Multi-omics data integration methods and their applications in psychiatric disorders

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Figure 1: Outline of the various aspects discussed in this review

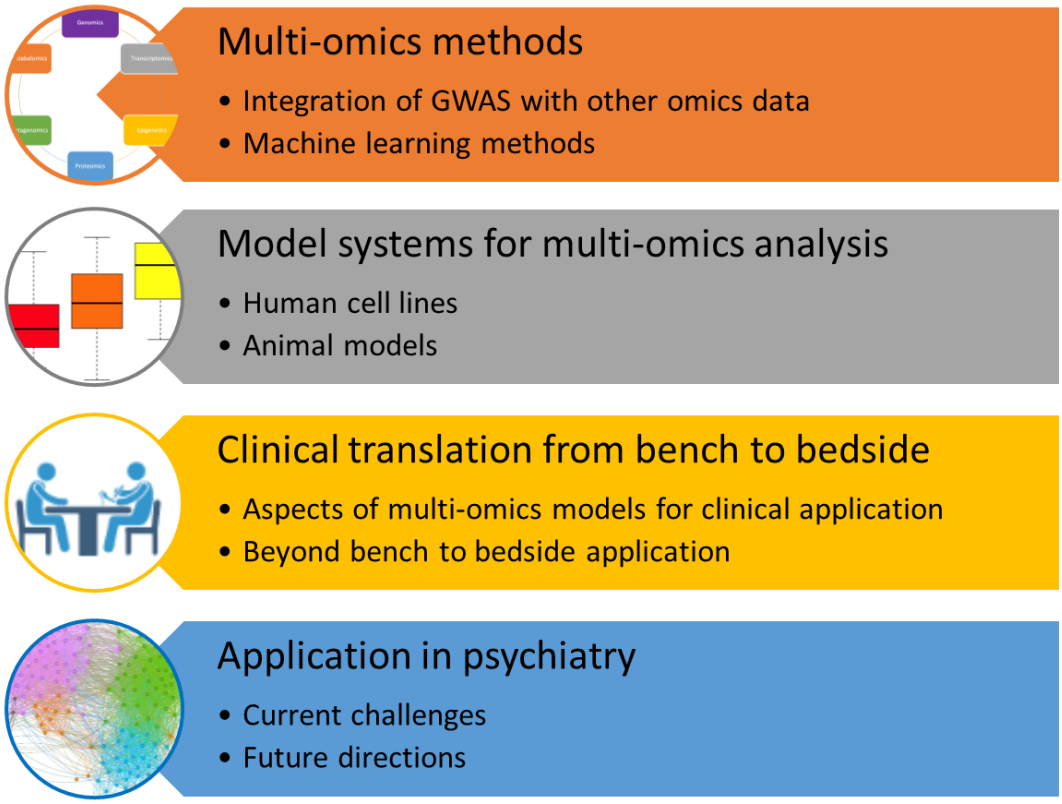
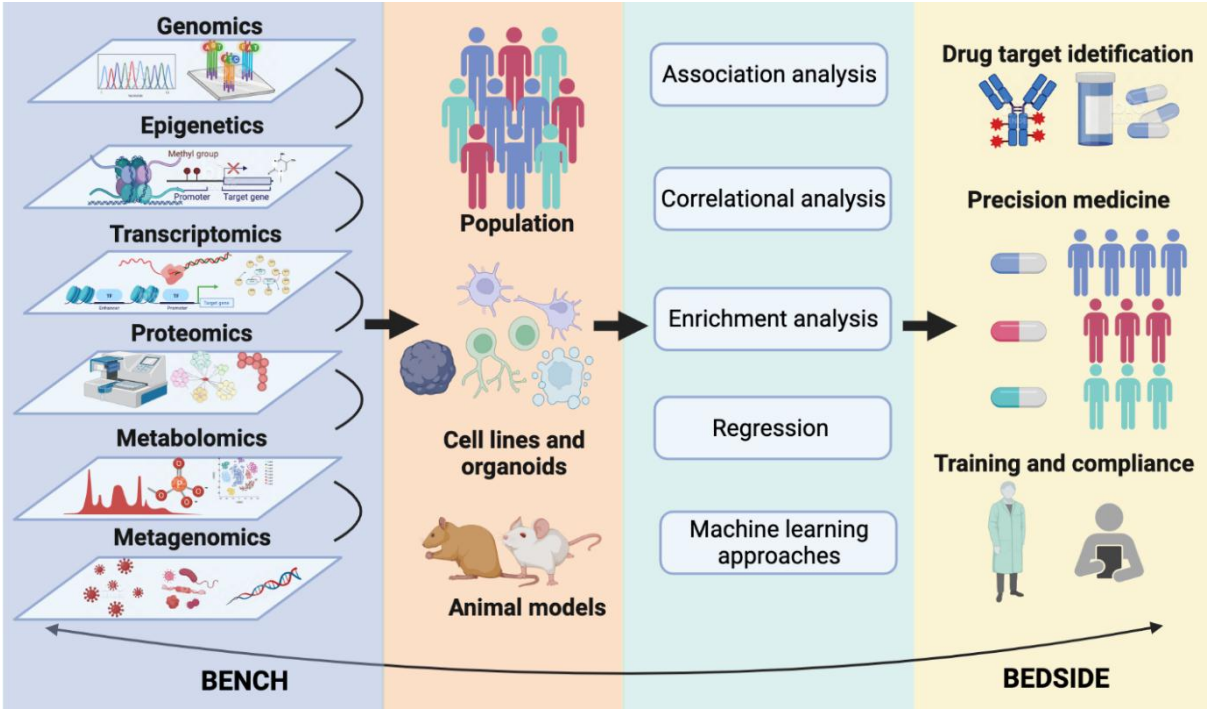


Figure 2: Multi-omics research from bench to bedside in psychiatry



Notes: The blue panel displays the various omics in cell that are commonly sequenced; the orange panel displays the populations from which multi-omics data is obtained; the green panel displays the various mathematical approaches used for multi-omics integration; and the yellow panel displays the clinical applications of multi-omics research in psychiatry.

Abstract

To study mental illness and health, in the past researchers have often broken down their complexity into individual sub-systems (e.g., genomics, transcriptomics, proteomics, clinical data) and explored the components independently. Technological advancements and decreasing costs of high throughput sequencing has led to an unprecedented increase in data generation. Furthermore, over the years it has become increasingly clear that these sub-systems do not act in isolation but instead interact with each other to drive mental illness and health. Consequently, individual subsystems are now analysed jointly to promote a holistic understanding of the underlying biological complexity of health and disease. Complementing the increasing data availability, current research is geared towards developing novel methods that can efficiently combine the information rich multi-omics data to discover biologically meaningful biomarkers for diagnosis, treatment, and prognosis. However, clinical translation of the research is still challenging. In this review, we summarise conventional and state-of-the-art statistical and machine learning approaches for discovery of biomarker, diagnosis, as well as outcome and treatment response prediction through integrating multi-omics and clinical data. In addition, we describe the role of biological model systems and *in silico* multi-omics model designs in clinical translation of psychiatric research from bench to bedside. Finally, we discuss the current challenges and explore the application of multi-omics integration in future psychiatric research. The review provides a structured overview and latest updates in the field of multi-omics in psychiatry.

Keywords: Multi-omics; genomics; transcriptomics; statistics; machine learning; psychiatry

1. Introduction

The study of psychiatric disorders in the past involved examination of the different systems such as genomics (genetic variants, copy number variations), transcriptomics (gene expression), epigenomics (DNA methylation, chromatin and histone modifications), proteomics (protein expression), metabolomics (metabolite expression), brain networks, and clinical data independently due to the technological limitations. Traditional single omics analysis approaches include genome-wide association studies (GWAS), differential gene expression and differential methylation analyses. Advancements were limited due to small sample size, difficulty in holistic interpretation of results, and computational resources.

With the advent of high throughput sequencing and decrease in sequencing costs, generation of large-scale omics data has become highly feasible. International consortia such as Psychiatric Genomics Consortium (PGC)(Sullivan et al., 2018), European College of Neuropsychopharmacology (ECNP), UK Biobank(Bycroft et al., 2018), and several research groups across the world collate and analyse largescale GWAS of several psychiatric disorders routinely. There has been remarkable success in identifying robust disorder-associated risk loci for schizophrenia (Trubetskoy et al., 2022), depression(Levey et al., 2021), bipolar disorder(Mullins et al., 2021), and post-traumatic stress disorder (PTSD)(Stein et al., 2021). However, inability to pinpoint causal variants and difficulty in biological interpretation have limited the clinical translation of GWAS results(Tam et al., 2019).

Massively parallel reporter assay has enabled measuring many more features on the genome than ever before. For example, the Illumina's Infinium MethylationEPIC beadchip measures methylation intensities at ~850,000 regions on the genome. Together with the largescale omics sequencing projects across the world has led to the era of Big Data in psychiatry. The boom in largescale multi-omics data have made integrative investigations of multiple omics and clinical subsystems feasible. Psychiatric disorders are multifactorial disorders, i.e., caused by multiple genes and molecular features in conjunction with significant contribution from physical and social environment. Thus, to answer questions regarding the underlying biological mechanisms in aetiology of psychiatric disorders, it is pertinent to conduct multi-omics research. Apart from holistic understanding of the

biological processes, it also enables the discovery of novel biomarkers and informed preventative approaches(Fusar-Poli et al., 2021).

Several approaches using statistical and machine learning methods have been developed for optimal integration of the multiple omics data. While development of accurate computational models that aim to understand the underpinning biology is one of the big challenges, the application of multi-omics research in clinical setting in psychiatry is equally challenging. The use of multi-omics data in clinical settings is promising as it can provide information for accurate diagnosis and targeted therapy. However, challenges pertain to the development of software tools with robust and transparent mathematical methods, active engagement and training of clinicians in new technologies, awareness among the public and implementation of policies towards safe and ethical use of automated decision-making software tools.

In this review we aim summerise the current state of psychiatric multi-omics research and its clinical application. This work is hereby divided into four parts outlined in **Figure 1**. We begin this review by providing an overview of the commonly employed multi-omics integration methodologies including statistical and machine learning (ML) concepts followed by multi-omics research using human and animal model systems. Next, we discuss on the desirable features of multi-omics based decision-making software tools for clinical translation and discuss the migration from bench to bedside. This development, including all relevant aspects, is visualized in **Figure 2**. Finally, we outline the opportunities and pitfalls of multi-omics research in psychiatry. Thus, we offer holistic insights which can inform researchers from diverse fields of psychiatry on the current state of multi-omics models from wet and dry lab to real world implementation.

2. Multi-omics methods for discovery and disease mechanisms

The integration of multi-omics data can be broadly classified into two approaches–multi-stage and meta-dimensional(Ritchie et al., 2015). Multi-staged approaches generally involve the integration of different omics in stepwise or hierarchical manners. For example, each omics data are analysed independently followed by an integration of the results. Multi-staged integration could also be carried

out through association analyses between measurements from two omics data for the same genes or molecular features. Multi-stage integration can inform on cause-effect links between the omics as well as identify the significant molecular features associated with the disorders. The meta-dimensional integration approach involves analysing two or more omics information simultaneously. This approach employs advanced statistical or ML strategies such as concatenation (where all omics data for each sample are concatenated prior to analysis), transformation (where each omics are transformed to an intermediate form such as network graph or kernel matrix) or integration of models (where models developed based on different omics are combined to develop the final model)(Ritchie et al., 2015). These strategies utilise genome-wide data and hence require some kind of feature selection prior to integration to overcome computational limitations and inclusion of noisy data. As meta-dimensional integration conducts a sample-level investigation, it is commonly used for diagnostic, classification, prognostic, and predictive purposes(Fusar-Poli et al., 2018). Below various statistical and ML methods utilised for multi-omics integration and their application in psychiatric research are summarised. These methods may fall in one or both of the aforementioned integration approaches.

2.1 Methods integrating GWAS with other omics

The majority of the GWAS significant variants lies in non-coding regions. This challenges the functional interpretation and clinical translation of GWAS results. Other limitations include requirement of large sample sizes, and inability to pinpoint causal variants(Tam et al., 2019). Integrating of genomics with other omics data has shown to aid in mapping the functional mechanisms of the GWAS-associated SNPs. It follows the rationale that when a disease-associated SNP is also associated with other molecular features such as gene expression or DNA methylation, then the SNP along with the associated omics feature is likely to play a crucial role in the disease mechanism(Schaid et al., 2018). Given the success of GWAS in psychiatric disorders as well as other complex disorders, several methods and ready-to-use software tools are developed routinely.

Enrichment-based methods

Enrichment-based approaches generally use overlap, correlation, or association analysis techniques independently or in combination to integrate GWAS data with more omics.

The quantitative trait locus (QTL) analysis is a widely used method to integrate SNPs with a quantitative phenotype (including omics measurements). Here, association between genotypes of SNP and molecular features such as gene expression levels or DNA methylation levels is done by conducting univariate regression analysis. The SNPs that are significantly associated with molecular features are known as QTLs. QTLs of gene expression are known as expression QTLs (eQTLs), of methylation intensities are known as methylation QTLs (meQTLs), of protein levels are known as protein QTLs (pQTLs) and so forth. The GTEx(Consortium, 2020), ENCODE(Moore et al., 2020), Roadmap Epigenomics(Kundaje et al., 2015), and proteome map(Jiang et al., 2020) are examples of databases that have systematically catalogued the association between SNPs and various molecular features using multiple omics data sequenced in healthy individuals. In addition, to understand various molecular mechanisms in the human brain during development, function, and disease, the compilation and analysis of different QTLs from post-mortem brains for different conditions and at different time points is carried out by brain-centric consortia such as PsychENCODE (Akbarian et al., 2015) and BrainSpan(Li et al., 2018). The PsychENCODE has generated largescale multi-omics data, including bulk transcriptome, chromatin, genotype, and Hi-C datasets and single-cell transcriptomic data from ~32,000 cells for major brain regions. The PsychEncode resource has developed a wealth of information using this data. This includes expression, splicing-isoform, chromatin, and cell fraction QTLs as well as derived data such brain-expressed genes, disease-associated genes, co-expression modules, gene regulatory networks, and epigenomics data including histone modification, K enhancers, chromatin loops, and topologically associating domain (Wang et al., 2018). Recently, omics analysis is moving toward single-cell analysis. This has enabled single cell focussed QTL analysis of different brain cell types(Bryois et al., 2022; Wang et al., 2018). In a study(Ziffra et al., 2021) investigating the single cell assay for transposase accessibility by sequencing (scATAC-seq) of the human forebrain found a total of 459,953 peaks that were enriched in gene regulatory elements, such as enhancers. Integration of the peaks with cleavage under targets and tagmentation data

identified 25,659 gene-linked enhancers. The authors subsequently found that the genes linked to predicted cell-type-specific enhancers were enriched for biological processes strongly associated with cell-type identity. Such studies inform on the contribution of different regulators to the emerging patterns of cell type diversity in the brain and can inform on the potential mechanisms in brain disorders.

Extensive databases cataloguing the functional role of SNPs have also allowed immediate integration between GWAS significant variants and various regulatory variants such as QTLs for functional characterisation of the GWAS results. The GWAS significant variants and QTLs are usually combined through overlap or positional mapping with functional annotation(Watanabe et al., 2017). Testing for enrichment involves a statistical test to check if the observed overlap between GWAS SNPs and QTLs is more than what is expected by chance. The statistical methods employed include binomial(O'Dushlaine et al., 2009), fisher's(Purcell et al., 2007), hypergeometric(Lee et al., 2012), Kolmogorov-Smirnov(Wang et al., 2007), and ad-hoc overlap statistical approaches based on permutation or related iterative approaches(Consortium, 2013; Hannon et al., 2016; Jaffe et al., 2018; Pers et al., 2015). Ad-hoc approaches involve simulating the overlap several times, e.g., 10,000 times, using randomly selected SNPs. Subsequently, the proportion of iterations with overlap more than observed is assigned as the empirical p-value for the observed enrichment between disease-associated SNPs and regulatory features. Such integrations of GWAS data with QTLs from multiple cell or tissue types can provide information on the likely pathogenic tissues and mechanistic pathways involved in the disorder. For example, Hannon et al.(Hannon et al., 2016) showed that schizophrenia-associated risk loci were enriched in meQTLs of fetal brain thereby suggesting implication of altered DNA methylation in fetal brain in schizophrenia. In another study(Andrews et al., 2017), Andrews *et al.* examined the enrichment of autism spectrum disorder (ASD)-associated GWAS SNPs in meQTLs from cord blood, peripheral blood, fetal brain, and lung tissues and found evidence for enrichment in peripheral blood and fetal brain. The DNA methylation sites regulated by ASD-associated GWAS SNPs were enriched for immune response pathways. The study also reported that five ASD-associated GWAS SNPs were meQTLs in cord blood, peripheral blood, and fetal brain tissues and that the genes

associated with the meQTLs were novel genes. While overlap enrichment approaches can aid in functional annotation and discovery of novel biomarkers, the estimates can be biased due to linkage disequilibrium, presence regulatory variants, and other unknown confounders(Trynka et al., 2015). Different statistical approaches have been designed to address these issues. Some examples include hierarchical Bayesian modelling(Pickrell, 2014), logistic regression(Iotchkova et al., 2019), permutation approach while taking into account the LD(Trynka et al., 2015) and incorporating SNP heritability(Finucane et al., 2015). Selected examples of enrichment-based software tools are provided in **Table 1**.

Statistical fine-mapping methods

Integration of GWAS with QTLs can also aid in identifying of causal variants. Approaches to identify causal variants are commonly termed as statistical fine-mapping(Schaid et al., 2018) and include colocalisation and mendelian randomisation (MR). Colocalisation analysis aims to determine if a single variant is responsible for the GWAS signal and QTL in a given genomic location. Thus, colocalisation analysis can identify putative causal SNPs and provide evidence for possible genes, tissues and mechanistic pathways involved for expression of a disorder. A popular approach for colocalisation analysis is Bayesian statistical method(Giambartolomei et al., 2014; He et al., 2013). It estimates the posterior probability for the existence of a single causal variant common to two traits of interest. High posterior probability estimate (>0.80) indicates colocalisation. Schwartzentruber et al. investigated the colocalisation between 36 risk variants of Alzheimer's disease and 109 eQTL datasets from various cell-types, tissues, and conditions(Schwartzentruber et al., 2021). A total of 391 colocalisations (posterior probability estimate > 0.80) representing 80 distinct genes at 27 loci were observed. The genes included novel genes such as *FCER1G*, *TSPAN14*, *APH1B* and *ACE*.

MR is conceptually similar to a randomised clinical trial and assesses if there is a causal relationship between a modifiable exposure (a molecular feature such as gene expression and protein expression) and an outcome (complex disease) with instrumental variables (genetic variants) affecting the exposure. MR has a strong assumption that the genetic variant is associated with the disorder only through the mediated molecular feature and is represented as *genetic variant → molecular feature →*

disorder. A study investigating the protein and gene expression levels in the brain with depression GWAS(Deng et al., 2022) through MR analysis found genetically regulated protein levels of eight genes to be causally associated with depression. Furthermore, colocalisation analysis showed the variants affecting brain protein levels (pQTLs) of six of the eight genes (*RAB27B*, *GMPPB*, *CNNM2*, *TMEM106B*, *PSMB4*, and *P2RX7*) to be colocalised with depression variants (posterior probability estimate for $H_4 > 0.80$). The authors also replicated the MR and colocalisation results using brain gene expression and eQTLs for *RAB27B*, *GMPPB*, and *TMEM106B* genes. While *TMEM106B* and *GMPPB* are known targets for depression, *RAB27B* is a novel target. Selected examples of colocalization and MR software tools are provided in **Table 1**. Both colocalisation and MR provide inference on the causal relationship between the genetic variants and disease. A significant colocalization typically implies a likelihood of a causal relationship mediated through exposure in MR; however, not vice-versa.

Imputation-based methods

The imputation-based integration method is a recently developed method that leverages the largescale GWAS and publicly available multi-omics data from databases such as GTEx and ENCODE. These methods require a reference panel of robust genetic prediction models developed using genotype data and molecular feature measurements (such as gene or protein levels) from the same healthy individuals. The prediction models are developed using different statistical methods such as LASSO, ridge regression, and elastic net (Fryett et al., 2020). Using the reference panel, the imputation-based methods impute the molecular features in a GWAS dataset and subsequently identify the association between genetically predicted molecular features with the GWAS trait to identify the trait-associated molecular features. Molecular features with significant associations are those which are significantly differentially expressed in GWAS cases compared to controls. Several ready to use software tools implementing this approach are shown in **Table 1**.

Imputation-based methods that integrates GWAS and gene expression are known as transcriptome-wide association studies (TWAS)(Wainberg et al., 2019). Thanks to the availability of large-scale gene expression data, the TWAS approach has been successfully applied to numerous psychiatric

disorders. For example, the investigation of depression using the TWAS approach identified 48 novel genes associated with the disorder(Dall'Aglio et al., 2021). Further analysis showed colocalization between eQTLs of 53 TWAS significant genes and GWAS SNPs, suggesting mediation of genetic risk of depression via gene expression regulation. Similarly, TWAS identified nine genes, of which six were novel in ADHD(Gusev et al., 2018; Liao et al., 2019). The fine mapping of TWAS hits suggested *KAT2B* and *TMEM161B* as likely causal genes. TWAS of schizophrenia identified 35 genes associated with schizophrenia risk in novel genomic loci(Gusev et al., 2018). Several such TWAS studies have been conducted in depression(Fabbri et al., 2021; Li et al., 2021), schizophrenia(Gandal et al., 2018; Zhu et al., 2016), and bipolar disorder(Gandal et al., 2018; Mullins et al., 2021). Recently, imputation-based integration has been replicated for other features such as DNA methylation(Freytag et al., 2018) and protein levels(Brandes et al., 2020; Wingo et al., 2021). However, the imputation-based integrations of DNA methylation, proteins and other omics are yet to be employed widely like TWAS.

It is important to mention that while integrative analysis using GWAS is popular in psychiatry, integration of transcriptomics, epigenomics, and other omics using similar enrichment-based methods are also conducted. Often in such studies, the results obtained from the analysis of two or more omics independently are integrated through overlap analysis(Lin et al., 2021; Xie et al., 2021) and correlation analysis(Bam et al., 2016; Fan et al., 2022; Zhao et al., 2022). Such studies can provide details on the cross talk between different omic layers occurring during pathogenesis. For example, Fan *et al*.(Fan et al., 2022) conducted integrative analysis of intestinal microbiota, serum metabolome, and serum inflammatory cytokines in 63 schizophrenia patients and 57 healthy controls. The authors using weighted gene co-expression network analysis(Langfelder and Horvath, 2008) identified 18 and co-abundance clusters of metabolites and gut bacteria, respectively. Both abundance groups showed association with cytokines. Correlation analysis between the cluster groups of metabolites and gut bacteria identified 15 metabolite groups significantly correlated with nine gut bacteria groups, indicating certain bacteria might affect inflammatory cytokines by modulating host metabolites. Such analysis also showcases that integrative analysis can conducted using omics data measured

specifically for a network of biological pathway of interest especially since several subsystems like the gut-brain and gut-immune axis have become focal themes in psychiatric research(Cryan et al., 2019).

Table 1: *Selected software tools for integrating GWAS with other omics*

Tool	**Omics**	**Reference**
Enrichment-based methods		
DEPICT	GWAS variants + Gene expression data	(Pers et al., 2015; Watanabe et al., 2017)
fGWAS	GWAS variants + functional annotations	(Pickrell, 2014)
FUMA	GWAS variants + functional annotations	(Watanabe et al., 2017)
GARFIELD	GWAS summary statistics + functional annotations primarily from ENCODE and roadmap Epigenomics	(Iotchkova et al., 2019)
GoShifter	GWAS variants + functional annotations	(Pickrell, 2014; Trynka et al., 2015)
Statistical fine-mapping tools		
Coloc	Colocalisation	(Giambartolomei et al., 2014)
EpiColoc	Colocalisation analysis for epigenomics variants	(Zhou et al., 2020)
HyPrColoc	Colocalisation analysis for multiple traits	(Foley et al., 2021)
SMR/HEIDI	Mendelian randomisation	(Zhu et al., 2016)
Imputation-based tools		
EpiXcan	GWAS Summary statistics + Gene expression while taking into consideration DNA methylation regulation	(Gusev et al., 2016; Zhang et al., 2019)
EstiMeth	GWAS Summary statistics + DNA methylation	(Freytag et al., 2018)
FUSION	GWAS Summary statistics + Gene expression	(Gusev et al., 2016)

MOSTWAS	GWAS Summary statistics + Gene expression while taking into consideration DNA methylation regulation	(Bhattacharya et al., 2021)
S-PrediXcan	GWAS Summary statistics + Gene expression	(Barbeira et al., 2018)

2.2 Machine learning methods

ML methods offer ever-increasing potential for holistic understanding of complex systems and may contribute for achieving to personalised treatment for mental disorders. The application of ML in psychiatric research is well established through numerous studies using single omics data. For example, a recent study(Enrico et al., 2021) used ML algorithms to distinguish between three patient groups based on immune profiles: first-episode psychotic patients, patients affected by chronic psychiatric disorders with psychosis, and healthy controls. The authors included immune-markers as predictive omics and demonstrated notable classification accuracy. In another example, ML was successfully used to identify a subgroup of schizophrenic patients (first episode and drug-naive) based on functional brain connectivity(Cao et al., 2020). During model development, some ML methods like tree-based models and penalised regression were used for feature selection i.e., selection of predictive biomarkers. These successful applications show that there is a lot of potential to utilize advanced ML methods for multi-omics data in psychiatric research.

In the following, we introduce the main ML methods, commonly employed in the area of multi-omics analysis for psychiatric disorders and refer to some of their concrete applications. A summary of those methods, their application area, and the multi-omics data that was used, can be found in **Table 2**. These ML methods include penalised regression(Joyce et al., 2021), principal component analyses(Campeau et al., 2022), trees-based methods such as Random Forests (RFs) and decision trees(Bhak et al., 2019), as well as clustering methods such as K-means or Gaussian mixture models(Athreya et al., 2018). Examples of ready to use multi-omics integration tools incorporating such methods include similarity network fusion(Wang et al., 2014), iclusterBayes(Mo et al., 2018), and mixOmics(Rohart et al., 2017). A rather newly introduced method, that lends itself well for

applications that require an integration of multi-modal data are Graph Neural Networks (GNNs). They enable ML to be directly applied to data structures like graphs and networks are therefore used frequently for multi-modal datasets such as multi-omics. MOGONET (Multi-omics graph convolutional networks)(Wang et al., 2021) is an example of a graph-based multi-omics integrative method for biomedical classification. The authors show that it outperforms previous state-of-the-art methods due to the additional utilisation of the interconnectivity of the data. Broadly, multi-omics integration through machine learning has three major applications: diagnostic classification, prognostic (natural outcome), treatment response. The following sub-sections introduce some successful applications of ML methods to integrate multi-omics data in those areas of psychiatric research.

Diagnostic Classification

One key application is diagnostic classification based on omics and/or clinical data. This involves the correct assignment of patients into pre-defined classes that represent psychiatric diagnoses or accurate differentiation between patient groups. Psychiatric disorders share genetic and environmental risk factors, symptoms, and comorbidities. Hence, it is pertinent to develop tools that assist in guiding diagnosis formulation, so appropriate treatment can be provided to each patient. Xie *et al*.(Xie et al., 2021) used gene expression and DNA methylation data to identify genes that exhibited upregulated expression and hypo-methylation, and down-regulated expression and hyper-methylation in major depressive disorder (MDD) compared to healthy controls using differential expression/methylation followed by overlap analysis. Next, using the identified genes and random forests, diagnostic models to distinguish between MDD and healthy controls were developed independently based on gene expression and DNA methylation data. The gene expression classifier showed better predictive power compared to DNA methylation classifier. Similarly, Bhak *et al*.(Bhak et al., 2019), also used gene expression and DNA methylation to develop random forests model to differentiate individuals with MDD, suicide attempters (SAs), and healthy controls. The models displayed high accuracies to distinguish SAs from MDD, MDD from healthy controls, and SAs from healthy controls, respectively. The upside are very promising results calling for replication in large multi-centric

studies, whereas overfitting and generalisability still remain methodological challenges(Manchia et al., 2020). Statistical control of ML analyses e.g., via permutation tests against chance-level, pre-selecting features, or applying regularisation constraints can be used to address the aforementioned challenges(Manchia et al., 2020).

A sub-area of diagnostic classification is disease subtyping which focuses on employing ML-based clustering techniques for identification of subgroups of psychiatric disorders. Psychiatric disorders are typically diagnosed in a symptom-guided manner to define categorical groups. Interest in the detection and exploration of data-supported subgroups has increased recently, particularly in terms of subtypes showing defined biological features. The clustering can be performed using a variety of data such as multi-omics data, clinical, and/or MRI data. Successful subtyping based on clinical and multi-omics data has been carried out for autism spectrum disorders (ASD). For more details about these approaches, we for example refer to a review by Higdon et al.(Higdon et al., 2015).

Outcome and risk prediction

The second key application of ML in multi-omics analysis for psychiatric disorders is generating a prognosis for a subject which intends to predict the natural outcome. One main application is hereby risk prediction. Informative molecular features associated with a disease or trait can be prioritised through single omics analyses or the aforementioned integration approaches or through ML-based feature selection approaches. The identified features can then be used to develop statistical models to predict individual risk. For example, using genetic variants associated with other molecular features in a polygenic score for risk of a disease can be estimated. In such cases, the risk score for an individual is estimated as a sum of risk SNPs the individual has, weighted by the GWAS effect size of the risk SNP. ML methods used to predict the risk scores include penalised regression methods such as LASSO, elastic net, ridge regression or Bayesian approaches(Joyce et al., 2021; Tasaki et al., 2019). A variation to this approach includes development of PRS scores using GWAS SNPs followed by association testing between PRS scores and other omics(Mooney et al., 2020; Tasaki et al., 2019). However, the implementation of risk prediction models is a big challenge, only less than 1% of risk prediction models are implemented in clinical practice(Oliver et al., 2021; Wang et al., 2020).

Treatment response prediction

The third main application area of ML in multi-omics settings is the prediction of patients' response to treatment for example, the response to pharmacotherapy, psychotherapy, psychopharmacotherapy, or neurophysiological stimulation. Prognosis, relapse, or diagnosis can also serve as outcomes of the respective ML models. Joyce *et al.*(Joyce et al., 2021), examined the utility of genomics and plasma metabolomics to predict the outcomes of combination pharmacotherapy to treat MDD. Here, the authors built two models—metabolomics only and metabolomics with genomics (multi-omics)—to predict treatment response. Penalised linear regression and XGBoost algorithms were used to build the models. The authors reported a higher AUC measure for multi-omics models compared to models utilising metabolomics data only. This suggests that multi-omics data achieves accurate predictions of treatment response across classes of antidepressants. In two meta-reviews of unipolar depression (MDD), the authors report combined multi-omics and clinical approaches to identify predictors of treatment response in MDD(Gillett et al., 2020; Perlman et al., 2019). Further examples include reviews on pharmacogenomics by Lin *et al*. (2020)(Lin et al., 2020) and van Westrhenen *et al*. (2020)(van Westrhenen et al., 2020). The authors review studies that use ML to investigate the role of genomic data in the effects of psychotropic drugs for the treatment of MDD (antidepressants) and bipolar disorder (lithium). They suggest that ML should already be taken into account when planning future clinical trials using multi-omics and connectomics. Exome sequencing may be also combined with clinical data using a gradient boosting algorithm, a study on treatment-resistant depression reached an AUC of 0.75 for extreme genetic percentiles genetic predictors plus a clinical score(Fabbri et al., 2020).

Similar studies have been conducted on other mental disorders for instance, in treatment-resistant schizophrenia as reviewed in Pisanu and Squassina, 2019(Pisanu and Squassina, 2019). For a comprehensive overview across different psychiatric diseases and treatment types, such as medication, psychotherapy, neurobiological treatments (TMS; ECT), and digital interventions, see Chekroud *et al*., 2021(Chekroud et al., 2021).

Table 2: *Selected machine learning methods and their application in psychiatry*

Machine learning method	**Omics data integrated**	**Psychiatric disorder**	**Reference**
Clustering	Genomics, metabolomics	Depression	(Athreya et al., 2018)
Graph neural networks	Genomics, transcriptomics, epigenomics	Alzheimer's Disease	(Wang et al., 2021)
	Genomics, transcriptomics, proteomics	Autism spectrum disorder	(Higdon et al., 2015)
	Genomics, proteomics	Autism spectrum disorder	(Zhang et al., 2020)
Penalised regression	Genomics, plasma metabolomics	Depression	(Joyce et al., 2021)
Principal component analysis	Proteomics, metabolomics	Schizophrenia	(Campeau et al., 2022)
Linear models	Genomics, epigenomics	Attention deficit hyperactivity disorder	(Mooney et al., 2020)
Linear/logistic regression	Genomics, transcriptomics, epigenomics, proteomics,	Dementia	(Tasaki et al., 2019)
Random forests	Transcriptomics, Epigenomics	Depression	(Bhak et al., 2019)
	Genomics, transcriptomics, epigenomics	Depression	(Xie et al., 2021)

3. Multi-omics based functional enrichment using model systems

Understanding disease mechanisms aids better diagnosis and treatment of psychiatric diseases. Post-mortem brains provide the ability to directly study the brain tissues to identify disease-related cellular and molecular alterations. However, obtaining well characterised, high quality, and sufficiently large samples and deriving causal inferences has many challenges. Omics studies from model systems including human cell lines and animals can aid in overcoming the limitations and provide useful insights into psychiatric disease aetiology and mechanisms.

3.1 Human cell lines

Advances in stem cell technology has led to the development of disease models based on novel, cutting edge induced pluripotent stem cells (iPSCs) technology. iPSCs are somatic cells that have been reprogrammed to a pluripotent stage and can be triggered to differentiate into all human cell types including neurons, fibroblasts, keratinocytes, and epithelial cells derived from urine and hair follicles. iPSCs and the derived differentiated cells retain the genetic signature of the donor. Thus, iPSCs from patients or high-risk individuals represent relevant disease models and hence, can be subjected to experimental manipulation and drug testing. Furthermore, iPSCs allow the study of development and function of live human cells which is not possible in animal models. iPSC models combined with multi-omics analysis could aid in gaining insights on pathogenesis as well as determining therapeutic efficacy of potential drugs.

iPSC models have been applied to a range of psychiatric disorders including autism, schizophrenia, bipolar disorder, and Rett syndrome(Marchetto et al., 2017; Quadrato et al., 2016). Marchetto et al. (Marchetto et al., 2017) derived iPSCs, neural progenitor cells and neurons using skin fibroblasts from ASD individuals with early brain overgrowth and non-ASD controls with normal brain size. The authors found increased cell proliferation of neural progenitor cells of ASD individuals because of dysregulation of a β-catenin/BRN2 transcriptional pathway. Weighted correlation analysis of gene expression of derived neurons identified clusters overrepresented with genes that showed ASD-associated copy number variations and genes affected by ASD-associated protein-disrupting and

missense rare *de novo* variations. These clusters were also found to be significantly associated with ASD status. Provencal *et al*.(Provençal et al., 2020) used human fetal hippocampal progenitor cell lines to measure the molecular changes upon exposure to glucocorticoid, a stress hormone, during neurogenesis. The authors estimated 27,812 DNA methylation sites and 3,857 gene expression transcripts to be dysregulated and further demonstrated lasting changes in epigenetic and transcriptional profiles of genes(Provençal et al., 2020). Another study verified the importance of Wnt signalling pathway in the pathogenesis of neuropsychiatric disorder through integrative analysis of genomic, transcriptomic, and epigenomic data of iPSCs converted to induced neurons from the same individuals with 15q13.3 microdeletion and matched controls(Zhang et al., 2021). Omics data from human-derived cell lines have also been used to develop biomarkers that predict treatment response to antipsychotics. Readhead *et al*.(Readhead et al., 2018) identified drugs that reverse schizophrenia-associated transcriptomic signatures by integrating transcriptomic data from human iPSCs and chemogenomic data; thereby, proving the importance of transcriptomic-based drug screening in psychiatry. While iPSC-based disease models provide a suitable representation of the disease especially if they are derived from patient and disease-relevant tissues, their use can be limited as most complex diseases are likely caused by interaction between multiple cell types. Other caveats associated with iPSCs and derived cell lines include artifactual heterogeneity, due to factors such as somatic mosaicism in donor cells and de novo mutations occurring during cell reprogramming, loss of epigenetic modifications, and the developmental immaturity of iPSC-derived neurons(Vadodaria et al., 2018). Newer approaches to development of disease models include using brain organoids that more closely resemble the cells' natural environment and in vivo cytoarchitecture. Such models allow modelling brain development and brain diseases and providing an alternate to the 2D iPSC models(Shou et al., 2020). Such methods have been applied in psychiatric disorders(Forsberg et al., 2018; Raja et al., 2016); however, to understand the complexity and communication between different systems in psychiatric disorders, multiple organoids such as brain and gut organoids can be investigated together to recapitulate brain-gut interactions(Kim et al., 2020).

3.2 Animal models

Compared to human studies, animal models have several advantages, including easier manipulation of environmental factors, reproducibility, accessibility and availability of relevant tissues and replicates for diseases. Animal models are valuable to study the neurobiological basis as well as for the development of new biomarkers and drug targets for psychiatric disorders(Scarpa et al., 2020). Preclinical animal models allow for rapid monitoring of disease progression(Jones et al., 2011), permit invasive studies of structural and molecular changes across development of the disorder, and allow for testing of potential therapeutic agents and targets. Still, animal models are limited by their genetic background, and complexity of accurate disease phenotyping, especially for neuropsychiatric disorders(Nestler and Hyman, 2010). Therefore, studies that combine both human cell lines and animal models are an elegant approach to multi-omics insights into disease. One such study(Misiewicz et al., 2019) investigated well-characterized mouse model of chronic social defeat stress (CSDS) in two inbred mouse strains, C57BL/6NCrl (B6) and DBA/2NCrl (D2). The authors conducted genome-wide integrative analysis of gene expression, and microRNA expression and protein abundance in the bed nucleus of the stria terminalis and identified involvement of mitochondrial pathways in stress response. Validation analyses based on gene expression of mice and human blood cells after exposure to chronic stress confirmed the dysregulation of mitochondrial pathways. Similar patterns of differential expression of mitochondrial-related genes and proteins were found in both mice and humans. These findings were further strengthened by differences in specific microRNAs and demonstrated the role of mitochondrial-related gene expression changes in stress-related behaviours and suggest that chronic stress may critically affect cellular energy metabolism.

Interventional methods such as optogenetics, which combines genetic and optical methods to cause or inhibit well-defined events in specific cells of living tissue or animals, offer alternatives to establish causative pathways between genes and behaviour(Deisseroth, 2015). There will also be a need to model developmental effects and the variability of phenotypic outcomes (genetic background, environmental exposures).

4. Clinical translation from bench to bedside

Bedside translation and integration are hoped to increase the practical benefit for patients and clinicians. In recent times, omics data and machine learning techniques have typically been used in clinical settings, for instance to identify biomarkers for mental illness, predict treatment success, cluster subgroups of disorder, and to make data-driven distinctions between patient groups. This section presents results and ideas on how integrated multi-omics data and ML models can be combined with clinical research and translated from bench to bedside. An important consideration for further research is the in-depth evaluation of the cost-effectiveness of multi-omics ML tools, which would go beyond the scope of this review. Further challenges and limitations are discussed in section 5; the interested reader might also refer to Tarazona et al. (2021)(Tarazona et al., 2021).

With the aim of discussing clinical application possibilities, we summarise recent research and cluster our suggestions in three thematic areas: (1) multi-omics model design for bedside translation, (2) computational training for psychiatrists, (3) translation from bench to bedside to large social groups.

4.1 Multi-omics model design for bedside translation

The question of design and usability of algorithms/tools poses a key challenge for the application of multi-omics data integration and advanced statistical and machine learning models in the clinical setting. The acceptance of such models among clinical psychiatrists is yet moderate(Bourla et al., 2018). We therefore postulate the following characteristics for these methods, in particular for ML-based models, to increase trust and acceptance among clinicians and facilitate bedside application: a) data availability, b) clinical applicability and explainability, c) utility, d) scalability, and e) transferability.

Data availability

Development of reliable and robust multi-omics models require largescale data sets. While genomics data is widely available for various psychiatric disorders, there is a paucity of other omics data. Currently this gap is being filled by international consortia, such as PGC, ECNP, and UK Biobank, which investigated multi-omics sequencing of various disorders. Easy access to largescale health data

including multi-omics and phenotypic data is crucial as data sharing is the key step for transparency, scaling, rapid discoveries and translation(Conroy et al., 2019). A recent review by Dong *et al*.,(Dong et al., 2021) summarises the multi-omics resources for human disorders. Often during development of a ML model, a dataset for training and testing, as well as a blind independent dataset for validation, are required. Both these datasets need to be sufficiently powered, particularly the dataset used for training and testing. This is due to the high dimensional nature of multi-omics datasets and the consequent 'curse of dimensionality', which can lead to unreliable models in small datasets. Hence, while generating new multi-omics datasets, it is important to sequence sufficiently large samples to develop meaningful and reliable models. Partnering with hospitals and clinicians can overcome this limitation to ensure regular inclusion of newer data to models to improve accuracy and prediction.

Clinical applicability and explainability

Clinicians are most likely to use software tools they understand and trust to protect their patients. Therefore, advanced diagnostic or predictive models should be applied in a way that their output can be easily and unambiguously interpreted by psychiatrists and other clinical professionals. To increase bedside application, it is necessary that clinicians are part of setting up comprehensive models that are easy to use. Therefore, intrinsically interpretable models like regression and random forests have been used to increase interpretability in medical decision support in a variety of applications(Byeon, 2021; Müller and Lio, 2020; Vázquez et al., 2021). More complex ML methods, however, are known as 'black box' approaches, as only the input and output of a model are known, while the internal learning processing remains hidden or hard to interpret. There is a high risk of rejection of multi-omics diagnostic and/or treatment prediction models employing such methods. White box techniques allow direct insight into internal learning mechanisms and the steps from input to output can be easily traced; thus, offering a high degree of explainability, which might stimulate clinical uptake. Grey box approaches combine white and black box internal mechanisms. While efforts are made or improving explainability, there is still a lack of generally agreed-upon metrics that evaluate explainability(Chekroud et al., 2021).

Increased interpretability can also be achieved through simplification or feature restriction, feature ranking, and simply the use of clinical language and clear visualization of model outputs. For example, a recent study presented meta-modelling as a method to facilitate interpretation through simplified ML models with at most half of the number of features compared to original ML models(Weyant and Brandeau, 2022). Class-contrastive reasoning has also been applied to create more interpretable ML models in the prediction of mortality of schizophrenia patients(Banerjee et al., 2021). Another example is usage of attention mechanisms, which have for example been explored to identify the impact of different factors to outcome of the algorithm. Yang *et al*.(Yang et al., 2019) explored the application of attention graph networks to identify bipolar disorder by investigating attention maps and gradient sensitivity of nodal features.

While easy to interpret models have clear advantages, they often lead to decreased performance. This highlights a potential dilemma of interpretable multi-omics models: simplification vs. accuracy. For a comprehensive review on interpretation of deep neural networks, see Sheu, 2020(Sheu, 2020). Another active research area with the goal of increasing clinical applicability of ML models is the implementation of human-in-the-loop concepts, where experts can influence the decision-making process of ML models. For a more detailed review refer to Budd *et al*.(Budd et al., 2021).

Utility

Utility stands for a) the practical benefit that clinicians receive using multi-omics models (e.g., reduction of further tests, reduced time for diagnosis/prognosis formulation/treatment, recommendations) and b) high usability of multi-omics software applications. While scientists focus on model performance, accuracy and knowledge gain on a formal level, a user-friendly Graphical User Interface (GUI) must be the next step taken towards clinical practice. In the multi-omics research field, currently the majority of the ready to use tools are command-line based. For the development of such GUIs, the needs of users, i.e., clinicians, must receive detailed attention. Yet, there is little mention of usability, GUIs, or user-friendly frontends within research articles. User experience and usability should also be considered from the initial developmental phase of the model. For the

translation from bench to bedside, the multi-omics models must therefore be embedded in user-friendly software applications adapted to the needs of clinicians.

There are promising possibilities for the application of ML-based models once prerequisites for independent use of the trained models (e.g., external validation, implementation trials) are provided(Chekroud et al., 2021). Clinical Decision Support Systems (CDSS) apply machine learning and active knowledge management to offer clinical advice for medical professionals. CDSS applications seem a very promising ML technology in the context of precision psychiatry but have not yet reached psychiatric practice. A recent review presents findings in multi-omics integration in ASD and the (theoretical) usage as biomarkers in CDSS for patient stratification and treatment(Richter et al., 2021). In depression and anxiety disorders, an attempt for a mechanism-based clinical diagnostic support system has recently been made(Richter et al., 2021). A random forest classifier was used to diagnose patients based on their cognitive performance. In sum, we are still in the early stages of developing CDSS in precision psychiatry. For widespread use of CDSS during clinical practice, the underlying ML models must satisfy performance criteria and, as a further step, the development of a user-friendly front-end is needed. Powerful predictions delivered via intuitive GUIs should together increase the clinical advantages of CDSS.

Scalability

Scalability constitutes a desirable characteristic of multi-omics analysis as well as ML algorithms and other computational tools. In systems science, scalability means the 'ability of a system to accommodate an increasing number of elements or objects, to process growing volumes of work gracefully, and/or to be susceptible to enlargement'(Bondi, 2000). In the field of psychiatry, scalable ML techniques seem important in the following ways. First, scalability of the psychiatric entity of interest; this refers to the development of models based on algorithms that are suited for diverse psychiatric entities such as multiple omics, single-cell level, organoids, animal models, single human case studies, up to clinical trials. Second, scalability of integrated data types; this requires statistical and ML methods for the multi-systemic integration of multi-omics data and other data, such as neurophysiological time-series data, clinical rating data, as well as medical report text files or

ambulatory data as collected through wearable devices. Third, scalability of the clinical target group; this leads from individual patients to group therapy, from acute psychiatric to outpatient settings to relapse prevention for specific patient populations and preventive measures for the general population. When developing ML algorithms and models for psychiatric clinics, it is crucial to keep scalability in mind, as highly scalable multi-omics models remain flexible and extendable. Scalability is not a prerequisite; however, it is gaining increasing importance in current research.

Transferability

Transferability means that it should be made as easy as possible for clinical professionals to use scientifically developed multi-omics statistical/ML tools. In addition to the above-mentioned user-friendly GUI, this also includes easy usability on local clinical IT systems. Browser-based applications are ideal if clinicians want to work independently of operating systems; the development and installation via version control systems (e.g., GitHub, GitLab, Gitea) create transparency and trust. Conversely, if multi-omics models require training data to be collected during daily clinical practice, this process should also be designed in a user-friendly manner and/or automated involving clinical staff already at the stage of development. It may sound trivial, but, in clinical practice, it is often precisely these hurdles that prevent staff from accepting and using new technologies.

4.2 Computational Training for Psychiatrists

Computational training of clinical professionals counteracts user-friendly design of multi-omics tools. Of course, not all clinical professionals can be computer scientists; moreover, software should ideally be usable by the end user without a technical or mathematical background. However, we believe that the development of clinically usable ML technologies can be promoted if more clinical professionals actively engage with and learn about them. We encourage clinicians to educate themselves in the field of multi-omics data and integration approaches. Ideally, this education includes technological knowledge and basic computational skills, e.g., data handling, programming concepts, logic and abstract thinking, and mathematical problem formulation. It enables clinicians to a) understand the nature of multi-omics data, b) formally define integration problems, c) apply advanced statistical and

ML-based technology in patient care and interpret as well as communicate their results to patients. While understanding the nature of multi-omics data places the least demands on current clinical training - because a biomedical background is already part of medical training; the latter points are more challenging. The benefits of technically trained clinical staff are apparent: When clinical professionals become more technologically and mathematically proficient, it is likely to increase acceptance of advanced multi-omics tools(Bourla et al., 2018). Trained clinicians are probably more likely to use advanced technologies frequently, gain real benefits from them, and help to increase patients' trust in technologies. At the same time, computational training for clinicians creates synergies among bioinformaticians, data scientists, and clinicians. When used increasingly during clinical practice, multi-omics models can be improved through regular input of real-time data and may consequently increase their performance and generalisability. Moreover, if clinicians themselves can formulate the processes and problems in everyday clinical practice as logical or mathematical problems, they can more easily stimulate further research with their ideas. However, traditional training for psychiatrists and other professionals in psychiatric care, e.g., clinical psychologists, psychotherapists, nurses, physiotherapists, usually includes little or no courses on computations or technology. These are more likely to be found in specialised postgraduate programmes, which often lay the foundation for a career in science. Their courses could as well be opened for clinical training. Those who work both scientifically and clinically, as well as technically interested clinicians, could take on the role of facilitators for bench to bedside transition.

4.3 From Bench - to Bedside - to Large Social Groups

Psychiatric research has the potential to develop advanced multi-omics models into clinical applications and beyond for the benefit of large social groups. Such social groups may include patient populations or subgroups of diseases, but also span towards the mental health of the public. This raises the question of how individual-based medicine using multi-omics data, single-cell, or organoid models, can stimulate research on large social groups. It is worth striving for developing largescale ML models that can connect individual-based psychiatry and population-based psychiatry and enable mutual translation of findings. The so-called digital phenotyping serves as example from a

biopsychosocial perspective. The term has been introduced as the ‘moment-by-moment quantification of the individual-level human phenotype in-situ using data from smartphones and other personal digital devices’(Torous et al., 2016). Digital phenotyping allows for individual, yet naturalistic data assessment scalable to large groups(Taliaz and Serretti, 2022) There is ample research on digital phenotyping methods and tools. For instance, Sequeira *et al*.(Sequeira et al., 2019) provide an overview of digital phenotyping in the context of childhood and adolescent depression. Another interesting use case is provided on autism using crowd sourcing(Washington et al., 2020). The aim of the study was to create a high-quality, yet naturalistic labelled data set suitable for supervised ML. The authors recruited participants via crowd sourcing platforms to rate the behaviour of children with ASD. These naturalistic ratings were then fed into an ML algorithm to determine the quality of ratings and their diagnostic accuracy. Results were promising with varying degrees of data quality and thus called for specific recruitment strategies(Washington et al., 2020).

5. Application of multi-omics in psychiatry – pitfalls and next steps

Psychiatric disorders are classified according to diagnostic categories with a broad range of symptoms, but patients with the same diagnosis typically present a great clinical heterogeneity. This clinical heterogeneity together with the incomplete knowledge of the biological mechanisms underlying psychiatric disorders and comorbidity of psychiatric disorders with other disorder, have so far contributed towards the limited efficacy of current treatments. Given the complexity of genetic and environmental interplay in psychiatric diseases, single methods or single-level data make it impossible to fully capture dynamic characteristics of the development and progression of the disorders. Translation of research from bench to bedside will require a combined effort from multidimensional omics datasets, larger studies, deeper clinical and biological phenotyping of the disorders, and more integrated models. Multi-omics integration of data provides one such avenue to identify biomarkers in psychiatry to facilitate stratification of patients within a diagnosis, allowing more focused treatment options. Still, several challenges remain in multi-omics research on psychiatric disorders, as outlined below.

5.1 Challenges of multi-omics research in psychiatry

A key challenge multi-omics research is knowing where to start. Different approaches have been outlined including genome-first, phenotype-first, and environment-first, although most of the multi-omics research has so far focussed only on the genome-first method. Another issue of multi-omics studies in psychiatry has been the focus on European populations. Given the ethnic differences in multi-omics markers, it is important to generate more multi-omics resources and findings for less represented ethnic populations to reduce the health disparity across groups and find universal biomarkers for psychiatric disorders. Outlined below are specific challenges faced during each step from biomarker discovery to clinical implementation of multi-omics research.

Biological sample and sequencing challenges

Tissues involve several cell types, each having a unique omics profile and depending on the location of a tissue sampled (e.g., sections of brain), or an individual's physiological condition (e.g., peripheral leukocytes after acute infection), proportions of multiple cell types within a tissue sample can vary substantially, causing cell heterogeneity, affecting the levels of the biomarkers, and leading to associations related to cellular differences rather than the disease. Statistical methods have been developed to adjust for potential confounding effects due to cell-type heterogeneity and are now routinely used in omics research(Houseman et al., 2012; Houseman et al., 2014) yet it is not fully known if this statistical correction accounts for the cell differences or even over-corrects some of the true biological effects. Ideally, omics profiles in each distinct cell type should be measures, so called single-cell omics but this is often unrealistic due to costs and amount of material required to assess all cell types. Multi-omics studies using single cells will likely help addressing the major unanswered question of which cell types should be studied in modelling psychiatric disorders.

Technical artefacts such as sampling and batch effects occur during sequencing. While the genetic data are relatively robust to the technical artefacts, other omics data which are dynamic in nature are highly sensitive to technical artefacts. Ensuring that comparison groups and data are processed in a similar fashion and at the same time, if possible, reduces such technical variation and provides more

confidence in multi-omics data. In terms of biological variation, tissue and cell-type specificity led to two important issues in multi-omics studies, selection of tissues and cell types, and heterogeneity of tissues. Due to ease of accessibility, blood-based specimens such as plasma, serum, and leukocytes are often used in omics association studies of psychiatric disorders due to the limited access to other disease-relevant tissues (e.g., brain). Although the use of blood as surrogate tissue is sometimes relevant (e.g., autoimmune diseases and inflammatory processes), the biological relevance of blood-based omics profiles for psychiatric disorders is often questioned. There is some evidence that several blood-based omics markers share similar profiles as brain-based omics markers(Smith et al., 2015), suggesting the use of blood as a surrogate tissue in psychiatry. Still, other consortia studies have demonstrated that there are distinct patterns of omics profiles across tissues and cell types(Kundaje et al., 2015). Using blood-based specimens is a convenient start for searching novel disease-related biomarkers, however, using blood as a surrogate tissue requires cautious validation and interpretation when the study aims to develop biomarkers for clinical use or to unravel disease mechanism.

Data challenges

Multi-omics data generated using different platforms often have different formats and require to be pre-processed using common validated methods to allow efficient integration of data(Subramanian et al., 2020). Such pre-processing is hindered by the lack of universal standards and can influence the integrative analysis. There exists some comparative analysis of integration tools(Rappoport and Shamir, 2018; Sathyanarayanan et al., 2020), but more comprehensive studies are needed to integrate the biological data with the clinical data and provide a standard and robust multi-omics pipeline. All individual omics datasets might not have the four v's associated with integration of 'big data', namely volume, variety, velocity, and veracity, hence pose similar challenges, especially in large-scale human studies. For high-dimensional datasets of over 1000 variables, the 'curse of dimensionality' is a critical issue, with large and sparse variances among samples(Ronan et al., 2016), further posing challenges in the interpretation of integrated omics datasets.

Integration method challenges

Methods integrating GWAS with other omics provide a wealth of information with respect to the functional role of GWAS variants, putative causal variants and genes, and novel biomarkers. It is becoming clear that investigation using a single integration approach is not sufficient. The different approaches provide complementary information and thus, a holistic understanding of the complex mechanistic interactions between the various omics. However, these approaches are not without limitations. One of the main challenges in enrichment-based methods is the bias in enrichment estimate that can be caused due to linkage disequilibrium, colocalisation of multiple functional variants and unknown confounders(Trynka et al., 2015). With respect to fine-mapping and imputation-based methods, these methods are sensitive to the accuracy of the reference linkage disequilibrium matrix which is a necessary input. Thus, it is important to use accurate and population-matched linkage disequilibrium information. This is particularly important when focusing on development of biomarkers to ensure maximum applicability in target population. In addition, imputation-based methods also rely on genetic reference models for a molecular feature such as gene expression or methylation. Obtaining genetic models for molecular features other than gene expression is challenging. Caution must be used when investigating tissues with no clear mechanistic relation as the architecture of QTLs vary substantially across tissues(Consortium, 2020). and. We also advise the readers to familiarise with the biological assumptions, statistical limitation and computational limitations specific to the software tools prior to use.

ML is a fast-evolving field with ever increasing opportunities for application in psychiatry. One major challenge is the limited availability of multi-omics data for research and biomarker development in psychiatry. This shortage imposes limitations on the validation of models using an external dataset to make the developed models generalisable. Indeed, a recent systematic review found that only 5% of all clinical risk prediction models is externally validated in psychiatry(Meehan et al., 2022; Salazar de Pablo et al., 2021). Differences between study designs, variable types, and samples characteristics are obstacles in the search of suitable data sets for external validation(van Bronswijk et al., 2021). Longitudinal multi-centre studies (e.g., UK Biobank(Bycroft et al., 2018), EMBARC(Trivedi et al., 2016)) and pre-registered studies with detailed protocols published before study conduction appear

especially suited for external validation. Even though such multi-centre studies have been collecting multi-omics, neuroimaging, and clinical data, scientists set their focus on the analysis of subsystems interactions (e.g., behaviour and clinical data, brain-behaviour, brain-gene, brain-gut, gut-immune axis). This could partly be contributed by the multi-modality of the datasets. Different data types need to be transformed into one usable format for ML methods to recognise the underlying patterns and relevant features contributing to the patterns. However, to obtain an overarching understanding it is important to embrace multi-systemic ML approaches to understand psychiatric diseases more holistically. In patient-specific ML models, which aim to enable precision medicine, ideally, multi-omics and clinical data should be combined to identify the best possible treatment for individual patients. One example from clinical research is the Patient Advantage Index (PAI). PAIs indicate individual treatment recommendations and constitute a clinically tailored application of ML. In a study on MDD, an ML-computed PAI identified about 31% of the clinical sample who would benefit from a specific antidepressant treatment compared to placebo(Webb et al., 2019). Those identified patients who also actually received pharmacotherapy showed indeed lower depressive symptoms than placebo.

Implementation challenges

A primary challenge is the lack of psychiatric staff(Butryn et al., 2017). Increased burnout and emotional exhaustion are often reported by psychiatric staff(Korkeila et al., 2003). Furthermore, there is an increasing demand for psychiatric care concurrent with limited financial resources and rising healthcare costs(Butryn et al., 2017). The current COVID-19 pandemic has also contributed to increasing psychiatric demands among COVID-19 patients and healthcare workers(Hossain et al., 2020). Despite this, there unwillingness in general among psychiatric staff to adopt new methods either due to lack of time or proneness of psychiatrists to focus more on social interaction than multi-omics results. The use of advanced tools like CDSS which can offer clinical advice, may help psychiatric staff care for more patients in lesser time and costs.

Policy, privacy, and fairness challenges

Potential challenges exist in the application of the developed automated multi-omics prediction models for the general population. Several surveys have shown that there is distrust of advanced technology and fear of abuse of personal data among the public(Kieslich et al., 2021). In effect, the European commission and the UK have provided clear guidelines on the use of automated decision-making tools. These guidelines have been developed for safe, sustainable, and ethical use of automated decision-making models. We recommend researchers adhere to policies and ensure the safety and validity of the multi-omics models prior to implementing in a clinical set-up. Furthermore, privacy and fairness concerns need to be addressed carefully, ensuring the protection of sensitive (patient) data(Kaissis et al., 2020) as well as fair model performances across diverse groups of individuals(Chen et al., 2021).

5.2 Future directions

Measuring the genome as a static entity has several disadvantages as both genetic and environmental factors contribute to psychiatric disorders. Such a static genome is limited in its ability to capture time-varying changes caused by environmental and/or physiological conditions. Through a multi-omics approach, several modalities such as epigenomics, transcriptomics and metabolomics complement genomics data by providing dynamic trajectories in genes, pathways and networks associated with environmental exposures and disease progression. Yet these complex models may paradoxically be more difficult to implement in clinical practice or too expensive, these caveats should be addressed.

Ideal datasets for integrative multi-omics analyses would include different omics data collected from the same set of individuals. Often this is not possible, given the costs or inaccessibility to tissues. Several international consortia and national biobanks have been established aimed at filling this major gap in psychiatric research, including the Psychiatric Genomics Consortium (PGC), the ECNP and the UK Biobank, which collect not only detailed phenotypic data but are increasingly collecting biospecimens for measuring different omics biomarkers. Despite the appealing scientific gain, the implementation of multi-omics studies has been hampered mainly due to the lack of feasible technologies for large-scale population studies, availability of biospecimens, and the high cost

attached to them, as well as for black -box development of algorithms that are too complex, expensive or logistically untenable to be understood by clinicians and patients and therefore implemented in clinical practice. This is reflected by the dearth of clinical prediction models that is currently implemented in clinical practice(Salazar de Pablo et al., 2021). In recent years, the core technologies behind the high-throughput assays, such as sequencing and mass spectrometry (MS), have become more and more sensitive, accurate, and affordable. Interrogation of complementary omics beyond a single omics layer has been explored for several diseases and model systems to demonstrate the utility and feasibility of multi-omics research. Multi-omics approaches have emerged as a promising and power tool for comprehensive study of human diseases at a system level across several types of functional layers over time.

Multi-omics data analyses and interpretation of psychiatric data require a vast number of resources as well as expertise in different subject areas ranging from genomics, laboratory science, psychiatry, statistics, and bioinformatics, encouraging close collaborations between scientists and clinicians. Investment in the study design and development of analytical frameworks of multi-omics data is as crucial as technological development and data generation.

In the end, psychiatric disorders are very complex, and the brain comprises of intricate and highly organised interconnected networks of neurons, the so-called connectome. Only by identifying how these brain networks adaptively or maladaptively respond to pathological perturbations, can lead to better understanding of the onset, manifestation and progression of psychiatric disorders(Fornito et al., 2015). Multi-omics methodologies will improve our understanding of psychiatric disorders and will facilitate more effective treatments and better preventive strategies, a giant leap in precision medicine. Future longitudinal integrative multi-omics studies in large and well-characterised cohorts combined with clinical trials will allow identification and implementation of rigorous biomarkers with high specificity, sensitivity, and predictive value. It is not long before one or more omics technologies will be incorporated as a routine part of standard precision medicine panels which, in conjunction with genetic risk, will provide more accurate diagnosis, more optimal treatment and prevention of psychiatric disorders.

ECNP TWG Network

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