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Genomics of Major Mental Illness

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Abstract:

The major psychiatric disorders of adult life, schizophrenia (SZ), bipolar disorder (BD) and major depressive disorder (MDD), contribute substantially to premature mortality and morbidity globally. Treatments are suboptimal, there is no diagnostic pathology or biomarkers, and pathophysiology is poorly understood. Novel therapeutic and diagnostic approaches are thus badly needed. Given the high heritability of psychiatric disorders, psychiatry has potentially much to gain from the application of genomics to identify molecular risk mechanisms and to improve diagnosis. Recent large-scale genome-wide association studies (GWAS) and sequencing studies, together with advances in functional genomics, have begun to illuminate the genetic architectures of psychiatric conditions and to identify potential biological mechanisms. Genomic findings also point to the aetiological relationships between different diagnoses and to the relationship between adult psychiatric disorders and childhood neurodevelopmental conditions.

Introduction.

Psychiatric disorders are characterised by clinically significant disturbances in thinking, emotional regulation and behaviour. Their global burden on individual health and societal welfare is considerable, and they are major causes of premature mortality and morbidity [1]. Schizophrenia (SZ), bipolar disorder (BD) and major depressive disorder (MDD), the focus of this review, are among the most severe adult-onset psychiatric disorders in terms of impact on the individual and society [2] and show substantial overlap in clinical features (BOX, Table 1).

From the late 18th, and throughout the 19th century, physicians and psychiatrists regarded heredity as among the strongest risk factors for “insanity” [3]. The 20th century saw the recognition of different syndromes in mental illness and the development of broadly agreed diagnostic criteria that form the basis of current nosology and clinical practice. It also saw the development and refinement of the key tools of classical genetic epidemiology: family, twin and adoption studies. Psychiatric disorders were extensively studied using these methods, with robust evidence emerging for the heritability of the different diagnostic categories (Table 1).

Psychiatric genetics was thus placed on a sound empirical footing for the application of molecular genetic approaches. These offered the prospect of identifying specific risk alleles and genes, thereby providing routes into understanding biological mechanisms and the development of novel approaches to stratification and diagnosis, as well as biomarkers to aid diagnosis and treatment targeting. This was particularly attractive in psychiatry as, given the complexity and inaccessibility of the brain, pathophysiology remains poorly understood,

and available drug treatments are largely based on serendipitous discoveries and do not target established disease mechanisms.

Linkage and candidate gene approaches beginning in the 1980s were unsuccessful. However, robust findings have steadily accumulated since the advent of genome-wide association studies (GWAS) and copy number variant (CNV) analysis, and the development of next-generation sequencing methods, together with the formation of consortia assembling large and sufficiently powered samples [4]. Over the past 10 years, a massive collaborative effort in psychiatric genomics, culminating in recently published large GWAS and whole exome sequencing studies, has identified many common and rare risk alleles and loci and begun to reveal the genetic architectures of psychiatric disorders.

The focus of this review is the genomics of SZ, BD and MDD, [the three adult-onset](#) psychiatric disorders for which genomics have so far provided the greatest insight. We do not cover neurodegenerative disorders such as Alzheimer's disease as these are largely genetically and neuropathologically distinct from psychiatric disorders [5]. Nor do we focus primarily on childhood-onset neurodevelopmental conditions (NDCs) such as autism, attention deficit hyperactivity disorder (ADHD) and intellectual disability (ID), although we do discuss the genetic relationship between NDCs and [adult](#) psychiatric disorders. We also briefly consider other psychiatric disorders in relation to genetic overlap (pleiotropy) with SZ, BD and MDD.

To provide context, we briefly summarise the main features of psychiatric disorders. We describe current understanding of their genetic architectures, and the degree to which genomic findings account for heritability estimates from genetic epidemiology. We consider the biological insights that have emerged from genomic studies, including the brain regions and cell types that are likely to mediate genetic risk. We discuss the evidence for pleiotropy across psychiatric disorders and how this informs our understanding of the aetiological relationships between different diagnostic groups. We present evidence implicating genes, biological pathways, cell types and potential mechanisms that cross traditional diagnostic boundaries and consider the clinical and research implications of these findings as well as the challenges that lie ahead. There have been recent reviews of [genomic studies of specific psychiatric disorders](#) [6-9] as well as of psychopathology more broadly [10, 11]. Here, focussing upon the three major adult psychiatric conditions, we provide a concise summary of the most robust findings, [including very recently published large-scale studies of BD and MDD](#). We emphasise evidence for the genetic similarities and differences between SZ, BD and MDD and how these conditions differ regarding their genetic relationships with NDCs and the contribution of neurodevelopmental processes. We also highlight the implications of variations in diagnostic stringency on the outcomes of genomic studies and the need for more research integrating deeper phenotyping and biomarkers with genomics research.

Main sections:

Heading 1: An Introduction to Psychiatric Disorders.

Subheading 1: Clinical features of SZ, BD and MDD.

Psychiatric diagnoses are syndromic, based solely on the presence or absence of constellations of signs and symptoms as there are no clinically validated diagnostic tests and biomarkers (**Box**). The main clinical features of SZ, BD and MDD are psychotic symptoms (delusions and hallucinations), negative symptoms (impaired motivation, reduction in spontaneous speech, and social withdrawal), disturbances of mood and activity that can either be low (depression) or elevated (mania or hypomania), and impairment of cognition (**Table 1**). While the relative prominence of each of these varies across the three diagnoses, there is substantial clinical overlap (**Box**).

Subheading 2: What is known of pathophysiology?

There is no diagnostic neuropathology, and despite decades of neurobiological research and many hypotheses, pathophysiology remains poorly understood, apart from evidence that psychosis results, at least in part, from dopamine dysfunction [12]. There is evidence from a variety of sources that SZ partly reflects disturbances in brain development [13, 14] and that these might lie on a neurodevelopmental continuum along with BD, MDD and childhood NDCs, with a gradient of decreasing severity from congenital and childhood NDCs, through SZ, to mood disorders (BD and MDD) [15, 16].

Brain imaging studies have not identified circumscribed structural differences that allow individuals with the three disorders to be distinguished from each other or from controls. While structural abnormalities have been found including reductions in cortical surface area/thickness and in the size of subcortical structures [17-22], these are heterogeneous, and widespread. Across disorders, the effect sizes are generally in the same direction and scale in the order of SZ>BD>MDD [23]. Some of the measures, especially cortical thickness, appear to be influenced by severity and duration of illness and pharmacological treatment [23].

Subheading 3: Heritability of psychiatric disorders from genetic epidemiology

Heritability estimates (**Table 1**) [derived from twins ascertained in hospital settings](#) are generally higher than those obtained from population studies. These differences might reflect greater diagnostic homogeneity in hospital-based twin studies and/or the inclusion of more severe cases with a stronger genetic component. However, the lower estimates from population studies likely align more closely to samples ascertained for genomic studies [24] and may be more relevant to discussions of unexplained heritability. Genetic epidemiology also points to a potential role for definable environmental factors, particularly in MDD. Finally, genetic epidemiology provided evidence that these disorders are not completely distinct from each other genetically, with both shared and unique genetic risk factors [25-27].

Heading 2: Genetic Architectures (Figure 1)

Subheading 1: Summary of genomic findings.

Common variation

SZ, BD and MDD are among the most polygenic of human disorders [28], with around 10,000 or more common variants estimated to contribute to each, MDD being the most polygenic [29, 30]. Large-scale GWAS have identified hundreds of common risk loci for these disorders at genome-wide significance (**Figure 1A**), with the most significantly associated variants at each locus typically residing in non-coding regions. An important limitation of GWAS in psychiatry, as in other disorders, has been the disproportionate dependence on participants of European ancestry (**Figure 1B**).

Schizophrenia: The largest GWAS (**Figure 1B**) identified 287 distinct associated genomic loci [31], many containing multiple independent association signals. Fine mapping integrated with functional genomic data prioritized 120 genes as candidates for mediating associations. Only 16 genes contained a credible nonsynonymous or untranslated region (UTR) variant, with the strongest evidence (posterior probability [PP] >0.99) for a missense variant in *SLC39A8* and a 3' UTR variant in *FURIN*. A key finding was that fine-mapped associations were enriched for genes implicated by rare coding variants in SZ as well as autism and ID.

Depression:

GWASs of clinical cases have met with limited success (**Figure 1B**) due to the power challenge of studying a modest heritability-high prevalence disorder (Table 1) [32]. The need for larger studies has been met by including cases with diagnoses based on minimal phenotyping, many of whom may not meet diagnostic criteria for MDD (**Box, Figure 1B**). We use the term depression rather than MDD to describe the phenotype of such studies.

The minimal phenotype approach has been highly effective for identifying risk variants, although while definitions ranging from research based clinical diagnosis to self-report are highly correlated (r_g 0.78-0.88) [33], this approach may fail to detect alleles that are specific to MDD while enriching for those that are shared with other psychiatric and behavioural traits [34, 35]. The largest published GWAS of depression to date, in which most cases were defined by minimal phenotyping or electronic health records, identified 635 risk loci [33] (**Figure 1B**). Gene prioritization highlighted 308 candidates for mediating the associations, 21 of which were prioritised in the SZ study including *SP4*, *FURIN*, and *CACNA1C*.

Another key observation from this study was the demonstration of the portability of PRS derived from this predominantly European ancestry sample to index liability in people of non-European ancestry; in Europeans, the PRS methodology indexed around 4% of liability, but the corresponding figures in Asian and African ancestry (including African-American) populations were around 1% and 0.2%, respectively.

Bipolar Disorder:

The largest GWAS identified 298 associated loci [36], powered primarily from self-report cases which comprised 58% of the sample. Compared with cases with a research diagnosis, self-report BD showed lower SNP heritability (0.08 vs 0.21) and stronger genetic correlations with a broad range of disorders (**Figure 2b**), the latter implying gain of power comes at the cost of some loss of specificity for the clinical disorder. Gene prioritization incorporating

fine-mapping and multiple functional genomics annotations particularly highlighted 36 genes, 15 of which were also prioritised in the depression study and 3 in the SZ study. Notable among these are *SP4* and *FURIN* which have been prioritised in all 3 phenotypes [31, 33, 36]. Reminiscent of the findings in SZ [31], fine-mapped associated genes were enriched for deleterious rare coding variants in exome sequencing studies of BD as well as SZ.

Copy Number Variants (CNVs)

Schizophrenia:

Recurrent 22q11.2 deletions were the first genomic variants to be unequivocally associated with SZ [37]. There is now strong evidence for up to 13 schizophrenia-associated recurrent large (>20kb) rare (frequency <0.01) CNVs [38, 39] and that the reciprocal duplication at the 22q11.2 locus is protective for the disorder [39-41]. Apart from deletions within *NRXN1*, all robustly associated CNVs are multi-genic. Specific associated CNVs have a frequency in cases of 0.01% – 0.6% and have relatively moderate to large effect sizes (**Figure 1A**). Collectively, around 2% of cases carry a known associated CNV, but discovery is incomplete [38, 39]. As discussed later, CNVs implicated in SZ have also been implicated in a range of NDCs.

Bipolar Disorder

CNVs appear to play less of a role in BD than in SZ. The biggest studies of *de novo* (>100kb) [42] or case-control CNVs [43] found no excess in BD. Moreover, the latter found no evidence for enrichment for sets of CNVs implicated in SZ or NDCs, although there was some evidence for enrichment in a small sample of cases with schizoaffective disorder (**Box**).

Depression

NDC-associated CNVs are enriched in people with self-reported depression in the UK Biobank [44] and in people with MDD diagnoses derived from electronic records in a US multi-ancestry biobank [45]. In the UK Biobank, those with the most conservative definition had the strongest enrichment (OR 1.51), somewhat lower than for the same set of CNVs in SZ (OR 2.56) [38]. Three of the NDC CNVs (1q21.1 duplication, Prader-Willi syndrome duplication, and 16p11.2 duplication) reached experiment-wide significance, although larger studies are required to confirm these at stringent levels.

Rare coding variants (RCVs)

Schizophrenia:

Elevated *de novo* mutation rate [46] and burden [47] established the involvement of RCVs in SZ. In the largest exome-wide study, that of the Schizophrenia Exome Meta-Analysis (SCHEMA) consortium [48], cases were enriched for ultra-rare (MAF <0.00002) damaging missense variants and protein truncating variants (PTVs) in loss-of-function mutation intolerant (LoFI) genes, particularly in genes expressed in neurons and at synapses, genes with evidence for association in the recent SZ GWAS [31] and genes implicated by RCVs in NDCs. More importantly (**Figure 1A**), 10 genes were enriched at exome-wide significance for RCVs, 2 of which (*GRIN2A*, *SP4*) were prioritized by fine-mapping in the recent SZ GWAS [31]. A subsequent meta-analysis of sequencing data from 161 genes and the SCHEMA

dataset identified 2 additional risk genes at exome-wide significance [49], but many more remain to be discovered [48].

Around 1% of cases carry a qualifying RCV in an associated gene [48]. The rarity of the implicated mutations, with a frequency typically less than 0.00002, precludes estimation of allelic effect sizes, but at the gene-burden level, point estimate ORs are similar to CNVs (**Figure 1A**).

Bipolar Disorder:

Burden tests suggest rare PTVs in LoFI genes contribute to BD [50], but less so than for SZ (BD OR = 1.11, SZ OR = 1.26) [51]. While the largest study [51] did not identify any BD associated genes, it did find enrichment in BD cases of PTVs within genes implicated in SZ, and a single exome-wide significant gene, *AKAP11*, in a combined SZ-BD analysis.

Depression:

Evidence for RCVs in depression comes from a UK Biobank study [52] in which cases defined according to electronic health records were enriched for PTVs (OR = 1.17), slightly higher than the rate in BD but less than in SZ. Cases were also enriched (OR = 1.08) for damaging missense RCVs. RCVs were enriched in genes implicated by RCVs in SZ, DD/ID, and autism, and in genes with relatively high specificity for brain expression. That specificity was not seen for broader definitions of depression.

Subheading 2: Heritability explained

Only a fraction of the heritability expected from genetic epidemiology is currently explained (**Table 1**). Some of this heritability gap might be explained by diagnostic misclassification and/or high levels of heterogeneity, and consistent with this a study based on a sample in which most cases met operational criteria for MDD rather than broader-based depression diagnoses found a much higher SNP heritability (SNP_{h^2}) of 0.24 (SE 0.03) [53] than observed in the larger meta-analyses of depression (**Table 1**). Similar conclusions can be inferred from a recent study of BD [36]. Other explanations for are not specific to psychiatric disorders and are extensively discussed elsewhere [e.g. 54, 55].

Heading 3: Pleiotropy. (Figure 2)

Family studies provide evidence for familial co-aggregation between SZ, BD and MDD, with genetic correlation estimates of 0.30-0.7 [24, 26, 56-58]. Genomic studies are now beginning to confirm that, at least in part, these correlations reflect pleiotropy. [These findings also point to a lack of pathogenic validity of psychiatric diagnoses, which are syndromic and lack diagnostic tests and biomarkers \[5\] \(Box\).](#)

Subheading1: Common variants

Common variant liabilities for many psychiatric diagnoses are correlated [5] (**Figure 2A**) suggestive of widespread pleiotropy. There is substantial genetic correlation (r_g) between SZ and BD, and moderate correlation between depression and both SZ and BD. Consistent with

genetic heterogeneity within bipolar disorder, liability to BD1 is strongly correlated with SZ but only weakly correlated with depression, while the converse is true for BD2 (**Figure 2B**).

The extensive genetic correlations imply the existence of widespread allelic pleiotropy (shared risk alleles) but there is evidence the level of genic pleiotropy (shared genes) may be even greater if we ignore allelic directions of effect [29]. Thus, it has been estimated that almost all variant sites that influence liability to BD also do so for SZ, while around 90% of those sites are also shared with depression, with around 80% of shared variant sites in both instances showing allelic concordance [59]. These findings imply the biological processes underlying these disorders are more closely related than is evident from genetic correlations, though co-action with the unshared (or allelic discordant) variants and environmental exposures may mean even the shared effects may be exerted in different brain regions, cell types, and developmental stages in different disorders.

A caveat to the implication of widespread pleiotropy is that genetic correlation estimates can be inflated by assortative cross-disorder mating and by reciprocal diagnostic misclassification (where each discrete disorder is mistaken for the other) [60, 61]. It is unlikely that these factors fully account for the correlations observed, particularly the very high correlation between SZ and BD, which if entirely spurious, would require unrealistically high reciprocal misdiagnosis rates [61, 62]. Moreover, misclassification can also deflate genetic correlations if additional cases are incorrectly assigned to one of a pair of the disorders in question. **Figure 2B** illustrates both inflationary and deflationary effects likely due to misdiagnosis [36]. There is a progressive deflation in r_g between BD and SZ as BD diagnostic stringency decreases from clinical research diagnosis to diagnoses based on minimal (community) and low depth (self-report) phenotyping, and in parallel, a substantial increase in r_g between BD and other conditions. These, and broadly similar findings from studies of depression [63], unsurprisingly suggest low depth phenotyping results in lower diagnostic specificity. Investigations aiming to distinguish alleles that are truly shared and, perhaps more interestingly, specific to individual disorders, will require deep phenotyping of large numbers of participants.

The question of whether genetic correlations are better accounted for by misdiagnosis of distinct disorders than by pleiotropy also needs to consider the fact that, as well as lacking biological validity, psychiatric diagnoses are heterogeneous and lack clear diagnostic boundaries between them (**Box**). Put simply, if the case for there being distinct diagnostic categories is *a priori* weak, then this undermines the argument that genetic correlations reflect misdiagnosis rather than pleiotropy. If, as seems increasingly likely (discussed below), the clinical picture expressed by an individual is the result of a confluence of partly orthogonal transdiagnostic symptom dimensions and their underlying genetic risk factors, genetic correlation could be a consequence of genetics driving clinical similarity rather than reflecting misdiagnosis of genetically distinct disorders. If this is true, the substantial overlaps in biological pathways implicated in the disorders (see *Biological Insights*) may point to the biological basis of particular clinical features better than they do to the clinical diagnoses.

Studies aiming to exploit genomics for diagnostic stratification have shown that SZ liability is highest in people with SZ followed by schizoaffective disorder-bipolar subtype, then BD1

followed by BD2, and then unaffected individuals [64-66]. Moreover, in people with BD, SZ liability is highest in those with psychotic symptoms and higher still in those with mood-incongruent psychotic symptoms, the symptoms most akin to schizophrenia [64, 65]. Conversely, in those with SZ, BD liability is associated with the level of manic symptoms [65] and MDD liability is associated with depressive symptoms [67]. Finally, there is evidence that in people with BD, the SZ polygenic risk score (PRS) associations seen with mood-incongruent psychosis do not derive from shared SZ and BD alleles but from a component of liability that is fairly specific to SZ [68]. Thus, pleiotropy not only points to the genetic relationships between psychiatric diagnoses but is also beginning to offer explanations for heterogeneity in transdiagnostic clinical features within diagnostic categories. In addition, both SZ and depression PRS are associated with poorer treatment response and worse outcomes in those with BD [69-71].

Subheading 2: Rare variants

The same CNVs and the same genes in which RCVs are associated with SZ are enriched in depression and BD respectively (discussed above). They are also often pleiotropic for NDCs [38, 48, 72-76] and, moreover, the specific mutations that confer risk of NDCs [77], are enriched in people with SZ, implying a degree of overlap in the primary molecular pathology.

The overall contribution of CNVs and RCVs to the associated conditions is not uniform, enrichments being greatest in disorders with the strongest neurodevelopmental contribution (as inferred from childhood onset and greater cognitive impairment) (**Figure 2c**). Thus, ID is most strongly enriched, then autism and ADHD, then SZ [16], with lower contributions to both MDD and BD. There is also evidence that genes and mutation sites are most highly conserved in ID, then autism, then SZ [46]. For some genes, different classes of rare mutation might be implicated in NDCs and SZ [48], but there is yet no evidence concerning the relative severity of the different classes. Within SZ, autism and ADHD the burden of rare mutations is also not uniform, being higher in those with severe cognitive impairment, although it is still elevated in those without it [76, 78, 79].

Subheading 3: Common variants modulate effects of rare variants.

Evidence from studies of SZ [80-82], depression [52] and NDCs [83] indicates that specific outcomes in rare variant carriers are at least in part a consequence of additive co-action with common variant liability to these disorders. These findings suggest that rare and common variants confer risk together in a manner consistent with a polygenic liability threshold model rather than that the two classes of variant lead to distinct, heterogeneous outcomes [81]. This also implies that PRSs and indeed likely other risk factors, genetic and environmental, have potential utility in risk stratification in those with rare, large effect but incompletely penetrant risk alleles [81].

Heading 4: Biological insights (Figure 3)

Subheading1: Neuroanatomical and cellular insights

Analyses of genomic data in relation to brain region- and cell- specific gene expression have provided insight into the likely neuroanatomical and cellular mediators of genetic liability to psychiatric disorders (**Figure 3**). Consistent with neuroimaging data [17-22], common variants associated with these conditions are strongly enriched in genes with high expression specificity for the cerebral cortex, along with subcortical brain regions involved in cognitive and affective processes, including the hippocampus, amygdala and striatum [29, 31, 84]. In SZ, the pattern of RCV enrichment according to regional brain gene expression mirrors that of common variation [48]. RCV studies of the other two disorders are underpowered, but a small enrichment of RCVs in genes expressed in the amygdala has been reported for BD [51].

Tests of common risk variant enrichment in predicted regulatory genomic elements and in genes with high expression specificity for individual cell populations have shown that liability for each of the disorders operates primarily through neurons (rather than glia) [in the post-natal brain](#) [85, 86]. The most strongly implicated neuronal populations are glutamatergic neurons of the cerebral cortex, hippocampus and amygdala, cortical GABAergic interneurons, and GABAergic medium spiny neurons of the striatum [29, 31, 85-87]. [Common risk alleles for these disorders are also enriched in putative regulatory genomic elements identified in the prenatal human brain \[88-90\]; however, there is conflicting evidence as to the prenatal cell types mediating common variant liability to these conditions, with some studies reporting pronounced enrichment in regulatory elements operating in neural progenitor cells \[89, 91\], while others \(based on cell-specific gene expression and / or regulation\) have reported more specific enrichments in developing post-mitotic neuron populations \[92-96\].](#) For SZ, genes containing an excess of RCVs have higher expression specificity for neurons in both the developing and adult brain [48, 93].

While there is considerable overlap in the cell types implicated in each disorder, there is evidence that certain cell populations may play a more important role in individual diagnoses. For example, a recent study found enrichment of common variants associated with depression, but not SZ or BD, in regulatory genomic regions mapped in fetal midbrain GABAergic neurons [97]. Larger single cell datasets and the incorporation of spatial transcriptomics (see [Emerging tools for biological insights](#)) should further resolve the cell populations most important for mediating genetic risk for these conditions.

Subheading 2: Biological processes

Ontology analyses of GWAS findings for SZ, BD and depression are consistent with neuronal disturbances in these disorders, with enrichment of common risk variation in genes involved in synaptic function, ion channels and neuronal development [29, 31, 98]. CNVs identified in SZ are also enriched for synaptic genes [39, 99, 100], while RCVs in the disorder are enriched in genes associated with synaptic function, ion channel activity and chromatin modification [48]. The observations that genes related to chromatin modification are also enriched for RCVs in NDCs [102] but are not notably enriched for SZ common variant associations [31] may partly explain the particular role postulated for rare variation in the neurodevelopmental pathology of SZ [16].

Individual genes with strong support from both GWAS and RCV analyses of SZ include *GRIN2A*, encoding a subunit of the glutamatergic NMDA receptor, and *SP4*, encoding a transcription factor known to regulate NMDA receptor subunit expression [102], substantiating the long-hypothesised role of this receptor in SZ pathophysiology [103, 104]. Common genetic variation in several genes with roles in neuronal development and function (e.g. *FURIN*, *SP4*, *DCC*, *CACNA1C* and *ZNF804A*) appear to confer risk for BD and depression as well as SZ [29, 31, 33, 98]. However, there is evidence that variation at other genes confers risk to specific disorders. For example, SZ-associated variation affecting expression of *C4A* [105] does not seem to be associated with depression [106] or BD [29], while discordant risk alleles at a locus on chromosome 5 for SZ and depression [107, 108] are respectively associated with increased and decreased expression of genes in the protocadherin alpha cluster [108, 109].

Subheading 3: Emerging tools for biological insights

Translation of genetic findings into an improved understanding of molecular and cellular risk mechanisms will benefit from advances in functional genomic and cell/organoid culture technologies. For example, information from spatial 'omics assays [e.g. 110] - through which global gene expression and epigenomic features can be measured in individual cells in their native tissue context - will help determine the precise location of cells mediating genetic risk for these conditions [e.g. 111]. Single cell RNA sequencing can be combined with genotype data to identify expression quantitative trait loci (eQTL) operating in individual brain cell populations, which, when integrated with GWAS data, can shed light on cell-specific molecular risk mechanisms through which common, non-coding risk variants operate [112]. Advances in CRISPR technology (e.g. CRISPR activation and interference) can be used to model these effects on gene regulation (as well as RCVs) in relevant human neural cell types or multicellular brain organoids *in vitro* [113], with single cell RNA sequencing providing an efficient means of assaying effects of multiple gene perturbations on cellular gene expression in parallel [114]. Given extensive alternative exon usage in the human brain transcriptome [115], it is important that such modelling takes into account the specific RNA transcripts of each gene that are principally affected by genetic risk variation, as well as the developmental timing of these effects.

Heading 5: Clinical implications

The potential benefits, limitations and challenges of genomic testing in psychiatry have been reviewed elsewhere [116-118], and a detailed treatment of these complex issues is beyond the scope of this article.

Subheading1: Population screening

Clearly risk prediction for psychiatric disorders in the population using genomic data alone will be limited by genetic factors accounting for only a proportion of variance in liability [119]. In addition, only a fraction of liability is currently attributable to known genomic variation (Table 1). The specificity of population testing will also be limited by the low

population prevalences particularly of SZ and BD. In any case, given the lack of proven preventative health management interventions in psychiatry, the current utility of population screening is questionable and, in some instances, may be harmful.

Subheading 2: Diagnostic/prognostic potential of PRS

Even though common variants currently account for only a proportion of heritability, it seems likely that, as genomic data accumulate, PRSs, alongside lifestyle information, clinical data and biomarkers may improve patient stratification, outcome prediction, and aid clinical decision making in symptomatic individuals [who do not meet diagnostic criteria but where the clinical picture points to a risk of illness that is higher than in the general population \[116\]. For example, in the latter instance, a combination of clinical information and PRS might identify individuals in whom early treatment or closer follow-up is required \[116\]. However, high quality, large-scale clinical studies are required to determine the clinical utility of PRSs and their integration with other data sources, to identify the patient groups that will benefit and the outcomes that are best predicted. Moreover, the current unrepresentative nature of published genetic studies, particularly with respect to ancestry, raises challenges to the equitable application of PRS in clinical contexts, \[as illustrated above in the section on the genetic architecture of depression.\]\(#\)](#)

Subheading 3: Clinical testing for rare variants.

Clinical testing for rare variants is available in many countries for children with NDCs. As data implicating rare variants, and particular CNVs, have accumulated in adult psychiatric disorders, there have been calls for testing to be available at least in high-risk groups such as those with premorbid cognitive impairment, a history of childhood onset neurodevelopmental disorder, congenital malformations, dysmorphic features, developmental delay or a family history of SZ or NDCs [120]. The value of such testing is now recognised in several guidelines and is being implemented internationally [121]. Nonetheless further research to clarify the benefits and harms of testing, particularly beyond high-risk groups, is required, as is close integration with genetic counselling services [117, 122]. Moreover, given many of the rare variants conferring risk to psychiatric disorders are also associated with other NDCs as well as physical health conditions which may be treatable or preventable, appropriate cross disciplinary assessment and care should be accessible [123].

Subheading 4: Pharmacogenomics

[Pharmacogenomics seeks to characterise the genetic contribution to inter-individual variation in response to drugs, both in terms of efficacy and safety \[124\]. Perhaps the greatest potential for the clinical translation of pharmacogenomics in psychiatry is with pharmacokinetics, particularly the genetic basis of drug metabolism. The accumulation of evidence in recent years, including the identification of drug-gene pairs for psychotropic medications \[125\] has led to expert recommendations for the testing of cytochrome P450 genes \(*CYP2D6*, *CYP2C19*\) to inform medication selection and dosing of several commonly-used antidepressant and antipsychotic medications, as well as testing for human leukocyte](#)

antigen genes when using some mood stabilisers, including carbamazepine [126]. These recommendations were supported by findings of a large-scale study that undertook pre-emptive pharmacogenetic testing and demonstrated that genotype-guided dosing reduced the incidence of adverse drug reactions, including to antidepressants and antipsychotics [127]. The importance of considering ancestry to optimise antipsychotic dosing has been shown for clozapine [128]. Furthermore, equitable access to clozapine, the only licensed medication for treatment-resistant schizophrenia, would be enhanced through the implementation of pre-initiation genetic testing of the duffy-null genotype to ensure those of African ancestries can safely receive this medication [129].

The genetic basis of treatment response has proven more challenging to delineate [130]. Nonetheless, a genetic basis for variation in lithium [131] and antipsychotic [132] response has been demonstrated, though these findings are not currently clinically impactful. Whilst the above evidence supports the use of pharmacogenomic testing in some clinical settings, there remain challenges to its implementation within healthcare systems and these need to be overcome if the potential of pharmacogenomics is to be realised [133].

Subheading 5: Roadblocks to clinical application of genomics

Currently, the **impact of** genomics on psychiatric care is limited, but it seems likely that this will change. Beyond the requirement for more research, the challenges for effective and ethical implementation are not trivial and are different to those in other branches of medicine [118]. There is a need for improved genetics training to give psychiatrists and other members of the clinical team the knowledge and confidence to initiate testing and interpret the results [118]. Professional organisations will need to develop practice guidelines to ensure appropriate standards of care, and more extensive collaboration with other clinicians and disciplines is required [118]. It will also be important for clinicians to consider issues around patient engagement, choice and informed consent, given the potential for harmful medical and social outcomes [118]. Finally, given the uptake of direct-to-consumer testing and the greater public awareness of genomics in medicine, there is a need for more genomic education for the public as well as clinicians.

More multi-ancestry studies and genome reference panels reflecting human population ancestral diversity are essential to ensure that the clinical benefits of genomics are realised globally, as well as to obtain novel genetic and biological insights. Achieving those benefits will also require skills development and research infra-structure building in many places across the globe [134]. There is a great deal to be done here, but this is starting to be addressed in psychiatry within the Psychiatric Genomics Consortium and through specific initiatives focussing on non-European Ancestries, examples of which include the Latin American Genomics Consortium (<https://www.latinamericangenomicsconsortium.org/>), Neuro-GAP and the affiliated Global Initiative for Neuropsychiatric Genetics Education in Research programme [135] and the Ancestral Populations Network, (<https://www.nimh.nih.gov/about/organization/dnbbs/genomics-research-branch/ancestral-populations-network-apn#organization>), and Depression Genetics in Africa (<https://wellcome.org/grant-funding/people-and-projects/grants-awarded/depression-genetics-africa-depgenafrica>).

Conclusions and perspective

While much heritability remains to be explained, genomics is beginning to characterise the genetic architectures of psychiatric disorders. They are highly polygenic, risk is conferred by a mix of common alleles of small effect and rare alleles of large effect, with the relative contribution of the latter being higher in NDCs than psychiatric disorders. Genes implicated suggest that these are primarily disorders of CNS neurons, with important roles for neurodevelopmental processes and perturbation of neuronal and synaptic function, particularly of glutamatergic and GABAergic neurons across many regions of the forebrain, in line with brain imaging studies. These findings are consistent with the hypothesis that SZ, BD and MDD are syndromes resulting from widely distributed neuronal pathology. While the reported patterns of neuroanatomical and cellular enrichment of common variant liability in the three disorders are similar (Figure 3), further work is required to understand the extent to which these may differ between and within diagnostic groups and their relationships with individual clinical features.

Larger sequencing studies, exome, whole genome (WGS) and long-read can be expected to refine emerging biological insights and possibly explain more heritability. Given current and emerging technology, progress is likely to come initially from studies of the exome and of structural variation but the reduction in the cost of whole WGS has made the study of rare non-coding variation (ncRV) tractable. Specific associations are beginning to emerge for traits that are well represented in large biobanks [136] but studies of ncRV in adult psychiatric disorders are small, and the findings are provisional and restricted to reports of excess burdens proximal to particular genomic features [137] in people with schizophrenia. It seems inevitable ncRVs will contribute to adult psychiatric disorders, but there are important analytic challenges. The very low frequencies of RCV of large effect has meant that insights from exome sequencing have required burden tests of RCVs predicted to be deleterious within the coding exons of gene, not tests of individual variants. Similar considerations will hold for ncRVs but, for now, there is no obvious unit for mutation burden testing and no robust methodology for predicting the subset of ncRCVs highly likely to be highly deleterious. Developments in the functional annotation of the genome linking regulatory elements to specific genes [e.g. 96] are likely to improve the prospects here.

Biological insights will also depend upon better annotation of the brain transcriptome and proteome, with greater spatial and temporal resolution [138]. Understanding the balance between neurodevelopmental impairments and direct effects on adult brain function across the different diagnostic groups - and the specific processes impacted - are key knowledge gaps for future research.

Rare variant studies support the hypothesis that psychiatric disorders share pleiotropic neurodevelopmental abnormalities with NDCs, the severity of which varies across and within traits as is indexed by cognitive impairment and rare variant burden (Figure 2c) [15, 16]. These findings point to the potential importance of cognitive impairment as a stratifier in psychiatry indexing the involvement of neurodevelopmental abnormalities [139].

Common variant studies have revealed a high genetic correlation between SZ and BD with risk for both conditions being moderately correlated with MDD. Early transdiagnostic studies of these disorders suggest that the clinical picture expressed by an individual is the result of a confluence of partly orthogonal [transdiagnostic](#) symptom dimensions and their underlying genetic risk factors. In this sense, genomics provides validation for stratification approaches based on symptom features within and across disorders. There is increasing interest in approaches modelling the latent structure of the pleiotropic relationships between multiple psychiatric disorders and these have identified broad factors that may underlie cross-disorder correlations [68, 107, 140]. [These cross-disorder findings, perhaps coupled with the transdiagnostic symptom research discussed above, have the potential to identify valid, biologically informed strata that cross existing diagnostic categories and advance nosology.](#) The lack of consistency and availability of clinical phenotypic measures across disorders presents a challenge to these advancements and hence deep phenotyping that is aligned transdiagnostically should be a priority for the field. Genomic studies of depression have shown the value of increasing sample sizes, regardless of the depth of phenotyping, for estimating the risk of MDD, but studies of cases meeting diagnostic criteria might better inform understanding of [the specific](#) neurobiology of clinical forms of the disorder [35]. Moreover, to identify biologically valid strata and to understand the genetic basis of heterogeneity, there is also the need for a greater focus on deeper phenotyping at the symptom level, including cognition and other biomarkers.

Despite substantial progress in psychiatric genomics, we are still some way from the goal of more effective and better targeted treatments. Challenges to identifying tractable biology are posed by the highly polygenic nature of psychiatric disorders, the complexity and inaccessibility of the brain, the involvement of neurodevelopmental as well as adult mechanisms and the heterogeneity inherent in psychiatric diagnoses. On the positive side, there is potential for genomics to illuminate novel and more biologically valid strata, and the availability of in vitro cell and organoid models means that it is now possible to investigate the impact of current and emerging risk alleles, singly and in combination, on human neural function [113]. Progress will depend upon coordinated interactions between geneticists, neurobiologists and clinical researchers.

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[H1] Author contributions

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Table 1 | **Main features of psychiatric disorders**

	Schizophrenia	Bipolar Disorder	Major Depressive Disorder
Core features	Delusions, hallucinations, formal thought disorder, negative symptoms.	Episodes of mania (BD1) or hypomania (BD2) and episodes of depression	Episodes of depression
Additional features	Cognitive impairment, episodes of mania and depression	Delusions and hallucinations, cognitive impairment.	Delusions and hallucinations, cognitive impairment.
Estimated global prevalence ^a	24M cases	40M cases	280M cases
Usual age at diagnosis	16-30	15-30	25-35
Commonly used drug treatments	Antipsychotics, antidepressants, mood stabilisers.	Mood stabilisers, antipsychotics	Antidepressants, antipsychotics, mood stabilisers.

Heritability estimates from twin studies	0.64-0.81	0.59-0.85	0.32-0.75
Liability from RCVs	0.02 ^b	0.02 ^d	0.007 ^e
Liability from CNVs	0.02 ^b	unknown	unknown
SNPh2	0.25 ^b	0.21 ^c	0.08 ^d
SNPh2 from GWS variants	0.03 ^b	0.04 ^c	0.01 ^d

Table 1.

[Refs 24, 25, 27, 141-146]. ^a World Health Organization [147]. ^b [7], ^c [36], ^d [33], ^e extrapolated from [52]. SNP heritability (SNPh2) estimates are derived from European populations which currently are over-represented in genome wide association studies. Note that estimates from rare variants include contributions from transmitted and *de novo* mutations, although the latter do not contribute to heritability. BD 1 and 2- Bipolar disorder types 1 and 2 (**Box**), RCVs- rare coding variants, CNVs – copy number variants, GWS – genome-wide significant.

Figure 1a. Effect size and frequency of known risk variants for schizophrenia, bipolar disorder, and depression

Effect sizes (odds ratios (OR)) versus general population minor allele frequencies for copy number variants (CNVs), damaging rare coding variants (RCVs: protein-truncating variants (PTVs) or missense variants), and common single nucleotide polymorphisms (SNPs). Y-axis spacing is on log(10) scale. CNV and RCV effect sizes are from studies of schizophrenia [39, 48]. For most CNVs, we give cytogenetic location. Dup and del refer to duplication and deletions respectively. For CNV loci attributed to named syndromes, we provide abbreviations. WBS denotes region deleted in Williams-Beuren syndrome, PWS/AS denotes Prader-Willi and Angelman Syndrome region. RCV associated genes are from Refs 48, 49. **AKAP11** was also identified in a meta-analysis of bipolar and schizophrenia datasets [51]. RCV effect sizes refer to the excess burden of RCVs in the named gene. CNV and RCV effect sizes are imprecise due to the small number of observations. Schizophrenia, depression and bipolar disorder genome wide SNP association data are from refs. 31, 33, and 36 (also represented top row Figure 1b). We also plot the OR for Polygenic Risk Scores based on the largest test samples (i.e. those of European ancestry). The PRS data for bipolar disorder are from ref. 29 as equivalent data were not reported in the more recent publication [36]. The suffixes 10M or 100M denote comparisons between top PRS decile (10M) or top centile (100M) and the median decile. The suffix 100B denotes comparison between the top and bottom PRS centiles (data for bipolar disorder not available). Adapted with permission from Ref 7.

Fig 1b. GWAS sample sizes, ancestries, and associated loci.

Pie charts illustrate the proportions of cases denoted as of European (EUR), East Asian (EAS), South Asian (SAS), African or African American (Afr), Latino/Hispanic (LA/HISP), or multiple/mixed background in largest published genome wide association studies (GWAS) of schizophrenia (SZ), depression (DEP) and bipolar disorder (BD). Top row shows the largest available GWAS data: schizophrenia [31]; depression [33]; bipolar disorder [36]. Bottom row shows the largest studies of cases described as meeting clinical diagnostic criteria for Major Depressive Disorder [148] and BD [29] demonstrating the relatively low yield of associations per case meeting clinical criteria, particularly for depression, that has motivated inclusion of minimal phenotype cases (see text).

Figure 2a. Genetic correlations between psychiatric diagnoses.

Numbers represent genetic correlations between pairs of disorders with standard errors in brackets. Bold font indicates significant correlations after Bonferroni correction. Data are taken from Ref. 107. SZ, schizophrenia; DEP, depression; BD, bipolar disorder; ADHD, attention deficit hyperactivity disorder; TS, Tourette's syndrome; AN, anorexia nervosa; OCD, obsessive compulsive disorder. Coloured bar denotes correlation values.

Figure 2b. Effect of diagnostic method on genetic correlations between bipolar disorder and other psychiatric conditions.

Numbers represent genetic correlations with standard errors in brackets. Data from Ref. 36; bold font indicates significant correlations after Bonferroni correction applied in the study [36]. SZ, schizophrenia; DEP, depression; BD, bipolar disorder; PTSD, post-traumatic stress disorder; ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder, BD1 and BD2 see Box. Diagnoses in decreasing order of stringency are clinical (based on structured or semi-structured clinical interviews), community (based on data extracted from medical records, registries and questionnaires), and self-report (based on self-reported surveys). Coloured bar denotes correlation values.

Figure 2c. The neurodevelopmental continuum and gradient.

This illustrates the relationship between the relative burden of rare damaging mutations (CNVs and RCVs) and neurodevelopmental and psychiatric diagnoses. ID-intellectual disability, cNDCs-childhood onset neurodevelopmental conditions (e.g. autism and ADHD), SZ-schizophrenia, SAD-schizoaffective disorder, BD-bipolar disorder, MDD-major depressive disorder. The model postulates a gradient of neurodevelopmental impairment with associated cognitive impairment and structural brain abnormalities. References in text.

Figure 3. Neuroanatomical and cellular enrichment of common variant liability to

schizophrenia based on gene expression specificity. Neuroanatomical heat map shows the mean $-\log_{10}$ P -values for enrichment of schizophrenia common variant genetic liability, as assessed by MAGMA [149] and S-LDSR [150] by Trubetskoy et al. [31], in genes whose RNA shows high expression specificity for each of 10 adult human brain regions assayed by the GTEx Consortium [151]. The most significant enrichments are observed in genes with high expression specificity for assayed regions of the cerebral cortex, while least significant enrichments are observed in genes with preferential expression in the substantia nigra and spinal cord (cervical C1). The GTEx Consortium did not provide RNA assays for non-coloured brain regions and therefore no conclusions can be drawn as to their enrichment. Genes with

high expression specificity for glutamatergic pyramidal cells and GABAergic interneurons of the cerebral cortex, glutamatergic granule cells and pyramidal neurons of the hippocampus, glutamatergic pyramidal cells of the amygdala and GABAergic medium spiny neurons of the striatum are prominently enriched for schizophrenia common variant associations [31, 86, 87]. Similar patterns of neuroanatomical and cellular enrichment of common variant liability to bipolar disorder [29] and major depressive disorder [84] have also been reported.

Box 1. Psychiatric diagnoses.

In the absence of diagnostic tests and biomarkers, psychiatric diagnoses are solely based on clinical signs and symptoms. The need for diagnostic standardisation and inter-rater reliability has been addressed by operationalised classifications codified in the DSM and ICD [152]. These have had many benefits to clinical practice and research but were never intended to be valid descriptors of distinct disease entities sharing an underlying pathogenic process [153, 154]. This lack of discrete biologically valid diagnostic categories in psychiatry provides a plausible explanation for the pervasive pleiotropy seen between psychiatric diagnoses and is consistent with observations that the genetic liability to specific clinical features (e.g. depression, mania, psychosis) is at least partially shared regardless of the primary categorical diagnosis (see main text).

The clinical features of SZ, BD and MDD substantially overlap (Table 1). Consequently, the boundaries between disorders are indistinct, as are the boundaries between these disorders and psychological phenomena present in people who are not classified as being unwell [152]. Moreover, individuals with the same diagnosis vary widely in symptoms, severity, course and outcome, suggesting mechanistic heterogeneity within diagnostic groups [152]. The lack of clear boundaries between diagnoses and heterogeneity within them is reflected in the common assignment of diagnoses in addition to the three cardinal groupings. Schizoaffective disorder is a diagnosis given to individuals who have the psychotic features of schizophrenia as well as prominent symptoms of mood disorder. This is sometimes divided into bipolar and depressive subtypes depending on whether manic episodes have occurred. Genetic epidemiology suggests schizoaffective disorder shares genetic risk with SZ and BD and may represent an intermediate form in a SZ-BD continuum [26]. Moreover, two types of BD are recognised. BD 1 is characterised by the presence of mania and usually episodes of depression, and BD2 characterised by hypomania (similar but less severe than mania) and episodes of depression.

Early genomic studies used DSM or ICD definitions of SZ, BD and MDD derived from structured interviews. Subsequently, responding to the need for large samples, researchers have increasingly used less stringent approaches, potentially resulting in the inclusion of cases who meet diagnostic criteria for another disorder or who have relatively mild symptoms and do not meet criteria for any disorder [34]. Such studies also lack granular clinical data upon which explorations of heterogeneity and transdiagnostic syndromes and symptoms can be based. This has led to calls for new cohorts for genomic research with deeper and more diverse phenotypes [34, 155].

[H1] Glossary terms

Psychotic symptoms- symptoms, particularly delusions and hallucinations, in which there are difficulties in determining what is real and what is not.

Mood-incongruent psychotic symptoms-hallucinations or delusions that are not aligned with the person's current mood state.

Delusion- a fixed false belief that is not amenable to change in the light of conflicting evidence.

Hallucination- a perception in the absence of an external stimulus that has a compelling sense of reality.

Depression- a mental state that involves low mood and decreased activity.

Mania- a mental state that involves elevated mood, which can be euphoric or irritable, and increased activity.

Hypomania- a less severe form of mania that is not accompanied by significant functional impairment (e.g. to occupation or personal relationships).

Formal thought disorder- a disruption of the form, or structure, of thought that is manifest as disorganised speech.

Polygenic Risk Score (PRS)-summarises the estimated effect of many genetic variants on an individual's phenotype. It is typically calculated as a weighted sum of trait-associated alleles.

Pleiotropy – the phenomenon when a variant or a gene influences more than one phenotype. The language of pleiotropy is evolving but the terms direct, horizontal, and biological pleiotropy imply that the effects on the phenotypes are independent. The terms mediated, vertical, or indirect pleiotropy imply that the effects on one phenotype are mediated through the other, for example alleles that influence smoking behaviour are likely to have mediated pleiotropic effects on all traits for which smoking is a risk factor. For further discussion, see ref. 156.

Common Variants- variants that are present in the population at frequencies of 1% or more. They include single-nucleotide polymorphisms (SNPs) that can be assayed in parallel across the genome in genome-wide associations studies (GWAS).

Copy Number Variants (CNVs) -variants in which the number of copies of a specific segment of DNA varies in the population. These structural differences may have come about because of duplications, deletions or other changes.

Rare Coding Variants (RCVs) – variants in the coding sequence of a gene that are present in less than 1% of the population. They can be detected by genome-wide sequencing studies.

Protein Truncating Variants (PTVs)- variants predicted to shorten the coding sequence of a gene and which may result in reduced expression of that gene and its protein due to nonsense mediated decay. They include nonsense, frameshift and essential splice site variants.

Loss-of-function mutation intolerant (LoFi) genes – genes with near complete depletion of PTVs in population studies suggesting strong direct selection against such mutations.

Genetic Correlation (r_g) - an estimate of the average similarity of causal allelic effects on two traits. This usually refers to the genome-wide average, though can be specified to be locus-or chromosome wide. Is usually indicative of pleiotropy but see main text and [60]