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Review

Mapping the Heterogeneity of Major Depressive Disorder: A Systematic Review of Multi-Omics Integration Studies

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Abstract

Major depressive disorder (MDD) has a widespread heterogeneity as per the psychiatric nosology, and traditional symptom-based diagnosis frameworks do not offer many clues regarding tailored therapy techniques. The recent development of multi-omics and data-driven solutions has now provided evidence for pathophysiologically different subtypes of MDD, moving the field toward precision psychiatry. The systematic review aggregates multimodal studies that combing neuroimaging, genomics, transcriptomics, epigenomics, metabolomics, and proteomics to define MDD subtypes. There are two to four candidate clusters that have been formed across these heterogeneous modalities, and each has a neurobiological and clinical profile. Cognitive subtypes are characterized by executive failure and loss of prefrontal and temporal gray matter. Neuroimaging-derived subtypes show specific patterns of functional connectivity that may predict response to selective serotonin reuptake inhibitors (SSRIs) or repetitive transcranial magnetic stimulation (rTMS) in

preliminary studies. There are immune-metabolic subtypes characterized by increased inflammatory cytokines and dysregulation of metabolic pathways. Molecular subtypes appear to be differentiated by cellular mechanisms such as mitophagy and pyroptosis. Taken together, these results indicate that multi-omics integration, in addition to explaining the molecular architecture of MDD, also characterizes patient subgroups with pathophysiological mechanisms, dimensions of symptoms, and disease treatment. The growing body of literature demonstrates that there is a shift in psychiatry toward a more mechanistic approach and that biomarker-based diagnostics and personalized treatment regimens are urgently needed to improve clinical outcomes in depressive diseases.

Keywords
Major depressive disorder; multi-omics integration; biological subtypes; precision psychiatry; biomarker-based diagnosis; immune-inflammatory depression; neuroimaging clustering

1. Introduction

Heterogeneity is associated with major depressive disorder (MDD). It poses a significant barrier to the nosological categorization of the disorder for successful therapeutic interventions and to how the underlying pathophysiology of this illness is understood. MDD is very heterogeneous in terms of the symptoms; the patients show a wide range of symptom combinations, which makes it difficult to implement standard treatment practices [1, 2]. Furthermore, subjective self-report-based clinical diagnoses often lead to misdiagnosis and worsen the effectiveness of treatment and recovery procedures [3]. The heterogeneity of MDD includes differences at neurobiological, genetic, and environmental levels, leading to variations in symptom manifestations and response to treatment. Systemic inflammation, dysregulation of the hypothalamic-pituitary-adrenal axis, and gut-brain axis interactions are all involved in the pathophysiology of MDD [4, 5]. As a result, the current diagnostic criteria do not reflect the complexity of biological heterogeneity defining MDD, which makes more specific classifications based on the exploration of valid biomarkers a necessity [4-6]. Even though progress has been achieved in terms of determining physiological characteristics and genetic vulnerability [7], the strong heterogeneity of MDD remains a significant challenge to accurate diagnosis and creating individualized treatment plans [8].

Precision psychiatry provides an exciting prospect of improving the care of MDD by personalizing the treatment in relation to the biological, genetic, or behavioural peculiarities of the particular patient. This paradigm aims to leverage large multi-omics datasets, including genomics, proteomics, and metabolomics, to identify biomarkers that explain MDD and its heterogeneous forms [9, 10]. The integrative method may eventually allow clinicians to categorize patients based on their individual profiles, which could establish more successful treatment strategies than traditional trial-and-error approaches [11, 12]. The introduction of artificial intelligence and machine learning offers new prospects for analysing large-scale datasets of various populations, thus giving the opportunity to identify new therapeutic targets and optimise predictive models of treatment response [9, 13]. The increased patient awareness of precision medicine can also lead to a high level of engagement and compliance with personalized treatment plans to achieve better health outcomes. Nevertheless,

there are still obstacles, such as the need to train medical professionals in these advanced methods and to address health equity to ensure everyone has access to these new developments [14, 15].

The omics method is a new approach to studying MDD, which incorporates several layers of biology and provides a complex picture of disorders. The method uses genomes, transcriptomes, proteomes, and metabolomes data to explain the heterogeneity in MDD populations [16]. Genome-wide association studies have reported many single-nucleotide polymorphisms that are associated with depression; these data offer clues to tissue-specific changes and pathways involved in the disease, as opposed to the gene-expression and metabolite profiles [16]. The integrative models also have the potential to identify signals of biomarkers that can predict the effect of treatment and the individual therapeutic outcome [17]. The multi-omics approach can show a crosstalk between different biological systems, including inflammatory cytokines and neuroplasticity, which is essential to comprehending the pathogenesis of MDD and its clinical trajectory [18, 19]. Mental-health outcomes can be altered by environmental and psychosocial elements, such as neighbourhood perceptions; as such, they confound analyses, and links between such perceptions and depression may be mediated by allostatic load, a concept that signifies accumulated stress due to chronic stress [20]. These methodological issues would be critical in developing therapeutically relevant models that use multi-omics datasets to understand the progression of MDD [20].

The review is a critical assessment of the emerging literature on the integration of multi-omics in the context of MDD, aiming to disentangle the disorder's heterogeneity and move towards precision psychiatry. The purpose of the study was to establish a set of biologically derived subtypes of MDD by integrating neuroimaging, genomics, transcriptomics, proteomics, metabonomics, and epigenomics and, therefore, to identify a discontinuous neurobiological phenotype and clinical phenotype. Such actions are essential for illuminating the pathophysiological processes involved in MDD and for estimating individual responses to treatment. Further issues that arise when consolidating heterogeneous biological data are also noted in the paper, and the need to have standardised methodologies to guarantee research reproducibility is also highlighted. In general, the results highlight the potential of multi-omics methods to find the biomarkers that help in creating a transition between symptom-based treatment approaches and biology-based, personalized interventions.

2. Materials and Methods

This systematic review was performed and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21].

2.1 Search Strategy

A literature search was conducted in Scopus and PubMed from database inception till October 2025. The Scopus search term used was:

TITLE-ABS-KEY ((“major depressive disorder” OR “depression”) AND (“subtype*” OR “subgroup*” OR “biotype*”) AND (“multi-omics” OR “integrat* omic*” OR “genomics” OR “transcriptomics” OR “epigenomics”) AND (“bioinformatics” OR “computational biology” OR “network analysis”)).

In PubMed, the query used was equivalent to the following:

(“major depressive disorder” [Title/Abstract] OR “depression” [Title/Abstract]) AND (“subtype*” [Title/Abstract] OR “subgroup*” [Title/Abstract] OR “biotype*” [Title/Abstract]) AND (“multi-omics”

[Title/Abstract] OR "integrat* omic*" [Title/Abstract] OR "genomics" [Title/Abstract]) OR ("transcriptomics" [Title/Abstract] OR "epigenomics" [Title/Abstract]) AND ("bioinformatics" [Title/Abstract] OR "computational biology" [Title/Abstract] OR "network analysis" [Title/Abstract]).

Duplicates were excluded, and data from both databases were merged. Also, the reference lists of the included articles and relevant reviews. English language articles were considered.

2.2 Eligibility Criteria

Studies were considered for inclusion in the study if they fulfilled the following criteria:

- Original research articles that include human participants with a diagnosis of major depressive disorder (MDD).
- Provided some biological information (neuroimaging, genomics, transcriptomics, epigenomics and/or proteomics and/or metabolomics and/or immunological markers).
- Utilized data-driven computational approaches (machine learning, cluster analysis, unsupervised learning, network analysis, etc.) to detect subtypes, biotypes, or subgroups.

Animal studies, reviews, case reports, editorials, and studies without biological data or computational subtyping were excluded.

2.3 Study Selection

All titles and abstracts were screened by two independent reviewers, and full text was assessed for potentially relevant articles. The disagreements were settled by consensus or with the help of a third reviewer. From the Scopus and PubMed databases, 53 and 6 records, respectively, were identified (total 59). After removing duplicates, 55 records remained and were screened. A PRISMA flow diagram (Figure 1) was used to explain the selection process.

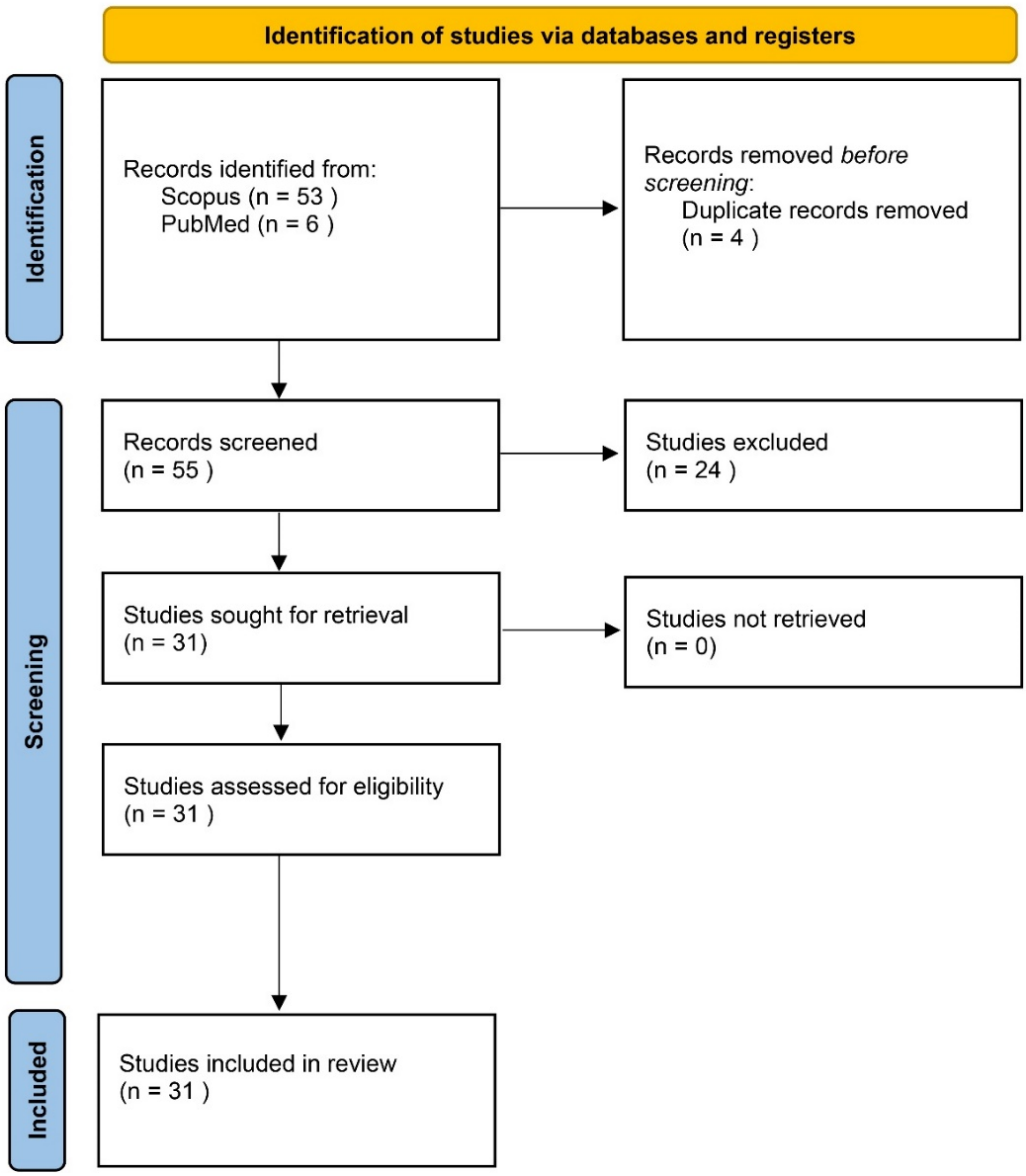

Figure 1 PRISMA flow diagram for selection process of the study. A total of 59 records were identified from Scopus (n = 53) and PubMed (n = 6). After duplicate removal, 55 records remained for screening. Of these, 31 full-text articles were assessed for eligibility, and all 31 met the inclusion criteria.

2.4 Data Extraction and Synthesis

The following information was extracted: author(s), year, sample size and characteristics (such as first-episode vs. recurrent MDD, treatment status), biological modalities used, computational methods, identified subtypes, key findings, and clinical correlates. All included studies are summarized in Table S1.

The study designs, omics platforms, and clustering methodologies were quite variable, and a quantitative meta-analysis was not possible. Rather, a cross-modal convergent patterns synthesis was done. Further, there were no uniform tools to evaluate the risk of bias because all of the studies included were observational and exploratory. The methodological quality and limitations were, however, discussed narratively in the Discussion section.

Additionally, as this field is still developing, many subtypes were first defined based on results from single landmark studies [22] for multi-omics integration and neuroimaging. Studies were prioritized based on the use of reproducible data-driven methods, the sample size (where available), and multi-modal validation. In systems biology, cross-validation and sensitivity analysis are used frequently as validation strategies [23]. If a finding was mainly based on a single study, it was identified as such in the Results and Discussion and interpreted with caution as only hypothesis-generating.

3. Results

3.1 Neuroimaging-Based Subtypes

Neuroimaging has also made significant contributions to understanding the heterogeneity of MDD, demonstrating that subtypes can be identified using structural and functional brain measures. In this regard, we have reviewed papers that used brain structure and function as input to clustering, and it is important to note the high number of neuroimaging-based subtypes of MDD.

The systematic review used a multi-omics integration approach to identify putative subtypes of major depressive disorder (MDD), using a standardised workflow synthesising heterogeneous data modalities to obtain strong clustering and trustworthy derivation of subtypes (see Figure 2).

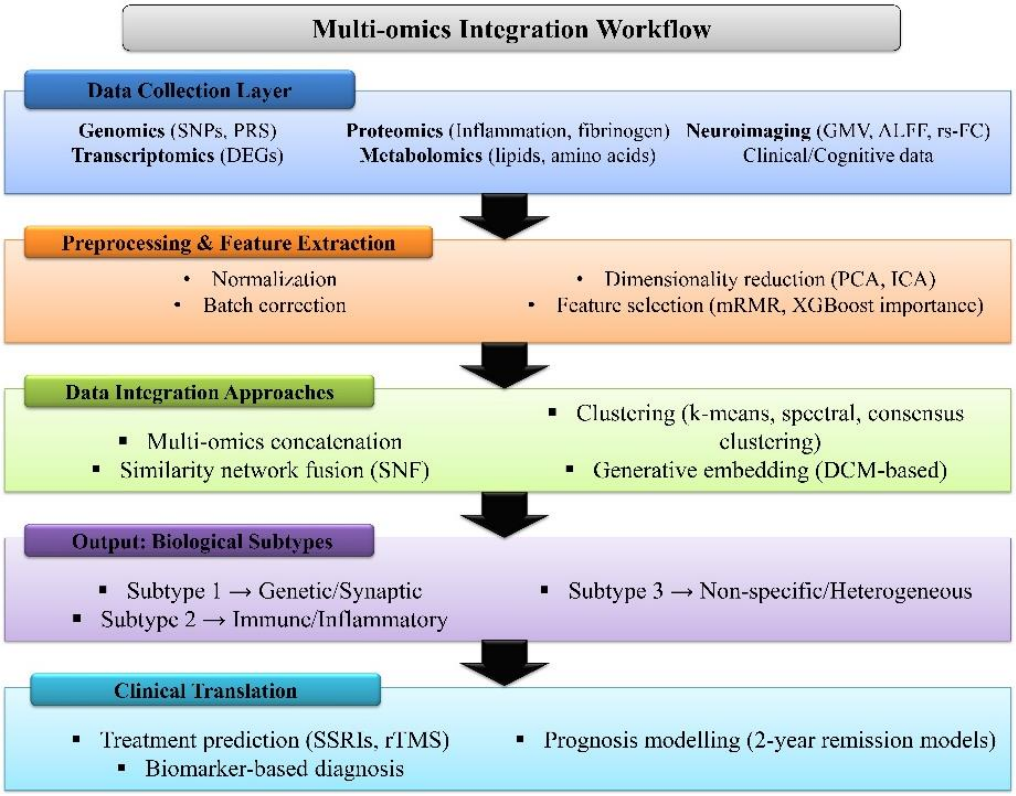

Figure 2 Multiple-omics assimilation approach to MDD subtyping. The diagram outlines consecutive steps that include, data acquisition (genomics, proteomics, metabolomics, neuroimaging), preprocessing, integration through methods such as multi-omics concatenation and similarity-network fusion, clustering and generation of biologically relevant subtypes, which in turn can be used in clinical processes, such as prediction of therapy and biomarker-based diagnostics.

The figure illustrates that clustering algorithms like k-means and generative embeddings using dynamic causal modeling can be helpful for incorporating heterogeneous data, thus alleviating the problem of batch effects and high dimensionality and eventually yielding subtypes with translational applicability to precision psychiatry.

3.1.1 Structural Neuroimaging Subtypes (sMRI)

Research on structural neuroimaging in MDD has shown that subgroups can be differentiated based on variation in the volume of gray matter (GMV) and cortical thickness. Such categories are often connected with exposure to trauma and resistance to therapy. Colombo et al. and Pfarr et al. emphasized that GMV in particular brain regions (especially the dorsolateral prefrontal cortex and the medial temporal lobe) is associated with cognitive deficits, as well as with the response to treatment [24, 25]. Colombo et al. suggested that persons with an intense gray matter atrophy have higher cognitive impairments, which can make them less receptive to treatment. The findings imply that the presence of altered brain structures may be used as a biomarker to identify those at high versus low risk in the MDD population, especially in cases where MDD is experienced following trauma [24].

3.1.2 Functional Neuroimaging Subtypes (fMRI/rs-fc)

Idle-state functional connectivity (rs-fc) and task-based functional MRI (fMRI) have demonstrated that MDD can be subclassified into subtypes based on connectivity patterns. Kashiwagi et al. [26], Liang et al. [27], Tokuda et al. [28], Ichikawa et al. [29], and Jing et al. [30] have presented unique patterns of functional connectivity, including thalamus-motor and default mode network (DMN) connectivity, which may predict treatment response. Kashiwagi et al. expressed that the stratification of patients based on biological data such as rs-fc (in addition to the standard clinical characteristics) has the potential to enhance treatment outcome prediction [26]. Their findings show that particular patterns of connectivity are linked to better response to treatment in some studies, suggesting that these functional subtypes might serve as potential biomarkers to help tailor antidepressant treatment [26, 27, 31].

3.1.3 Multimodal Subtypes of Neuroimaging

Integrative structural and functional neuroimaging studies have made it possible to identify multimodal subtypes of MDD, and they have added to the knowledge of heterogeneity in the disorder. Collective measures (e.g., GMV and amplitude of low-frequency fluctuations (ALFF)) have been used to identify subgroups with different cognitive and clinical results. Tang et al. name the subtypes of MDD based on neuroimaging and discuss their biological basis with references to multi-omics profiles such as genetic profile, epigenetic profile, metabolomic profile, and pro-inflammatory cytokine profile [22].

These 807 participants were 327 MDD patients and 480 healthy controls. They were clustered into subgroups, depending on resting-state ALFF, a functional neuroimaging measure, and unsupervised machine-learning clustering was used to categorize subsets of MDD participants [22]. Three subtypes of MDD were distinguished based on neuroimaging patterns, and each had varying changes in ALFF compared with healthy controls [22]. A follow-up multi-omics study would clarify

these differences and further the research into idiosyncratic etiological factors with each subtype [22].

Subtype1 was defined by increased activity in the limbic system and key cortical areas, with ALFF values significantly higher in the hippocampus, cingulate cortex, and amygdala in comparison to the primary visual sensorimotor areas. The subtype is very much hereditary and is mainly associated with brain development and synaptic-regulation mechanisms and is associated with the most severe signs and symptoms of depression and the cognitive declines in later life stages [22].

Subtype 2, which is an immune-inflammatory/metabolic subtype, had a different ALFF imbalance with more cortical activity [22]. It was characterized by the increased expression of immunoinflammatory indicators, such as interleukin-1β (IL-1β) and other related epigenetic inflammatory markers, and a variety of metabolites linked to the levels of IL-1β [22]. There were no statistically significant biological markers of Subtype 3 (indeterminate subtype) [22]. These results also support establishing mechanism-based interventions against MDD and indicate that individually tailored treatment approaches based on a neurobiological and molecular profile are urgent [22].

The studies outlined above aimed to categorize different manifestations of MDD with multidimensional cognitive profiles with the help of a semi-supervised learning algorithm and later used multimodal neuroimaging findings to reveal specific neural patterns of each type [32, 33]. The findings show that specific cerebral abnormalities in MDD patients who present with cognitive impairments can be detected with the help of neuroimaging. Morphometric studies of MDD have demonstrated decreased hippocampal volume as well as impaired working memory and executive functioning, whereas atrophy of gray matter in the medial temporal lobe, motor and prefrontal regions is correlated with visuospatial memory and language impairments, respectively [32].

MDD causes cognitive impairment in various domains as a result of increased ALFF in the lateral frontal cortex and pericalcarine cortex, which is positively related to visual learning [32]. In addition, the association between GMV/ALFF and computerized working-memory training is linked to serotonergic distribution, dopaminergic activity, and NMDA receptor involvement, elucidating the underlying neurochemical processes [32]. This method aims to resolve the cognitive heterogeneity of MDD using data-driven subtyping, which connects the resultant subtypes to a neural substrate spectrum, thus improving the insights into the neurobiological connections between cognition [32].

Xiao et al. developed a precision-medicine framework of neuroimaging in depression, which identifies an objective neurobiomarker strategy of disease subtyping and personalized treatment [34]. Machine-learning algorithms were used to distinguish between two subtypes of depression, including typical and atypical, using ALFF patterns. The detected subtypes supported the earlier results and strengthened the assumption that frontal-posterior functional imbalance is a putative neurobiomarker of depression. The authors pinpointed the dorsal medial prefrontal cortex (dmPFC) and occipital cortex (OCC) as separate regions of interest in repetitive transcranial magnetic stimulation (rTMS) to treat prototypical (archetypal) and atypical depression, respectively [34].

During the second follow-up (T2), patients with the typical subtype (90.00%) and patients with the atypical subtype (70.73%) reported positive treatment outcomes. At T2, 30.00% of the archetypal subtype and 46.34% of the atypical subtype attained remission [34]. In terms of suicidality, the typical and atypical subtypes had response rates of 100.00% and 81.25% at T2, respectively, and remission rates of 100.00% and 56.25%, respectively, at T2 [34].

3.2 Cognitive and Behavioral Subtypes

A study proposes a neuroimaging-based subtyping framework to guide mechanism-oriented rTMS treatment, which may help address gaps in precision psychiatry for depression in translational research [34]. In addition to neuroimaging evidence, cognitive performance and symptom pattern provide complementary solutions to explain MDD heterogeneity. This paper reviews studies that began subtyping based on cognitive measures or symptom groups. These studies identified subsets of individuals who showed divergent clinical features and treatment responses.

3.2.1 Cognitive Performance Subtypes

Two types of biotypes of MDD have been distinguished in terms of cognitive performance: the Cognitive Deficit (CD) and Cognitive Preservation (CP) subtypes. These groups come with different anatomical-imaging patterns of the brain and different clinical outcomes after taking antidepressants. Data-driven cognitive subgroups in major depressive disorder were examined by Tao et al. [32] and how they are related to atrophy of gray matter. They outlined two cognitive subtypes. There were 75 patients in the Cognitive Deficit subtype, and most had significantly worse scores in the cognitive domains than the 43 patients in the Cognitive Preservation subtype. The former became the CD subtype, the latter the CP subtype. More specifically, the CD subtype performed significantly worse across multiple cognitive domains compared to the CP subtype. More specifically, individuals with the CD subtype showed clear cognitive deficits compared to those with the CP subtype, and these differences were observed across several tests. Like with the Delayed Matching to Sample (DMS) task, for instance. Their Immediate Percentage Correct was quite a bit lower (73.10 ± 12.80% compared to 89.40 ± 7.61% for the CP group, $p < 0.0001$), and on top of that, they were slower to respond correctly too (4040.00 ± 1300.00 ms versus 3620.00 ± 999.00 ms, $p = 0.014$).On top of that, the CD group took longer on average during the Rapid Visual Processing (RVP) test (456.00 ± 131.00 ms vs. 407.00 ± 87.90 ms, $p = 0.035$) and committed more total errors on the Spatial Working Memory (SWM) test (32.90 ± 19.30 vs. 20.70 ± 15.00, $p = 0.002$).

Moreover, the CD subtype showed much higher pre-extra-dimensional errors and total errors in the Intra-Extra-Dimensional Set Shift (IED) test, and significantly fewer stages were passed. Whereas the voxel-wise analysis of the total brain volume that survived the family-wise error (FWER) correction did not find any significant voxels, a significant cluster was found after the false-discovery rate (FDR)-corrected cluster-level correction was applied. Furthermore, left fusiform gyrus and cerebellar atrophy were also noticed, thus showing that cognitive impairments can be traced to distinct neuroanatomical alterations. Hack et al. described a cognitive biotype of depression, which occurs in about 27% of depressed people, and involves pronounced behavioral impairments in both executive functioning and inhibition of responses in situations of cognitive control [31]. An individual pattern of pretreatment depressive symptoms and impaired psychosocial functioning (d = -0.25; 95% CI, -0.39 to -0.11; $p < 0.001$) and lack of activation of the cognitive control network, right dorsolateral prefrontal cortex included (d = -0.78; 95% CI, -1.28 to -0.27; $p = 0.003$) [31]. Remission rates were considerably lower in this cognitive biotype subgroup (38.8% vs. 47.7% of the non-cognitive biotype group; $p = 0.04$) [31], and even when the symptoms had been cut to less than 0.2 of z-score standard deviations below the control mean, cognitive deficits persisted [31]. These results implicate cognitive dysfunction as a contributing factor to poor response to antidepressant treatment by showing that the magnitude of symptomatic and functional change was best explained

by cognitive change. Therefore, a personalized treatment plan aimed at alleviating cognitive impairments, as opposed to using only conventional antidepressants, can be more successful [31].

Architecture Coexistence of neuroimaging and multi-omics information points to recurrent candidate subtypes of major depressive disorder (MDD), as shown in the next diagram, grouped into genetic-synaptic, immune-inflammatory and heterogeneous groups, which have different clinical correlates (Figure 3).

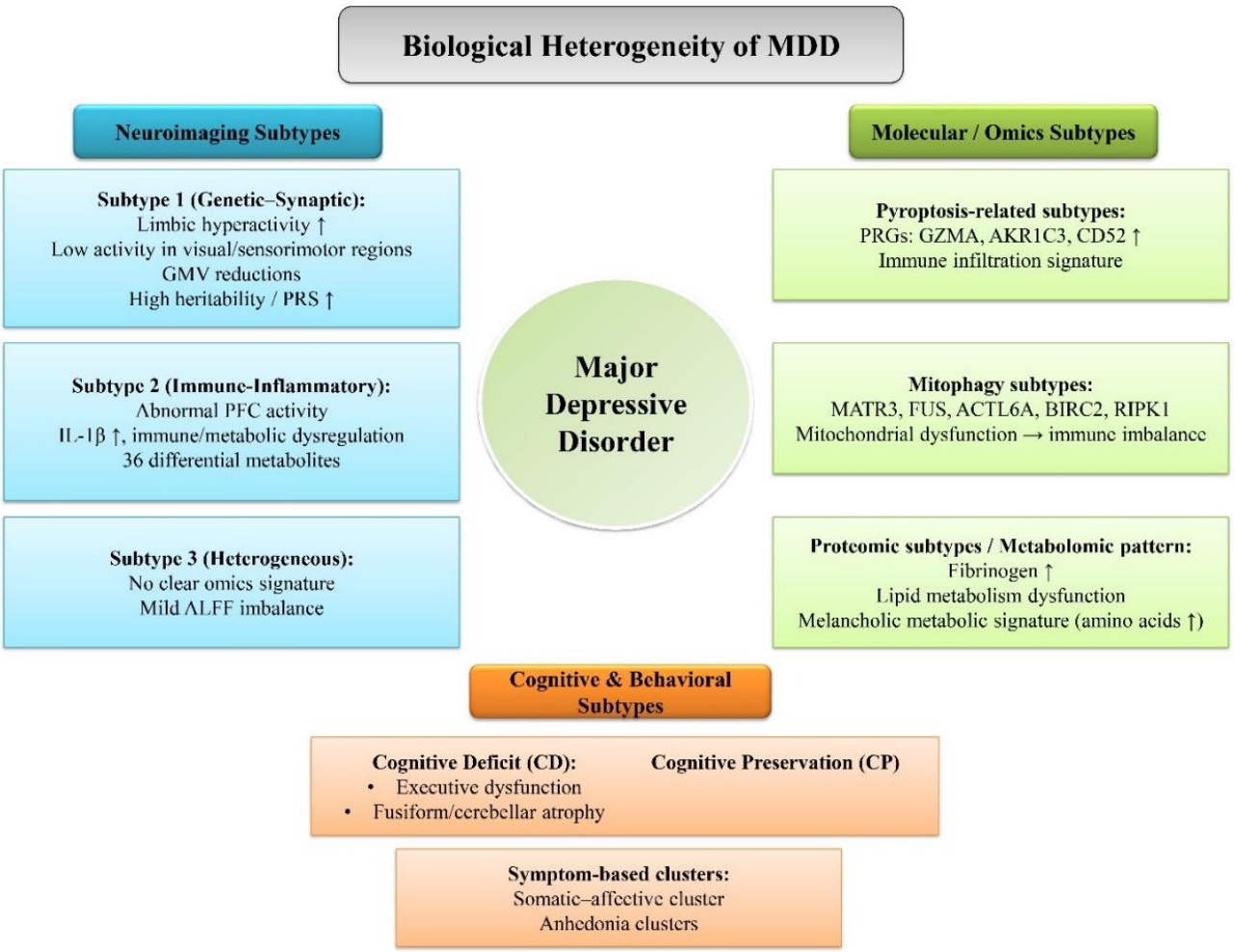

Figure 3 Biological heterogeneity of any MDD. The figure represents main neuroimaging, molecular-, and cognitive-behavioral subtypes, which have been identified with multi-omics integration, with highlights on a differentiation of pathophysiological mechanisms, such as genetic-synaptic hyperactivity, immune-inflammatory dysregulation, and cognitive impairment.

This model emphasizes that there is a lack of modalities, (e.g. upregulation of pyroptosis-related genes in immune-infiltrated subtypes and mitochondrial dysfunction in others), informing the future biomarker panels.

3.2.2 Symptom-Based Clusters

Patterns of affective, somatic, and anhedonic symptoms have been used to characterize the clinical heterogeneity of MDD and may provide insights into differences in treatment response and

possible therapeutic targets. In STAR*D, Collins et al. tested the hypothesis of symptom clusters in depression and the relationship between symptom clusters and treatment response [35]. Using a cluster analysis on baseline Inventory of Depressive Symptomatology (IDS) scores from 1,491 patients with MDD, nine clusters of naturally occurring symptoms were identified, including core affective, core somatic, and core anxiety [35]. Two patient groups were identified by K-means clustering, with differences across seven of the nine symptom clusters [35]. Patients in Cluster 1 (experiencing more intense somatic symptoms) experienced a slight decrease in depressive symptoms after treatment with citalopram compared with Cluster 2 (more severe core affective symptoms) [35]. These results are consistent with previous studies suggesting that higher pretreatment somatic symptom burden may be associated with decreased response to monoaminergic treatment and that SSRIs may have differential effects across symptom dimensions. Collectively, these observations suggest that assessing both somatic and psychological symptoms could be clinically informative, although further validation is required.

Ding et al. investigated the neural correlates of anhedonia subtypes in MDD. The study was conducted on subcategories of anhedonia (anticipatory and consummatory pleasure) using resting-state functional magnetic resonance imaging (rsfMRI) [36]. Two groups (Group M and Group N) were formed using the scores of anticipatory and consummatory pleasure. The study revealed associations between certain regions of the reward network, such as the pallidum and the dorsal striatum, and anticipatory and consummatory pleasure [36]. These findings may generate hypotheses regarding opioid-related therapeutic approaches, although they do not establish clinical utility. Changes in reward-related circuits observed here are consistent with hypotheses regarding the potential involvement of opioid signaling in a subset of patients with MDD, which will need to be investigated directly in clinical studies [36].

3.3 Molecular/Omics-Motivated Subtypes

Neuroimaging and cognitive knowledge is also expanded with molecular and omics-based studies, which have revealed particular biological mechanisms of depressive subtypes. These approaches can be used to classify people into anatomically distinct categories and this may help in shedding more light on common pathophysiological mechanisms, including immune dysfunction and metabolic disruptions, thus making it easier to create more specific therapeutic interventions.

3.3.1 Genomic and Transcriptomic Signatures

The subcategories of MDD have been defined based on individual risk factors, including genetic and expression markers of cellular processes such as pyroptosis and mitophagy, some of which relate to immune dysfunction. Tang et al. described Subtype 1 (genetic-synaptic subtype) as having a highly heritable elevated genetic risk of MDD; the polygenic risk score (PRS) of MDD explained 5.9 per cent and 8.1 per cent at PT thresholds of 0.01 and 0.001, respectively [22]. The genes associated with these PRS were strongly expressed in pathways essential for brain cell development and synaptic plasticity, such as synapse organization, regulation of neuron projection development, axonogenesis, postsynaptic membrane, and neuron-to-neuron synapse with monoatomic ion-gated channel activity [22]. Conversely, Subtypes 2 and 3 found no significant genetic markers associated with MDD. According to these findings, Subtype 1 is mostly related to genetic factors [22]. The three-subtype solution, combining ALFF neuroimaging with multi-omics (genomics, cytokines and

metabolomics), was mainly adopted from Tang et al. [22] (n = 327 MDD patients), as one of the few studies to achieve a successful integration of neuroimaging-defined subtypes with deeper biological layers. Some subsequent research has started to demonstrate a certain degree of convergence with these patterns, especially in regard to immune-metabolic dysregulation.

The article by Feng et al. explored the activation of a pro-inflammatory programmed cell death named pyroptosis in MDD. They described molecular subtypes of pyroptosis and developed a DNA diagnosis model. They used consensus clustering on pyroptosis-related genes (PRGs) to detect changes in molecular subtype characteristics of MDD [37]. In this research, three overlapping genes were identified, namely GZMA, AKR1C3, and CD52, as candidate biomarkers of MDD [37]. This paper has identified three intersecting genes (GZMA, AKR1C3, and CD52) that may serve as highly reliable biomarkers of major depressive disorder (MDD). The MMI model was developed using maximum relevance/minimum redundancy features and is elaborated herein. Furthermore, it was found that the development of MDD is regulated by immune responses; at the same time, three pyroptosis-related genes (PRGs) were differentially expressed and significantly associated with the immunologic infiltrate pattern in MDD patients [37]. These particular PRGs were also validated by in vitro biological tests as crucial components of the diagnosis of MDD, and strongly correlated with the immunological inflammatory response [37]. Pyroptosis, an inflammation-related form of programmed cell death, can also contribute to the inflammatory immune environment that worsens disease progression [37]. In the case of mitophagy-related mechanisms, the findings are based on less research, such as [38], given the early stage of this field. Five candidate genes (MATR3, ACTL6A, FUS, BIRC2 and RIPK1) consistently appeared in that set, but they must be replicated. In the same way, pyroptosis-related subtypes [37] are promising molecular markers that need to be validated with larger independent cohorts.

Zhang et al. investigated the importance of mitophagy, which is the specific destruction of dysfunctional mitochondria by the autophagic apparatus, and its correlation with MDD. They wanted to determine mitophagy-related biomarkers and clarify the molecular pathways behind it in terms of immune infiltration [38]. This current research identified 315 differentially expressed genes that were involved in mitophagy in MDD, which were significantly overrepresented in the biological process of mitophagy and neurodegenerative disease-linked pathways [38]. Two different clusters of MDD with unique patterns of immune infiltration were discovered [38]. It was identified that five mitophagy-related genes, MATR3, ACTL6A, FUS, BIRC2, and RIPK1, showed promise as candidate biomarkers of major depressive disorder [38]. These genes showed a range of differences in the association with immune cells; ACTL6A, BIRC2, and RIPK1 were up-regulated in one cluster/subtype, but both FUS and MATR3 were not up-regulated in any of the clusters/subtypes [38]. The results highlight that mitophagy plays a role in MDD diagnosis and immune response regulation; therefore, it is possible that the severity of MDD is linked to the balance and regulation of mitophagy-induced inflammation [38].

3.3.2 Proteomic and Metabolomic Profiles

Subgroups of MDD have been defined based on their circulating metabolites and proteins, which proves promising in making predictions about the progression of the disease and response to treatment.

Habets et al. examined the predictive value of a variety of biological data modalities, including whole-blood proteomics, lipidomic metabolites, transcriptomics, and genetic information, for predicting two-year remission in MDD individuals. Their machine-learning results showed that the proteomics data also gave the most discriminative unimodal predictive accuracy with an area under the receiver operating characteristic curve of 0.68 [39]. Addition of proteomic data into clinical baseline attributes significantly increased two-year prediction of MDD remission, and the AUROC increased to 0.78 (p = 0.013) [39]. Addition of additional layers of omics (lipid metabolomics, transcriptomics, or genetics) and clinical data did not provide a better model performance [39]. Both have shown relevance and enrichment analysis results showing that proteomic analytes, especially those related to inflammatory responses and lipid metabolism, played a decisive role; the most significant variable was fibrinogen level [39]. The combination of proteomic and clinical variables in this trial generated a distinct multimodal signature of MDD remission with therapeutic implications in the prediction of disease trajectories in a personalized manner. The machine-learning models were more accurate than psychiatrists in predicting remission status at 2 years (balanced accuracy of 71% compared with 55% for psychiatrists) [39].

Liu et al. used metabolomic biosignatures to discriminate between patients with melancholic depression and healthy controls, thus distinguishing a particular subpopulation within major depressive diseases [40]. Their computer system, based on a Random Forest classifier, demonstrated better claims with melancholic depression compared with anxious depression or MDD in general, implying that the metabolome contains much more melancholy-specific information and that the sub-condition may be more biologically homogeneous [40]. This method achieved around 80 per cent classification, sensitivity and specificity of melancholic depression [40]. The cluster of discriminating features was analyzed and showed metabolic classes and pathways that differed in response to cortisol activation during chronic stress [40]. A large percentage of identified metabolites (48/56) were higher in melancholic depressed individuals than in healthy people [40]. Namely, the amino acids were regularly found in this subtype; out of 56 metabolites evaluated, 11 were amino acids, and the rest of the metabolites were the products of amino acid breakdown. It has been reported that fourteen lipid-related metabolites were mainly upregulated, and three stress-hormone-signaling component metabolites were also detected as upregulated [40]. The analysis revealed that the two immune-relevant markers were lower in those who were subjected to melancholic sadness. The high heritability of melancholia identified by the authors is an indicator of an underlying biological pathology that can manifest as molecular phenotypes [40].

With regard to many studies, the corresponding publications describe a network-science approach to obtain an integrative genomic-metabolomic signature of antidepressant response and lifetime history of attempted suicide in individuals with major depressive disorder [35, 41]. This investigation aimed to identify biomarkers that can predict suicide risk and antidepressant treatment sensitivity, highlighting that patients with MDD who have a history of suicidal behaviour often have muted suicide responses to these therapeutics [41]. Possible biological markers of those who attempt suicide can be determined by the combination of metabolomics and genomic data as the metabolome also demonstrates consistent abnormality in stress response similar to those found in suicide attempts [41]. However, the current discussion does not directly state that there exist discrete metabolomic subtypes of suicide, as it is evident in melancholic depression or in MDD in general, as quoted in the article in question. It focuses on finding a multi-omics signature and

explaining its connection to the effectiveness of antidepressants, as well as the prevalence of suicide attempts [41].

3.3.3 Immuno-Inflammatory Subtypes

One subtype of MDD is associated with an immunoinflammatory phenotype, characterized by elevated levels of pro-inflammatory cytokines and specific clinical features. The integrative multi-omics study of depression phenotypes performed by Hagenberg et al. has found that about 30 % of patients with the diagnosis of MDD exhibited a pro-inflammatory profile, which is also referred to as low-grade inflammation, confirmed by high C-reactive protein (CRP) levels [42]. In this study, four separate clusters of symptoms were identified, two of high immune-related-depression symptoms (HIRDS) cluster, one of mild depression symptoms (MIDS) cluster, and another of low immune-related-depression symptoms (LIRDS) cluster. The HIRDS clusters had greater immunological proxies, elevated body mass index (BMI), and severity of depression. CRP, tumour necrosis factor (TNF), interleukin 1 receptor antagonist (IL-1RA), placental growth factor (PlGF), CCL2, CCL4, and CCL13 were found to be elevated in these clusters of inflammatory markers. Up-regulated anti-inflammatory cytokine IL-1RA was shown to have substantial effects in the HIRDS clusters and was linked to the changes in appetite, depression levels, BMI, and disturbed sleep patterns [42].

This evidence supports the notion of immunometabolic depression, indicating that there is a correlation between increased inflammatory response and the breakdown in energy homeostasis, which can be the cause of both obesity and fatigue [42]. It was proven that patients in the non-regulated metabolism state (immunometabolic depression) had increased inflammatory markers, which were associated with anhedonia and changes in appetite, eating behaviour, and fatigue [42]. A subgroup of persons with the highest levels of monocytes, $CD4^+$ T cells, and neutrophils also exhibited high levels of CRP and interleukin-6 (IL-6), which were also correlated with severe depressive symptomatology [42]. The integration of multi-omics revealed that HIRDS clusters exhibit cell-type-specific inflammatory signatures, with higher levels of vascular endothelial growth factor-A (VEGF-A) and an inverted expression pattern of SERPINF1, which is mostly expressed by dendritic cells [42].

Subtype 2, in contrast to healthy controls, showed much higher levels of the pro-inflammatory cytokine IL-1β as well as strong metabolic regulation [22]. Complement component C3 was highly correlated with IL-1β and demonstrated the presence in the metabolic profile of fragile × syndrome, which exhibits changes in the metabolism of fatty acids, triglycerides, and amino acids. Pre-mutation variants of C3 were characterised, which implied implications on its branching behaviour in this subtype [22]. In a different study, 44% (16 of 36) of disease manifestations were detected at the same time in people with Subtype 2 chronic regional pain syndrome were strongly correlated with the level of IL-1β [22]. There were negative associations of five of six amino acids (N-acetylleucine, acetyl-N-formyl-5-methoxykynurenamine, N-acetylisoleucine, N-lactoylvaline, and methylglutaconic acid) with plasma IL-1B, and six of seven organic acids also showed strong negative relationships with IL-1β [22]. The available literature provides abundant evidence of a strong correlation between immune-inflammatory pathology and MDD in both human and animal literatures. As an example, in MDD patients, pro-inflammatory cytokines, including IL-1β, and immune cells, including neutrophils and monocytes, have increased numbers [22]. Clinical evidence has revealed that cytokine therapy can induce depressive mood, and anti-depressive mood

symptoms may be improved with anti-inflammatory interventions, thus highlighting the significance of anti-inflammatory-specific therapy in a group of patients with immune-inflammatory phenotypes. Subtype 3 [22], on the other hand, had no significant effect on inflammatory mediators.

3.4 Combination of Multi-Omics Data

Expanding on results from single modalities, multi-omics integration is the most comprehensive and gives the most complete picture of MDD heterogeneity. Without considering all the dimensions of the complex syndrome of MDD and predicting its course, it is impossible to fully grasp it. A combination of multi-omics research (including various types of biological data) is the future of such research. These high-level studies provide a clearer overall picture of the disorders under study and which biomarkers may be helpful in the future. The above advanced studies utilize a variety of data types and no longer rely solely on single-omics studies to explain the complex relationships between genetic disposition, molecular profiles, and phenotypic manifestations. In this area, research indicates that integration of clinical data with other omics profiles, including proteomics, may significantly improve predictive models of long-term outcomes in MDD.

One of the investigations was by Habets et al., who studied the predictive value of different biological samples (whole-blood proteome, lipid metabolism, transcriptome, and genetics) individually and collectively, in combination with baseline clinical data to predict two-year remission at the individual level in MDD. A machine-learning solution based on data analysis was used to train and cross-validate predictive models using data from 643 MDD patients, and then performance was evaluated on 161 individuals [39]. Unimodal predictions were best with proteomics data alone, with an area under the curve (AUC) of 0.68.

When proteomic data were added to clinical baseline parameters, the 2-year MDD remission prediction was significantly improved (AUROC rose to 0.78 vs 0.63 (p = 0.013) [39]. The addition of omics (lipidomics, transcriptomics, genetics) to the clinical data did not improve model performance [39]. The importance of the features and enrichment analysis revealed that the inflammatory response and lipid metabolites of proteome analytes were also important predictors, with fibrinogen being the most critical, followed by the severity of symptoms [39]. Machine learning models performed better than psychiatrists in predicting 2-year remission status, with balanced accuracy totals of 71% among machine learners and balanced accuracy totals of 55% among clinicians [39]. Findings: The comparison revealed increased predictive power when including proteomic, not clinical, data, which was observed with nonlinear machine learning (e.g., XGBoost) rather than linear models, suggesting even stronger detection of more complex multimodal predictive patterns by nonlinear models [39]. XGBoost multimodal predictions were found to account for variance in 2-year remission without consideration of the possible confounding variables, such as antidepressant and other psychopharmaceutical use, the level of education attained, body mass index (BMI), age, and sex. In the current research, the integration of proteomic analysis with clinical data has created a new multimodal signature of MDD remission. To determine the developmental course of an individual patient, estimating disease progression is therapeutically significant during the initial assessment [39].

Frässle et al. produced and experimented with a generative embedding (GE) learning model to determine how patients with MDD progressed over two years with a combination of clinical, neuroimaging, and omics features [43]. In 85 patients with MDD, they compared effective directed

connectivity between key face-processing and emotion-related areas (such as the Occipital Face Area, Fusiform Face Area, and amygdala) using dynamic causal modeling (DCM) based on fMRI data of an emotion face-perception task. The parameter estimates of the generative model yielded features of physiological interest, which could be used for supervised classification with support vector machines. The patients were categorized into three clinical trajectory groups (remitted, improved and chronic) based on the variation in symptom severity. The chronic/rapid tendency of the remission trajectory was adequately predicted by GE classifiers, with a moderate accuracy of 79, which was significantly better than that of classifiers using classical FC or local BOLD activity features alone. The source of predictive value is, to a considerable extent, related to trial-by-trial variations in effective connectivity, which depend on emotional valence, with the significance of dynamic modulation of emotion-processing networks being a primary indicator. Frässle et al. showed that clinical trajectory prediction was improved when neuroimaging-derived effective connectivity features, rather than broad multi-omics data, were incorporated into clinical models [43]. Clinically, the prediction was very low (albeit 66 percent), but with the addition of omics data alongside the neuroimaging-based EC indices, the mechanistic interpretability and predictive utility significantly increased. Dynamic variation in the connection to various emotional faces (i.e., happy, angry, fearful, and sad) was most predictive in the long-term curve, which depicts the neural network response to emotional experiences and the validity of biomarkers that demonstrate the pathophysiology of diseases. We are also aware that the limitations of the study include its small sample size and the wide scope of naturalistic treatment because it would be advisable to focus on completely standardized, prospective datasets to prove the validity. This work also shows significant advances in the combination of clinical, neuroimaging, and omics predictors of personalized prognosis in MDD and shows how physiologically based computational models can be translated to precision medicine in psychiatry.

Common patterns in the subtyping of MDD across the studies reviewed are summarized in the following table. The table combines neuroimaging, omics, and clinical results to explain biologically-based collections (Table S1).

Interestingly, multimodal techniques, including the simultaneous dependencies between the areas of the brain (e.g., components of the limbic system) and immune biomarkers, display direct correlations between the brain regions and the immune biomarkers. These results have serious implications for treatment resistance in subtypes that are caused by atrophy of the gray matter or an exaggeration of inflammatory processes.

4. Discussion

4.1 Biologically Distinct MDD Subtypes are Converged on Evidence

Such neurobiologically defined subtypes are promisingly associated with clinical heterogeneity. For instance, the genetic-synaptic subtype (Subtype 1) has been previously linked to early onset, more severe cognitive impairment and a more poorly predicted long-term course, and shares these risk factors with recurrent and treatment-resistant depression. The immune-inflammatory/metabolic subtype (Subtype 2) is often accompanied by increased BMI, metabolic syndrome, chronic inflammation-related comorbidities (e.g., cardiovascular disease, obesity), somatic symptoms, and a more chronic course of illness. There is a description of systems immunology approaches for integrating multi-omics data [44]. Cognitive Deficit subtypes are

associated with more functional impairment, severity, and the risk of continued disability despite resolution of mood symptoms. Neuroimaging, cognitive-behavioral and multi-omics research has shown increasing support for two to four different candidate subtypes of MDD. Several multimodal investigations (e.g., [22, 34]) have proposed three main candidate subtypes: a genetic-synaptic subtype with hyperactivity of the limbic system and an enrichment of genes associated with synapses, an immune-inflammatory/metabolic subtype characterized by increased IL-1β and metabolic dysregulation, and cognitive deficit versus preserved subtypes (e.g., [31, 32]). Two additional groups, anhedonic and somatic-affective, have been identified in symptomatic clusters [35, 36].

These candidate subtypes appear promising based on their clinical features. For example, patients with immune-inflammatory type tend to have recurrent episodes, increased BMI, metabolic comorbidities, and somatic symptoms. Cognitive Deficit subtypes are more likely to be associated with worse functional impairment and long-term outcomes. Most of these associations are based on cross-sectional analyses and need to be replicated in studies with a longitudinal design, which will take illness course, burden of comorbidities and treatment history into account [22, 37, 38, 42].

4.2 Clinical Association and Treatment

Preliminary studies have found differences in symptoms and treatment response between biological subtypes, although there is significant variation in patient characteristics (such as first-episode vs recurrent MDD, comorbidities, and treatment resistance status) among the studies. In recurrent or treatment-resistant depression, the genetic-synaptic subtype is often comorbid with symptoms of severe cognitive dysfunction and anhedonia, whereas the immune-inflammatory subtype is usually comorbid with somatic symptoms, fatigue, increased BMI and possibly decreased responsivity to conventional antidepressants, especially SSRI drugs [22, 31, 42]. This subtype may be more responsive to anti-inflammatory and/or metabolic interventions in preliminary studies [42].

A trial with neuroimaging-informed targets and reporting varying remissions by subtype (30-46%) [34] suggested subtype-specific rTMS targets. Results of analyses of the anhedonia subtypes have indicated possible associations with dysfunction of the reward circuits [36]. However, these observations are hypothesis-generating and need to be confirmed in larger prospective trials that better characterise patients (single episode, recurrent, comorbid conditions and treatment resistance).

These multi-omics subtypes have been further investigated using biomarker-guided stratification approaches, strengthening their translational. For example, metabolomics studies have revealed distinct metabolomic signatures for responses to ketamine and esketamine, which may provide a basis for selecting patients likely to benefit from glutamatergic or anti-inflammatory interventions. This is especially important for our immune-inflammatory/metabolic Subtype 2, which has higher levels of IL-1β and metabolic dysfunction. Complementary neuroimaging and cognitive biotype methods have also been shown to help inform treatment allocation, e.g. differential rTMS targeting or cognitive remediation approaches [26, 45]. The identified neurobiological subtypes also have significant clinical dimensions that correspond to the subtypes. The immune-inflammatory subtype is often associated with more medical comorbidities (e.g., metabolic syndrome, obesity), more severe somatic symptoms, and differential treatment response, with standard SSRIs having less

efficacy for this subtype and potential efficacy of anti-inflammatory and/or metaboli-targeted medications. Adjunctive cognitive remediation is needed because cognitive biotypes with executive dysfunctions are more severe, have more psychosocial dysfunction and have lower remission rates with conventional antidepressants. Such overlaps between the neurobiological profiles and clinical characteristics (etiology, co-morbidity, clinical course and treatment response) further support the clinical relevance of multi-omics-driven subtyping.

Finally, we have pointed out that a biologically informed subtyping could increase the accuracy of treatments, based on a neurobiological profile rather than simply on symptom severity.

4.3 Methodological Considerations

The reviewed studies offer important insights into the biological heterogeneity of MDD, but a few methodological limitations should be noted. A large number of studies included small sample sizes, and the analysis of multi-omics and neuroimaging datasets with high-dimensional data and unsupervised clustering algorithms carries a risk of overfitting. Data preprocessing workflows, molecular platforms for assays, and clustering parameters vary across studies, further hindering direct comparisons and reproducibility due to high dimensionality. In psychiatric diseases, gene expression studies have identified inconsistent molecular signatures [46].

Importantly, most methods used to identify subtypes were based on internal cross-validation and only a few studies conducted external validation in independent cohorts. Confounding factors (e.g., batch effects, scanner differences (neuroimaging), site effects and clinical heterogeneity (e.g., recurrent versus first-episode MDD, medication status and comorbidities) were present and often inadequately addressed. Also, many the subtyping definitions in use are derived from a single study (e.g. Tang et al. [22]), so there is a need for replication.

The caveats reflect the fact that the proposed subtypes are not full-fledged taxonomies. To enhance the robustness and clinical utility of multi-omics subtyping of MDD, future large-scale, multi-site, prospective studies with pre-registered protocols and external validation are needed.

4.4 Challenges and Future Directions

Despite positive developments, the inclusion of biological categories into clinical practice is cumbersome. The pace of computational science advances is high, and longitudinal and standardized datasets are scarce, making it difficult to maintain progress in this area. Future research priorities thus consist of removing biases in the analysis procedures, encouraging the dissemination of open data, or performing multisite replication studies to achieve the ability to reproduce. The combination of omics and imaging-based subtyping with real-world clinical parameters (e.g., treatment-response trajectories, comorbidities, etc.) can be utilized to determine subgroups that have clinical relevance. Additionally, future research should stratify participants by treatment arm to determine whether distinct physiologically defined subgroups exhibit differential therapeutic benefits. Future research will be done to develop commercially viable instruments (e.g. composite biomarker panels or machine-learning-driven diagnostic platforms) that can differentiate patient subtypes at the time of intervention to enable true precision psychiatry of MDD. Recent literature on biomarker-guided treatment allocation in MDD further supports this direction. Cavaleri et al., for instance, summarized recent progress in biomarker-based stratification and treatment

selection, and emphasized the increasing promise of multi-omics and neuroimaging markers to facilitate personalized interventions [45].

5. Conclusions

Accumulating evidence suggests that MDD is a heterogeneous disorder comprising potentially distinct biological subgroups. In the studies examined, integrative analyses have indicated candidate clusters based on genomic, proteomic, metabolomic, and neuroimaging data, such as genetic-synaptic clusters, immune-inflammatory/metabolic clusters, and cognitive-control clusters. These candidate subtypes are associated with different symptom dimensions such as anhedonia, cognitive impairment, and somatic fatigue, and may be relevant for predicting treatment response to antidepressants, neuromodulation, and/or anti-inflammatory treatments, though this needs to be validated in prospective studies. The combination of results from the independent studies is encouraging, and there is a need for replication and external validation. Emerging evidence also supports the potential for translating multi-omics findings into clinical practice; however, prospective clinical studies are needed to validate candidate biomarkers, develop diagnostic algorithms, and assess the clinical value of these approaches. In summary, these strategies could contribute to improved diagnosis and treatment selection by using biomarkers, if they are substantiated in large, well-defined cohorts. Recent research developments such as biomarker studies focusing on antidepressant response to ketamine and stratification for antidepressant therapy based on functional connectivity networks also demonstrate the promise of moving from symptom-based toward biologically informed selection of treatment, but challenges remain for routine clinical use. Overall, our synthesis suggests that integrating multi-omics is a promising step towards precision psychiatry in MDD and highlights the need for further validation before clinical use.

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Author Contributions

EA carried out the gathering and analyzing of studies. BS participated in the design of the study and drafted the manuscript. EA and BS conceived of the study and participated in its design and coordination as well as the analyses of data. All authors read and approved the final manuscript.

Competing Interests

The authors have declared that no competing interests exist.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Table S1: Comprehensive Summary of Data-Driven MDD Subtyping Studies.

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