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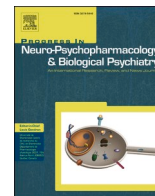
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The molecular pathophysiology of mood disorders: From the analysis of single molecular layers to multi-omic integration

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ABSTRACT

Next-generation sequencing now enables the rapid and affordable production of reliable biological data at multiple molecular levels, collectively referred to as “omics”. To maximize the potential for discovery, computational biologists have created and adapted integrative multi-omic analytical methods. When applied to diseases with traceable pathophysiology such as cancer, these new algorithms and statistical approaches have enabled the discovery of clinically relevant molecular mechanisms and biomarkers. In contrast, these methods have been much less applied to the field of molecular psychiatry, although diagnostic and prognostic biomarkers are similarly needed. In the present review, we first briefly summarize main findings from two decades of studies that investigated single molecular processes in relation to mood disorders. Then, we conduct a systematic review of multi-omic strategies that have been proposed and used more recently. We also list databases and types of data available to researchers for future work. Finally, we present the newest methodologies that have been employed for multi-omics integration in other medical fields, and discuss their potential for molecular psychiatry studies.

1. Introduction

Mood disorders are defined in the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as a group of psychiatric disorders characterized by the recurrence of clinically significant changes in mood state, energy, cognitive processes, sleep, or appetite. Among this group, Bipolar Disorder (BD) and Major Depressive Disorder (MDD) are the most prevailing syndromes in the general population. Indeed, BD affects around 1% of the global population (Ferrari, 2015),

whereas MDD reaches a 12-months prevalence of 10.4% and a lifetime prevalence of up to 20.6% (Hasin et al., 2018). Mood disorders impose a substantial burden on patients and caregivers due to their recurrence and the frequently associated psychiatric comorbidities, including substance use, anxiety disorders, and suicidal behaviors (Isometsä, 2014). Consequently, they represent an economic and public health issue that needs to be addressed. Unfortunately, their heterogeneous etiology, ranging from genetic predisposition to environmental factors, complicates understanding underlying biological mechanisms. Furthermore,

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the development of prognostic and diagnostic biomarkers in psychiatry is still at its debut, and the need for personalized approaches to improve therapeutic outcomes is rising (Nemeroff, 2020).

Over the last decade, researchers have turned to high-throughput technologies to try and bridge the gap between the lack of biological insights into mood disorders and their worldwide impact. Indeed, the emergence of Next Generation Sequencing (NGS) tools and their financial and technological accessibility has enabled the production of petabytes of biological data at different molecular levels, thereby accelerating the shift from a monogenic paradigm to a holistic view, where numerous molecular regulatory mechanisms interact to drive phenotypes. The relationship between these different omic layers turns out, in most cases, to be non-linear and to involve intricately mechanisms, such as transcriptomic adaptations under epigenetic regulation. In this context, multi-omic data integration is proposed as a set of tools to identify the main processes guiding these interactions and test hypotheses on molecular etiologies. This approach, which takes full advantage of multidimensional databases, creates new research avenues to explore and new challenges to overcome. Applied to psychiatry, it is expected to help refine diagnosis and patient stratification and improve therapeutic decisions (Fig. 01).

The present systematic review aims to describe the contribution of omics data integration to psychiatry, focusing on mood disorders. Omics data integration can be classified into two main categories, as illustrated in Fig. 02:

- i) **Horizontal integration (indirect):** This “meta-analysis” strategy combines datasets related to the same molecular layer, generated on distinct clinical cohorts but with a given phenotype as a common denominator.
- ii) **Vertical integration (direct):** This approach associates data on multiple layers generated from the same cohort of individuals, allowing a more comprehensive view of the different layers’ interactions and identifying omics-phenotype causal relationships with higher statistical power.

In the first part of our systematic literature review, we first briefly summarize the most significant contributions and recommend dedicated reviews on mood disorders studies based on unique or horizontally (indirect) integrated single omic data. Then, we present our systematic literature search focused on identifying studies that combined at least 2 omic approaches (as defined in the Methods section below; see Fig. 03), to assess which strategies have been prioritized for data integration in

the field, and what results were obtained when compared to previous single-layer approaches. Finally, we discuss how similar endeavors are ongoing in other medical areas and may guide future developments in molecular psychiatry.

2. Materials and methods

2.1. Search strategy

A systematic literature search was performed using the MEDLINE, Crossref, and Scopus databases to identify research and review articles published between January 1st, 2000 and May 15, 2021. Selected articles had to include one of the following terms: “Genome-wide association study (GWAS)”, “RNA-Seq”, “Transcriptomics”, “Transcriptome”, “Epigenetics”, “miRNA”, “DNA Methylation”, “Histone methylation”, “Chromatin Conformation,” and “Proteomics.” These terms were associated with either “Bipolar Disorder” or “Major Depressive Disorder”. Furthermore, the term “Multiomics” was also associated with each of the following: “Bipolar Disorder”, “Major Depressive Disorder”, and “Psychiatry”. Papers resulting from these queries were investigated according to the Preferred Reporting Items for Systematic Reviews (PRISMA) protocol (Moher et al., 2009), as shown in Fig. 03.

2.2. Inclusion and exclusion criteria

Papers investigating BP or MDD patients and integrating more than two datasets either horizontally (meta-analyses of a single type of omics data – single-omics) or vertically (multi-omics) were included. Publications that did not include patients with either BD or MDD in their discovery cohort were excluded. No other specific study design was required for inclusion in our corpus, but a description of samples (biological origin, size, and diagnosis) was necessary. Research on non-human species was considered out-of-scope and excluded. Regarding multi-omics studies, we considered relevant all genome-wide studies that conducted an integration of more than one “omic” level.

3. Results

Below, we present the meta-analyses for patients with mood disorders identified during the systematic search summarizing the main findings from each single omic approach.

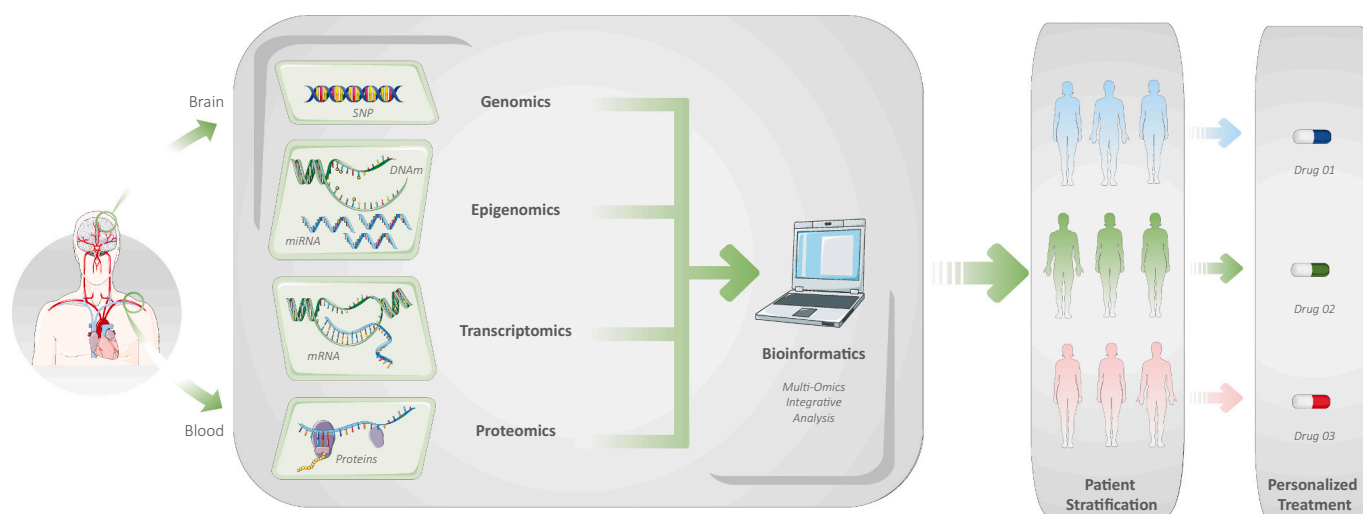


Fig. 01. Illustration of the concept of multi-omics data integration enhancing patient stratification and precision medicine. Different omics data-levels are collected from the brain and peripheral tissues which are then integrated using computational biology tools, providing complementary information on the studied diseases resulting in better patient stratification and adapted treatments.

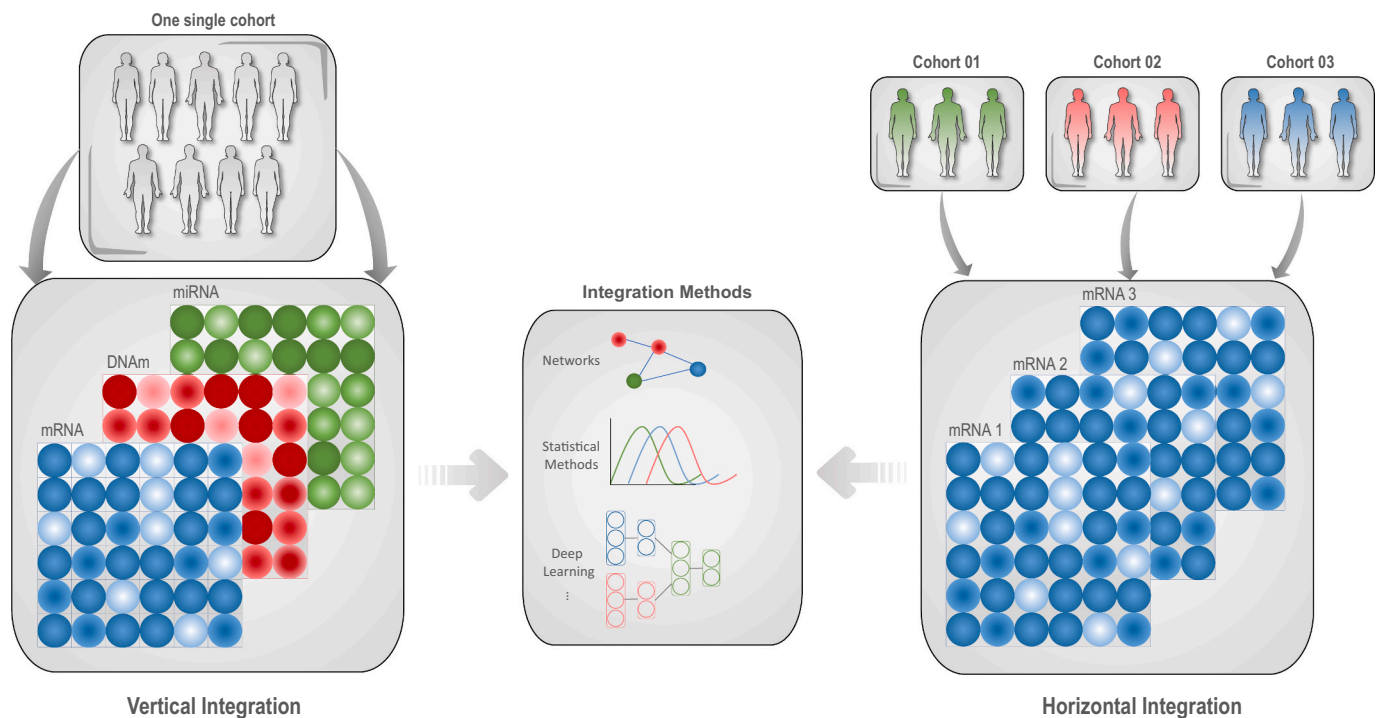


Fig. 02. Data integration approaches. a. Horizontal integration: the same molecular data-layer is retrieved from different cohorts. b. Vertical integration: multiple omics data are available from the same cohort.

3.1. Horizontally integrated single-omic studies of mood disorders

3.1.1. Genomics

GWAS meta-analyses are commonly applied to capture the shared genetic background of mood disorders. Among the 20 eligible studies listed in Supplementary Table 1, eight focused solely on BD, ten on MDD, one on both BD and MDD, while the last one covered a broader spectrum (ASD, ADHD, BP, MDD, and SCZ). It is worth noting that the latest published GWAS add new subjects to previous ones, which explains their concordance. Regarding BD-associated variants, Stahl et al. (2019) highlighted 30 loci, among which loci within the *ANK3* gene were already identified several times in earlier studies. *ANK3* encodes ankyrin-G, a protein associated with the cell membrane, notably present at nodes of Ranvier and the initial axon segment. In addition, the *ODZ4* gene encoding a transmembrane protein which plays a role in neural development (Ikeda et al., 2018; Psychiatric GWAS Consortium Bipolar, 2011; Mühleisen et al., 2014), and *POU3F2* a DNA-binding transcription factor acting notably in neuronal differentiation (Hou et al., 2016; Mühleisen et al., 2014; Stahl et al., 2019), were also pointed out in several coupled BD GWAS.

Similarly, for MDD, successive GWAS aggregating depressive cohorts identified specific loci, including *DCC*, which encodes a functional transmembrane receptor for NETRIN-1 and mediates neurite outgrowth (Howard et al., 2019; Okbay et al., 2016; Wray et al., 2018); *SORCS3*, a cell surface receptor localized at the postsynaptic density of hippocampal neurons (Howard et al., 2019; Hyde et al., 2016; Wray et al., 2018), both *SORCS3* and *DCC* genes significance associations were replicated in the Coleman et al., 2020's mood disorder GWAS; and *NEGR1*, a cell adhesion molecule promoting neuronal spine plasticity (Li et al., 2018). It is worth mentioning that only the *MAD1L1* gene, which plays a role in the cell cycle, was significantly associated in multiple studies with both MDD and BD (Hou et al., 2016; Howard et al., 2019; Howard et al., 2018; Ikeda et al., 2018). Recently, the *MAD1L1* locus has been significantly associated with anxiety (Levey et al., 2020) and found differentially methylated in post-traumatic stress disorder (Snijders et al., 2020). However, this association was not replicated in a recent

mood cohort GWAS meta-analysis (Coleman et al., 2020). The lack of other loci associated with both MDD and BD, despite common symptoms, likely reflects their heterogeneous and complex pathophysiology. Some authors suggested that inconsistent patient phenotyping may also partly explain this low overlap (Ormel, 2019). Of note, copy number variants (CNVs), single nucleotide variants (SNVs), and other genomics polymorphisms were investigated in MD and are not discussed here further (see Gordovez and McMahon, 2020 and McIntosh et al., 2019 for reviews). Even though these extensive analyses may facilitate identifying genomic variants associated with mood disorders, the post-single-omic GWAS challenges reside in prioritizing functional and causal variants and characterizing their biological mechanisms.

3.1.2. Transcriptomics

The advent of microarrays and NGS technologies has permitted transcriptomic genome-wide investigation of mood disorders. These studies, similar to the other types of functional omic analyses detailed further in this review, focuses mainly on two tissues: i) the brain (with different regions examined, and a gradual shift from whole-tissue to single cell-type, or even single-cell analyses), which is biologically more relevant but difficult to collect in large sample size cohorts, and is currently available for retrospective investigation only; and ii) peripheral tissues, such as blood or saliva, which are easier to collect and can be used in longitudinal designs and for biomarkers identification. The following paragraphs first describe studies on brain and blood separately before concluding on possible convergence between the two tissues.

Among the 4 reported meta-analyses of our systematic screening focusing on peripheral tissues Supplementary Table 2, Hess et al. (2019) have conducted a meta-analysis of seven studies, including BD ($n = 95$) and schizophrenia ($n = 258$) patients. They reported significant enrichments for both differentially expressed genes (DEG) and WGCNA co-expression modules in the immune system's biological function, oxidative stress, and apoptosis pathways. More recently, Wittenberg et al. (2020) reviewed whole-genome data generated from blood samples (whole blood, lymphocytes, or PBMC) in case-control studies (1754 depressed cases and 1145 healthy controls compiled from 10 studies).

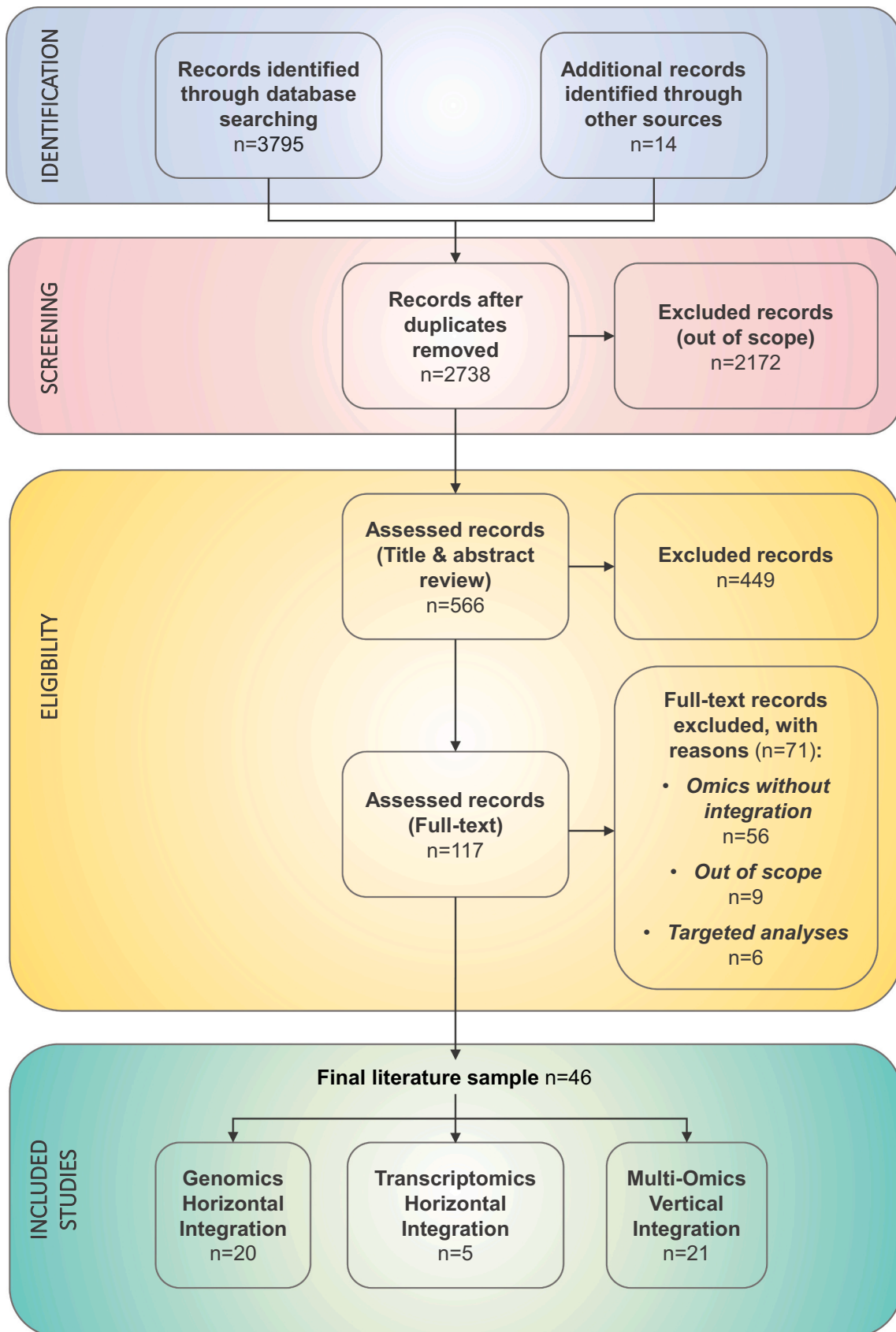


Fig. 03. The PRISMA flow diagram for the systematic review detailing the searched database, the number of abstracts screened and the full texts reviewed.

The meta-analysis was done at two levels: i) by compiling DEGs identified by at least 2 studies, and ii) by conducting a homogenized re-analysis of subject-level data, when such data were available ($n = 8$), or using standardized mean difference otherwise (whole blood studies, $n = 4$). The three approaches highlighted genes associated with the immune response system, especially neutrophil activation. Noteworthy, they also explored sample type (whole blood/PBMC) and data heterogeneity issues with respect to such meta-analysis. Results showed that MDD-related adaptations were more consistent within (e.g. whole blood vs. whole blood) than across (whole blood vs. PBMC) sample type. Importantly, findings were also more concordant among whole blood than among PBMC studies, indicating that neutrophils (not present in the PBMC fraction) and related GO terms exhibit a more robust association with MDD and highlighting the importance of investigating relevant cell types.

Regarding brain tissue-based meta-analyses, Seney et al. (2018) were interested in opposite transcriptional alterations in men and women. They focused on three brain regions (dorsolateral prefrontal cortex, subgenual anterior cingulate cortex, and basolateral amygdala), with a total cohort of 26 MDD cases and 13 controls in men, and 24 MDD cases and 9 controls in women. The authors reported sex-specific changes in MDD, with relatively few overlapping DEG. The altered pathways included opposite transcription gene variations with a decrease in synapse-related genes in male MDD and an increase in female MDD.

In addition to Ciobanu et al. (2016)'s review of replicated finding, only one cross-tissue investigative meta-analysis have been published (Forero et al., 2017). First, in their review, Ciobanu et al. (2016) included transcriptomic datasets obtained from peripheral ($n = 10$ articles) and brain ($n = 15$ articles) tissues in MDD covering adrenal gland, colon transverse, and whole blood along with ten brain structures (dorsal prefrontal cortex, hippocampus, or cerebellum as main examples). The authors reported 57 replicated DEGs in the brain and 21 in peripheral tissues. Their findings suggest more significant overlaps and greater homogeneity among brain regions than peripheral tissues. Second, Forero et al. (2017) investigated brain and blood transcriptomics profiles in MDD. This meta-analysis was of a larger scale than the previous one, as 24 primary datasets were used: 6 from blood, 18 from 4 brain regions (amygdala, cerebellum, prefrontal, and anterior cingulate cortices). The authors identified several enrichment pathways involving synaptic plasticity in the brain datasets but, surprisingly, no significant pathway enrichment in blood.

Altogether, even if MDD-related DEGs vary according to tissue type (blood/brain), results from pathways enrichment appear relatively convergent towards an implication of groups of genes associated with the immune system and/or inflammation. But, one should be concerned that blood-based analyses can be less informative than investigations based on brain tissue, where mood disorders pathophysiological mechanisms primarily occur.

3.1.3. Epigenetics

The mood disorders heritability has been estimated via monozygotic twin studies between 31% to 42% for MDD (Flint and Kendler, 2014), and between 70% to 90% for BD (Gordovez and McMahon, 2020). Despite these significant genetic contributions, it is widely acknowledged that mood disorders and their clinical course involve additional factors, including environmental ones and life events, such as childhood trauma (Aldinger and Schulze, 2017). While mechanisms potentially mediating interactions between genetic determinism and environmental exposure have long remained elusive, their importance is not to neglect. Recently, convincing illustrations of the relevance of G x E interactions have been published in relation to epigenetic consequences of prenatal or early-life factors, which act as distal risk factors for mood disorders (Czamara et al., 2021; Czamara et al., 2019).

Epigenetics refers to physical and chemical substrates that regulate the architecture and activity of the genome without any change in the underlying DNA sequence. They include chromatin conformation, DNA

methylation, histone modifications, miRNAs, and other non-coding RNAs (Penner-Goeke and Binder, 2019). In their critical review, Legrand et al. (2021) questioned the epigenetics of BD, retracing the evolution of this emerging field and significant discoveries. Here, we focus on whole-genome epigenetic approaches, mostly related to DNA methylation and miRNAs in the current literature.

3.1.3.1. DNA methylation. DNA methylation (DNAm) is the addition of a methyl group at the 5' position of cytosine. The modification influences gene expression through multiple mechanisms (Jones, 2012) and globally acts as a repressor on gene expression. Accumulating evidence indicates that DNAm contributes to gene x environment interactions, including for monozygotic twins discordant for psychiatric phenotypes (van Dongen et al., 2014), or following severe traumatic life experiences (Wolf et al., 2018). While initial DNAm studies focused on candidate genes, like brain-derived neurotrophic factor (BDNF) or the glucocorticoid receptor, advance in NGS technologies (MBD-seq, MeDIP-Seq, RRBS, WGBS) and the development of relatively affordable microarrays (450 k and more recently Infinium EPIC arrays), now allow conceiving genome-wide case/control analyses to identify differentially methylated regions (DMRs) or perform MWAS (methylome-wide association study).

As observed for transcriptomics studies, the tissues characterized in mood disorders DNAm studies vary widely, including studies investigating different brain regions and others focusing on peripheral tissues (whole blood). For example, for genome-wide MDD investigations, Li et al. (2019) outlined genes related to neurogenesis, neuroplasticity, and estrogen signaling regardless of the sample's tissue origin. On the other hand, for BD DNAm analyses, Teroganova et al. (2016) highlighted differentially methylated genes in peripheral tissues of BD and schizophrenia patients, including well-known BDNF promoter regions involved in neuroplasticity and dopaminergic pathways.

Of note, Li et al. (2019) underlined a limited number of systematic reviews and meta-analyses on DNAm and MDD, and we observed a similar issue for BD. This lack of quantitative reviews is even more pronounced for genome-wide studies. Thus, we notice an urgent need for genome-wide meta-analyses of DNAm in mood disorders.

3.1.3.2. Micro-RNAs. Recently, non-coding RNAs and particularly micro-RNAs (miRNAs), have become the focus of significant attention. It is now acknowledged that they play an extensive role in regulating gene expression (He and Hannon, 2004). Their canonical mode of action involves silencing mRNAs with complementary target sequences. A miRNA can act on numerous mRNAs, and reciprocally, an mRNA is regulated by various miRNAs. Many public repositories list predicted and experimentally validated targets of miRNAs, such as MiRBase (Kozomara et al., 2019).

Ferrúa et al. (2019) focused on bioinformatic analysis of peripheral miRNAs in patients with depressive symptoms. This systematic review emphasized *AKT*, *BRAF*, and *PIK3CA* as the target of many differentially expressed miRNAs. The study also inferred potentially affected pathways such as mTOR, phosphoinositide 3-kinase PI3K/Akt, and MAPK signaling pathways.

These pathway enrichment analyses of the miRNA targeted genes concur with those uncovered at other molecular levels mentioned above. Furthermore, miRNAs were also identified as potential biomarkers of BD, schizophrenia (Amoah et al., 2019; Fries et al., 2018), MDD (Gururajan et al., 2016), suicidal behavior in BD patients (Squassina, 2020), and nausea intensity in MDD patients treated with mood stabilizers (Yroni et al., 2020). Altogether, these results suggest that miRNAs may be potential diagnostic and predictive biomarkers in psychiatric disease (Gibbons et al., 2020).

3.1.3.3. Metabolomics. Metabolomics in mood disorders is an emerging field of research. This omics aims to depict the state of the metabolism's

end products (metabolites) and establish metabolic profiles for various pathways, including carbohydrate, protein, and fatty acid metabolism. MacDonald (2019) performed an extensive systematic review on metabolomics biomarkers of mood disorders, looking at 266 studies measuring metabolites using different techniques: in vivo brain imaging, chromatography, nuclear magnetic resonance, and mass spectrometry. Among the metabolites identified, 122 were reported in two or more BD or MDD studies, and involved mainly in neurotransmission and energy metabolism. Recently, Bot et al. (2020) investigated the metabolic profile of a large cohort of patients with depressive symptoms ($N = 5283$ MDD and 10,145 Controls) in a meta-analysis. Of the 21 metabolites that met the significance criteria ($FDR < 0.05$), higher blood levels of very-low-density lipoprotein triglycerides, and lower concentration of high-density lipoproteins were related to depression and were consistent with previous findings.

Despite the growing appeal towards metabolomic-based biomarkers in psychiatric diseases, few meta-analyses are to be reported, especially for BD, for which no specific meta-analysis seems to be available. In the same way, no meta-analysis or systematic review on mood disorders and proteomics was identified during the systematic search.

3.1.3.4. Metagenomics. Lately, the influence of the gut microbiota on mood disorders has attracted increasing attention, with the hope that related studies may lead to innovative treatments and diagnosis tools. Despite these promises, a lack of functional and publicly available data has to be deplored. Indeed, the only comprehensive meta-analysis on gut microbiota and depression available at the time of literature screening, from Sanada et al. (2020), focused solely on the gut microbiota composition, with no functional data available, therefore falling outside the scope of the present review.

3.2. Multi-omics integration methods

Understanding complex pathologies such as mood disorders require a holistic vision. These diseases result from an intricate interplay between different actors (genomics, transcriptomics, epigenetics, proteomics, and metabolomics) and environmental factors that regulate the neuronal mechanism underlying cognitive and emotional processes. Although single-omic approaches have brought a better understanding of psychiatric illness, it is now proposed that combining multiple types of data through systems biology may harness further progress. Therefore, in the second part of this review, we also provide a systematic review of the application of multi-omics approaches to mood disorders. Several reviews described multi-omics data integration methodologies and their mathematical aspects. Available approaches can be categorized differently according to various criteria: horizontal, vertical or neither vertical nor horizontal integration methods as illustrated by Eidem et al. (2018). The machine learning criteria distinguishing unsupervised, semi-supervised or supervised approaches are also widely used (Bersanelli et al., 2016; Huang et al., 2017; Wu et al., 2019). This distinction reflects, for example, whether one proceeds in an exploratory manner or applies clinical labels to individual cases. Another categorization criteria distinguish early, intermediate, and late integration approaches (Cantini et al., 2021; Rappoport and Shamir, 2018). For example, step by step combination of results obtained from single omics can be processed concatenating omics before clustering with an “early” integration approach or after clustering using a “late” integration approach (Rappoport and Shamir, 2018). Genuine “intermediate” joint multi-omics integrative methods remain rarer and constitute a highly active area of research (Cantini et al., 2021). Below, we first list the most commonly used methods (with concrete examples from other research fields), and then detail their application to mood disorders.

3.2.1. Step by step methods

These methods simplify data integration by finding correlations and

overlaps after analyzing each data type separately while respecting its specificities. Ready-to-use tools or pipelines are not available for this kind of approach. An example of a typical pipeline begins with a differential analysis carried out on each omic, followed by integration via overlaps (identifying entities commonly dysregulated across distinct layers) or correlation (to assess the covariance of omics quantitative data). A major drawback of these methods lies in their oversimplification of the problematic as, among others, known biological interactions between omic types are not taken into account. As the full range of information extractable from the data is not exploited, only strong effects can be unveiled, potentially missing the subtle interactions at stake in psychiatric disease.

3.2.2. Network-based methods

Network theory is widely used at the single-omic level, notably with gene-gene expression correlation methods. Graph theory and network methods are often used in systems biology, and can also help characterize the interconnectivity between multi-omic layers. Various tools have been developed based on the adaptability of network modeling methodologies. Some rely on pre-existing knowledge, such as the Protein-Protein Interaction networks (PPI), as an integration guide. For example, iOmicsPASS has been applied to breast cancer data and revealed a molecular signature for the basal-like subtype that could not be identified using single-omic analyses (Koh et al., 2019). Other tools explore the inherent characteristics of the generated networks, such as their topology features (network connectivity patterns; node degree: number of connections with other nodes; and centrality: number of times a node acts as a bridge between pairs of nodes in the network). Among network-based approaches, similarity network fusion (SNF) was able to identify differential survival profiles among subtypes of 5 cancer types from the TCGA research network, allowing a better patient stratification (Wang et al., 2014).

3.2.3. Dimension reduction methods

Dimensionality reduction methods for the joint analysis of multi-omics datasets were reviewed and benchmarked using simulated data, cancer datasets, and, more recently, single-cell datasets (Cantini et al., 2021; Tini et al., 2018; Wu et al., 2019). Matrix decomposition algorithms offer an answer to the multidimensionality issue of NGS data (a much higher number of features than samples). In order to extract the nature of the data variance, dimension reduction methods aim at decomposing a matrix of N samples by M measures into a matrix product of smaller matrices representing the components that best summarize the data. The most commonly used algorithms include Principal Component Analysis (PCA), and Canonical Correlation Analysis (CCA). Among other examples, the DIABLO method of the mixOmics R package (Rohart et al., 2017) relies on Partial Least Squares (PLS) regression and proposes to integrate several omic matrices by maximizing correlations between the extracted components and phenotypic variables. This package also encapsulates all the algorithms mentioned above (PCA, CCA and PLS) and their variants and has been used in numerous multi-omic studies. Matrix factorization methods are another toolset to circumvent the growing size of data matrices, of which JIVE (Joint and Individual Variation Explained) (Lock et al., 2013) is a popular multi-channel integration method. JIVE decomposes the matrices into a combination of matrix pairs representing each omic’s specific and common variation. It has been applied to glioblastoma to uncover miRNA-mRNA interactions and improve the stratification of tumor subtypes (Lock et al., 2013).

3.2.4. Bayesian methods

One major advantage of Bayesian models is the possibility of enhancing the statistical model with a priori information. Thus, these methods are particularly interesting when one wishes to assess the probability of a sample clustering assignment. However, these models often require proper attribution of a prior probability distribution for

each omic type, based on one or more parameters, and a posterior probability distribution of expected results to identify the clustering pattern (Bersanelli et al., 2016). In addition, these models are costly in terms of computing resources. Among these, iRIGS is a framework adapted to identify genes associated with the risk of developing schizophrenia, using GWAS results combined with a gene-gene network integrating multi-omic data (differential expression, de novo mutations, chromatin states (Wang et al., 2019a).

3.2.5. Advanced machine learning

Machine learning and artificial intelligence (AI) have seen remarkable advances over the last decade. The complexity and quantity of NGS data are ideally suited for machine and deep learning algorithms, as these methods rely on extensive data as training sets to improve from experience. Multi-omic integration can be described as a variant of a known AI clustering problem named multi-view clustering. iClusterPlus (Mo et al., 2018), an improvement of the iCluster method (Shen et al., 2009), is among the most commonly used methods. It relies on a generalized linear regression to formulate a joint model, uncover insights on mechanisms driving the phenotype of interest, and was initially applied to colorectal cancer to reveal tumor subtypes.

Further, iClusterBayes (Mo et al., 2018) is a Bayesian computational and statistical enhancement of iClusterPlus, that has been applied to glioblastoma data generated by the TCGA Research Network. Rappoport and Shamir (2018) benchmarked iClusterBayes and other machine learning methods, including those cited previously (JIVE, CCA, and SNF), on 10 cancer datasets. They concluded that no single method systematically outperformed the others, and advocated for their careful use to analyze omics data, as these methods largely disregard their specificities (inter-omic dependency).

3.3. Multi-omic integration applied to mood disorders

Here, we systematically identified and reviewed 21 multi-omic publications described in detail in Table 1. Several factors likely account for this relatively modest number of papers, among which the relative youth of the field and the low amounts of publicly available data, notably for brain tissue. In addition, the majority of these articles have used step-by-step approaches due to the current absence of state-of-the-art methods. Below, we summarize their main findings, subjectively organized from simplest to most advanced approaches.

3.3.1. Step-by-step approach – overlap

Zhao et al. (2015) investigated the relation between DNAm and the transcriptome (RNA-seq) in BA9 tissue from a cohort of 5 SCZ, 7 BD patients, and 6 controls. They found that 11 of the 146 genes with hypermethylation in the promoter region showed a down-regulation at the expression level, and 4 of the 411 hypomethylated showed an up-regulation, indicating that a vast majority of DMRs had no detectable effect on gene expression, at least when analyzing such a small sample size. A high percentage of intronic DMR overlapped with miRNAs that were predicted to target genes identified as differentially expressed, indicating that DNAm may alter gene expression in part via intronic miRNAs. The down-regulated genes showed significant enrichment in neurogenesis and nervous system development. Ju et al. (2019) also overlapped DNAm and gene expression analyses. They investigated molecular predictors of response to antidepressant treatment in peripheral blood samples from 177 MDD (comparing 82 responders to escitalopram and 95 non-responders, sampled before treatment initiation – a predictive approach) and 102 healthy controls. They identified 303 differentially methylated CG sites, among which, again, only a minority ($n = 16$) were located within DEGs (with *CHN2* and *JAK2* the 2 most significant DEGs, involved respectively in neurodevelopmental hippocampal axon pruning and synaptic plasticity). Recently Xie (2021) reprocessed available mRNA and DNAm data from studies by Leday et al. (2018) and Crawford et al. (2018). The analysis included 128 MDD

and 64 healthy controls' transcriptomic data and methylomic data for 100 distinct MDD patients and 50 controls. The overlap study identified: 46 hypomethylated and up-regulated genes involved in PI3K-Akt, IL-17, and axon guidance signaling pathways, among others; and 71 hypermethylated and down-regulated genes involved in the MAPK and NF-kappa B signaling pathways. Furthermore, from these overlaps, the authors also developed a random forest-based classifier to discriminate MDD cases and controls, using mRNA and DNAm data separately; comparison of the 2 classifiers showed a better predictive power for the one based on gene expression (AUC > 0.95).

3.3.2. Step-by-step approach – correlation

The integration of different molecular layers by correlation testing has been used mainly to assess relationships between DNAm and gene expression in mood disorders. Chen et al. (2014) used Pearson correlation to identify candidate genes with differential methylation and expression patterns in cerebellar samples from 39 SCZ and 36 BD patients, as well as 43 controls. Among the 20 genes where 204 significantly differentially methylated CpGs were identified, four (*PIK3R1*, *BTN3A3*, *NHLH1*, and *SLC16A7*) were differentially expressed. Fries et al. (2017) combined correlation and pathway analyses to identify molecular differences between PBMCs from 6 young BD patients, 6 unaffected subjects at high-risk of BD, and 6 healthy controls, using DNAm and transcriptomics. Results identified 135 genes with a significant correlation between gene expression and DNAm, while Ingenuity pathway analysis on the 43 genes either differentially expressed ($n = 33$) or methylated ($n = 10$) at individual level implicated circadian rhythms, immune system, synaptic scaffolding, and glucocorticoid receptor signaling. Abdolmaleky et al. (2019) used Spearman correlation to analyze transcriptomic (10 BD, 10 SCZ, and 10 healthy control) and DNAm (27 k CpG sites analyzed in 3–4 individuals from each group) brain data. Among other findings, an anti-correlation between DNAm (increased) and gene expression (decreased) was observed for the *CCND1* locus in SCZ and BD patients. Zhu et al. (2019) used both partial correlation and an overlap test to identify methylation differences associated with changes in gene expression in circulating monocytes in 79 monozygotic twin pairs discordant for MDD. Results indicated that differentially methylated genes were significantly overrepresented in previous GWAS MDD loci (2.32 times, P value = 2.4×10^{-4}) and, interestingly, were more likely to be differentially expressed (2.44 times, P value = 1.1×10^{-4}). Correlations were also assessed between miRNA and mRNA data from patients with mood disorders. Pisanu et al. (2019) tested for, and identified, negative correlations between miRNA expression and differentially expressed mRNAs in 10 responders and 10 non-responders to lithium BD patients. This resulted in correlations among 30 miRNAs and 277 mRNAs, with one downregulated and one up-regulated sub-cluster network centered on miR-320a and miR-155-3p, respectively, which are involved in the inflammatory response and the regulation of G-protein signaling. Chen et al. (2018) applied correlation analysis to identify miRNA/mRNA co-expressed modules using WGCNA and sequencing data generated using brain tissue from a larger cohort composed of 95 patients with SCZ, 74 with BD, and 225 healthy individuals. They identified a disease-associated module (daM) enriched for rare and de novo variants (but not for GWAS loci), which included 545 mRNAs and 5 miRNAs (miR-320b, miR-320c, miR-320d, miR-320e and miR-585). Among this module's hub genes were 6 transcription factors, including *POU3F2*, which plays a role in brain development and was identified as a key regulator.

3.3.3. Step-by-step approach – regression

Regression approaches were applied several times to mood disorders, often determining the relationship between genomic variations and other molecular layers. Mehta et al. (2014) used a regression approach to uncover 293 eCNVRs (expression-influencing copy number variation regions) that significantly influenced 429 unique transcripts in prefrontal cortex tissue from 35 controls, 34 BD, and 35 SCZ patients, with

Table 1
Selected multi-omic studies applied to mood disorders.

Paper	RNA	DNAme	miR	SNP	ChIP	Cohort	Biological samples	Integration method	Covariate correction	Relevant results	Code available
Abdolmaleky et al., 2019	x	x				mRNA: 10 BD, 10 SCZ, 10 HC DNAme: 4 BD, 4 HC, 4 SCZ	Brain (BA46, DLFC)	Spearman correlation	Matching samples	Anti-correlation between DNAm and expression of the <i>CCND1</i> locus	No
Aberg et al., 2018		x		x		812 MDD, 320 HC	Whole blood	Regression analysis	Quantity of DNAm captured, batches, peak location, age, gender & blood cell composition	23 CpG-SNPs with case/control methylation effect involved in neural function	No
Bhak et al., 2019	x	x				56 MDD SAs, 39 MDD, 87 HC	Whole blood	Random forest*	Not mentioned	Suicidal vs non suicidal MDDs classifier with an accuracy of 92.6%	Upon request
Belzeaux et al., 2019	x		x			237 MDD	Whole blood	Multiple logistic regression	Not mentioned	Combined MLRA of treatment-worsening suicidal ideation including miR-5695, <i>STMN1</i> mRNA, and <i>MADRS</i>	No
Chen et al., 2014	x	x				36 BD, 39 SCZ, 43 HC	Brain	Pearson's correlation & linear regression	Age, gender, brain pH & PMI	20 significantly correlated CpGs / gene expression showed correlated DEGs and DMGs patterns in psychotic patients brains	No
Chen et al., 2018	x		x	x		26 BD, 25 SCZ, 24 HC	Brain	Correlation	Gender age, brain pH, RIN & PMI	SCZ/BD associated module enriched for genes implicated in rare and de novo variants, and for miRNA targets with key regulators including <i>POU3F2</i> , <i>SOX9</i> , <i>PAX6</i> , <i>SOX5</i> , <i>EPAS1</i> , and <i>ZNF423</i>	No
Ciuculete et al., 2020	x	x		x		mRNA: 15 MDD, 15 HC DNAm & meQTL: 23 MDD, 36 HC	Brain & whole blood	Regression analysis, Spearman correlation	Blood cell composition & batches	Lower methylation at cg24627299 was observed in MDD patients, associated with expression levels of the MET ligand HGF in blood	No
Fries et al., 2017	x	x				6 BD, 6 BD HC offsprings, 6 HC	PBMCs	Pathway analysis & Pearson's correlation	Matching samples	42 combines DEGs and DMGs enriched in the circadian rhythm, immune system and synaptic scaffolding	No
Gandal et al., 2018	x			x		222 BD, 51 ASD, 559 SCZ, 963 HC	Brain (frontal, temporal cortices)	Regression analysis	RIN, PMI & hidden factors	5 gene/isoform networks enriched in inflammatory and postsynaptic density/receptor-mediated presynaptic signaling pathways as well as endothelial and pericyte genes	No
Ju et al., 2019	x	x				177 MDD, 102 HC	Whole blood	Overlap test	Age & gender	16 DMPs overlapping with <i>CHN2</i> and <i>JAK2</i> DEGs involved in the inflammatory response and neurodevelopment	No
Li et al., 2020	x			x		eQTL: $n = 2251$ GWAS: 246.363 MDD & 561.190 HC	Brain	SMR & Bayesian framework *	Diagnosis, gender, institution, AOD, PMI, RIN, Batches & hidden factors	<i>LRFN5</i> and <i>DCC</i> genes identified as depression risk genes involved in synaptic plasticity	No
Mehta et al., 2014	x			x		23 BD, 23 SCZ, 26 HC	Brain	GLM Likelihood ratio test	Age, gender, ethnicity & PMI	429 transcripts significantly associated with CNVR, enriched in the corticotrophin-releasing hormone signaling pathway	No
Pai et al., 2019	x	x		x		RNA seq: 17 BD & SCZ, 17 HC EWAS & Genotypes: 26 BD, 29 SCZ, 27 HC	Brain: PFC neurons	Regression analysis	Age, gender, PMI & ancestry	Concordance between DEG and DMG and enrichments related to embryonic development, synaptic function and immune cell activation	https://github.com/shraddhapai/EpiPsychosis_IGF2

(continued on next page)

Table 1 (continued)

Paper	RNA	DNAme	miR	SNP	ChIP	Cohort	Biological samples	Integration method	Covariate correction	Relevant results	Code available
Pisanu et al., 2018	x			x		mRNA: 10 BD LR, 10 NR Genotype: 59 LR, 146 NR	LCL	Multiple linear principal components regression	Matching samples	<i>ZNF429</i> and <i>ZNF493</i> as potential lithium-responsive biomarkers	No
Pisanu et al., 2019	x		x			mRNA: 10 BD LR, 10 NR miRNA: 12 BD LR, 12 NR H3K27ac: 117 SCZ, 109 HC.	LCL	Negative correlation between	Matching samples	A 30 miRNAs and 277 genes correlation network centered on miR-320a and miR-155-3p	No
Wang et al., 2018	x			x	x	mRNA: 259 BD, 630 SCZ, 1094 HC SNP: 172 BD, 497 SCZ, 619 HC	Brain (DLPFC)	WGCNA & Deep Boltzmann Machine*	Matching samples between training and test datasets	An improved model linking regulatory network including immunological, synaptic, and metabolic pathways and higher psychiatric level phenotypes	https://github.com/gersteinlab/PsychENCODE-DSPN
Wang et al., 2019a	x			x		mRNA: 258 SCZ, 279 HC GWAS: 36.989 SCZ, 113.075 HC	Brain & Whole blood	Bayesian framework*	Not mentioned	104 high-confidence risk genes involved in neurogenesis	https://www.vumc.org/cgg/irigs
Wang et al., 2019b	x			x		23 BD, 24 SCZ, 24 HC	Brain	Vertical & horizontal approaches: regression model *	No correction	<i>MAPK1</i> , <i>YWHAE</i> , <i>TPH1</i> and <i>AKT1</i> as key features genes in BD and SCZ	https://github.com/shuanggema/VHinteg
Xie, 2021	x	x				mRNA: 128 MDD, 64 HC. DNAme: 100 MDD, 50 HC.	Whole Blood	Overlap	Batch effect	46 Hypomethylated and up-regulated genes involved in -among others- PI3K-Akt IL-17 and axon guidance signaling pathways, 71 Hypermethylated and down-regulated genes involved in the MAPK and NF-kappa B signaling pathways 7,5% of hypermethylated BD genes showed decreased expression and less than 1% of the hypomethylated ones showed and increase.	No
Zhao et al., 2015	x	x				7 BD, 5 SCZ, 6 HC	Brain (BA9)	Overlap Test	Matching samples	DMR-related miRNAs down-regulated genes in neurogenesis and nervous system development	No
Zhu et al., 2019	x	x				72 MDD and 72 non MDD twins	PBMCs	Partial correlation	Blood cell composition estimation & batches	DMGs are 2.44 times more likely to be DEGs and are significantly enriched in previous MDD GWAS loci	No

Legends: AOD, alcohol and other drug; ASD, acute stress disorder; BA, Brodmann area; BD, bipolar disorder; CNVR copy number variation regions; DEG, differentially expressed gene; DLPFC, dorsolateral prefrontal cortex; DMG, differentially methylated gene; DMP, differentially methylated probe; DMR, differentially methylated region; DNAme, DNA methylation; eQTL, expression quantitative trait locus; EWAS, epigenome-wide association study; GLM, generalized linear model; GWAS, genome wide association study; HC, healthy controls; LCL, lymphoblastoid cell lines; LR, lithium responder; MDD, major depressive disorder; meQTL, DNA methylation quantitative trait locus; miR, micro RNA; NR, non responder; PBMC, peripheral blood mononuclear cells; PFC, prefrontal cortex; PMI, post mortem intervals; RIN, RNA integrity number; SA, suicidal attempt, SCZ, schizophrenia; SMR, summary data-based Mendelian randomization; SNP, single nucleotide polymorphism; WGCNA, weighted correlation network analysis. * Advanced integration approaches.

enrichment in the corticotrophin-releasing hormone signaling pathway. The PsychENCODE consortium generated brain RNA-seq and genotype data from a large cohort of 51 patients with autism, 559 SCZ, 222 BD, and 963 controls (Gandal et al., 2018). After a comprehensive investigation of this new transcriptome dataset (including alternative splicing, non-coding genes, and co-expression analyses), the authors combined transcriptome with genotype data to compute both gene- and isoform-level expression quantitative trait loci (eQTL). Expression prediction regression models were also tested by conducting a transcriptome-wide association study (TWAS). Taking advantage of these new brain eQTL and large publicly available GWAS in SCZ, autism, and BD, they identified genes whose expression, although not significantly different across disease groups, is regulated in *cis* by disease-associated variants. Pisanu et al. (2018) used a multiple linear principal components regression model to analyze gene expression changes induced by lithium chloride exposure in LCLs from 10 lithium responders (LR) and 10 non-responders (NR) BD patients, as well as genotype data of 56 LR and 141 NR patients. Among the 29 genes whose expression was significantly affected by lithium treatment, two (*ZNF429* and *ZNF493*) were also associated with lithium response using genotype data (analyzed at gene level). Regarding treatment response, regression methods were also applied by Belzeaux et al. (2019) to analyze mRNA, miRNA, and clinical data in relation to antidepressant treatment-worsening suicidal ideation (TWSI) in 237 MDD patients from a double-blinded trial. The authors compared multiple logistic regression models and found that the model that included miR-5695, *STMN1* mRNA, and the MADRS (Montgomery-Asberg Depression Rating Scale) score at baseline significantly outperformed those based on a single omic, or clinical data alone. Regression approaches were also applied for methylome or epigenome-wide association studies (MWAS or EWAS) and for integrating meDNA data with genotype or transcriptome several times. Aberg et al. (2018) concurrently analyzed genotype and DName using Methyl-binding domain sequencing (MBD-seq) from blood and brain for the NESDA MDD collection (320 controls and 812 cases). They focused on CpGs created/deleted by SNPs (with minor allele frequency > 10%). Twenty-three CpG showed a significant methylation quantitative trait locus (meQTL) effect. These so-called CpG-SNPs were over-represented among three recent MDD GWAS findings, with genes involved in neural function. Pai et al. (2019) also investigated genetic-epigenetic interactions, focusing on frontal cortex tissue. DName was assessed using neuronal nuclei (sorted using FACS in 29 SC, 26 BD patients, and 27 controls), while gene expression was investigated at whole tissue level (in 17 randomly selected cases and 17 controls), and SNPs were also characterized. Results showed a concordance of enriched pathways in both transcriptomic and methylomic analyses, including immune activation, embryonic development, and synaptic transmission. The cis-meQTL analysis (SNP-CpG regression) showed a significant genetic-epigenetic interaction in 13 out of the 18 differentially methylated CpG sites. Ciuculete et al. (2020) considered a step-by-step approach with regressions using blood and brain DName data. In their discovery cohort of 59 adolescents, they first identified an increase in blood DName at the cg24627299 site that was associated with higher depression scores and suicidal ideation during a 1-year follow-up. Then using genotype data from the same discovery cohort, they identified that rs39748 a SNP located at ~16 kb downstream, was associated with the level of DName at this CpG site. Using a replication cohort with brain DName data for 45 individuals and multiple published datasets, they found that this site was inversely correlated with *MET* expression in blood and hypomethylated with an increased *MET* expression in MDD subjects' brains.

3.3.4. Advanced approaches

Elaborated approaches have been used to integrate GWAS with eQTL data – see (Reynolds et al., 2021) for a comprehensive review of post-GWAS data integration strategies. In most cases, these studies use data from non-overlapping cohorts of patients. One of the exceptions, Li et al.

(2020) identified risk genes for MDD in Europeans and Han Chinese using SMR 'Summary-based Mendelian Randomization' coupled with a 'Bayesian integration risk gene selectors' (iRIGS) algorithms. The authors integrated GWAS data and eQTL, RNA-seq data in the DLPPFC, and chromatin conformation data (Hi-C) from multiple sources and very large cohorts. Results identified several genes, the most significant of which was *LRFN5*, involved in the formation and differentiation of synapses, and *DCC*, involved in synaptic plasticity.

Among advanced approaches, machine learning classification was used by Bhak et al. (2019) to distinguish depressive subjects with ($n = 56$) or without ($n = 39$) suicidal behavior and healthy controls ($n = 87$). Using a random forest classifier, the authors integrated blood data on DEGs and differentially methylated CpG sites with leave-one-out cross-validation. This resulted in an MDD suicidal vs. MDD non-suicidal classifier with an accuracy of 92.6%, and 63 features composed of differentially methylated sites only. Strikingly, Wang et al. (2018) was the only study using deep learning algorithms on mood disorder data despite its growing popularity. Both WGCNA and deep Boltzmann machine algorithm were applied to the transcriptome, genome (SNP), and chromatin conformation (Hi-C) PsychENCODE data from DLPPFC tissue of BD, SCZ patients, and controls. It resulted in an enhanced model linking psychiatric phenotypes to omics data, with genes involved in immunological and synaptic processes common to both schizophrenia and bipolar disorder.

Because of the rarity of studies leveraging such advanced approaches, we broadened our scope of analysis to SCZ and identified two additional relevant studies. In the first one, Wang et al., 2019a applied the iRIGS framework to infer risk gene probability from the GWAS data generated by the Schizophrenia Working Group of the PGC (36,989 SCZ cases and 113,075 controls). As a result, they built 104 networks derived risk genes (NRGs) and identified 104 high-confidence risk genes (HRGs) collectively involved in neurogenesis, glutamatergic neurotransmission, synaptic plasticity, and calcium channel and signaling, and targeted by miR-137. In the second SCZ publication, Wang et al. (2019b) proposed two integrative approaches of CNV and gene expression data from the same individuals (24 SCZ, 23 BD, and 24 controls from the Stanley foundation). The vertical approach, which aims to override collinearity among different omics, used a "reverse regression" of the CNVs on gene expression, and sparse PCA to reduce the number of selected features within a logistic regression model. The approach, which aims to study the impact of CNV on the expression of genes common to the two diseases, was based on linear regression with LASSO penalties. The sparse PCA in the vertical integration identified previously known SCZ and BD genes (*MAPK1*, *YWHAE*, *TPH1*, and *AKT1*). In contrast, the horizontal one showed *BRCA1* as a potential SCZ biomarker, suggesting that visualizing data using multiple analysis strategies and methods can help identify key disease-associated genes and biomarkers.

4. Discussion

This review first summarized recent studies that used single omic approaches in mood disorders and then looked in more detail at integrative studies that included more than one omic. Cohort size varied a lot among both single and multiple omics studies. We also noted that most recent research focused on the epigenetic aspect of mood disorders in both cases, emphasizing the contribution of DName and miRs, followed by their transcriptomic impact.

Up to now, despite the insights that single omic based studies have provided on the etiology of mood disorders, these studies failed at identifying reliable classifiers or molecular signatures that would improve diagnosis or patient stratification, neither for MDD nor BD. Most of these studies have observed small effect sizes, which contributes to the difficulty in uncovering reproducible functional perturbation in mood disorders. This could be explained by the subtlety and heterogeneity of molecular signatures associated with these disorders, among other factors. Accordingly, the well-known complexity of the brain

Table 2
Available multi-omic data on mood affective disorders.

Studies	DOI	Technologies	RNA	DNAm	SNP	Description	Biological samples	Phenotype data availability	Molecular data availability	Papers
Netherlands Study of Depression and Anxiety (NESDA) & Netherland Twin Register (NTR)	doi: https://doi.org/10.1002/mpr.256 doi: https://doi.org/10.1375/twin.5.5.401	Affymetrix 6.0 Human SNP & Human Genome U219 Array	x		x	SNP Genotypes: 5061 samples mRNA Expression: 5429 samples	Blood & Sliva	MDD Diagnosis, menopausal status, BMI, alcohol consumption, smoking habits, and sociodemographic data	dbGaP Study Accession: phs000486.v1.p1	Aberg et al., 2018
Stanley Medical Research Center (SMRC)	doi:10.1002/ajmg.b.32691	Illumina Infinium Human Methylation 27 k & Human Genome U133 Plus 2.0 array	x	x		mRNA: 10 BD, 10 SCZ, 10 HC DNAm: 4 BD, 4 HC, 4 SCZ RNA seq: 17 BD & SCZ, 17 HC	Brain (BA46, DLPFC)	Not publically available	GEO: GSE120342	Abdolmaleky et al., 2019
Pai et al., 2019	doi:10.1038/s41467-019-09786-7	Illumina NextSeq 500 Illumina MethylationEPIC BeadChip Illumina Human PsychArray-24 v1.1	x	x	x	DNAm & Genotypes: 26 BD, 29 SCZ, 27 HC RNA Seq: 353 SCZ, 128 BD/MD, 501 HC SNP: n = 1076 RNAseq: 259 BD, 630 SCZ and 1094 HC	Brain: PFC neurons	Age, gender, ethnicity, brain weight, smoking habits, PMI, antipsychotics use, valproate use, and lithium use	GEO: GSE112525	Wang et al., 2019b and Pai et al., 2019
CommonMind Consortium	doi:10.1038/s41597-019-0183-6	HiSeq 2000 or HiSeq 4000 HumanOmniExpressExome 8 v 1.1b chip, HumanHap650Y, Human1M-Duo, and HumanOmni5M-Quad	x		x	SNP: n = 1076 RNAseq: 259 BD, 630 SCZ and 1094 HC	Brain	RIN, library batch, diagnosis, age of death, genetic ancestry, PMI, and gender	https://www.synapse.org/#!/Synapse:syn2759792/wiki/69613	Wang et al., 2019a and H. J. Li et al., 2020
The PsychENCODE project	doi:10.1038/nn.4156	Details for each study available in supplimetry data of https://doi.org/10.1126/science.aat8464	x		x	SNP: 172 BD, 497 SCZ and 619 HC	Brain (DLPFC)	Age, gender, ethnicity	http://resource.psychencode.org/#Raw	Gandal et al., 2018

Legends: BA, Brodmann area; BD, bipolar disorder; DLPFC, dorsolateral prefrontal cortex; DNAm, DNA methylation; HC, Healthy Controls; GEO, gene expression omnibus accession; MD; Mood disorders; MDD, major depressive disorder; miR, micro RNA; PFC, prefrontal cortex; PMI, post mortem intervals; RIN, RNA integrity number; SCZ, Schizophrenia; SNP, single nucleotide polymorphism.

histological and structural organization, with multiple intricately glial and neuronal cell types, participates in this heterogeneity, and its underlying genetic architecture. In addition to such variable interactions at each omic level, these studies also likely suffer from their relatively small sample size, diagnostic heterogeneity, as well as insufficient consideration of meaningful additional factors, in particular, patient's medications.

From a systems biology point of view, it, therefore, appears that restricting analyses to a single biological level may not have the capacity to capture the complexity of molecular relationships and regulatory processes involved in mood disorders. With the aim of improving the identification of biomarkers with clinical potential, recent studies have moved towards multi-integrative methods, as reviewed in the second part of the present work. Over the last decade, rapid technical progress and increased availability of large datasets through collaborative and open-source efforts have opened new avenues for multi-omics data integration strategies. Among the 21 multi-omic studies reviewed herein (Table 1), most used step-by-step approaches. Such approaches, however, by definition only allow extracting information whose variance is strong enough to be detected as significant at the level of a single omic layer. Surprisingly, only one publication used a deep machine learning approach (Wang et al., 2018), despite the outstanding progress and popularity that such methods have gained recently, particularly in other research fields such as cancer. This is explained at least in part by technical challenges and higher costs associated with generating multi-omic data on large collections of biological samples. Yet, the application to multi-omics data of approaches based on matrix factorization and dimensionality reduction, as benchmarked recently by Cantini et al. (2021), would help the research community to prioritize genes and molecular biomarkers, and to uncover regulatory principles driving their pathophysiological dysregulation, as well as their potential as targets for drug repurposing programs. Furthermore, the clustering of patients using network-based methods such as SNF (Wang et al., 2014), or best consensus among various clustering methods (Brière et al., 2021), should improve patient stratification, and help better understand disease heterogeneity by identifying more homogeneous sub-groups of patients with MDD or BD.

We note that studies identified in the present systematic review mainly use case-control designs, with a striking paucity of studies based on other potentially relevant designs (e.g. longitudinal, dimensional). This could be explained by the relative novelty of multi-omics tools and integration methods designed around case-control studies. Furthermore, these methods could be used to cluster patients into molecularly homogeneous subgroups, which could potentially help in getting a finer understanding of the mood disorder spectrum. The current lack of statistically significant and reliable molecular signatures for mood disorders could be potentially overcome in the future by studies exploiting larger cohorts, and including groups of individuals at high risk for mood disorders, in prodromal phases of MDD and BD, or with variable symptom severity, using dimensional approaches. Additionally, future studies should seek to gather extensive longitudinal multi-omics profiling, which would likely help acquiring a better understanding of biological processes associated with mood disorders and their interaction with environmental factors at their earliest stage. Despite their substantial financial and logistics requirements, such prospective studies could notably mitigate the impact of significant confounding factors (e.g. medication), and ultimately lead to predictive biomarkers.

Lastly, the limited availability of bioinformatic code used for data analysis is concerning, as only 3 studies made their scripts public. Greater transparency is necessary to encourage the generalized use of multi-omics integration in molecular psychiatry. Even if some of the methods are already released as packages, many of their adaptations applied to molecular psychiatry need to be better documented to facilitate their use, determine their limitations, and ultimately lead to proper applicative recommendations. Besides, almost half of the studies reviewed here did not report corrections for known confounding

covariates and were limited to matching sample groups in terms of demographic and clinical variables. Above all, none of the multi-omic studies has taken medications into account (let alone frequent combinations of medications), although available evidence suggests that this factor may be critical.

5. Conclusion

In conclusion, we would like to advocate for the use of multi-omics data in psychiatry. Indeed, applying advanced integration methods could greatly benefit patients with mood disorders by promoting the discovery of biomarkers and, ultimately, precision psychiatry. This would help to overcome the lack of stratification indicators in the current nosology. It is, therefore, necessary to encourage collaboration between clinicians, biologists, and computational biologists. It is also essential to promote data availability, notably through public, freely accessible databases, as performed e.g. in oncology with the cancer genome atlas project (TCGA). Within this line, publicly available multi-omic data discussed in the present review are gathered in Table 2.

Further initiatives should be encouraged to generate multi-omic datasets for higher numbers of individuals, with prospective longitudinal data collection complemented by clinical and phenotypic data (eg brain imaging). The specificities of each data type, their increasing amounts, and analysis of their dynamic interactions raise new challenges for multi-omics and multi-view integration methods. Overall, developing such approaches is nevertheless expected, in the long term, to strongly benefit affected patients and their families.

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Declaration of Competing Interest

None.

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