]. Therefore, piRNA in neurons may be involved in the occurrence of various neurological disorders.

SINGLE-CELL RNA-SEQUENCING APPROACH IN DEPRESSION AND SUICIDE

Single-cell sequencing technology has enabled us to identify specific cells that cause transcriptome changes in specific diseases [101, 102]. The brain, as the most important material for the study of neuropsychiatric diseases, contains countless cell types with individual, specific, and spatial functions [103]. Cluster analysis, cell type markers for specific gene clusters, and annotation analysis of gene expression based on single-cell omics data can not only identify transcripts that are differentially expressed in specific cell types between cases and controls but also draw pseudo-time trajectories to characterize transcriptional changes across age [104]. However, there are obstacles to isolating whole cells from postmortem brain tissue, and single-nucleus isolation has become the first choice for research. Compared with bulk tissue RNA sequencing technology, its transcript coverage is relatively low, and it cannot identify missing or under-expressed transcripts [105]. In recent years, deconvolution analysis algorithms have been developed to infer cell-type proportions [106] and even cell-type-specific expression [107] from bulk tissue gene expression data. Multiple studies have performed single-cell sequencing on postmortem brain samples related to MDD, revealing gene expression changes specific to certain cell types. Recently, one study applied single-cell sequencing technology in the prefrontal cortex tissue of male and female patients with depression and compared the gene expression patterns in terms of cell types [108]. The study found differences in differentially expressed genes between men and women. DEGs in women were primarily enriched in microglia and parvalbumin interneurons, while DEGs in men were primarily enriched in deep excitatory neurons, astrocytes, and oligodendrocytes. More recently, a study integrated GWAS data with single-nucleus RNA sequencing data of the dorsolateral prefrontal cortex from elderly depressed patients and conducted a transcriptome-wide association study (TWAS) and Mendelian randomization analysis [109]. The results showed that 68 depression-related core genes were enriched in excitatory and inhibitory neurons. TWAS studies found that genetic risk genes, highly associated with depression, had greater transcriptomic differential expression levels. At the same time, genes such as KCNN2 and SCA1 were identified as being associated with specific cell subtypes and late-life depressive symptoms. In the animal model of acute stress, singlenucleus RNA sequencing (snRNAseq) and multi-omics analysis have been done to explore the effects of stressors of different severity on cell types in the hippocampus [110]. The findings underscored that glial and vascular cells play a significant role in the overall transcriptional response to stress, which is also notably specific to each cell type. In summary, single-cell RNA sequencing provides an important research basis for studying brain tissue with complex cell types.

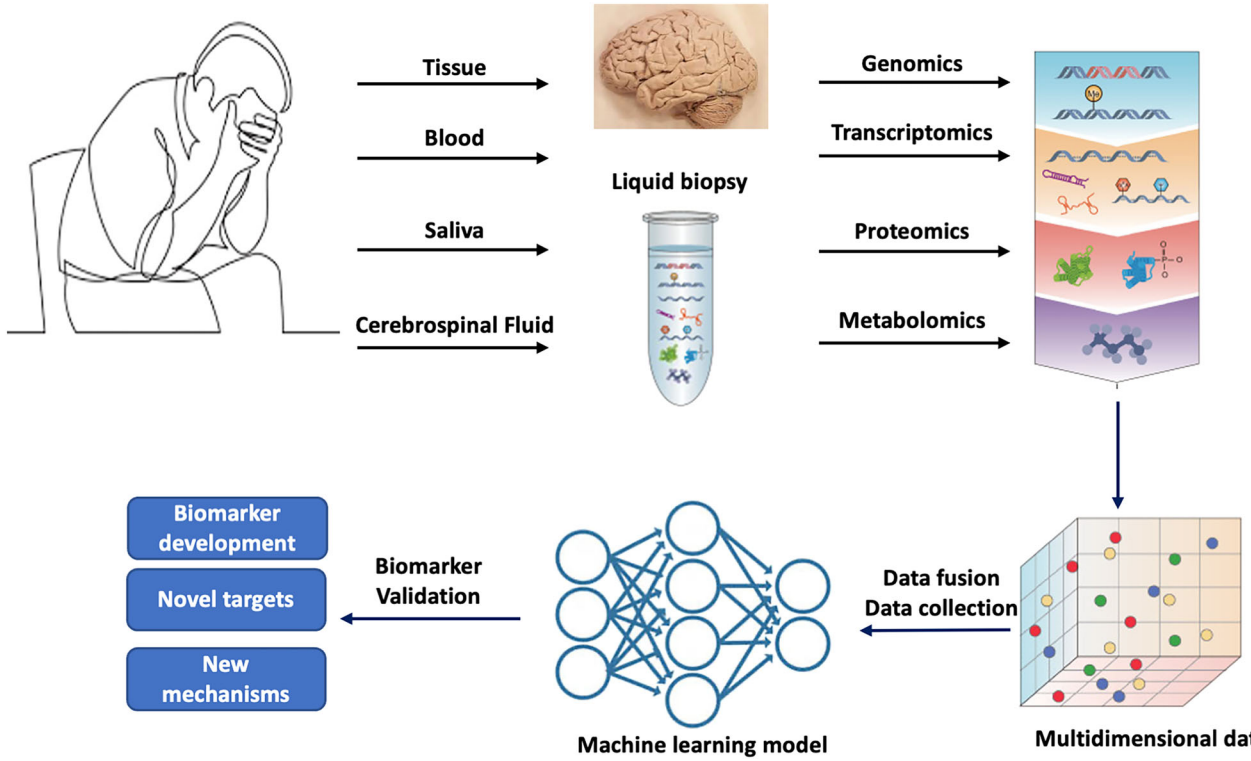

Fig. 2 Multi-omics approaches and machine learning contributing to biomarker discovery of early diagnosis in depression and suicide. Different materials from patients with depression, including brain tissue and body fluids such as blood, saliva, and cerebrospinal fluid, can be analyzed through multi-platform omics technologies such as genomics, transcriptomics, proteomics, and metabolomics mass spectrometry. These multidimensional omics data are then analyzed through machine learning and high-dimensional bioinformatics to explore the overall molecular analysis of depression and the discovery of biomarkers in early diagnosis.

MULTI-OMICS APPROACHES TO DEPRESSION AND SUICIDE

Studies have found that complex diseases such as depression and suicide are caused by interactions between genes and the environment [8]. This can be studied at different levels, including genomics, transcriptomics, epigenetics, proteomics, and metabolomics. Therefore, molecular mechanisms associated with these complex disorders should be explored and analyzed from a holistic and systematic perspective (Fig. 2). From the systems biology perspective, a single biological level cannot attain the complex molecular relationships and regulatory mechanisms [111]. Combining transcriptomics data with proteomics, epigenomics, and microbiome data can provide a broader insight into the potential disease mechanisms associated with a condition. Currently, the main methods of multi-omics integration are (1) overlap or regression, (2) graph theory and network methods, (3) Bayesian algorithm, (4) dimensionality reduction, and other methods [14, 112]. With the help of these research methods, several studies have carried out relevant multi-omics data analysis in materials such as blood and postmortem brain tissue and successfully mined out some novel risk genes. Recently, we integrated the mRNA-seq data, DNA methylation, and scRNA-seq data and identified some important dysregulated genes influenced by DNA methylation in two brain regions of MDD and suicide individuals. Interestingly, we found that oligodendrocyte precursor cells (OPCs) contribute most to cell-type proportions related to differential expression genes and methylated sites in suicidal behavior [113]. Meanwhile, we also used strategies for identifying tissue-specific modules, annotated pathways for elucidating biological functions of tissues, and tissue-specific genes based on WGCNA and robust rank aggregation with transcriptional profiling data from different human tissues and GWAS data to mine out those important risk genes for the development of MDD [32]. We reported that tissue-specific genes from the PFC were involved in MDD-related functions.

OMICS AND AI APPROACHES IN DEPRESSION AND SUICIDE

There are a few studies that have utilized transcriptomic data in combination with machine learning in dissecting MDD phenotypes from controls. For example, one study applied a support vector machine (SVM) approach to blood gene expression data to classify drug-free, first-episode cases with subsyndromal symptomatic depression (SSD), MDD, and matched controls [114]. They tested various combinations of signatures from the three pairwise compartmental results and identified 48 gene expression signatures with 100% accuracy. These signatures may be significant for diagnostic purposes and for classifying SSD, MDD, and healthy controls. Another study also applied an SVM approach to classifying MDD cases and controls based on expression data of preselected blood RNA markers [115]. This SVM model provided a cross-validated sensitivity and specificity of 90.6% for the diagnosis of MDD using a panel of 10 transcripts. When the logistic equation on the SVM model was applied, it quantified the likelihood of a depression score, which provided the probability of an MDD diagnosis. Recently, a random forest classifier was used on blood transcriptomic and methylomic data to distinguish between cases of MDD, suicide attempters, and controls. The data provided high classification accuracies ranging from 80–100% [116]. Additionally, using these data sets, the authors developed regression models for predicting psychiatric scales with R^2 values of 0.961 and 0.943 for the Hamilton Rating Scale for Depression 17 and Scale for Suicide Ideation, respectively, which were used to construct psychiatric status prediction models for improved mental health treatment. More recently, machine learning for the gene expression data from the dorsolateral prefrontal cortex and blood of MDD subjects identified gene sets and covariates to predict the occurrence of MDD [117]. In human postmortem brain tissues, transcriptomic and epigenetic changes in depression and suicide have been recapitulated that directly reflect changes

relevant to the neurobiology of suicide and psychiatric disorders [118–122]. Additionally, our group used machine learning to analyze the gene expression profiles of postmortem brain tissues from patients with suicidal depression, non-suicidal depression, and non-depressed suicide and identified several lncRNAs and mRNAs with high area under the curves (AUCs) as molecular markers for distinguishing depression with or without suicidal [123].

In the machine-learning analysis of miRNAs, one study analyzed gene expression data from MDD and controls and established supervised and unsupervised miRNA machine-learning analysis to identify potential molecular markers predicting depression and antidepressant efficacy [124]. In the view of machine learning analysis, we integrated lncRNA microarray data in the brain of rats who showed depression resiliency and susceptibility before and after fluoxetine treatment with machine learning and cross-validation analysis, and successfully identified potential biomarker lncRNAs, which were specifically associated with depression, resiliency, and fluoxetine treatment [85]. Overall, a combination of transcriptional data and a machine-learning approach can provide the key gene sets and pathways as predictors for depression and suicide.

NOVEL OMICS APPROACHES AND AI-BASED ANALYSIS IN DEPRESSION AND SUICIDE

So far, transcriptomic studies based on postmortem brain tissue have mainly focused on bulk mRNA-seq in total tissue homogenates, which cannot provide heterogeneity of cell types within brain regions and is affected by cell types and other confounding factors. In recent years, the rapid development of single-cell sequencing technology has allowed researchers to observe transcriptome changes in specific cell types. This advancement is crucial for studying mental illness. Single-cell sequencing technology can not only provide molecular characteristics of transcripts in specific cell types but also identify differential expression information of transcripts between cases and controls and map transcriptional changes in pseudo-time trajectories. Currently, mononuclear cell transcriptomics has been applied to the study of depression using postmortem brain tissue as material. Chromatin accessibility sequencing (ATAC-seq) can be an important supplement to regulating gene expression through higher-order chromatin structure. Combining scATAC-seq and scRNA-seq can be used to evaluate the epigenetic regulatory mechanisms of transcripts that produce variations in specific cell types in postmortem brain tissue.

Spatial transcriptomics can capture the local context of transcriptional activity at the regional or individual cell level within intact tissue [125]. When tissue cryosections are placed on spatial transcriptomic slides, barcoded primers bind to and capture adjacent mRNAs in the tissue. Subsequent cDNA libraries incorporate the spatial barcodes of the primers, which, after RNA sequencing, allow data from each individual mRNA transcript to be mapped back to its origin within the tissue section [126]. Spatial transcriptomics has transformed how we identify cellular function and state in intact tissues. Although studies of the human brain remain scarce [127], spatial RNA sequencing has captured the cellular diversity of the hippocampus [128] and the six prefrontal cortical layers in humans [129] and mice [130–132], providing novel tools to study the detailed anatomy of these processes in the brains of MDD and suicidal individuals.

The proteome is the entire set of proteins produced or modified by an organism or system. Proteomics allows the identification of an ever-increasing number of proteins. The proteome level in the body dynamically changes over time after the subjects receive different stressors in the cell or organism [133]. Much proteomics data is collected using high-throughput technologies such as mass spectrometry and microarrays. The rapid development of single-cell mass spectrometry (scMS) in recent years has provided the opportunity to analyze more proteins and post-translational modifications (PTMs) without the need for affinity reagents, providing an attractive alternative to single-cell multimodal analysis [134]. Proteomic studies in human brain homogenates, combined with spatial techniques such as DBiT-seq spatial proteomics, focusing on regions of interest associated with, will enable the characterization of the molecular features associated with depression and suicidal behavior [135].

The above-mentioned new omics methods can provide rich and detailed data from different perspectives. Recently, AI has become a powerful tool for data analysis, automatically mining data and providing insights into the complex relationships between different datasets. One of the commonly used AI algorithms is machine learning. The core of this algorithm is pattern recognition. The main processes include feature extraction and selection, classification model construction, generalization ability testing, etc [136]. Currently, the frequently used classification diagnosis models include random forest, k-nearest neighbor (kNN), logistic regression, support vector machine (SVM), and Gaussian process classifier (GPC) [137]. Among them, random forest and SVM are the most widely used pattern classification models in the study of neuropsychiatric diseases [138]. One study employed the random deep forest algorithm in machine learning, integrating leave-one-out cross-validation to analyze blood data of differentially expressed genes (DEG) and differentially methylated CpG sites. This approach successfully distinguished between suicidal and non-suicidal behaviors in individuals with MDD with an accuracy of 92.6%. Of these, 63 features were composed only of differentially methylated sites [116].

The other commonly used AI method is deep learning. This algorithm uses a specific network structure and training to learn meaningful representations of input images for subsequent image classification. The main processes of deep learning algorithms (feature extraction, selection, classification, etc.) can be implemented by building a deep learning framework [139]. The study used deep learning algorithms and WGCNA to study the transcriptome, genome (SNP), and chromatin conformation (Hi-C) PsychENCODE data from dlPFC from bipolar and schizophrenia patients and controls. They found that some important genes were involved in the immune and synaptic processes shared by these two disorders [140].

Deep learning can effectively manage the high dimensionality and complexity of mental health data. Automatically constructing models from diverse data sources is anticipated to facilitate early detection and intervention strategies while providing more accurate, personalized treatment methods. The data sources currently employed for deep learning include: (1) extracted information from clinical notes and interviews; (2) Electronic Health Records (EHRs); (3) neuroimaging data (e.g., MRI, fMRI); and (4) genetic and molecular data. These models can assist in identifying language markers of depression and suicidal ideation, thus enabling early risk detection and intervention as well as uncovering the neurobiological mechanisms of suicide and depression. One example is a study that applied deep neural networks to textual data from social media to identify markers of depression, demonstrating the potential of deep learning for mental health screening [141]. Another study has used deep learning models to analyze EHR data, improving the prediction of suicide risk by extracting meaningful patterns from clinical narratives [142]. Recent reviews have also summarized the growing body of work on deep learning applications in mental health, highlighting advances in both text-based and imaging-based analyses [143].

Natural language processing (NLP) is another algorithm that can convert text from unstructured formats to structured formats. NLP can effectively create organized datasets to train and develop useful algorithms [144]. This algorithm is widely used in mental

health clinics. The diagnosis of mental illness primarily relies on voice analysis during interviews between doctors and patients. Clinicians use their skills in recognizing behavioral patterns to convert this information into relevant medical data for recording and diagnosis [145].

SUMMARY AND FUTURE DIRECTIONS

Depression and suicide are intricate conditions affected by genetic factors, environmental influences, and their interplay. The most relevant result from the multi-omics data analysis discussed above indicates that depression may be influenced by multiple genes. These susceptible genes can be easily affected by environmental factors and undergo epigenetic regulation, which consequently alters their gene expression and leads to the onset of depression. Therefore, it is essential to understand their molecular basis at various levels to discover new treatment targets and identify potential biomarkers for individuals at high risk. Omics technology and artificial intelligence research methods can help identify new key target genes and signaling pathways at the whole genome level. These key genes may lay the foundation for clinical research on depression and the identification of new targets for drug development. Additionally, AI can enhance precision medicine, as not all depressed patients respond to antidepressants. Furthermore, it is critical to identify the causal factors for suicidality among depressed patients. This is clinically relevant because not all depressed patients develop suicidal ideation or behavior. A prediction-based approach will be useful in preventing future suicides. Based on the current study, key pathogenic genes and signaling pathways need to be identified. Although research in this area is currently underway, pinpointing the networks associated with specific phenotypes would be highly desirable. Besides, multi-omics approaches should be used to design specific drugs based on druggable targets. This will offer valuable insights for developing more effective antidepressant therapies, particularly for those who are treatment-resistant. Regarding research strategy, omics can provide information on molecular characteristics related to disease. However, the brain has a variety of cell types. Therefore, transcriptomics analysis needs to be further integrated with clinical phenotypes and environmental factors to identify the systemic nature of the cause of the disorder. Regarding research materials, currently, studies are mostly carried out from cadaveric brain tissue and blood. With the advancement of neurosurgical technology, it has become possible to obtain relevant brain tissue sources from living bodies. However, these tissues are limited to case samples. It is believed that with the generation of large-scale omics data from postmortem brain tissues and patients' blood, more subtype classifications and precision therapies for affective disorders will emerge. Research approaches that use multi-omics and artificial intelligence to identify specific biomarkers for MDD aim to select the best antidepressant for each patient and predict treatment response. These methods are the most promising for achieving objective diagnosis and accurate treatment. The proposed biomarkers for clinical practice have several limitations. Implementing multi-omics as a standard clinical approach could lead to more effective diagnostic and treatment strategies. This may reduce the burden of MDD while improving patients' quality of life, satisfaction, and overall well-being.

Future research in the transcriptomics of depression and other psychiatric illnesses should focus on the following areas. Single-cell RNA-sequencing, multi-omics integration, and comparative overlap of animal models with postmortem findings are necessary. The brain is comprised of a myriad of cell types, and we must understand how these individual cells contribute to the mechanistic function of the cell types involved, as some gene pathways may have effects in only single cell types or opposite effects in different cell types. Bulk-tissue transcriptomics would miss the roles of such genes and pathways. Applying machine learning to combine different multi-omics data types may improve prediction accuracy. The advent of newer approaches and analytical tools is promising. As shown in a few studies, integrating blood and brain-based data would also be critical for AI-based molecular findings, given that blood-based approaches are much more accessible to the patient population. In this regard, large-scale AI-based studies in exosomes derived from the brain could be a game changer. Multi-omic approaches should be explored as well. Currently, most genetic variants fall within non-coding regions, and their impact on the transcriptome and cell biology is obscured. snATAC-seq and HiC-seq will be crucial for understanding how the genomic and nuclear structure of the cell regulates the transcriptome. Spatial transcriptomics is emerging as one of the most promising genomic technologies. The spatial organization of the brain defines many of its functions, with different regions exhibiting differing patterns of cell morphology and physiology. Other methods, such as using 3-dimensional organoids, will be crucial. Another interesting approach would be to combine multi-omics data with brain MRI and EEG data and use integrated machine learning analysis, which could lead to clinically useful results. Future research should also improve the accuracy of prediction and diagnosis, solve the problem of insufficient sample size, and continuously improve the combination of AI technology and omics data so that it can be put into clinical application, reduce the waste of medical resources, improve work efficiency, and provide more effective personalized treatment plans for patients with depression.

Comparing brain and blood transcriptome data offers a unique perspective that can significantly enhance the utility of specific biomarkers. Brain tissue provides direct insight into neuropathology, revealing changes in gene expression that relate to underlying disease mechanisms. However, limited access to brain tissue makes blood biomarkers an appealing option for routine clinical diagnosis. By comparing transcriptome profiles from both sources, researchers can validate and refine candidate biomarkers to ensure they accurately reflect changes in the central nervous system while remaining accessible in peripheral samples. This integrated approach helps distinguish changes specific to brain pathology from those representing systemic responses, ultimately enhancing the specificity and sensitivity of biomarkers. Furthermore, advanced computational and network-based methods can identify shared molecular signatures, providing a panel of biomarkers that are both clinically useful and biologically informative. Newer technologies, particularly those that utilize extracellular vesicles, are highly useful, as these vesicles can cross the blood-brain barrier and can be tracked at their point of origin using specific surface markers. The genetic materials within the vesicles can act as a window to the brain and be used as predictive biomarkers.

REFERENCES

1. Andrade L, Caraveo-Anduaga JJ, Berglund P, Bijl RV, Graaf RD, Vollebergh W, et al. The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. Int J Methods Psychiatr Res. 2003;12:3–21.
2. Schmidt HD, Shelton RC, Duman RS. Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. Neuropsychopharmacology. 2011;36:2375–94.
3. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med. 2013;10:e1001547.
4. Kennedy SH. Core symptoms of major depressive disorder: relevance to diagnosis and treatment. Dialogues Clin Neurosci. 2008;10:271–7.
5. Malhi GS, Mann JJ. Depression. Lancet. 2018;392:2299–312.
6. Coryell W, Young EA. Clinical predictors of suicide in primary major depressive disorder. J Clin Psychiatry. 2005;66:412–7.
7. Mann JJ. Neurobiology of suicidal behaviour. Nat Rev Neurosci. 2003;4:819–28.

8. van Heeringen K, Mann JJ. The neurobiology of suicide. Lancet Psychiatry. 2014;1:63–72.
9. Dong M, Wang S-B, Li Y, Xu D-D, Ungvari GS, Ng CH, et al. Prevalence of suicidal behaviors in patients with major depressive disorder in China: a comprehensive meta-analysis. J Affect Disord. 2018;225:32–9.
10. Dong M, Zeng L-N, Lu L, Li X-H, Ungvari GS, Ng CH, et al. Prevalence of suicide attempt in individuals with major depressive disorder: a meta-analysis of observational surveys. Psychol Med. 2019;49:1691–704.
11. Cui L, Li S, Wang S, Wu X, Liu Y, Yu W, et al. Major depressive disorder: hypothesis, mechanism, prevention and treatment. Signal Transduct Target Ther. 2024;9:30.
12. Pompili M, Venturini P, Palermo M, Stefani H, Seretti ME, Lamis DA, et al. Mood disorders medications: predictors of nonadherence - review of the current literature. Expert Rev Neurother. 2013;13:809–25.
13. Mariani N, Cattane N, Pariante C, Cattaneo A. Gene expression studies in depression development and treatment: an overview of the underlying molecular mechanisms and biological processes to identify biomarkers. Transl Psychiatry. 2021;11:354.
14. Manzoni C, Kia DA, Vandrovcova J, Hardy J, Wood NW, Lewis PA, et al. Genome, transcriptome and proteome: the rise of omics data and their integration in biomedical sciences. Brief Bioinform. 2018;19:286–302.
15. Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. Genome Biol. 2017;18:1–15.
16. Niu X, Zhang J, Zhang L, Hou Y, Pu S, Chu A, et al. Weighted gene co-expression network analysis identifies critical genes in the development of heart failure after acute myocardial infarction. Front Genet. 2019;10:1214.
17. Bouzid A, Almidani A, Zubrikhina M, Kamzanova A, Ilce BY, Zholdassova M, et al. Integrative bioinformatics and artificial intelligence analyses of transcriptomics data identified genes associated with major depressive disorders including NRG1. Neurobiol Stress. 2023;26:100555.
18. Nickson D, Meyer C, Walasek L, Toro C. Prediction and diagnosis of depression using machine learning with electronic health records data: a systematic review. BMC Med Inform Decis Mak. 2023;23:271.
19. Wang Z, Gerstein M, Snyder M. RNA-Seq: a revolutionary tool for transcriptomics. Nat Rev Genet. 2009;10:57–63.
20. Hwang B, Lee JH, Bang D. Single-cell RNA sequencing technologies and bioinformatics pipelines. Exp Mol Med. 2018;50:1–14.
21. Liang M, Cowley JrAW, Greene AS. High throughput gene expression profiling: a molecular approach to integrative physiology. J Physiol. 2004;554:22–30.
22. Sibille E, Wang Y, Joeyen-Waldorf J, Gaiteri C, Surget A, Oh S, et al. A molecular signature of depression in the amygdala. Am J psychiatry. 2009;166:1011–24.
23. Cruceanu C, Tan PPC, Rogic S, Lopez JP, Torres-Platas SG, Gigek CO, et al. Transcriptome sequencing of the anterior cingulate in bipolar disorder: dysregulation of G protein-coupled receptors. Am J psychiatry. 2015;172:1131–40.
24. Zhou Y, Lutz P-E, Wang YC, Ragoussis J, Turecki G. Global long non-coding RNA expression in the rostral anterior cingulate cortex of depressed suicides. Transl Psychiatry. 2018;8:224.
25. Kim B, Kim D, Schulmann A, Patel Y, Caban-Rivera C, Kim P, et al. Cellular diversity in human subgenual anterior cingulate and dorsolateral prefrontal cortex by single-nucleus RNA-sequencing. J Neurosci. 2023;43:3582–97.
26. Pantazatos SP, Huang Y, Rosoklija GB, Dwork AJ, Arango V, Mann JJ. Whole-transcriptome brain expression and exon-usage profiling in major depression and suicide: evidence for altered glial, endothelial and ATPase activity. Mol Psychiatry. 2017;22:760–73.
27. Yoshino Y, Roy B, Kumar N, Shahid Mukhtar M, Dwivedi Y. Molecular pathology associated with altered synaptic transcriptome in the dorsolateral prefrontal cortex of depressed subjects. Transl Psychiatry. 2021;11:73.
28. Dóra F, Renner É, Keller D, Palkovits M, Dobolyi Á. Transcriptome profiling of the dorsomedial prefrontal cortex in suicide victims. Int J Mol Sci. 2022;23:7067.
29. Mahajan GJ, Vallender EJ, Garrett MR, Challagundla L, Overholser JC, Jurjus G, et al. Altered neuro-inflammatory gene expression in hippocampus in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2018;82:177–86.
30. Bagot RC, Cates HM, Purushothaman I, Lorsch ZS, Walker DM, Wang J, et al. Circuit-wide transcriptional profiling reveals brain region-specific gene networks regulating depression susceptibility. Neuron. 2016;90:969–83.
31. Mehta D, Menke A, Binder EB. Gene expression studies in major depression. Curr Psychiatry Rep. 2010;12:135–44.
32. Han M, Yuan L, Huang Y, Wang G, Du C, Wang Q, et al. Integrated co-expression network analysis uncovers novel tissue-specific genes in major depressive disorder and bipolar disorder. Front Psychiatry. 2022;13:980315.
33. Labonté B, Engmann O, Purushothaman I, Menard C, Wang J, Tan C, et al. Sex-specific transcriptional signatures in human depression. Nat Med. 2017;23:1102–11.
34. Mansouri S, Pessoni AM, Marroquín-Rivera A, Parise EM, Tamminga CA, Turecki G, et al. Transcriptional dissection of symptomatic profiles across the brain of men and women with depression. Nat Commun. 2023;14:6835.
35. Sun S, Liu Q, Wang Z, Huang Y-y, Sublette ME, Dwork AJ, et al. Brain and blood transcriptome profiles delineate common genetic pathways across suicidal ideation and suicide. Mol Psychiatry. 2024;29:1417–26.
36. Seney ML, Glausier J, Sibille E. Large-scale transcriptomics studies provide insight into sex differences in depression. Biol Psychiatry. 2022;91:14–24.
37. Liew C-C, Ma J, Tang H-C, Zheng R, Dempsey AA. The peripheral blood transcriptome dynamically reflects system wide biology: a potential diagnostic tool. J Lab Clin Med. 2006;147:126–32.
38. Harrington CA, Fei SS, Minnier J, Carbone L, Searles R, Davis BA, et al. RNA-Seq of human whole blood: Evaluation of globin RNA depletion on Ribo-Zero library method. Sci Rep. 2020;10:6271.
39. Hennings J, Uhr M, Klengel T, Weber P, Pütz B, Touma C, et al. RNA expression profiling in depressed patients suggests retinoid-related orphan receptor alpha as a biomarker for antidepressant response. Transl Psychiatry. 2015;5:e538–e538.
40. Ju C, Fiori LM, Belzeaux R, Theroux J-F, Chen GG, Aouabed Z, et al. Integrated genome-wide methylation and expression analyses reveal functional predictors of response to antidepressants. Transl Psychiatry. 2019;9:254.
41. Le-Niculescu H, Kurian S, Yehyawi N, Dike C, Patel S, Edenberg H, et al. Identifying blood biomarkers for mood disorders using convergent functional genomics. Mol Psychiatry. 2009;14:156–74.
42. Le-Niculescu H, Levey D, Ayalew M, Palmer L, Gavrin L, Jain N, et al. Discovery and validation of blood biomarkers for suicidality. Mol Psychiatry. 2013;18:1249–64.
43. Woo HI, Lim S-W, Myung W, Kim DK, Lee S-Y. Differentially expressed genes related to major depressive disorder and antidepressant response: genome-wide gene expression analysis. Exp Mol Med. 2018;50:1–11.
44. Geng R, Li Z, Yu S, Yuan C, Hong W, Wang Z, et al. Weighted gene co-expression network analysis identifies specific modules and hub genes related to subsyndromal symptomatic depression. World J Biol Psychiatry. 2020;21:102–10.
45. Wang Q, Timberlake IIMA, Prall K, Dwivedi Y. The recent progress in animal models of depression. Prog Neuropsychopharmacol Biol Psychiatry. 2017;77:99–109.
46. Wang Q, Dwivedi Y. Advances in novel molecular targets for antidepressants. Prog Neuropsychopharmacol Biol Psychiatry. 2021;104:110041.
47. Peng S, Zhou Y, Lu M, Wang Q. Review of herbal medicines for the treatment of depression. Nat Prod Commun. 2022;17:1934578X221139082.
48. Roy B, Wang Q, Dwivedi Y. Long noncoding RNA-associated transcriptomic changes in resiliency or susceptibility to depression and response to antidepressant treatment. Int J Neuropsychopharmacol. 2018;21:461–72.
49. Svenningsen K, Venø MT, Henningsen K, Mallien AS, Jensen L, Christensen T, et al. MicroRNA profiling in the medial and lateral habenula of rats exposed to the learned helplessness paradigm: candidate biomarkers for susceptibility and resilience to inescapable shock. PLoS ONE. 2016;11:e0160318.
50. Gui S, Liu Y, Pu J, Song X, Chen X, Chen W, et al. Comparative analysis of hippocampal transcriptional features between major depressive disorder patients and animal models. J Affect Disord. 2021;293:19–28.
51. Bondar N, Bryzgalov L, Ershov N, Gusev F, Reshetnikov V, Avgustinovich D, et al. Molecular adaptations to social defeat stress and induced depression in mice. Mol Neurobiol. 2018;55:3394–407.
52. Peña CJ, Kronman HG, Walker DM, Cates HM, Bagot RC, Purushothaman I, et al. Early life stress confers lifelong stress susceptibility in mice via ventral tegmental area OTX2. Science. 2017;356:1185–8.
53. Peña CJ, Smith M, Ramakrishnan A, Cates HM, Bagot RC, Kronman HG, et al. Early life stress alters transcriptomic patterning across reward circuitry in male and female mice. Nat Commun. 2019;10:5098.
54. Wang Q, Roy B, Dwivedi Y. Co-expression network modeling identifies key long non-coding RNA and mRNA modules in altering molecular phenotype to develop stress-induced depression in rats. Transl Psychiatry. 2019;9:125.
55. Lei C, Li N, Chen J, Wang Q. Hypericin ameliorates depression-like behaviors via neurotrophin signaling pathway mediating m6a epitranscriptome modification. Molecules. 2023;28:3859.
56. Hing B, Mitchell S, Eberle M, Filali Y, Matkovich M, Kasturirangan M. et al. Transcriptomic evaluation of stressvulnerability network using single cell RNA-seq in mouse prefrontal cortex. Biol Psychiatry. 2024;96:866–99.
57. Ling H, Fabbri M, Calin GA. MicroRNAs and other non-coding RNAs as targets for anticancer drug development. Nat Rev Drug Discov. 2013;12:847–65.
58. Bartel DP. Metazoan micrornas. Cell. 2018;173:20–51.
59. Nock MK, Borges G, Bromet EJ, Alonso J, Angermeyer M, Beautrais A, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. Br J Psychiatry. 2008;192:98–105.
60. Wahid F, Shehzad A, Khan T, Kim YY. MicroRNAs: synthesis, mechanism, function, and recent clinical trials. Biochim Biophys Acta. 2010;1803:1231–43.
61. Smalheiser NR, Lugli G, Rizavi HS, Torvik VI, Turecki G, Dwivedi Y. MicroRNA expression is down-regulated and reorganized in prefrontal cortex of depressed suicide subjects. PLoS ONE. 2012;7:e33201.

62. Smalheiser NR, Lugli G, Zhang H, Rizavi H, Cook EH, Dwivedi Y. Expression of microRNAs and other small RNAs in prefrontal cortex in schizophrenia, bipolar disorder and depressed subjects. PLoS ONE. 2014;9:e86469.
63. Roy B, Wang Q, Palkovits M, Faludi G, Dwivedi Y. Altered miRNA expression network in locus coeruleus of depressed suicide subjects. Sci Rep. 2017;7:4387.
64. Yoshino Y, Roy B, Dwivedi Y. Differential and unique patterns of synaptic miRNA expression in dorsolateral prefrontal cortex of depressed subjects. Neuropsychopharmacology. 2021;46:900–10.
65. Yoshino Y, Roy B, Dwivedi Y. Altered miRNA landscape of the anterior cingulate cortex is associated with potential loss of key neuronal functions in depressed brain. Eur Neuropsychopharmacol. 2020;40:70–84.
66. Roy B, Dunbar M, Shelton RC, Dwivedi Y. Identification of MicroRNA-124-3p as a putative epigenetic signature of major depressive disorder. Neuropsychopharmacology. 2017;42:864–75.
67. Wang Q, Roy B, Turecki G, Shelton RC, Dwivedi Y. Role of complex epigenetic switching in tumor necrosis factor-α upregulation in the prefrontal cortex of suicide subjects. Am J Psychiatry. 2018;175:262–74.
68. Smalheiser NR, Lugli G, Rizavi HS, Zhang H, Torvik VI, Pandey GN, et al. MicroRNA expression in rat brain exposed to repeated inescapable shock: differential alterations in learned helplessness vs. non-learned helplessness. Int J Neuropsychopharmacol. 2011;14:1315–25.
69. McKibben LA, Dwivedi Y. Early-life stress induces genome-wide sex-dependent miRNA expression and correlation across limbic brain areas in rats. Epigenomics. 2021;13:1031–56.
70. McKibben LA, Dwivedi Y. Early life and adult stress promote sex dependent changes in hypothalamic miRNAs and environmental enrichment prevents stress-induced miRNA and gene expression changes in rats. BMC Genomics. 2021;22:701.
71. McKibben LA, Dwivedi Y. MicroRNA regulates early-life stress-induced depressive behavior via serotonin signaling in a sex-dependent manner in the prefrontal cortex of rats. Biol Psychiatry Glob Open Sci. 2021;1:180–9.
72. Lopez JP, Lim R, Cruceanu C, Crapper L, Fasano C, Labonte B, et al. miR-1202 is a primate-specific and brain-enriched microRNA involved in major depression and antidepressant treatment. Nat Med. 2014;20:764–8.
73. Lopez JP, Fiori LM, Gross JA, Labonte B, Yerko V, Mechawar N, et al. Regulatory role of miRNAs in polyamine gene expression in the prefrontal cortex of depressed suicide completers. Int J Neuropsychopharmacol. 2014;17:23–32.
74. Lopez JP, Fiori LM, Cruceanu C, Lin R, Labonte B, Cates HM, et al. MicroRNAs 146a/b-5 and 425-3p and 24-3p are markers of antidepressant response and regulate MAPK/Wnt-system genes. Nat Commun. 2017;8:15497.
75. Fiori LM, Lopez JP, Richard-Devantoy S, Berlim M, Chachamovich E, Jollant F, et al. Investigation of miR-1202, miR-135a, and miR-16 in major depressive disorder and antidepressant response. Int J Neuropsychopharmacol. 2017;20:619–23.
76. Mattick JS, Amaral PP, Carninci P, Carpenter S, Chang HY, Chen L-L, et al. Long non-coding RNAs: definitions, functions, challenges and recommendations. Nat Rev Mol Cell Biol. 2023;24:430–47.
77. Statello L, Guo C-J, Chen L-L, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol. 2021;22:96–118.
78. Karlsson O, Baccarelli AA. Environmental health and long non-coding RNAs. Curr Environ Health Rep. 2016;3:178–87.
79. Zimmer-Bensch G. Emerging roles of long non-coding RNAs as drivers of brain evolution. Cells. 2019;8:1399.
80. Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs. Mol Cell. 2011;43:904–14.
81. Issler O, van der Zee YY, Ramakrishnan A, Wang J, Tan C, Loh YE, et al. Sex-specific role for the long non-coding RNA LINC00473 in depression. Neuron. 2020;106:912–26.e915.
82. Cui X, Niu W, Kong L, He M, Jiang K, Chen S, et al. Long noncoding RNA expression in peripheral blood mononuclear cells and suicide risk in Chinese patients with major depressive disorder. Brain Behav. 2017;7:e00711.
83. Issler O, van der Zee YY, Ramakrishnan A, Xia S, Zinsmaier AK, Tan C, et al. The long noncoding RNA FEDORA is a cell type–and sex-specific regulator of depression. Sci Adv. 2022;8:eabn9494.
84. Punzi G, Ursini G, Viscanti G, Radulescu E, Shin JH, Quarto T, et al. Association of a noncoding RNA postmortem with suicide by violent means and in vivo with aggressive phenotypes. Biol Psychiatry. 2019;85:417–24.
85. Wang Q, Wang H, Dwivedi Y. Integrated long noncoding RNA and messenger RNA expression analysis identifies molecules specifically associated with resiliency and susceptibility to depression and antidepressant response. Biol Psychiatry Glob Open Sci. 2024;4:100365.
86. Xie R, Zhang Y, Zhang J, Li J, Zhou X. The role of circular RNAs in immune-related diseases. Front Immunol. 2020;11:545.
87. Yu C-Y, Kuo H-C. The emerging roles and functions of circular RNAs and their generation. J Biomed Sci. 2019;26:29.
88. Shi Y, Wang Q, Song R, Kong Y, Zhang Z. Non-coding RNAs in depression: Promising diagnostic and therapeutic biomarkers. EBioMedicine. 2021;71:103569.
89. Zimmerman AJ, Hafez AK, Amoah SK, Rodriguez BA, Dell'Orco M, Lozano E, et al. A psychiatric disease-related circular RNA controls synaptic gene expression and cognition. Mol Psychiatry. 2020;25:2712–27.
90. Cui X, Niu W, Kong L, He M, Jiang K, Chen S, et al. hsa_circRNA_103636: potential novel diagnostic and therapeutic biomarker in Major depressive disorder. Biomark Med. 2016;10:943–52.
91. Shi Y, Song R, Wang Z, Zhang H, Zhu J, Yue Y, et al. Potential clinical value of circular RNAs as peripheral biomarkers for the diagnosis and treatment of major depressive disorder. EBioMedicine. 2021;66:103337.
92. Huang Z-h, Du Y-p, Wen J-t, Lu B-f, Zhao Y. snoRNAs: functions and mechanisms in biological processes, and roles in tumor pathophysiology. Cell Death Discov. 2022;8:259.
93. Wajahat M, Bracken CP, Orang A. Emerging functions for snoRNAs and snoRNA-derived fragments. Int J Mol Sci. 2021;22:10193.
94. Lin R, Kos A, Lopez JP, Dine J, Fiori LM, Yang J, et al. SNORD90 induces glutamatergic signaling following treatment with monoaminergic antidepressants. eLife. 2023;12:e85316.
95. Aravin A, Gaidatzis D, Pfeffer S, Lagos-Quintana M, Landgraf P, Iovino N, et al. A novel class of small RNAs bind to MILI protein in mouse testes. Nature. 2006;442:203–7.
96. Girard A, Sachidanandam R, Hannon GJ, Carmell MA. A germline-specific class of small RNAs binds mammalian Piwi proteins. Nature. 2006;442:199–202.
97. Siomi MC, Sato K, Pezic D, Aravin AA. PIWI-interacting small RNAs: the vanguard of genome defence. Nat Rev Mol Cell Biol. 2011;12:246–58.
98. Weick E-M, Miska EA. piRNAs: from biogenesis to function. Development. 2014;141:3458–71.
99. Sato K, Takayama K-i, Inoue S. Role of piRNA biogenesis and its neuronal function in the development of neurodegenerative diseases. Front Aging Neurosci. 2023;15:1157818.
100. Nandi S, Chandramohan D, Fioriti L, Melnick AM, Hébert JM, Mason CE, et al. Roles for small noncoding RNAs in silencing of retrotransposons in the mammalian brain. Proc Natl Acad Sci USA. 2016;113:12697–702.
101. Piwecka M, Rajewsky N, Rybak-Wolf A. Single-cell and spatial transcriptomics: deciphering brain complexity in health and disease. Nat Rev Neurol. 2023;19:346–62.
102. Kashima Y, Sakamoto Y, Kaneko K, Seki M, Suzuki Y, Suzuki A. Single-cell sequencing techniques from individual to multiomics analyses. Exp Mol Med. 2020;52:1419–27.
103. Liao J, Lu X, Shao X, Zhu L, Fan X. Uncovering an organ's molecular architecture at single-cell resolution by spatially resolved transcriptomics. Trends Biotechnol. 2021;39:43–58.
104. Chen H, Albergante L, Hsu JY, Lareau CA, Lo Bosco G, Guan J, et al. Single-cell trajectories reconstruction, exploration and mapping of omics data with STREAM. Nat Commun. 2019;10:1903.
105. Cuevas-Diaz Duran R, González-Orozco JC, Velasco I, Wu JQ. Single-cell and single-nuclei RNA sequencing as powerful tools to decipher cellular heterogeneity and dysregulation in neurodegenerative diseases. Front Cell Dev Biol. 2022;10:884748.
106. Titus AJ, Gallimore RM, Salas LA, Christensen BC. Cell-type deconvolution from DNA methylation: a review of recent applications. Hum Mol Genet. 2017;26:R216–r224.
107. Momeni K, Ghorbian S, Ahmadpour E, Sharifi R. Unraveling the complexity: understanding the deconvolutions of RNA-seq data. Transl Med Commun. 2023;8:21.
108. Maitra M, Mitsuhashi H, Rahimian R, Chawla A, Yang J, Fiori LM, et al. Cell type specific transcriptomic differences in depression show similar patterns between males and females but implicate distinct cell types and genes. Nat Commun. 2023;14:2912.
109. Zeng L, Fujita M, Gao Z, White CC, Green GS, Habib N. et al. A single-nucleus transcriptome-wide association studyimplicates novel genes in depression pathogenesis. Biol Psychiatry. 2024;96:34–43.
110. von Ziegler LM, Floriou-Servou A, Waag R, Das Gupta RR, Sturman O, Gapp K, et al. Multiomic profiling of the acute stress response in the mouse hippocampus. Nat Commun. 2022;13:1824.
111. Pinu FR, Beale DJ, Paten AM, Kouremenos K, Swarup S, Schirra HJ, et al. Systems biology and multi-omics integration: viewpoints from the metabolomics research community. Metabolites. 2019;9:76.
112. Mokhtari A, Porte B, Belzeaux R, Etain B, Marie-Claire C, Lutz P-E, et al. The molecular pathophysiology of mood disorders: from the analysis of single molecular layers to multi-omic integration. Prog Neuropsychopharmacol Biol Psychiatry. 2022;116:110520.

113. Zhou Y, Xiong L, Chen J, Wang Q. Integrative analyses of scRNA-seq, bulk mRNA-seq, and DNA methylation profiling in depressed suicide brain tissues. Int J Neuropsychopharmacol. 2023;26:840–55.
114. Yi Z, Li Z, Yu S, Yuan C, Hong W, Wang Z, et al. Blood-based gene expression profiles models for classification of subsyndromal symptomatic depression and major depressive disorder. PLoS ONE. 2012;7:e31283.
115. Yu J, Xue A, Redei E, Bagheri N. A support vector machine model provides an accurate transcript-level-based diagnostic for major depressive disorder. Transl Psychiatry. 2016;6:e931–e931.
116. Bhak Y, Jeong HO, Cho YS, Jeon S, Cho J, Gim JA, et al. Depression and suicide risk prediction models using blood-derived multi-omics data. Transl Psychiatry. 2019;9:262.
117. Qi B, Ramamurthy J, Bennani I, Trakadis YJ. Machine learning and bioinformatic analysis of brain and blood mRNA profiles in major depressive disorder: a case–control study. Am J Med Genet B Neuropsychiatr Genet. 2021;186:101–12.
118. Zhang J, Kaye AP, Wang J, Girgenti MJ. Transcriptomics of the depressed and PTSD brain. Neurobiol Stress. 2021;15:100408.
119. Zhou Y, Lutz PE, Ibrahim EC, Courtet P, Tzavara E, Turecki G, et al. Suicide and suicide behaviors: a review of transcriptomics and multiomics studies in psychiatric disorders. J Neurosci Res. 2020;98:601–15.
120. Furczyk K, Schutová B, Michel TM, Thome J, Büttner A. The neurobiology of suicide-A review of post-mortem studies. J Mol Psychiatry. 2013;1:2.
121. Barnes J, Mondelli V, Pariante CM. Genetic contributions of inflammation to depression. Neuropsychopharmacology. 2017;42:81–98.
122. Allen L, Dwivedi Y. MicroRNA mediators of early life stress vulnerability to depression and suicidal behavior. Mol Psychiatry. 2020;25:308–20.
123. Peng S, Zhou Y, Xiong L, Wang Q. Identification of novel targets and pathways to distinguish suicide dependent or independent on depression diagnosis. Sci Rep. 2023;13:2488.
124. Qi B, Fiori LM, Turecki G, Trakadis YJ. Machine learning analysis of blood microRNA data in major depression: A case-control study for biomarker discovery. Int J Neuropsychopharmacol. 2020;23:505–10.
125. Williams CG, Lee HJ, Asatsuma T, Vento-Tormo R, Haque A. An introduction to spatial transcriptomics for biomedical research. Genome Med. 2022;14:68.
126. Du J, Yang Y-C, An Z-J, Zhang M-H, Fu X-H, Huang Z-F, et al. Advances in spatial transcriptomics and related data analysis strategies. J Transl Med. 2023;21:330.
127. Fang S, Chen B, Zhang Y, Sun H, Liu L, Liu S, et al. Computational approaches and challenges in spatial transcriptomics. Genom Prot Bioinform. 2023;21:24–47.
128. Thompson JR, Nelson ED, Tippani M, Ramnauth AD, Divecha HR, Miller RA, et al. An integrated single-nucleus and spatial transcriptomics atlas reveals the molecular landscape of the human hippocampus. Nat Neurosci. 2025. https://doi.org/10.1101/2024.04.26.590643
129. Maynard KR, Collado-Torres L, Weber LM, Uytingco C, Barry BK, Williams SR, et al. Transcriptome-scale spatial gene expression in the human dorsolateral prefrontal cortex. Nat Neurosci. 2021;24:425–36.
130. Bhattacherjee A, Zhang C, Watson BR, Djekidel MN, Moffitt JR, Zhang Y. Spatial transcriptomics reveals the distinct organization of mouse prefrontal cortex and neuronal subtypes regulating chronic pain. Nat Neurosci. 2023;26:1880–93.
131. Yao Z, van Velthoven CTJ, Kunst M, Zhang M, McMillen D, Lee C, et al. A high-resolution transcriptomic and spatial atlas of cell types in the whole mouse brain. Nature. 2023;624:317–32.
132. Joglekar A, Prjibelski A, Mahfouz A, Collier P, Lin S, Schlusche AK, et al. A spatially resolved brain region- and cell type-specific isoform atlas of the postnatal mouse brain. Nat Commun. 2021;12:463.
133. Cho WC. Proteomics technologies and challenges. Genom Prot Bioinform. 2007;5:77–85.
134. Lee S, Vu HM, Lee JH, Lim H, Kim MS. Advances in mass spectrometry-based single cell analysis. Biology. 2023;12:395.
135. Liu Y, Yang M, Deng Y, Su G, Enninful A, Guo CC, et al. High-spatial-resolution multi-omics sequencing via deterministic barcoding in tissue. Cell. 2020;183:1665–81.e1618.
136. Sarker IH. Machine learning: algorithms, real-world applications and research directions. SN Comput Sci. 2021;2:160.
137. Kocaman E, Erdem MK, Calis G. Machine learning thermal comfort prediction models based on occupant demographic characteristics. J Therm Biol. 2024;123:103884.
138. Sarica A, Cerasa A, Quattrone A. Random forest algorithm for the classification of neuroimaging data in Alzheimer's disease: a systematic review. Front Aging Neurosci. 2017;9:329.
139. Alzubaidi L, Zhang J, Humaidi AJ, Al-Dujaili A, Duan Y, Al-Shamma O, et al. Review of deep learning: concepts, CNN architectures, challenges, applications, future directions. J Big Data. 2021;8:53.
140. Gusev A, Mancuso N, Won H, Kousi M, Finucane HK, Reshef Y, et al. Transcriptome-wide association study of schizophrenia and chromatin activity yields mechanistic disease insights. Nat Genet. 2018;50:538–48.
141. Al Hanai T, Ghassemi M, Glass J. Detecting depression with audio/text sequence modeling of interviews. In: Proceedings of the Annual Conference of the International Speech Communication Association, INTERSPEECH. 9th Annual Conference of the International Speech Communication, INTERSPEECH 2018 - Hyderabad, India. 2018.
142. Walsh CG, Ribeiro JD, Franklin JC. Predicting suicide attempts in adolescents with longitudinal clinical data and machine learning. J Child Psychology Psychiatry. 2018;59:1261–70.
143. Quaak M, van de Mortel L, Thomas RM, van Wingen G. Deep learning applications for the classification of psychiatric disorders using neuroimaging data: systematic review and meta-analysis. NeuroImage Clin. 2021;30:102584.
144. Kreimeyer K, Foster M, Pandey A, Arya N, Halford G, Jones SF, et al. Natural language processing systems for capturing and standardizing unstructured clinical information: a systematic review. J Biomed Inform. 2017;73:14–29.
145. Birnbaum ML, Abrami A, Heisig S, Ali A, Arenare E, Agurto C, et al. Acoustic and facial features from clinical interviews for machine learning-based psychiatric diagnosis: algorithm development. JMIR Ment Health. 2022;9:e24699.

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ADDITIONAL INFORMATION

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