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Review

Translational bioinformatics and data science for biomarker discovery in mental health: an analytical review

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Abstract

Translational bioinformatics and data science play a crucial role in biomarker discovery as it enables translational research and helps to bridge the gap between the bench research and the bedside clinical applications. Thanks to newer and faster molecular profiling technologies and reducing costs, there are many opportunities for researchers to explore the molecular and physiological mechanisms of diseases. Biomarker discovery enables researchers to better characterize patients, enables early detection and intervention/prevention and predicts treatment responses. Due to increasing prevalence and rising treatment costs, mental health (MH) disorders have become an important venue for biomarker discovery with the goal of improved patient diagnostics, treatment and care. Exploration of underlying biological mechanisms is the key to the understanding of pathogenesis and pathophysiology of MH disorders. In an effort to better understand the underlying mechanisms of MH disorders, we reviewed the major accomplishments in the MH space from a bioinformatics and data science perspective, summarized existing knowledge derived from molecular and cellular data and described challenges and areas of opportunities in this space.

Keywords: translational bioinformatics; neuroscience; biomarker discovery; data science; mental health informatics

INTRODUCTION

How bioinformatics and data science contribute to biomarker discovery in MH

Thanks to the digitization of healthcare data, massive amounts of data are being generated and collected from electronic health record (EHR) systems, medical imaging, laboratory and genomics tests, mobile health and wearable technology. This surge in Big Data, projected to reach the zettabytes range annually [1, 2]. With advances in artificial intelligence (AI) methodologies and cloud computing technologies, scientists are able to apply machine learning (ML) and AI-based deep learning techniques to structured and unstructured data on a scale that was previously unimaginable.

In this Big Data revolution, bioinformatics and data science play a crucial role as it enables scientists to extract and integrate biological information from the DNA, mRNA, microRNA, genes, proteins and metabolites, environmental and lifestyle factors. The scalable computational power of cloud computing empowers researchers to delve into complex disease mechanisms, enabling a systems-level understanding [3, 4].

The US Food and Drug Administration (FDA) has defined various categories of biomarkers and their various areas of applications. They include diagnostic, prognostic and theranostic biomarkers and can enable identification of various disease subtypes, better prediction of disease progression and better monitoring of treatment response [5, 6]. A good biomarker must be reliable, reproducible and independently confirmed by more than one study [7].

In recent years, mental health (MH) disorders have become a promising venue for biomarker discovery and for improved patient outcomes due to increasing prevalence and rising treatment costs [6]. Exploration of underlying biological mechanisms is the key to the pathogenesis and pathophysiology of mental disorders [8]. This is also keeping with National Institute of Mental Health (NIMH)'s Research Domain Criteria (RDoC) which is a framework that enables the study of the mechanisms of mental illness [6]. At present, very few biomarker tests have been approved for use in the clinic for MH, making this research even more important [9]. The progressive identification of new biomarkers in the MH space could enable researchers to build advanced clinical description support systems (CDSS) empowered by sophisticated AI models to advance personalized medicine [10].

Translational bioinformatics plays a vital role in biomarker discovery as it bridges the gap from the bench to the bedside.

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Table 1: Summary of articles categorized by the type of omics analysis

Category of omics study	Number of published articles	Percentage of published articles
Proteomics	46	27
NGS; genomics	36	21
Cellular	21	12
Microbiome	17	10
Multiomics	16	9
microRNA	13	8
Gene expression	11	6
Epigenomics	11	6
Imaging	2	1
Total	173	100

Table 2: Summary of articles categorized by MH disorder

Category of MH disorder	Number of published articles	Percentage of published articles
Alzheimers	35	20
Major depressive disorders	33	19
Neurodegenerative disorders (in general)	26	15
Neuropsychiatric disorders (in general)	19	11
PTSD, general anxiety	18	10
ASD and ADHD	15	9
Other (neurological disorders, psychiatry)	15	9
SCZ and BD	12	7
Total	173	100

In order to better understand the various mechanisms of mental illnesses, we reviewed the major accomplishments in MH translational research from a bioinformatics and data science perspective, summarized computationally enabled discoveries of potential molecular and cellular biomarkers and described challenges and areas of opportunities for further exploration in this space.

This review is based on extensive search of relevant publications. A multiterm query for the following terms was performed in the NCBI Pubmed repository (bioinformatics OR transcriptome OR Proteomics OR genomics OR sequencing OR infection OR microbiome OR microRNA OR gene expression OR multiomics OR NGS OR RNA-seq OR RNAseq) AND (brain OR mental illness OR psychiatric OR psychiatry OR depression OR schizophrenia OR bipolar OR bi-polar OR autism OR anxiety OR PTSD OR Addiction OR Neurodegenerative diseases OR dementia OR memory loss. This resulted in 195,104 results from publications in 2009–2019, and 200 of the most relevant publications were downloaded for detailed review. The publications were then tagged based on two categories—category of MH disorder and molecular technology.

The scope of this review article was limited to the most common MH disease categories including major depressive disorders (MDD), Alzheimer's disease (AD) and common disorders including schizophrenia (SCZ), bipolar disorder (BD), autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD) and posttraumatic stress disorder (PTSD). The word 'biomarker' was not used in the query as that may have resulted in publications unrelated to molecular and cellular mechanisms. As a result, the final list of publications was 173 (Tables 1 and 2).

Summary of diseases reviewed

AD is a progressive neurodegenerative disorder that is estimated to affect one in nine senior adults. Its risk factors include age, family history and surrounding environment [11]. Many studies have been conducted to understand the underlying molecular mechanisms but no cure has been found so far [12]. MDDs is one of the most common MH disorders in the USA [13] and affects about 4.7% of the people in the world [14]. MDD which is associated with high mortality includes clinical depression, BD, suicide and other mood disorders. MDD is known to be heterogeneous and caused by a combination of genetic, environmental and psychological factors, and not many biomarkers are known to be effective in this domain [13].

According to the World Health Organization (WHO), SCZ is a psychiatric disorder that affects 1 in 300 people worldwide. SCZ is not as well studied as other psychiatric disorders like MDD. BD is a mental illness associated with extreme changes in mood from high to low and vice versa [15]. ADHD is one of the most common neurodevelopmental disorders that begin in early childhood. ASD is another neurological disorder that also begins in early childhood and impairs the ability to communicate and interact [16]. Anxiety disorders, such as PTSD among others, are one of the most common classes of psychiatric disorders and are known to be familial and heritable to a moderate degree [17].

Potential biomarkers from proteomics studies in various MH-related disorders

One of the most studied molecular datatypes in AD is proteomics-derived protein-based biomarkers. Advances in proteomics have allowed development of new biomarker discovery methods for early detection and diagnosis [18, 19]. The articles reviewed highlight the pivotal role of proteomics in unraveling intricate molecular mechanisms associated with AD, including the identification of protein-based biomarkers for early detection and diagnosis. Noteworthy findings encompass the characterization of over 400 proteins linked to amyloid plaques [20], the influence

of hyperphosphorylated tau protein on neuronal health [21] and the discovery of key proteins such as glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in AD progression [22, 25]. The mitochondrial dimension of AD is explored through proteomic analysis of mitochondrial proteomes, revealing distinct patterns between early-onset and late-onset AD [23, 24]. Additionally, mitochondrial dysfunction, oxidative stress and alterations in protein homeostasis and energy production emerged as crucial contributors to AD pathophysiology [25–27]. Exploration of the proteomic landscape of the hippocampal tissues pinpointed to the changes in protein expression and potential implications for calcium signaling and extracellular matrix dynamics [28]. In the clinic, reduced glucose utilization is used as a biomarker for AD detection [29].

We found proteomics to be one of the most common molecular profiling platforms applied in MDD as well. One hundred and seventy-one serum proteins were identified, and serum analytes were linked to diverse cell communication in MDD patients [30]. Changes in protein abundance that were associated with several biological functions, including inflammation, transcription, cell metabolism and cytoskeleton organization [31] and those related to energy metabolism-related were also identified [7, 32].

In MDD, the protein HINT1 displayed increased brain levels, while SCZ exhibited lowered HINT1 levels [32]. Other aberrations associated with SCZ included glutamate receptor N-methyl-D-aspartate receptor (NMDA-R) and gamma-aminobutyric acid (GABA) [33]. Clinicians needed to identify and differentiate BD from MDD at the first depressive episode as the treatment course is different. Ren *et al*. [34] studied the differences between the two disorders by using a proteomics technology that applied isobaric tags for relative and absolute quantification (iTRAQ) technology combined with liquid chromatography–tandem mass spectrometry (LC–MS/MS). The authors found nine proteins significantly changed between MDD and BD and shortlisted *B2RAN2* and *ENG* as potential biomarkers to distinguish BP from MDD.

The p140Cap protein interactome network associated with the *SRCIN1* gene has been found associated with SCZ, ASD and BD [35]. Da Silva *et al*'s [36] proteomic profiling elucidated molecular mechanisms underlying the effects of methylphenidate in ADHD, highlighting potential links between pathways related to neurotransmitter release and GABA transmission, with drug response. The findings are summarized in Table 3.

Potential biomarkers from genomics/NGS studies in various MH-related disorders

Affordable high throughput genome sequencing has spurred a wave of new studies utilizing next-generation sequencing (NGS) to uncover biomarkers and untangle the intricate pathology of MH disorders like AD [37]. Bertram *et al*'s [38] NGS investigations unveiled mutations in genes APP, TREM2 and PLD3. Verheijen *et al*. studied distinct subtypes of AD including early onset Alzheimer's disease (EOAD) and late onset Alzheimer's disease (LOAD). EOAD affects people before the age of 65 and often hereditary; was associated with genes like *APP*, *PSEN1* and *PSEN2* and characterized by amyloid accumulation. On the contrary, LOAD, affecting those over 65, with about 80% genetic contribution, is notably linked to APOE ε4 allele, which is a major risk factor [39].

Increased hypothalamic–pituitary–adrenal (HPA) axis activity has been known to occur in MDD leading to reduced mood and cognitive dysfunction [40], Nashed *et al*'s study on cancer-induced depression via RNA-seq revealed pathways tied to neuronal development, intracellular signaling, memory and learning [41]. *NR3C2* and *NR3C1* genes encoding mineralocorticoid and glucocorticoid receptors emerged as MDD risk factors, affecting HPA axis and cognitive functions [42]. Other candidate genes that have been linked with MDD include SNPs of CRHR1 that function through the HPA axis. [17, 43]. *RGS2* gene has been found associated with multiple MH disorders including PTSD, generalized anxiety disorder (GAD) and PD [17].

Pies *et al*. studied biomarkers in SCZ and identified four main potential biomarkers that included mutations in neuregulin-1 NRGI, a cell adhesion molecule which acts on the EGFR family of receptors. Mutations in this gene have been linked with increased risk of SCZ [7, 44]. Mutations in DISC1 have been found in multiple MH disorders including BD, SCZ, MDD and ASD [35, 45–47]. Li *et al*. studied 36 studies on 4 neuropsychiatric disorders including ASD, epileptic encephalopathy, intellectual disability, SCZ profiled by WES/WGS and found 764 candidate genes in these disorders. Of these, 53 genes were found in more than one disorder and indicated a shared etiology of those disorders, with *de novo* mutations in *SCN2A* mutations common to all. [48]. Common pathways found between SCZ and ASD were synaptogenesis and synapse function and epigenetic process [49]. *RGS2* gene has been found associated with PTSD, GAD and PD genes [17].

An interesting discovery was serotonin transporter *SLC6A4* gene was found associated with both ASD [50] and tandem repeats in the promoter region of this gene was associated with PTSD [17]. Mutations in dopamine transporter and D4 receptor have shown to have potential as biomarkers in ADHD [51, 52]. Overall, we saw the genes commonly found in biomarker studies to be linked with monoaminergic neurotransmitter systems, neuropeptides and HPA axis function and an increased activity of transporter genes in the SLC family. Table 4 summarizes these findings in more detail.

Potential biomarkers from gene expression studies in various MH-related disorders

A wide array of gene expression studies was examined across various MH disorders, offering interesting insights into the underlying molecular mechanisms. Wang *et al*. [53] suggest a potential link between abnormal AMP expression and AD onset in flies. Forero *et al*. [54] conducted a substantial meta-analysis of gene expression studies in MDD, revealing differentially expressed genes across various brain regions including blood, amygdala, cerebellum, anterior cingulate cortex (ACC) and prefrontal cortex (PFC) regions and highlighting 23 confirmed genes from their findings (Table 4). Dysregulated genes associated with MDD include *SLC1A2* (glutamate transporter), GABRD (GABA receptor [54, 55]), genes in the HTR serotonergic family [56] and *PXMP2* (ROS metabolism) [54]. Xiao *et al*'s [57] study on SCZ and BD revealed altered mRNA levels of *RELN*, while Kuan *et al*'s [58] research from World Trade Center responders who had PTSD identified 99 differentially expressed genes, including the upregulation of *FKBP5* in PTSD responders. Overall, we can see diverse gene expression patterns associated with different MH disorders, providing valuable insights into potential biomarkers and therapeutic targets. Table 5 summarizes these differentially expressed genes and findings in more detail.

Potential biomarkers from microRNA studies in various MH-related disorders

Forero *et al*. performed one of the largest meta-analysis of gene expression studies in MDD that covered 24 datasets that included a total of 753 samples. The authors identified 35, 793, 231, 668 and 252 genes differentially expressed from studies analyzed in the blood, amygdala, cerebellum, ACC and PFC regions, respectively [59, 60]. One particular microRNA reported

Table 3: Potential biomarkers from proteomics studies in various MH-related disorders

Author name or study ID	Disorder	Protein(s)/biological functions affected	Implications	Source
[22]	AD	GAPDH	Interaction with β-amyloid precursor protein [22]	Various
[24]	AD	Respiratory mitochondrial complex subunits including those from the NDUFA and NDUFB subunits of the enzyme NADH dehydrogenase	Mitochondrial proteomic differences in early-onset and late-onset AD [24]	Brain tissue
Multiple studies: Moya-Alvarado *et al.* [25–27]	AD	Proteins associated with mitochondria, phosphorylation and oxidation	Impaired glucose metabolism and energy production [25–27]	Multiple studies from blood and brain tissue
Hondius *et al.* [28]	AD	Calcium-dependent signaling proteins, extracellular matrix components	Protein expression changes in hippocampus [28]	Brain
[138]	AD	Novel peptide sequences identified (SpotLight)	Antibody variable region associations with potential to provide disease origin insights [138]	Blood
[29]	AD	Reduced glucose utilization	Biomarker for AD detection [29]	Brain
Bot *et al.*/Netherlands Study of Depression and Anxiety	MDD	171 serum proteins and serum analytes	Linked to diverse cell communication, signal transduction processes, immune response and protein metabolism [30]	Serum
Gellen *et al.*	MDD	Changes in protein abundance	Linked to several biological functions, including inflammation, transcription, cell metabolism and cytoskeleton organization [31]	Animal model
Comes *et al.* [139]	MDD	141 peptides and analytics analytes with combined m/z 1017, m/z 1042 and m/z 1479	Potential biomarkers	Blood
Multiple studies: [32, 140]; [7, 32]	MDD	DPYSL2 also known as CRMP2; CA2 and ALDOC	Regulating axonal guidance, neuronal growth cone collapse and cell migration [32, 140]; energy metabolism [7, 32]	Studies from blood and brain tissue
[32]	MDD versus SCZ	HINT1 increased in MDD and lower in SCZ.	Differential protein levels in brain of MDD and SCZ patients	Blood and urine
[139]	BD	Alpha-2-macroglobulin, Apolipoprotein A-I and C4b-binding protein alpha chain, Complement C3, Glutathione-S-transferase A3, hemopexin, Immunoglobulin M, Kit ligand, Macrophage migration inhibitory factor, MMP7 and sex hormone-binding globulin	Proteins belonging to the following pathways associated with BD: FXR/RXR activation, LXR/RXR activation, acute phase response signaling, clathrin-mediated endocytosis signaling and atherosclerosis signaling	Blood
Ren *et al.* [34]	BD versus MDD	Proteins upregulated: B2RAN2, B4E1B2, APOA1, ENG, SBSN and QSOX2. Proteins downregulated: ORM1, MRC2 and SLPI downregulated	B2RAN2 and ENG as potential biomarkers to differentiate BD and MDD	Blood plasma
Ristori *et al.* [10]	ASD	(APOE and APOA1) and (FN1)	Large presence of apolipoproteins proteins and fibronectin	Studies from blood and brain tissue
Junaid *et al.* [141]	ASD	Glyoxalase I (Glo1) [141]	Increase in polarity	Brain
[35]	SCZ, ASD and BD	p140Cap protein interactome network associated with the SRCIN1 gene	Common interactome network	Various

Table 4: Potential biomarkers from genomics/NGS studies in various MH-related disorders

Author name or study ID	Disorder	Genes/biological functions affected	Implications/key findings	Source
Bertram *et al.*'s [38]	AD	APP, TREM2 and PLD3	Gene mutations associated with AD	Various
Iacono *et al.* [142]	AD	A study of mouse models in AD using single-cell RNA sequencing (scRNA-seq) and functional analysis identified genes associated with gene expression or metabolic processes	Genes linked with multiple mouse organs were found to be associated	Brain
Verheijen [39]	EOAD	Increased accumulation of the amyloid-β ($A\beta)_{1-42}$ peptide. Genes associated included amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*)	Hundreds of pathogenic mutations were found in this inherited disorder	brain
Verheijen [39]	LOAD	APOE ε4 allele	Well-known risk factor	Brain
Pantazatos *et al.* [143]	MDD	Humanin-like-8 (MTRNRL8), interleukin-8 (IL8) and serpin peptidase inhibitor, clade H (SERPINH1) and chemokine ligand 4 (CCL4)	Altered gene expression identified using RNA-seq	Brain
Nashed *et al.* [41]	MDD	Neuronal development, intracellular signaling, learning and memory	Pathways implicated in depression using RNA-seq	Brain
Pantazatos *et al.* [144]	MDD	SSAT and SATX isoforms, SAT1	Low gene expressions in MDD	Brain
Pirooznia *et al.* [145]	MDD	Calcium signaling and dendrite regulation	Exons of synaptic genes potentially involved in the etiology of MDD	Brain
Howard *et al.* [146]	MDD	102 genomic variants and 269 genes including SORCS3 and NEGR1	Meta-analysis study of three large genome-wide association studies (GAWAS) studies	Brain
Keller *et al.* [42]	MDD	Variants in the NR3C1 gene including rs33388, rs10052957, rs10482633, rs41423247. variants in the NR3C2 gene included rs1879829, rs3910052, rs4835488, rs6535578, rs7658048 and rs5522	NR3C2, NR3C1 variants affecting HPA axis and cognition	Brain
Belzeaux *et al.* [147]	MDD	RORA, GCET2 and SMARCC2	Three potential biomarkers for treatment response	Various
Feng *et al.* [148]	MDD	EEF2, RPL26L1, RPLP0, PRPF8, LSM3, DHX9, RSRC1 and AP2B1	potential pathogenic genes associated with MDD and potential therapeutic targets	Various
Multiple studies [17, 43]	MDD	SNPs of CRHR1	Candidate genes reported	various; blood
Multiple studies [149–151]	MDD	Whole-genome sequencing was used to identify SNPs: one near gene SIRT1, an enzyme that deacetylates proteins that contribute to cellular regulation and the other SNP in an intron of LHPP gene [149–151]	Single nucleotide polymorphisms (SNPs) associated with MDD	Various; blood; saliva
Multiple studies [35, 152, 153]	SCZ and BD	Mutations and DNA methylation in BRD1 protein	Genetic associations	Various; blood; blood
Pies *et al.* [7, 44]	SCZ	Mutations in neuregulin-1 NRGI	Potential biomarkers for SCZ; increased risk of SCZ	Various; various
Multiple studies [35, 154, 155]	SCZ	ZNF804A [35, 155] and CRMP2 mutations [35, 154]	Increased risk of SCZ	Various; blood; mouse models, cell lines and DNA constructs
[49]	SCZ	Voltage-gated calcium channels, ARC-associated scaffold and FMRP interactors	The affected functional gene sets were identified using whole exome sequencing (WES)	Induced pluripotent stem cells (iPSC)
Demkow *et al.* [133]	ASD, ADHD	NGS testing justification in various clinical scenarios	Enables search for inherited conditions and new de novo mutations	Various
Goes *et al.* [156]	ASD	RPGRIP1L, FRAS1, AHNAK, KDM5B and SLC12A4	Shortlisted genes implicated in ASD using WES	DNA from lymphoblastoid cell lines
Multiple studies [51, 52]	ADHD	Mutations in dopamine transporter and D4 receptor	Potential biomarkers	Various
Li *et al.* [48]	ASD, epileptic encephalopathy (EE), intellectual disability (ID), SCZ	53 shared genes among four disorders, including SCN2A	Indicates a shared etiology of these disorders	Various
[49]	SCZ and ASD	Synaptogenesis and synapse function and epigenetic process	Common pathways found	Induced pluripotent stem cells (iPSC)
Wen *et al.* [157]	ASD	Mutations in MECP2	Used WES to identify several loss-of-function mutations that could lead to ASD	Peripheral blood
Multiple studies: Sjaarda *et al.* [17, 50]	ASD and PTSD	Serotonin transporter SLC6A4	Mutations linked to ASD and prenatal stress; GWAS-identified polymorphisms associated with PTSD	Mouse model; various
[17]	PTSD, generalized anxiety disorder (GAD) and Parkinson (PD)	RGS2	Only a few findings have been confirmed by multiple studies	Various

Table 5: Potential biomarkers from gene expression studies in various MH-related disorders

Author name or study ID	Disorder	DEGs/biological functions affected	Implications/key findings	Source
Wu *et al.* [158]	AD	ITGB5, RPH3A, GNAS, THY1 and SEPT6	Associated with AD disease progression	Brain tissue
Wang *et al.* [53]	AD	Abnormal AMP expression	Onset and development of AD in flies	Brain tissue
Forero *et al.* [60]	MDD	A list of 23 genes including ABCG4, ACTA2, AGAP1, AP2B1, ATP1A3, ATP2B1, ATP5A1, BMI1, C10orf10, C3orf70, CAMK2A, CD24, CDC37, CDH13, CDKN1B, CDO1, CLDND1, CPLX1, CSRNP3, GLDN, GRM8, IL17RD, TUSC3	Short list of 23 genes confirmed in other studies as well	Meta-analyses for GWES of MDD for four brain regions and for blood
Multiple studies: [54–56]	MDD	Glutamate transporter gene SLC1A2 [54]; GABAergic gene GABRD that codes for gamma-aminobutyric acid type A receptor delta subunit [54, 55]; genes in the serotonergic family including HTR1A, HTR1B, HTR2A, HTR2C [56] and the PXMP2 gene which is involved in reactive oxygen species (ROS) metabolism [54]	Dysregulated in various regions of the brain in MDD	Brain and peripheral tissues; blood
Multiple studies: [49, 159, 160, 161]	SCZ	GFAP [159], GLUL [160] and S100B [49, 161]	Genes implicated in SCZ	Brain tissue; brain tissue; blood
Xiao *et al.* [57]	SCZ and BD	mRNA levels of RELN were affected in patients	The study of the methylome and transcriptome	Brain tissue
Ansel *et al.* [74]	ASD	DIO2, Cirbp, DNMT3A, DNMT3B, TET1, TET3	Dysregulated genes identified	Multiple sources
McCaffrey *et al.* [162]	ADHD	ABCB5, RGS2, GAK, GIT1	This study of RNA markers could be studied further towards design of targets for diagnostics and therapeutics in ADHD	Blood

in most of the studies was *miR-132* which is one of the microRNAs regulating expression of *BDNF*, one of the key players in brain plasticity. This microRNA also targets the gens *MAOA* and *SLC6A3* that are implicated in neuropsychiatric disorders [61, 62]. Kohen *et al.* applied RNA-seq to patients with MH disorders including SCZ, MDD and BD and found that the level of expression of another microRNA: *miR-182* was changed in these disorders. *miR-182* was also found activated in patients with BD and healthy controls, while it was found downregulated in MDD and SCZ [63]. Nakata *et al.* [64] studied microRNA expression in peripheral blood from adults with high functioning ASD and compared with healthy controls and discovered miR-6126 as downregulated in ASD. Gupta *et al.* studied PTSD data from military veterans and found circulatory microRNAs to play an important role. Specifically, microRNAs associated with HPA axis regulation through *FKBP5* were found to play a key role in PTSD [65]. Detailed findings are summarized in Table 6. Overall, these diverse miRNAs implicated in MH disorders offers valuable insights into potential mechanisms and therapeutic avenues.

Potential biomarkers from epigenomics studies in various MH-related disorders

Zhang *et al.* employed whole genome bisulfite sequencing to identify novel differentially methylated sites in genes *DLGPAP1*, *TMEM51* and *EIF2AK2* that could serve as potential biomarkers for AD. [66]. Li *et al*'s review of 67 studies highlighted hypermethylation in *BDNF* and *SLC6A4* as associated with depression [67, 68]. Kuan *et al.* [69] studied epigenome-wide association studies (EWASs) of MDD of 473 World Trade Center responders and found phosphatidylinositol signaling and cell cycle pathways affected. DNA methylation changes in genes *CAMK2A*, *SLC1A2*, *HTR1A* and *HTR1B* have also been implicated in MDD [68, 70, 71]. Epigenetic changes in gene *BDNF* or receptor *TRKB* were found in multiple psychiatric disorders including MDD, BD, SCZ and borderline personality disorder [72].

Epigenetic changes in serotonin transporter *SLC6A4* have implications in MDD, BD, PTSD, SCZ, and ADHD.

Loke *et al.* [73] studied epigenetic changes associated with Autism and identified five candidate genes (*OXTR*, *GAD1*, *EN2*, *RELN*, *MECP2*) whose methylation was affected in the brains of ASD patients. One of the very commonly studied methylation changes is the addition of a methyl group on the fifth carbon of cytosine (e.g. 5-methylcytosine 5mC). This epigenetic marker in involved in important functions including X-chromosome inactivation, chromatin structure, gene silencing and genomic imprinting. Disruptions in 5mc has recently been linked to ASD with promising relevant in the clinic [74–76]. Kuan *et al.* [69] conducted EWASs of PTSD responders and found genes enriched in the following pathways including stress response, inflammation and physical health. Detailed findings are summarized in Table 7.

Potential biomarkers from imaging studies in various MH-related disorders

Imaging biomarkers play a crucial role in not only understanding MH disorders but also help with early detection in many MH disorders. In AD, functional and structural MRI, along with amyloid imaging using PET tracers, aid in detecting changes and amyloid

Table 6: Potential biomarkers from microRNA studies in various MH-related disorders

Author name or study ID	Disorder	Molecular features/biological functions affected	Implications/key findings	Source
Pang *et al.* [163]	AD	hsa-let-7d, hsa-miR-144, hsa-miR-374a, and hsa-miR-106b targeting genes in pathways PI3K-AKT signaling pathway, MAPK signaling pathway, oxidative phosphorylation, synaptic vesicle cycle, cell–cell adhesion, cytokine-mediated signaling pathway, proteasome, arginine, proline metabolism and pentose phosphate pathway [163]	Analysis of two important regions of the brain—entorhinal cortex (EC) and hippocampus (HIP) of AD patients revealed microRNAs that targeted genes in specific pathways	Blood
Multiple studies: Forero *et al.* [55, 59, 60, 164]	MDD	DEGs in various brain regions. MicroRNAs including hsa-miR-32, hsa-miR-33, hsa-miR-122, hsa-miR-429 associated with MDD. These microRNAs also known to regulate other MDD genes including GABA receptors, NOTCH2 and HNRNPU [60, 164]. Other miRNAs implicated include hsa-miR-370, hsa-miR-411, hsa-miR-433, hsa-miR-487b and hsa-miR-539 [165]	Studies analyzed in the blood, amygdala, cerebellum, ACC and PFC regions revealed microRNAs linked to chronic stress and fear and GABA receptors linked to chronic stress and fear [55, 164]	Various brain regions
Wang *et al.* [166–168]	SCZ	hsa-miR409-3p [166–168] which targets genes associated with SCZ including FAM117B, GABRA1, GAD1, and NUMBL. hsa-miR-370 targets several SCZ associated genes including BDNF, NRG1 and SYN2 [166, 169]. Other microRNAs affected include miR-30e, miR-7, miR-195, miR-34a and miR-346	microRN As that targets genes associated with SCZ	Tissue; blood; blood
Multiple studies [61, 170]	MDD and BD	miR-652 [61, 170]	microRNA affected in both MDD and BD	Various sources (microRNA affected in both MDD and BD); blood
Kohen *et al.* [63]	SCZ, MDD and BD	miR-182	RNA-seq revealed this microRNA was found activated in patients with BD and healthy controls while downregulated in MDD and SCZ [63]	Brain tissue
Multiple studies [61, 62]	Multiple neuropsychiatric disorders	miR-132, one of the microRNAs regulating expression of BDNF, and targets the genes MAOA and SLC6A3	One of the key players in brain plasticity and implicated in neuropsychiatric disorders [61, 62]	Various sources (microRNA affected in both MDD and BD); various sources
Srivastav *et al.* [171]	ADHD	microRNAs regulated the gene expression of BDNF, DAT1, HTR2C, HTR1B and SNAP-25	These microRNAs were also linked to ADHD etiology [171]	Various sources
Nakata *et al.* [64]	ASD	miR-6126 downregulated in ASD	Study of microRNA expression in peripheral blood from adults with high functioning ASD compared with healthy controls	Blood
Gupta *et al.* [65]	ADHD	microRNAs associated with HPA axis regulation through FKBP5 were found to play a key role in PTSD	Circulatory microRNAs to play an important role in PTSD	Blood
Martin *et al.* [172]	PTSD	Four upregulated microRNAs (miR-19a-3p, miR-101–3p, miR-20a-5p and miR-20b-5p) and four downregulated microRNAs (miR-15b-3p, miR-125b-5p, miR-128-3p and miR-486-3p) in PTSD samples	Implications of microRNA dysregulation in PTSD patients	Blood

Table 7: Potential biomarkers from epigenomics studies in various MH-related disorders

Author name or study ID	Disorder	Molecular features/biological functions affected	Study summary/key findings	Source
Zhang *et al.* [66]	AD	Novel differentially methylated sites in genes DLGPAP1, TMEM51 and EIF2AK2	Potential biomarkers for AD identified through whole-genome bisulfite sequencing in mouse brains	Brain
Li *et al.* [67, 68]	MDD	Hypermethylation in BDNF and SLC6A4 associated with MDD. DNA methylation changes in genes linked to MDD. [67, 68]	Review of 67 studies to summarize the relationship between DNA and depression	Blood; various
Multiple studies: Kuan *et al.* [68–71]	MDD	Phosphatidylinositol signaling and cell cycle pathways affected in MDD. Genes CAMK2A, SLC1A2, HTR1A and HTR1B also implicated	EWASs	Various; blood; various; various
[72]	MDD, BD, SCZ	Epigenetic changes in gene BDNF or receptor TRKB	Could be a potential biomarker as it was found in multiple psychiatric disorders	Various
Multiple studies [35, 57, 152, 153]	SCZ and BD	Mutations and DNA methylation in BRD1 protein. Methylation changes in RELN, PPP3CC, DNMT1, DTNBP1, NOS1, HTR1E, GRM5, PRIMA1, HTR2A and HTR2A [57]	The study of the methylome and transcriptome in SCZ and BD found changes in the methylation of many genes	Various; brain; various; brain;
Neumann *et al* [173]	ADHD	DNA methylation in CREB5 which is known to be important for neurite outgrowth was associated with ADHD [173]	DNA methylation at birth was associated with ADHD by performing an epigenome-wide association study (EWAS)	Blood
[72, 174]	MDD, BD, PTSD, SCZ and ADHD	Epigenetic changes in serotonin transporter SLC6A4	Could be a potential biomarker as it was found in multiple MH disorders	Blood; various
Loke *et al.* [73]	ASD	(OXTR, GAD1, EN2, RELN, MECP2)	Identified five candidate genes whose methylation was affected in the brains of ASD patients [73]	Various
Multiple studies [74–76]	ASD	5mC is a methylation marker involved in important functions including X-chromosome inactivation, chromatin structure, gene silencing and genomic imprinting	5mc methylation could be a potential marker in the clinic [74–76]	Various; brain; brain
[175]	PTSD	Methylation levels of FKBP5 and SLC6A4 genes studied for associations with PTSD	Epigenetic insights into genes associated with PTSD	Blood
Kual *et al.* health [69]	PTSD	Genes enriched in the following pathways including stress response, inflammation and physical health [69]. Epigenetic changes in HDAC4	Epigenetic changes were found in a gene in the blood of patients with PTSD	Blood

plaques in the brain [77–79]. For MDDs, MRIs reveal structural abnormalities in regions like the PFC, cingulate cortex, thalamus and hippocampus, offering insights into potential pathogenesis [80]. In ASD, white matter microstructure and amygdala growth abnormalities impacted brain networks in early life [81]. MRIs were also found to differentiate ADHD patients from controls based on alterations in the cortical shape in areas of the brain [82]. Such an approach could be explored further for clinical use to identify clinical symptoms and treatment response [83]. Detailed findings are summarized in Table 8.

Potential biomarkers from copy number studies in various MH-related disorders

Copy number variations (CNVs) in the genomic regions are linked to various MH disorders. From this summary, it is clear that there are common genomic regions of copy number instability across various MH disorders including 1p, 1q, 15q, 16p and 22q.

In AD, variations in regions of chromosome 1 and 2 were found including 1p36, 1q21,1q32, 2p23 and 2q14 [84]. People who inherit one copy of the *APOE* isoform APOE $\varepsilon 4$ have an increased chance of AD and those with two copies have an even greater risk [85]. In another study, MDD patients had a higher mitochondrial DNA copy number and could be relevant to the pathophysiology of MDD [86]. For SCZ and BD, Xiao *et al.* pinpointed CNV 'hot spots', i.e. regions of large CNV as 1q32 and 22q11.22 [87, 88]. Krgović *et al.* predicted that the rate of CNVs in patients with ADHD was 1.33 times higher when compared to healthy controls [89]. Duplications of 15q13.3 and 16p13.11 regions were found in ADHD patients [89, 90], while deletions in the 22q11.2 and deletions/duplications in 16p11.2 were commonly observed in ASD patients [91]. The mitochondria has been found to play a

Table 8: Potential biomarkers from imaging studies in various MH-related disorders

Author name or study ID	Disorder	Molecular features/biological functions affected	Study summary/key findings	Source
[77]	Alzheimer's disease (AD)	Functional and structural MRI	Functional and structural magnetic resonance imaging (MRI) can be used to indicate the changes in the cerebrospinal fluid (CSF)	Resting-state functional MRI (rfMRI)
[78, 79]	AD	Many AD patients have amyloid-β (Aβ) plaques present in their brains long before they develop the disease. Amyloid imaging i.e., using PET tracers for detecting changes and amyloid plaques	This amyloid imaging can help with early detection purposes, but are expensive and have a hazard of radiation [78, 79]	PET; PET
[80]	MDD	MRI reveals structural abnormalities in PFC, cingulate cortex, thalamus and hippocampus	These abnormal brain functions may also be associated with the pathogenesis of MDD and could be studied further for early diagnosis and intervention [80]	MRI
[176]	SCZ and BD	Genetic variants of the genes GFAP [159], GLUL [160] and S100B [49, 161] associated with cytoskeletal effects manifested in brain imaging	Potential for use in early detection	Various
Lainhart et al [81]	ASD	White matter microstructure and amygdala growth abnormalities impact brain networks in early life	Potential for use in early detection in ASD	MRI
Sun *et al* [82]	ADHD	MRIs differentiate ADHD patients from controls based on cortical shape alterations	Potential biomarkers for ADHD	Anatomic and diffusion-tensor magnetic resonance (MR) imaging
Zilcha-Mano *et al.* [83]	PTSD	Resting state MRIs and ML identify unique brain abnormalities for clinical differentiation and treatment response	Such an approach could be explored further for clinical use to identify clinical symptoms and treatment response [83]	Resting-state magnetic resonance images

crucial role in neurodegenerative diseases including AD, MDD, BD and others [23] [86]. Mitochondrial DNA copy number was found significantly lower in PTSD patients, which may reflect impaired energy metabolism [92]. Detailed findings are summarized in Table 9.

Potential biomarkers from metabolomics and glycomics studies in various MH-related disorders

Metabolites are the substrates and products of metabolism and include sugars, lipids, amino acids, fatty acids, phenolic compounds and alkaloids among others [93]. Glycans are long chain essential carbohydrate molecules that serve structure, energy storage and regulatory purposes [94]. The advantage of using metabolites as biomarkers is that they are found in blood and serum. They can be extracted and analyzed using noninvasive and inexpensive analysis techniques. Changes in glycosylation typically occur during disease progression and have been increasingly studied for biomarker development [95]. Table 10 shows key takeaways on research in this area.

Mapstone *et al.* [96] identified a set of 10 lipids from the peripheral blood of people who went on to develop AD 2–3 years later with 90% accuracy. Frenkel-Pinter *et al.* [97] studied the changes in glycosylation pathways associated with AD, found changed levels of glycans involved in protein *O*-GlcNAcylation and N-/O-glycosylation and proposed for the use as novel glyco-based biomarkers for AD [97]. Hashimoto *et al.* [98] found purine metabolism downregulation in MDD patients and amino acid metabolism involvement in MDD pathogenesis. Okamoto *et al.* [99] noted reduced metabolite peak values in SCZ, affecting pathways like glutamate metabolism. Ren *et al.* [100] identified potential BD biomarkers: lactate, trimethylamine oxide, N-acetyl glycoprotein and α-glucose. Orozco *et al.* [101] linked 11 plasma metabolites to ASD outcomes, revealing disturbances in one-carbon metabolism and the tricarboxylic acid cycle. Tian *et al*'s [102] ADHD study identified differentially changed metabolites including FAPy-adenine and dopamine 4-sulfate. Karabatsiakis *et al*'s [103] PTSD research found 13 significant metabolite changes including glycerophospholipids and an endocannabinoid signaling metabolite.

Potential biomarkers from multiomics studies in various MH-related disorders

Utilizing multiple omics data types enhances our understanding of brain-related disorders [39, 104]. In AD, multiomics approaches have been applied, integrating genomics, epigenomics, transcriptomics and proteomics data to gain insights into AD pathogenesis and identify potential biomarkers.

In MDD, integration of metabolomics and proteomics unveiled intricate molecular alterations that could contribute to the pathophysiology, offering insights for potential therapeutic strategies [105]. A multiomics analysis (RNA-seq, microRNA, ChiPseq) discovered dysregulation of nuclear FGFR1 signaling in SCZ, indicating a potential therapeutic target [106]. Another multiomics analysis comparing ASD and SCZ revealed affected biological processes including neural development, synaptic dysfunction neural networks, and enriched chromatin modification in ASD [107]. Another multiomics investigation unveiled the molecular

Table 9: Potential biomarkers from copy number studies in various MH-related disorders

Author name or study ID	Disorder	Molecular features/biological functions affected	Study summary/key findings	Source
Cuccaro *et al* [84]	AD	CNV identified in genomic regions1p36, 1q21,1q32, 2p23, and 2q14 [84]	Identification of CNVs in specific regions associated with AD (1p, 1q, 2p, 2q)	DNA
Multiple studies [85, 177]	AD	People who inherit one copy of the APOE isoform APOE ε4 have an increased chance of AD and those with two copies have an even greater risk [85]	APOE ε4 allele is known to affect normal brain function and early onset of memory loss. Potential biomarker	Blood
Chung et al [86]	MDD	Higher mitochondrial DNA copy number in MDD patients	Potential relevance of mitochondrial DNA copy number to MDD pathophysiology	Peripheral blood
Xiao *et al.* [87, 88]	MDD	Genomic regions 1q32 and 22q11.22 identified as 'hot spots' i.e. regions of large copy number variation for SC and BD [87, 88]	Identification of genomic regions with large CNVs in SCZ and BD	Genotyping and DNA pooling; genotyping
Krgović *et al.* [89]	ADHD	Patients with ADHD show higher CNV rate compared to healthy control	Association of higher CNV rate with ADHD	Genome-wide study
[89, 90]	ADHD	Duplications in 15q13.3, 16p13.11 regions found in ADHD patients	CNV in chromosomal regions 15p and 16p associated with ADHD	Genome-wide study; blood
[91]	ASD	Duplications in the 16p11.2 regions, and deletions in the 22q11.2 region	CNV in chromosomal regions 16p and 22q associated with ADHD	Genetic study
[23, 86]	AD, MDD and BD	Energy production impaired and higher levels of oxidative stress	The crucial role of mitochondria in neurodegenerative diseases	Mitochrondrial DNA
Bersani *et al.* studied [92]	PTSD	Lower mitochondrial DNA copy number (mtDNAcn) in PTSD patients	Impaired energy metabolism potentially reflected by mtDNAcn in PTSD patients	Mitochrondrial DNA

Table 10: Potential biomarkers from metabolomics and glycomics studies in various MH-related disorders

Author name or study ID	Disorder	Molecular features/biological functions affected	Study summary/key findings	Source
Mapstone *et al.* [96]	AD	Identification of a lipid panel in peripheral blood predicting AD development with 90% accuracy	Promising noninvasive biomarkers for early AD detection	Blood
Frenkel-Pinter *et al.* [97]	AD	Altered levels of glycans involved in protein O-GlcNAcylation and N-/O-glycosylation	Potential glyco-based AD biomarkers	Brain regions and serum
Hashimoto *et al.* [98]	MDD	Downregulation of prune metabolism and involvement of amino acid metabolism in MDD pathogenesis [98]	Identification of affected metabolic pathway in MDD	Various
Okamoto *et al.* [99]	SCZ	Lower peak values of metabolites in SCZ patients, affecting pathways like glutamate metabolism	Metabolic differences in SCZ patients, contributing to a better understanding of the disorder	Serum
Ren *et al.* [100]	BD	Identified potential BD biomarkers: lactate, trimethylamine oxide, N-acetyl glycoprotein and α-glucose	Discovery of metabolites with potential biomarker utility for BD	Serum
Orozco *et al.* [101]	ASD	Linked 11 plasma metabolites to ASD outcomes, revealing disturbances in one-carbon metabolism and the tricarboxylic acid cycle	Insights into metabolic changes in ASD and their potential roles	Plasma
Tian *et al.* [102]	ADHD	Identified differentially changed metabolites including FAPy-adenine and dopamine 4-sulfate	Metabolomic profiling in ADHD, highlighting potential metabolic contributors to the disorder	Urine
Karabatsiakis *et al.* [103]	PTSD metabolite	13 significant metabolite changes including glycerophospholipids and an endocannabinoid signaling	Insights into metabolic alterations in PTSD patients using peripheral blood, and suggesting candidate markers and pathways of interest	Blood

Table 11: Potential biomarkers from multiomics studies in various MH-related disorders

Author name or study ID	Disorder	Molecular features/biological functions affected	Study summary/key findings	Source
Pang *et al.* [163]	Alzheimer's disease (AD)	Measured genes and microRNAs expression, systems biology analysis	Identification of potential AD biomarkers, better understand AD pathogenesis	Entorhinal cortex, hippocampus and blood
Song *et al.* [178]	AD	Summarized studies and results based on the genome, transcriptome and epigenome, curated data into a database called AlzBase	Advancements towards candidate biomarkers and new hypotheses	Various
De Yager *et al.* [179]	AD	Multiomics analysis of the frontal cortex regions. The data had come from over 3000 patients that included 1179 samples from whole genome sequencing (WGS), 740 samples from DNA methylation, 712 samples from chromatin immunoprecipitation with sequencing (Chip-seq), 638 samples from RNA sequencing (RNA-seq) and 702 samples from microRNA expression profiling. The patients profiled were part of the Religious Orders Study (ROS) or the Rush Memory and Aging Project (MAP) [179, 180]	This dataset includes controls well and hence allows users to repurpose and offers opportunities for new findings	Various
Wang *et al.* [181]	AD	Generated WGS, whole exome sequencing (WES), RNA-seq and proteomic data from 258 AD brains along with clinical and pathophysiological data called the Mount Sinai cohort [181, 182]	This large-scale study of matched multiomics data in AD and control brains servers as an important resource for further analyses. The raw and processed data are publicly available.	Brain
Zhang *et al.* [105]	MDD	Studied the brains of chronic unpredictable mild stressed rat models by application of both metabolomics and proteomics. Significant changes were found in 30 metabolites and 170 proteins, related to these biological processes including impairment in amino acid metabolism and protein synthesis/degradation; dysregulation of glutamate and glycine metabolism; disturbances in fatty acid and glycerophospholipid metabolism; abnormal expression of synapse-associated proteins	Such multiomics studies could improve our understanding of the biology behind MDD and enable better treatments	Gas chromatography/mass spectrometry (GC–MS)
Narla *et al.* [106]	SCZ	Applied multiomics analysis including RNA-seq, microRNA and ChiPseq to find dysregulation of nuclear FGFR1 signaling in SCZ patients	Potential as a therapeutic target for SCZ	Plasmids expressing FGFR1 constructs and Human induced pluripotent stem cell lines, neuron committed cells
Goes *et al.* [156]	BD	Performed a large-scale meta-analysis using whole-exome sequencing (WES)and found three genes affected: MLK4, APPL2 and HSP90AA1	Identification of BD-affected genes	Various
Pineda-Cirera *et al.* [108]	ADHD	Studied genetic variation that influences brain methylation. They found that genetic variants for ADHD were correlated with higher gene expression and lower methylation of ARTN and PIDD1. On the other hand, Genetic variants for ADHD were correlated with a lower gene expression and higher methylation of C2orf82 [108]	Interplay of gene expression and methylation changes in ADHD	Brain
Hubers *et al.* [183]	ADHD	Performed an integrative analysis of genomics, epigenomics and metabolomics data from in 596 twins (cases and controls) from the Netherlands Twin Register (NTR) and looked for associations with ADHD. The top differentially changed features included TMEM, STAP2 and DNA methylation in MAD1L1 [183]	Identification of differentially changed features related to ADHD	Urine, buccal cell swabs

(continued)

Table 11: Continued

Author name or study ID	Disorder	Molecular features/biological functions affected	Study summary/key findings	Source
Nomura *et al.* [107]	ASD versus SCZ	Performed a multiomics analysis to compare ASD and SCZ and found the several biological processed affected in both disorders including neural development, synaptic dysfunctions and neural network. The authors also found chromatin modification process to be enriched only in ASD samples	Shared and distinct biological processes in ASD and SCZ	Various
Dean *et al.* [184]	PTSD	Studied warzone-related PTSD using multiomics technologies including genetics, DNA methylation, proteomics, metabolomics, immune cell counts, cell aging, endocrine markers, microRNAs and cytokines. They applied multistep ML models to identify candidate biomarkers for PTSD. At the end of their multi step analysis, 10 top performing candidate biomarkers were identified as most relevant to PTSD, including methylation markers cg01208318, cg20578780, cg15687973 (PDE9A) and 75,938,326 C2orf3; microRNA markers hsa-mir-133a-1-3p, hsa-mir-192-5p, hsa-miR-9-1-5p, metabolite marker gamma glutamyltyrosine; clinical labs insulin and mean platelet volume and physiological marker heart rate	Identification of top-performing candidate biomarkers for PTSD	Blood

interplay between genetic variation, gene expression and methylation, providing insights into ADHD-related mechanisms [108]. This multiomics approach is instrumental in understanding the complex biology of neuropsychiatric disorders, offering potential avenues for treatment and biomarker discovery. Table 11 summarizing key findings from these studies.

Potential biomarkers from cellular data in various MH-related disorders

Cellular data in the form biological functions and pathways offer another dimension to better understand the underlying mechanism in various MH disorders. While some biological functions may have come up along with the molecular markers in previous sections, the current section focuses solely on features at the cellular level. These could be pathways, biological functions and cellular processes associated with various MH disorders. Table 12 summarizes these key features. These could be used as potential targets for further research and potential therapeutic interventions.

Noteworthy themes of interest

Throughout this comprehensive review, we have encountered several noteworthy discoveries.

Dysregulation in the immune and inflammatory systems

Researchers have found that the immune system and inflammatory responses undergo a systemic change in patients affected with neurodegenerative diseases including dementia and neurodegeneration [109, 110]. Increased levels of circulating cytokines and other pro-inflammatory markers have been found and its role in these diseases is being studied in more detail [111, 112].

Heightened activity within the HPA axis

The heightened activity within the HPA axis has been consistently observed across various MH disorders and in this review. Furthermore, multiple NGS studies have implicated the role of serotonin transporter SLC6A4 in MH disorders. An interesting parallel was found in the involvement of the dopamine transporter gene SLC6A3 in neuropsychiatric conditions [113]. While dopamine predominantly resides in the brain and serotonin predominantly in the gut, both neurotransmitters play pivotal roles not only in MH but also in gut health [114]. Presently, the interactions between these neurotransmitters remain currently unclear. However, a detailed exploration of complex interconnections in the body (i.e. 'axis') may provide valuable insights interactions [115]. There are various connections in the body such as gut–brain, gut–lung and gut–skin axes. Interestingly, these axes are also linked with the immune system. Below, we discuss in more detail the gut–brain axis and potential for the gut microbiome in MH disorders as a future direction.

The gut–brain axis and the microbiome: an emerging biomarker in MH

The gut microbiome, comprising trillions of microorganisms in the gastrointestinal tract, is a novel biomarker with far-reaching implications for MH. Linked through the gut–brain axis, it exerts bidirectional influence over human behavior and brain function via the immune, nervous and endocrine systems [116]. Dysregulations in gut microbiota have been associated with neurodegenerative diseases, mood disorders and depression, often driven by chronic inflammation converting into mood symptoms [116, 117]. Stress influences neuroendocrine hormones affecting bacterial growth, and consequently, behavior, metabolism, appetite and immunity. Microbiome research is particularly extensive in MDD and neuropsychiatric conditions like SCZ and BD. MDD shows microbiota alterations, while SCZ and BD exhibit systemic immune changes [116–118]. Furthermore, ASD and ADHD have their unique microbiota profiles. Preclinical AD is associated with gut microbiome shifts correlating with pathological markers. [119–121, 214]. Complementary therapies like 'psychobiotics' and fecal transplants are being explored alongside traditional treatments, promising new avenues for MH understanding and intervention [122].

Table 12: Potential biomarkers from cellular data in various MH-related disorders

Author name or study ID	Disorder	Molecular features/biological functions affected	Study summary/key findings	Source
Sancesario *et al.* [185]	AD	A meta-analysis of 96 articles related to Alzheimer's disease that included 12 meta-analyses, 21 re-analyses of existing data and 63 original studies. Studies of brain tissues identified the following affected pathways including dopamine metabolism, mitochondrial function, oxidative stress, protein degradation, neuroinflammation, vesicular transport and synaptic transmission. Studies of the blood identified the following affected pathways including pathways involved in immune function, inflammation, RNA processing, protein chaperones, mitochondrial function and programmed cell death.	Pathways identified in both blood and brain tissue were mitochondrial function, protein degradation and inflammation indicated that AD was a systemic disease and not localized to any one region [185]	Both blood and brain tissue
Reitz et al [186]	AD	These included amyloid pathway, immune and inflammation system, lipid transport and metabolism, synaptic cell functioning, Tau pathology, cell migration, hippocampal synaptic function, cytoskeletal function and axonal transport and microglial and myeloid cell function	Identification of major pathways associated with AD, including immune system involvement and synaptic function	Various
Mirza *et al.* [187]	AD	The study of the electrophysiological changes indicated the following pathways contributed to the pathophysiology of AD including Glutamate receptor signaling, CREB signaling, dopamine- DARPP32 feedback in cAMP signaling and fMLP signaling in neutrophils	Implicates various neurotransmitter systems	Various
Li et al. [188]	AD	Identified nitric oxide, reactive oxygen species in macrophages (NOROS), NFkB and mitochondrial dysfunction and the major pathways associated with late onset AD (LOAD) [188]	Major pathways associated with late-onset AD, highlighting oxidative stress and immune response	Various
Mengsi *et al.* [158]	AD	Used gene expression data from 76 AD patients and discovered that the GABAergic (related to neurotransmitter GABA) system, neurons and synaptic function were affected in AD	AD affects neurotransmitter systems and synaptic function	Brain
Di Resta *et al.* [12]	AD	Reviewed the AD disease from an omics perspective. The molecular analyses shed light on AD pathogenesis, the cellular level analysis provided a systems biology perspective that could enable more effective treatment options	Concluded that an integration of molecular and cellular level analyses could better help with understanding of this complex disease	Various
Pang *et al.* [163]	AD	Several functional genes expressed together were affected in AD patients, including ERBB2, ERBB4, OCT3, MIF, CDK13 and GPI. Several pathways were found to be significantly dysregulated in EC and HIP brain regions, including PI3K-AKT signaling pathway, MAPK signaling pathway, oxidative phosphorylation, synaptic vesicle cycle, cell–cell adhesion, cytokine-mediated signaling pathway, proteasome, arginine and proline metabolism and pentose phosphate pathway	Analysis of two important brain regions in AD patients the entorhinal cortex (EC) and hippocampus (HIP) compared to normal controls	EC and HIP
[189, 190]	AD	In AD patients, the protein Tau is no longer able to help with forming structures that transport nutrients within nerve cells, which eventually leads to cell death. Hyperphosphorylation, i.e. signaling mechanisms used by the cell to regulate mitosis of this tau protein is known to be associated with AD	Importance of tau protein dysfunction and hyperphosphorylation	Clones of human brain τ isoforms

(continued)

Table 12: Continued

Author name or study ID	Disorder	Molecular features/biological functions affected	Study summary/key findings	Source
[191, 192]	AD	Researchers found S100A9 increased in the brains of AD patients. S100A9 is a calcium binding protein that plays an important role in the regulation of inflammatory processes and immune response [191, 192]	Increased S100A9	Various; ultracentrifugation-electrostatic repulsion hydrophilic interaction chromatography (UC-ERLIC) coupled mass spectrometry-based proteomics profiling of soluble and aggregated amyloidal plaque
Howard *et al.* [146]	MDD	Performed gene set enrichment analysis (GSEA) on the 269 genes that they found to be associated with MDD and found the following pathways as significantly enriched including post synapse, synapse, neuron spine, excitatory synapse, behavior, cognition, neuron projection, modulation of synaptic transmission and regulation of synapse structure or activity [146, 193, 194]	Pathways associated with MDD, revealing potential therapeutic targets	Various
Pantazatos *et al.* [143]	MDD	Used RNA-seq and found the following pathways affected in MDD including lower expression of immune-related pathways like chemokine receptor activity, chemotaxis and cytokine biosynthesis and angiogenesis and vascular development	Insights into immune system involvement in MDD.	Brain
Forero *et al.* [60].	MDD	Performed one of the largest meta-analysis of gene expression studies in MDD that covered 24 datasets that included a total of 753 samples. A functional analysis of the DEGs in MDD identified the following biological processes and KEGG pathways enriched with DEGs including synaptic transmission, neuron projection, Alzheimer's disease pathway and proteasome pathways	Identification of biological processes and pathways in MDD	Various
[139]	MDD	Studies have also identified a change in the abundance of pro-inflammatory and oxidative stress response proteins in MDD. Other pathways implicated include LXR/RXR activation, acute phase response signaling, FXR/RXR activation, agranulocyte adhesion diapedesis and granulocyte adhesion diapedesis	Changes in the abundance of pro-inflammatory and oxidative stress response proteins in MDD	Blood
Multiple studies [7, 32, 137, 140, 193, 195]	MDD	Dysfunctional metabolic pathways for ATP production have been observed in MDD [193, 195]. This includes mitochondrial dysfunction and issues with glucose transporter proteins [32, 140]. Changes in energy metabolism-related proteins have also been identified [7, 32]. Studies have explored dysregulation in the glutamate system in MDD, particularly in the context of ketamine studies [137]	Dysregulation in metabolic and glutamate systems	Various; various; various, various, brain; various
Silva-Costa *et al.* [196]		The study of proteomic-based biomarker studies associated with MDD found gene biomarkers as part of several biological processes including inflammatory system, immune and inflammatory systems, lipid metabolism, carboxypeptidase activity, retinoid metabolic process, artery morphogenesis, coagulatory systems, cell communication, protein metabolism, regulation of the nervous system, energy metabolism, oxidative stress, and cell communication and oligodendrogenesis [196].	Identifies potential gene biomarkers associated with MDD.	various

(continued)

Table 12: Continued

Author name or study ID	Disorder	Molecular features/biological functions affected	Study summary/key findings	Source
Multiple studies [197]. [198].	MDD	Mehta *et al.* reviewed gene expression and RNA-seq studies from postmortem brain and peripheral blood for potential links to MDD and found biological processes that include inflammatory response, cell survival, apoptosis and oxidative stress [197]. Lin and Tsai [198] also reviewed gene expression-based studies in MDD to identify biomarkers related to peripheral immune response and growth factors, endocrine factors and metabolic markers	Several systems implicated including immune and inflammatory, oxidative stress and more	Postmortem brain and peripheral blood; peripheral blood cells
[139]. [199].	SCZ	Multiple proteins associated with SCZ belonged to the following pathways including LXR/RXR activation, FXR/RXR activation, hepatic fibrosis and hepatic stellate cell activation and atherosclerosis signaling [139]. A total of 99 peptides were found associated with BD and 202 peptides [139]. The pathways altered in SCZ included oxidative phosphorylation, mitochondrial dysfunction, EIF2 signaling, protein ubiquitination Pathway, mTOR signaling, CDK5 signaling, among others [199]	Pathways associated with SCZ, suggesting targets for further research and potential therapeutic interventions.	Blood; prefrontal pyramidal cells
Multiple studies [49, 159–161, 176, 200–202]	SCZ	Genetic variants of the genes GFAP [159], GLUL [160] and S100B [161] [49] were implicated including astrocyte function, including signal transduction, tyrosine kinase signaling, G protein–coupled receptor signaling, small GTPase-mediated signaling, cell adhesion and gene transcription [49, 200]. Other cell processes found altered in SCZ include reduced migration in neural precursor cells [201], Cytoskeletal effects [176], aberrations in mitochondrial function [202]	Cell processes found altered in SCZ	Various; brain; brain; various; various; brain; brain; fibroblasts
Depino *et al.* [203]	SCZ	A review of animal models of SCZ found changes in dopaminergic function and reduction in neurogenesis (the process that produces the cells of the nervous system)	Altered dopaminergic function and neurogenesis in SCZ	Animal models
Multiple studies: Wang *et al.* [204].	SCZ	A review of RNA-seq-based studies in SCZ found GABA function, glutamate function, myelin and oligodendrocyte related processes affected. Other biological processes related to immune and inflammatory pathways (including genes IL6 and SERPINA3) and response to virus or bacteria were also affected [204]	Biological processes affected in SCZ	Various
[7, 44]	SCZ	Patients with SCZ were found to have abnormal smooth-pursuit eye movement and reduced anterior cingulate volumes; enlarged lateral and third ventricular volumes and white matters abnormalities [7, 44]	Potential biomarkers and structural anomalies associated with SCZ	Various; various
[7, 205, 206]	SCZ	Changes in oligodendrocytes, energy metabolism (NADPH) [7, 206], glutamatergic neurotransmission and cannabinoid metabolism [7, 205]	Dysregulations in SCZ	Various; cerebrospinal fluid (CSF); postmortem mediodorsal thalamus (MDT)
Arion *et al.* [199]	SCZ	Transcriptome alterations in pyramidal cells of prefrontal cortex (SCZ patients)	Transcriptome changes specific to SCZ, less prominent in BD and MDD	Prefrontal pyramidal cells
[61]	SCZ and MDD	Oxidative phosphorylation was the most affected pathway in MDD whereas glycolysis pathway was the most affected in SCZ brains. Pathways found commonly affected between SCZ and MDD include WNT pathway, MAPK, PTEN signaling pathways, glutamate signaling that includes SLC38A2, GRM7, GRIA2; neurodevelopment-related genes including RUNX3, ITGB1, FMR1, STAT3 and SCZ susceptibility genes PDGFRA and PPARG [61]	Shared and distinct pathways in SCZ and MDD; potential targets for understanding and treating these disorders	Blood, serum and plasma

(continued)

Table 12: Continued

Author name or study ID	Disorder	Molecular features/biological functions affected	Study summary/key findings	Source
[207]	BD	Mitochondrial dysfunction may be associated with decreased in mitochondrial respiration, downregulation of proteins involved in mitochondrial respiration. It could also cause changes in mitochondrial morphology, increased mitochondrial DNA polymorphisms [207]	Mitochondrial dysfunction's potential contribution to BD progression	Various
[7, 208, 209]	ASD	Fragile X syndrome is the most commonly studied genetic cause for Autism [7, 208]. Hormozdiari *et al*. studied WES data from 1116 patients with Autism to identify two sets of gene networks. One set was found associated with Wnt, Notch, SWI/SNF and NCOR complexes. The second set was associated with synaptic function, including long-term potentiation and calcium signaling [209]	Gene network analysis reveals two sets of genes associated with ASD, shedding light on molecular pathways involved in synaptic function and complex biological processes	Various; various; various
[7, 141, 210, 211]	ASD	Research has linked ASD with several biological processes including oxidative stress and mitochondrial dysfunction [210], increased polarity of glyoxalase 1 (GLO1) [141] and protein phosphorylation [7, 211]	Biological processes associated with ASD	Various; brain; various; saliva
Multiple studies [7, 162, 212–214]	ADHD	Biological processes affected in ADHD include prefrontal dopamine deficiency, central dopaminergic dysfunction, changes in oxidative metabolism and immunity [7, 212, 213]. In recent years, dopaminergic and noradrenergic systems have risen as potential genetic and biochemical markers in ADHD diagnosis [214]. McCaffrey *et al*. [162] studied RNA markers in case-controlled subjects and a study of twins which revealed the genes in the galactose metabolism pathway as affected	Biological processes associated with ADHD that could be studied further towards design of targets for diagnostics and therapeutics	Various; blood; various; blood; various
[58, 65]	PTSD	RNA-seq analysis in individuals with PTSD revealed glucocorticoid receptor signaling and immunity-related pathways. The authors found the key biological processes associated with PTSD to be immune dysregulation and HPA axis [58]. Gupta *et al*. studied PTSD data from military veterans, and the micoRNAs associated with immune response inflammation were found to play a pivotal role in PTSD in veterans [65]	The key biological processes associated with PTSD are immune dysregulation and HPA axis	Blood; various

DISCUSSION

A systems biology approach

We used the potential NGS biomarkers indicated in this article to demonstrate how the results could give us insights to the underlying mechanisms of Alzheimer's. We performed a systems biology analysis using an online interaction network tool *StringDB* (https://string-db.org/) [123] and subsequently an enrichment analysis using online tool *EnrichR* (https://maayanlab.cloud/Enrichr/) [124]. Figure 1 shows a gene interaction network obtained from the potential NGS biomarkers. The lines that connect the genes are the edges of this network and indicate gene associations obtained from various types of evidences including curated databases, experimentally determined connections or predicted interactions by published literature. From our enrichment analyses, we identified many of the genes to be associated with regulation of amyloid fibril formation and positive regulation of amyloid-beta clearance validating the gene results and its disease association (Figure 2).

A similar analysis was performed using the potential biomarker genes associated with MDD. We used StringDB which generated two gene interaction networks (Figure 3). Enrichment analysis was performed on the gene network on the left side using EnrichR and was found to be involved in serotonin signaling receptor pathway and serotonin metabolism. Serotonin binding deficits have been well documented in MDD literature [125]. Enrichment analysis performed on the genes network on the right side revealed RNA editing mechanisms which have been documented in association with MDD in a publication [126].

A third analysis was performed using the potential biomarker microRNAs and genes associated with PTSD (Figure 4). These molecular features were enriched by the annotation of common cell processes and diseases relevant to MH. This analysis was performed using Elsevier Pathway Studio software (www.pathwaystudio.com).

Such an evidence-based analysis demonstrates the power of connecting the candidate biomarkers to biology using a systems biology approach. It not only pinpoints the biological processes affected but also creates ideas and opportunities for new hypotheses generation and experiments for therapeutic intervention.

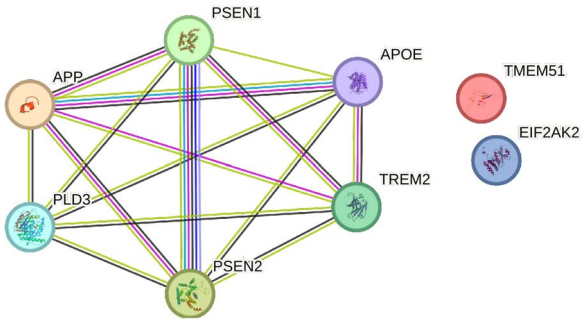

Figure 1. Alzheimer's disease gene interaction network input to this network: *TREM2*, *PLD3*, *DLGPAP1*, *TMEM51*, *EIF2AK2*, *APP*, *PSEN1*, *PSEN2*, *APOE*. Genes that are known to interact with each other are connected by cyan lines (information obtained from curated databases) or magenta lines (experimentally determined connections). The genes that could be in the same neighborhood are connected by green lines, those that could have gene fusions are linked by red lines and those genes that could co-occur are linked by blue lines.

Knowledge extracted and cataloged from research in the molecular and cellular domains could enable us to identify specialized pathways relevant to the MH domain. This would enable very sophisticated downstream system biology analysis and that could offer new insights into mechanisms of MH disorders. Such a cellular level analysis in conjunction with a multiomics analysis could help understand the functioning of the disorder at a systems level and improve our understanding of the disorders.

Taking advantage of publicly available MH datasets and resources

Throughout this review process for this article, we encountered many important large datasets and/or resources relevant to this topic. Many of these resources follow the FAIR principles of Findable, Accessible, Interoperable and Reproducible [127] and could empower researchers to kick-start their analyses without the need to apply for a federal grant to gather sample data. Data from such studies could be used in meta-analyses or case control association studies using powerful modern ML tools or AI-based models. Reuse of such publicly available resources enable researchers to perform an in-depth data analysis for their discovery or validation experiments. These resources have been summarized in Supplementary File 1.

Integration of molecular technologies in the clinic for MH disorders

The integration of molecular technologies into the clinical realm for MH disorders is a promising avenue for enhancing diagnosis and treatment. In the context of MDD, traditional diagnostic methods involving questionnaires and clinical assessments are being complemented by molecular omics technologies [128]. Researchers are exploring the potential clinical application of pharmacogenomic testing in MDD [129]. Antidepressant drugs have been found to influence the epigenome through multiple mechanisms. Drug *Genipin* has been found to reduce activity of enzyme *DNMT1* which preserves the DNA methylation patterns during replication [130]. Another drug *Paroxetine* was found to change phosphorylation of DNMT1 which again affects enzyme activity. Other drugs known as histone deacetylase (HDAC) inhibitors have been found to have antidepressant effects through regulation of gene transcription [131]. HDAC inhibitors and cyclooxygenase-2 (COX-2) inhibitors also show promise in treating MDD in animal models [7, 132]. Other examples include the use of pharmacogenomic markers of *CYP450* to predict drug response or adverse effects in psychiatric drugs. Another example includes confirming drug treatment in certain genetic conditions including Down syndrome, Fragile X syndrome, phenylketonuria and *22q11* deletion syndrome [133]. Understanding the functions and biological processes of the potential biomarkers would allow scientists to explore how they could be integrated into the clinic.

Towards clinical decision support systems

In the realm of clinical cancer care, sequencing-based results and reports, known as Molecular Diagnostic (MolDx) panels, are gradually making their way into practice. The FDA has approved an increasing number of NGS-based biomarkers that are covered by insurance for both diagnostic and treatment purposes. Genetic counseling often accompanies these tests, ensuring informed decision-making. A notable example in the field of MH is the GeneSight test (genesight.com) [134], which assesses genetic variants to guide drug selection for psychiatric disorders. These advancements open the door to creating tailored molecular diagnostic panels for each MH disorder. These panels could be integrated into CDSSs, along with patient medical and drug history, to suggest suitable medications. Clinicians could then use this information to devise more effective treatment plans, reducing the likelihood of adverse reactions or poor responses, ultimately lowering hospital readmissions and costs. This progress holds the potential to drive personalized medicine forward through sophisticated ML models within CDSS.

Challenges

Challenges and future directions in MH research are multifaceted. Patients with mental illness are at an elevated risk for other health issues like cardiovascular disease [135] and type 2 diabetes [136], emphasizing the need to bridge the gap between psychiatric disorders and their physiological manifestations. While progress has been made in identifying biomarkers, actionable ones are still limited [49], requiring more validation and research. There is a growing demand for increased funding in MH research, as well as the development of noninvasive diagnostic procedures, expanded insurance coverage and cost-effective diagnostic and treatment options [7].

Future directions

In the realm of future directions for MH research, several promising avenues emerge. Firstly, there is a growing interest in creating diagnostic panels using the potential biomarkers discussed in this article. This approach, already successful in cancer diagnostics and often covered by insurance, holds the potential to streamline and enhance MH disorder diagnoses, making them more accessible and cost-effective.

Moreover, the application of these potential biomarkers could lead to more sophisticated interaction analyses, a few examples of which were showcased in this article. These can provide deeper insights into the underlying mechanisms of these disorders. This includes exploring intricate relationships between various biological markers, shedding light on the complex nature of MH conditions.

To gain a comprehensive understanding, researchers could employ advanced statistical analyses, such as correlation or ML approaches to examine the multiomics biomarkers across various MH disorders listed in this article. This approach could uncover shared or distinct patterns, aiding in tailored diagnostic and treatment strategies.

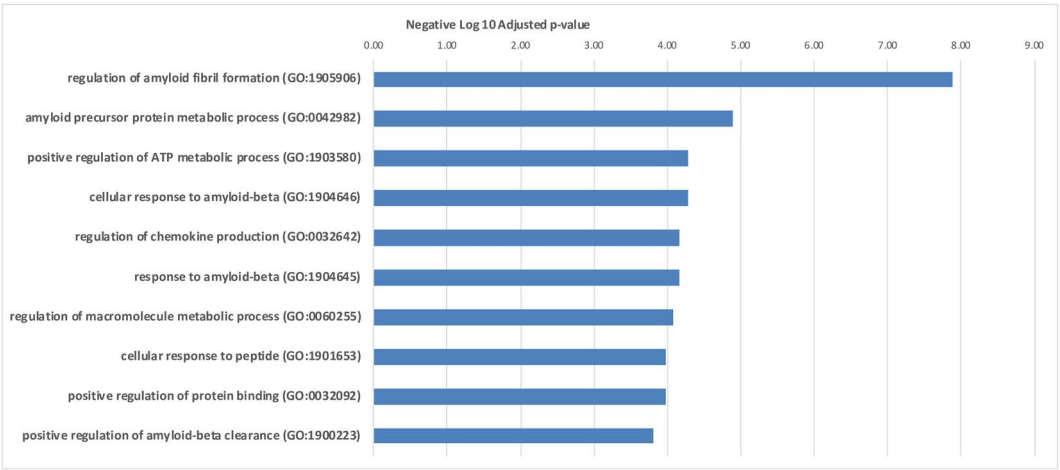

Figure 2. Top enriched gene ontology biological processes in AD. The x axis shows the negative log base 10 of the adjusted *P* value. The y axis indicates the various GO terms enriched.

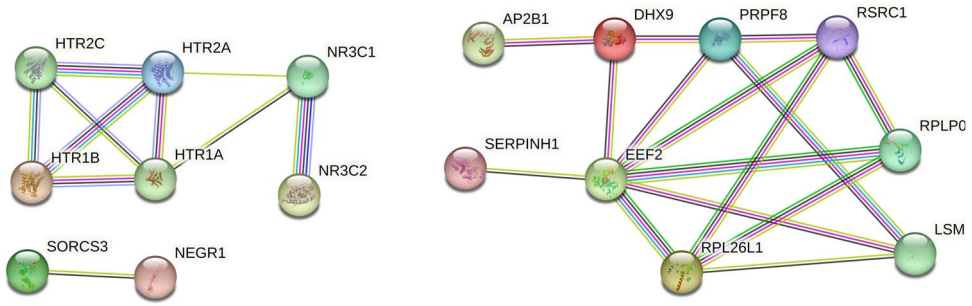

Figure 3. Gene interaction networks in MDD *Input gene list: SORCS3, NEGR1, NR3C2, NR3C1, MTRNRL8, SERPINH1, CCL4, SLC1A2, GABRD, HTR1A, HTR1B, HTR2A, HTR2C, PXMP2, EEF2, RPL26L1, RPLP0, PRPF8, LSM3, DHX9, RSRC1, AP2B1* Genes that are known to interact with each other are connected by cyan lines (information obtained from curated databases) or magenta lines (experimentally determined connections). The genes that could be in the same neighborhood are connected by green lines, those that could have gene fusions are linked by red lines and those genes that could co-occur are linked by blue lines.

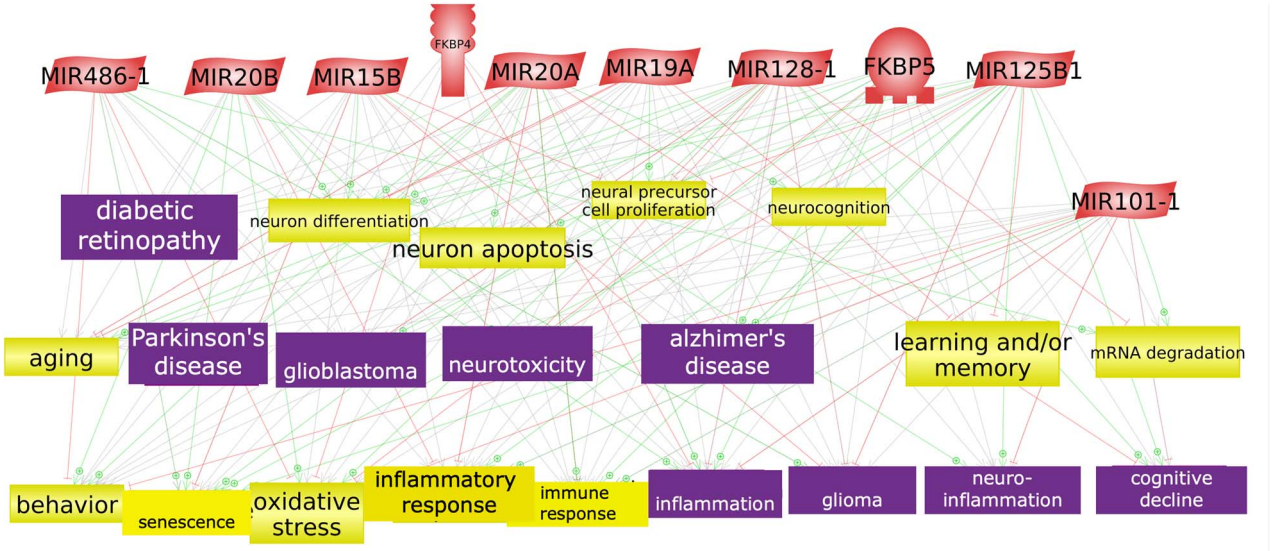

Figure 4. microRNAs and genes associated with PTSD enriched with common cell processes and diseases. The figure shows an interaction network between the microRNAs and genes associated with PTSD. First connections between the microRNAs and genes were found and then the common cell processes and diseases were added to the network. The microRNAs are represented as red parallelograms, the cell processes are the yellow colored boxes and the diseases are the purple colored boxes.

Additionally, the gut–brain axis and its connections to the immune system represent an intriguing area for further exploration. Investigating the role of the gut microbiome in MH disorders could yield critical insights into the connection between the gastrointestinal system and brain function, potentially opening new avenues for intervention.

Lastly, it is essential to expand this research beyond the disorders already discussed. Applying similar methodologies to other MH conditions could broaden our understanding of the molecular underpinnings of these disorders, ultimately paving the way for more effective diagnostics and treatments across the MH spectrum.

CONCLUSION

Neuroscience research has made tremendous progress in understanding the processes that govern the system. But not much progress has been made in translating this research into the clinic to treat psychiatric disorders. Biomarkers can bridge this gap which is why it is crucial to extract knowledge from molecular and cellular research using a broad array of bioinformatics and data analytics methods, tools and resources [121, 137]. The progressive identification of new biomarkers in the MH space could enable researchers to build advanced CDSS empowered by sophisticated ML models to advance personalized medicine.

Our findings suggest that MH disorders we reviewed in this paper involve complex molecular and cellular changes, affecting various pathways and processes, including protein function, phosphorylation, inflammation and immune responses, many of which could lead to new diagnostic or prognostic biomarkers. It also highlights the tremendous scope and opportunity for application of molecular and cellular data to further MH research. As we strive to integrate MH disorders into mainstream EHR systems, the power of translational bioinformatics and systems medicine will enable us to overcome the stigma associated with these disorders and accelerate new funding for research studies, *in silico* and lab analyses and findings.

Key Points

- Biomarkers in mental health disorders: The article discusses various potential biomarkers associated with different mental health disorders, shedding light on the molecular and cellular aspects of conditions like AD, MDD, SCZ, BD, ASD and ADHD.
- Omics technologies: The work emphasizes the importance of omics technologies, including genomics, proteomics, epigenetics, DNA copy number, microRNA and multi-omics analysis, in identifying and understanding these potential biomarkers. These technologies provide valuable insights into the biological processes underlying mental health disorders.
- Gut–brain axis and the immune system: The article highlights the emerging role of the gut–brain axis in mental health. It discusses how the gut microbiome and its interactions with the brain through the immune and endocrine systems can influence mental health conditions, paving the way for potential diagnostic and therapeutic interventions.
- Example evidence-based analysis: We used the published results in mental health disorders and performed evidence-based analysis to demonstrate the power of connecting the candidate biomarkers to biology using a systems biology approach. It not only pinpoints the biological processes affected but also creates ideas and opportunities for new hypotheses generation and experiments for therapeutic intervention.
- Clinical integration: The work explores the integration of molecular technologies, such as pharmacogenomic testing, into clinical practice for mental health disorders. It discusses how these technologies can aid in personalized treatment plans and improve treatment outcomes.

SUPPLEMENTARY DATA

Supplementary data are available online at http://bib.oxfordjournals.org/.

AUTHOR CONTRIBUTIONS

K.B. conceptualized and wrote the paper. Y.G. reviewed and edited the paper.

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