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Review

Defining the Genetic, Genomic, Cellular, and Diagnostic Architectures of Psychiatric Disorders

Patrick F. Sullivan[1,2,*] and Daniel H. Geschwind[3,4,*]
[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[2]Departments of Genetics and Psychiatry, University of North Carolina, Chapel Hill, NC, USA
[3]Departments of Neurology, Psychiatry, and Human Genetics, David Geffen School of Medicine, University of California, Los Angeles, CA, USA
[4]Institute for Precision Health, David Geffen School of Medicine, University of California, Los Angeles, CA, USA
*Correspondence: patrick.sullivan@ki.se (P.F.S.), dhg@mednet.ucla.edu (D.H.G.)
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Studies of the genetics of psychiatric disorders have become one of the most exciting and fast-moving areas in human genetics. A decade ago, there were few reproducible findings, and now there are hundreds. In this review, we focus on the findings that have illuminated the genetic architecture of psychiatric disorders and the challenges of using these findings to inform our understanding of pathophysiology. The evidence is now overwhelming that psychiatric disorders are "polygenic"—that many genetic loci contribute to risk. With the exception of a subset of those with ASD, few individuals with a psychiatric disorder have a single, deterministic genetic cause; rather, developing a psychiatric disorder is influenced by hundreds of different genetic variants, consistent with a polygenic model. As progressively larger studies have uncovered more about their genetic architecture, the need to elucidate additional architectures has become clear. Even if we were to have complete knowledge of the genetic architecture of a psychiatric disorder, full understanding requires deep knowledge of the functional genomic architecture—the implicated loci impact regulatory processes that influence gene expression and the functional coordination of genes that control biological processes. Following from this is cellular architecture: of all brain regions, cell types, and developmental stages, where and when are the functional architectures operative? Given that the genetic architectures of different psychiatric disorders often strongly overlap, we are challenged to re-evaluate and refine the diagnostic architectures of psychiatric disorders using fundamental genetic and neurobiological data.

Introduction

Psychiatric disorders are the most enigmatic maladies in medicine. Although their existence has been known for millennia (Porter, 2002) and their impact on public health well-documented, remarkably little is known about their causal risk factors and fundamental neurobiology despite a considerable corpus of research. In the past century, many have applied the best tools then available but, until recently, without reproducible successes. The lack of success using approaches that were fruitful elsewhere is attributable an inadequate toolkit and the intrinsic complexity of the brain. Psychiatric disorders impact higher cortical functions (mood, behavior, perception, and cognition), which are far more difficult to localize, quantify, and model than more basic neurological functions. In addition, psychiatric disorders are defined based on self-report and observation of cognition and behavior rather than on direct measurement of an etiological factor, making them syndromes rather than single diseases. These features strongly suggest diverse and complex etiologies.

Despite these challenges, there has been remarkable progress in the past decade in elucidating the genetic underpinnings of psychiatric disorders with numerous findings that meet modern criteria for significance and reproducibility (Geschwind and Flint, 2015; Sullivan et al., 2018). In this Review, we focus on the findings that have illuminated the "genetic architecture" of psychiatric disorders and the challenges of using these findings to inform our understanding of pathophysiology. Genetic architecture refers to the overall composition of the implicated risk variants in the population—the total number of variants and, for each, the frequencies in those afflicted and in the general population and the degree of risk conferred (Timpson et al., 2018). The concept of genetic architecture is applicable to any trait (e.g., Huntington's disease is caused by a rare, deterministic variant). Knowledge of genetic architecture can help optimize gene discovery (e.g., study design, ascertainment, choice of genotyping technology) (Timpson et al., 2018; Visscher et al., 2012). Genetic architecture can inform prospects for clinical utility: although many deterministic monogenetic conditions are predicted or diagnosed using genetic testing, application to most psychiatric disorders traverses far more murky, probabilistic terrain (Timpson et al., 2018).

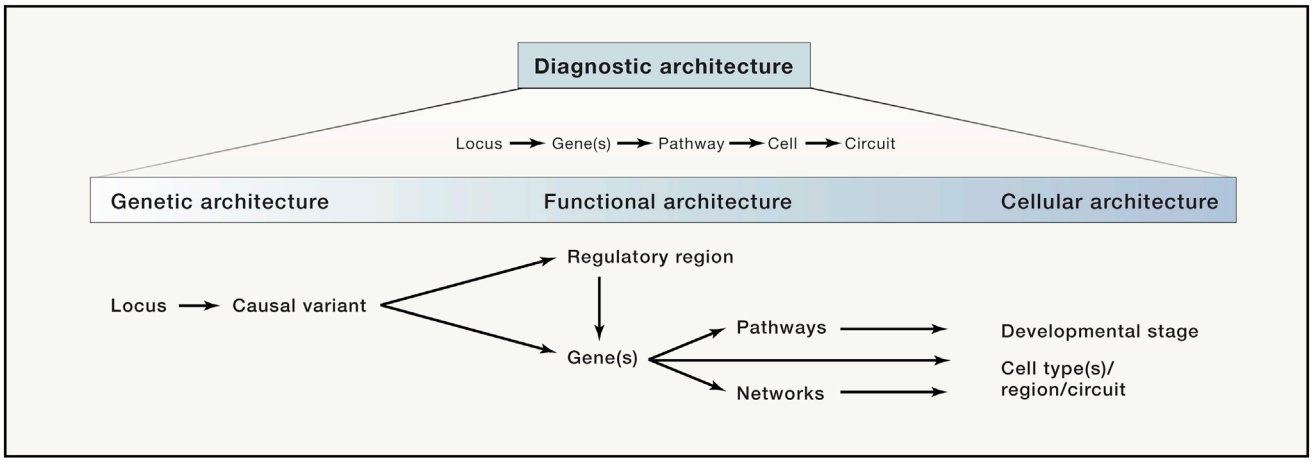

Figure 1. Relationship of the Levels of Disease Architecture to Different Stages of Analysis

Genetic studies identify the loci and causal variants that impact disease and thereby its genetic architecture. The subset of causal variants in coding regions are typically directly assignable to genes. As many loci are non-coding, regulatory regions and the genes they regulate need to be empirically defined and identified—such studies render the functional architecture of disease. As psychiatric disorders all appear to be polygenic, it is also necessary to consider the implicated genes in the context of biological networks and pathways. Sets of genes and networks can be placed in specific developmental stages and cell types to generate more precise understanding of their effects on brain regions and circuits. Diagnostic architecture—the structure of the interrelationships between psychiatric syndromes—is subsequently refined by increased knowledge at each of these levels.

The evidence is now overwhelming that psychiatric disorders have a "polygenic" basis—that many genetic loci, mostly with small effect sizes, contribute to risk (Visscher et al., 2017). In this respect, psychiatric disorders are broadly similar to other common biomedical diseases. The polygenic concept allows for the fact that some individuals can harbor genetic variants of far larger effects. This is particularly salient for autism spectrum disorder (ASD), where a large effect variant is present in ~15% of cases, along with smaller proportions of individuals with Tourette's syndrome (TS), attention-deficit hyperactivity disorder (ADHD), and schizophrenia (SCZ) (Iossifov et al., 2012; Sanders et al., 2012; Satterstrom et al., 2018b; Singh et al., 2016; Willsey et al., 2017). A polygenic model can include weak and strong genetic effects, as well as non-genetic influences (e.g., the impact of environmental exposures and life events [e.g., chronic fear], the impact of individual choices). A key empirical finding is that genetic risk can be non-specific and shared to varying extents across many adult- and childhood-onset psychiatric disorders (Antilla et al., 2018; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Schork et al., 2019).

As progressively larger studies of psychiatric disorders have uncovered increasingly more about their genetic architecture, the need to elucidate additional architectures has become clear (Figure 1). Even if we were to have complete knowledge of the genetic architecture of a psychiatric disorder, full understanding requires deep knowledge of the functional genomic architecture—how these loci interact in the nucleus (often across large distances), how gene and isoform expression are coordinated for many genes, and how these affect networks. Second, following from this, is cellular architecture—of all brain regions, cell types, and developmental stages, where and when are the functional architectures operative, and what circuits do they influence? Finally, the data used to diagnose psychiatric disorders consist of signs and symptoms determined during patient-clinician interactions that infrequently have recourse to objective biomarkers to support or refute a diagnosis. Furthermore, the internationally accepted definitions of psychiatric disorders were crafted by experts and influenced by traditions dating back a century or more. Given that the genetic architectures of different psychiatric disorders can strongly overlap, we are challenged to re-evaluate and refine the diagnostic architectures of psychiatric disorders with respect to fundamental genetic and neurobiological data.

Psychiatric Disorders and Genetics

Definitions

Many psychiatric disorders are internationally recognized (World Health Organization, 1993). In this Review, we focus on the 10 psychiatric disorders that have been the subject of the greatest scrutiny by geneticists and all are the focus of working groups in the Psychiatric Genomics Consortium (PGC) (Sullivan et al., 2018). We do not cover dementia and intellectual disability (ID), which are often considered neurological conditions with prominent psychiatric manifestations, but recognize the inherent arbitrariness of following this conventional delineation. Table 1 contains brief definitions of each condition, along with lifetime prevalence rates and twin heritabilities. The essence of each disorder is a persistent, pervasive, and pathological pattern of abnormal mood (as in mania or major depression), perception (e.g., auditory hallucinations in SCZ, bizarrely distorted body image in anorexia nervosa [AN]), behavior (e.g., repetitive hand-washing in obsessive-compulsive disorder [OCD], injurious ethanol consumption in alcohol dependence [ALC]), or higher-level cognition (e.g., delusions in SCZ). People with

Table 1. Descriptive Features of 10 Psychiatric Disorders

Abbreviation	Name	Lifetim Prevalence	Twin Heritability	SNP Heritability	GWA Cases	GWAS Loci	Essential Characteristics	Notable Impacts
ADHD	attention-deficit hyperactivity disorder	0.053	0.76	0.216	20,183	12	persistent inattention, hyperactivity, impulsivity	costs estimated at ~$100 billion USD per year
ALC	alcohol dependence	0.125	0.51	0.090	14,904	2	persistent ethanol use despite tolerance, withdrawal, dysfunction	most expensive psychiatric disorder (total costs > $225 billion/year)
AN	anorexia nervosa	0.009	0.58	0.110	16,992	8	dangerously low weight from self-starvation	notably high standardized mortality ratio
ASD	autism spectrum disorder	0.017	0.74	0.118	18,381	5	abnormal social interaction and communication beginning before age 3	wide range of function, from complete care to exceptional achievement
BIP	bipolar disorder	0.010	0.85	0.213	29,764	30	manic-depressive illness, episodes of mania usually with depressive episodes	nearly as disabling as SCZ
MDD	major depressive disorder	0.162	0.37	0.087	135,458	44	unipolar depression, persistent dysphoria with physical/cognitive symptoms	top five in burden of disease globally
OCD	obsessive-compulsive disorder	0.011	0.47	0.280	2,688	0	uncontrollable, persistent thoughts (obsessions) and repetitive behaviors (compulsions)	top 10 globally for lost income and decreased quality of life
PTSD	post-traumatic stress disorder	0.068	0.46	0.038	23,212	2	trauma-related re-experiencing, avoidance, negative thoughts, and hyperarousal[a]	high medical and psychiatric comorbidities (suicide, substance depdence)
SCZ	schizophrenia	0.004	0.81	0.244	40,675	145	longstanding delusions and hallucinations	life expectancy decreased by 12–15 years
TS	Tourette's syndrome	0.005	0.37[b]	0.350	4,819	1	vocal or motor tics (stereotyped, involuntary movement and utterances)	comorbid psychiatric disorders cause more disability than tics

All definitions are made more restrictive by requiring persistence over time (e.g., the criteria for SCZ require ≥6 months of symptoms), presence in different contexts (e.g., for ADHD, inattention at home, school, and in peer interactions), and significant impairment. See Table S1 for data and citations. Updated from Sullivan et al., (2012).

[a]PTSD is distinctive in requiring traumatic exposure to death, injury, or sexual violence.

[b]Heritability from national pedigrees is higher (0.77).

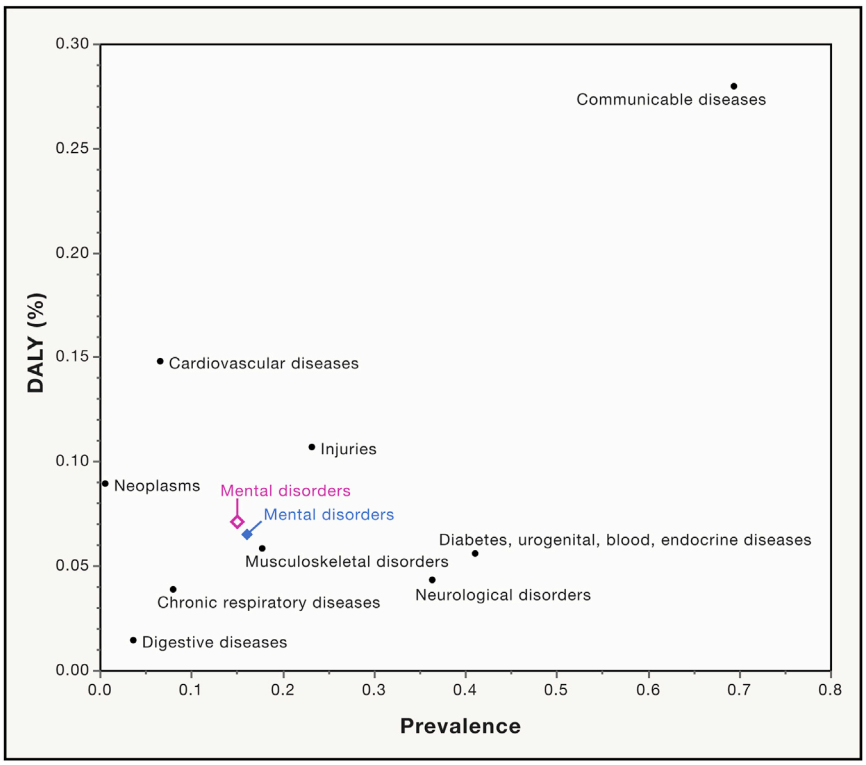

Figure 2. Prevalence and Impact of Psychiatric Disorders Compared to Other Major Diseases

Looking at both measures allows evaluation of how common and how impactful a psychiatric disorder is. These data are from global surveys, and we have included other major classes of disease. Prevalence (x axis) and disability-adjusted life years (DALYs, y axis) for 10 major classes of disorders. DALYs are a measure of overall disease burden due to the number of years lost due to poor health, disability, or premature mortality, here expressed as the proportion of total global DALYs. Psychiatric disorders rank fifth and account for 6.7% (females are the open diamond and males are the closed diamond) (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017).

See also Table S1.

serious psychiatric disorders are often acutely aware that their symptoms and behaviors "don't make sense" and have made exhaustive attempts to ameliorate their illness.

Each of these disorders has an explicit operational definition based on symptoms (reported by a person or an informant) and signs (observed by a clinician). Many diagnostic features from laboratory testing, brain imaging, or pathology have been evaluated, but few have acceptable positive and negative predictive values to support routine clinical use. One exception is the measurement of intelligence, which defines ID and which is an important clinical stratifier for many psychiatric disorders (particularly ADHD and ASD). Thus, these conditions are disorders or syndromes, not diseases due to their descriptive/syndromic definitions without objective defining features based on etiology. All are idiopathic with rare exceptions (single-gene disorders with prominent ASD features like *MECP2* and Rett syndrome).

Impact

Psychiatric disorders are among the conditions with the greatest impacts (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017), ranking fifth globally in causes of disability (Figure 2). These disorders are associated with considerable morbidity and increased rates of mortality due to suicide and ill health (e.g., 10- to 15-year reduction in life expectancy for SCZ) and cost (due to health care, disability, and lost income). The human impact of a severe mental illness on the lives of the people afflicted and their families and communities is not readily condensed into a statistic but is nonetheless often profound. In addition, empirical studies have demonstrated the effectiveness of social, psychological, and/or pharmacological therapies for all of these disorders. These are treatable conditions, and treatment often leads to marked improvements in symptoms and quality of life. However, particularly for severe psychiatric disorders, current therapies may only mitigate symptoms. Therapeutic failure is common.

Commonalities

Four clinical features of psychiatric disorders are notable. First, there is considerable clinical variability. For example, individuals with ADHD or OCD can have mild, transient symptoms in childhood or lifelong, incapacitating symptoms. People with ASD can have profound impairment requiring lifelong care, as well as high academic/occupational achievement (despite impairments in social relations and behavioral flexibility). Features of many psychiatric disorders are on a continuum: depressed mood is a normal human experience but becomes major depressive disorder (MDD) if present continuously for weeks or months. Second, many psychiatric disorders are chronic illnesses: MDD often begins in adolescence and recurs throughout adulthood. SCZ frequently begins in early adulthood and is often life altering. Most people with ASD in childhood continue to have ASD in adulthood (Billstedt et al., 2007; Howlin and Magiati, 2017). Third, given the syndromic nature of the definitions, it is unsurprising that these conditions are commonly comorbid (e.g., many people with AN or ALC also meet criteria for MDD, AN overlaps considerably with MDD and OCD, about half of people with ASD have ADHD symptoms) (de Bruin et al., 2007).

Finally, the neurological impact of psychiatric disorders can be subtle. Some individuals have important neurological impairments (e.g., epilepsy and motor or sensory abnormalities) or neurological "soft signs" (deficits in sensory integration, coordination, and complex motor sequencing). However, most people with a severe psychiatric disorder have little if any neurological impairment (e.g., consciousness, sensation, motor function, language, many aspects of memory). Individuals who are at the worst point in their illnesses—floridly hallucinating, severely manic, profoundly melancholic, or starved down to a body mass index of 10—usually have normal neurological exams

and unremarkable or only non-specific structural and functional brain-imaging findings. This again suggests relatively subtle and heterogeneous etiological processes.

A Brief History of Genetic Studies

For over 150 years, researchers have applied the best available methods to try to find the causes of serious psychiatric disorders. Many of these methods had been informative for other medical disorders but unsuccessful for psychiatric disorders. The most reproducible single clue that emerged was the tendency for psychiatric disorders to "run" in families—as established by 50+ years of twin, family, and adoption studies (summarized in Table 1) (Polderman et al., 2015). This observation logically led to attempts to identify the specific locations in the genome conferring risk. The progression of genetic studies mirrors technology development since the 1960s: single-protein biomarkers, small numbers of restriction-fragment-length polymorphisms, genome-wide panels of microsatellite markers for linkage analysis, small numbers of selected SNPs, arrays containing 10^5–10^6 genome-wide SNPs, and resequencing of genes and then exomes and whole genomes. Whenever a new technology emerged, a prominent early success was strongly influential. Examples include identification of a genomic region for Huntington's disease using linkage analysis of 12 markers in 1983, the association of common variation in *APOE* with Alzheimer's disease in a candidate gene study of 30 cases in 1993, identification of *CFH* as a risk factor for age-related macular degeneration using SNP arrays in 96 cases in 2005, and exome sequencing identifying the cause of Miller syndrome in four cases in 2009.

These early successes were a form of "winner's curse" (Ioannidis, 2005) that led to gross underestimation of the efforts that would ultimately be required (we note that geneticists working on most other complex human diseases were similarly misled). Linkage analysis is poorly powered for complex traits (Risch and Merikangas, 1996). Compared to current knowledge, the reproducible yield of candidate gene-association studies is negligible (Farrell et al., 2015). Linkage and candidate gene studies led to many claims of gene discovery (e.g., *COMT*, *DISC1*, *DTNBP1*, and *NRG1* for SCZ) that were not subsequently supported (Border et al., 2019; Farrell et al., 2015). Psychiatric genetics was bedeviled by reproducibility problems.

Global Consortia

The failure of simple models led to widespread acknowledgment of a need for sample sizes that were beyond the reach of any single group to achieve power to detect generalizable findings. The need for unprecedented levels of cooperation became widely recognized (Cichon et al., 2009; Fischbach and Lord, 2010; Geschwind et al., 2001; Lajonchere and AGRE Consortium, 2010; Moldin, 2003; Psychiatric GWAS Consortium Steering Committee, 2009). Many consortia emerged to combine efforts across research groups to elucidate reproducible genetic risk factors for psychiatric disorders. For adult-onset disorders, this began with transient efforts (e.g., GAIN, ISC, SGENE). For childhood-onset disorders, these efforts began in ASD with smaller consortia, such as the IMGSAC and PARIS, during the linkage era (International Molecular Genetic Study of Autism Consortium, 2001; Philippe et al., 1999). Subsequently, the formation of the Autism Genetic Resource Exchange (AGRE) enabled expansion to include multiplex families (Geschwind et al., 2001; Lajonchere and AGRE Consortium, 2010). The largest consortium in psychiatric genetics is the PGC, which began in 2007 (http://www.med.unc.edu/pgc/) (Sullivan et al., 2018) and has spearheaded many of the major genetic advances in the field. The PGC has 800+ members from 40+ countries and working groups for 11 psychiatric disorders. The PGC is a mega-analysis consortium that allows highly harmonized analyses, rigorous quality standards, and significance thresholds that maximize reproducibility. A feature of most consortia is making summary results freely available, along with paths for other researchers to get access to individual data or biological samples for independent research.

As whole-exome and whole-genome sequencing (WES, WGS) have become mainstream, the Whole Genome Sequencing for Psychiatric Disorders consortium is adopting a similar approach as the PGC but for modern resequencing (Sanders et al., 2017). Investigators conducting WES for ASD have formed multiple consortia. The Simons Simplex Collection focused on discovery of *de novo* variation via WES and played a major role in accelerating gene discovery in ASD (Fischbach and Lord, 2010). The SPARK initiative is conducting WES on 50,000 ASD cases, a rapid data-release policy (Spark Consortium, 2018). The Autism Sequencing Consortium rigorously harmonizes ASD resequencing data from multiple studies (Buxbaum et al., 2012), and combining data from multiple cohorts has enabled major advances (De Rubeis et al., 2014; Sanders et al., 2015).

Genetic Architecture

We review here what we have learned about the genetic architectures of the 10 psychiatric disorders in Table 1. Because some of the basic techniques may be unfamiliar, we provide in Table 2 brief definitions and accessible introductions to these topics that are beyond the scope of this Review. The results to date indicate that psychiatric disorder risk is imparted by many common variants of individually small effects, and several disorders also have contributions from rarer variants with larger impact on risk (Geschwind and Flint, 2015; Sullivan et al., 2018).

Background

Knowledge of genetic architecture is fundamental to rational study design and genotyping technology choice. For many decades, this was debated with various authors speculating architectures inferred from indirect clinical or epidemiological data. The extreme positions were the common-disease/common-variant model (psychiatric disorders result from the cumulative effect of many common variants of small effect) and the multiple-rare-variant model (strong genetic impacts on single genes cause psychiatric disorders, with each case having a different causal mutation). Neither model can explain all of the genetic risk, and many possible genetic architectures lie between these extremes.

Genetic variation lies on a continuum from common to extremely rare: a risk variant might be present on half the chromosomes in a population or be observed only once in 1 million people. We can consider a frequency continuum from ultra-rare (present once in a large sample, frequency <0.001%) to rare (present in a pedigree or in descendants of a recent ancestor, <0.1%) to uncommon (0.1% to 1%) to common (>1%). In general, rare variants arose recently, and common

Table 2. Brief list of "Omic" Technologies Used to Understand Psychiatric Disorders.

Initialism or Acronym	Reversed	Description
GWAS	genome-wide association study	Genomics: usually a case-control comparison of common genetic variation revealed by SNP arrays (prespecified set of reliably measured biallelic genetic markers selected for good performance and coverage of the genome). Can achieve coverage of >90% of common variants in the genome. Can also identify rare CNVs. Many studies of psychiatric disorders (Corvin et al., 2010; Sullivan et al., 2018; Visscher et al., 2017).
WGS	whole-genome sequencing	Genomics: *ab initio* resequencing of the genome. In concept, can identify all types of genetic variation. Increasingly used clinically for rare genetic syndromes. Few studies of psychiatric disorders to date (Wray and Gratten, 2018).
WES	whole-exome sequencing	Genomics: a version of WGS focused on the protein-coding parts of the genome (~3%) using one of several methods to pull down all known exons. This provides a focused and less expensive way to identify gene-disrupting or missense variants in exons. WES has identified ~100 genes for ASD and an increased "burden" of rare, protein-altering genetic variation differing between cases and controls in SCZ and a few other disorders (Biesecker and Green, 2014; Warr et al. 2015).
–	epigenomics	Unlike the (usually) static, body-wide nature of genomics (GWAS, WGS, WES), multiple readouts that capture changes that do not affect DNA sequence but act to alter the functional state of cells and tissues. These include DNA methylation, histone tail modifications, etc. Initial approaches required large numbers of cells, but improved versions can increasingly be applied to single cells. Epigenomic changes can be highly specific to a cell or tissue or common across the body; they generally reflect cell differentiation and function. (Ecker et al., 2012).
OC	open chromatin	Epigenomic: regions of the genome that are not histone bound in cell nuclei and thus open to gene regulatory processes. Main methods are ATAC-seq and DNase-seq (Ecker et al., 2012).
ChIP-seq	chromatin immunoprecipitation sequencing	Epigenomic: a class of methods to identify functional modifications to specific genomic regions. Many focus on changes to the N terminus tails of histone proteins. Such changes are part of the histone code that can dramatically alter gene expression. Examples of histone marks strongly associated with functional chromatin states include acetylation at the 27th lysine of the histone H3 protein (H3K27ac) and trimethylation of the 4th lysine of the histone H3 protein (H3K4me3) (Ecker et al., 2012).
Hi-C	none	Epigenomic: one of several chromosome-conformation capture methods that can capture genomic regions that are near each other in cell nuclei. Hi-C does this in an all-to-all manner, whereas other methods target more specific interactions. A subset of these DNA-DNA contacts these can mediate regulatory interactions between regions that are located far apart (Dekker et al., 2017; Rowley and Corces, 2018).
RNA-seq	RNA sequencing	Genomic: identify the amount of all RNA molecules in a cell or tissue, a transcriptomic technology. RNA-seq can also capture splicing and isoform level information. (Hardwick et al., 2017).
eQTL	expression quantitative trait loci	Genomic and epigenomic: identify genetic predictors of gene expression. Essentially, GWASs for every variable transcript in a tissue (~50,000) to identify genetic variants associated with RNA abundance. Many are highly tissue or stage specific (Conesa et al., 2016; Nica and Dermitzakis, 2013).

variants are far older. Given what we know now, common variants generally have small effects on disease risk (odds ratio [OR] < 1.15), and rare variants typically have larger effect sizes (>2.0), are more likely to be deleterious, and tend to be removed by natural selection (Fu et al., 2013; Nelson et al., 2012; Zeng et al., 2018). This is not an invariant rule, as rare variants may have a continuum of risk (Marouli et al., 2017), and a fraction of common variants have large effects (e.g., *APOE* and Alzheimer's disease).

Technology

Two main technologies have emerged for capturing germline genetic variation in individual subjects: resequencing and SNP arrays. Resequencing determines anew many types of genetic variation in the immediately accessible genome. It captures many types of genetic variation—SNPs, insertion-deletions, copy-number variation (CNV)—across the frequency spectrum, from ultra-rare to common. In concept, resequencing is the method of choice for psychiatric genomics. Costs for WGS have declined considerably ($800 per sample), but analyzing WGS data remains challenging. Most resequencing studies to date used WES, reducing expense and analytic burden via a focus on protein-coding regions, where the functional impact of variants is easier to interpret than in the non-coding genome. Study designs are usually either standard case-control comparisons or family-based methods. For the latter, trios of unaffected parents and an affected offspring are popular, as they enable

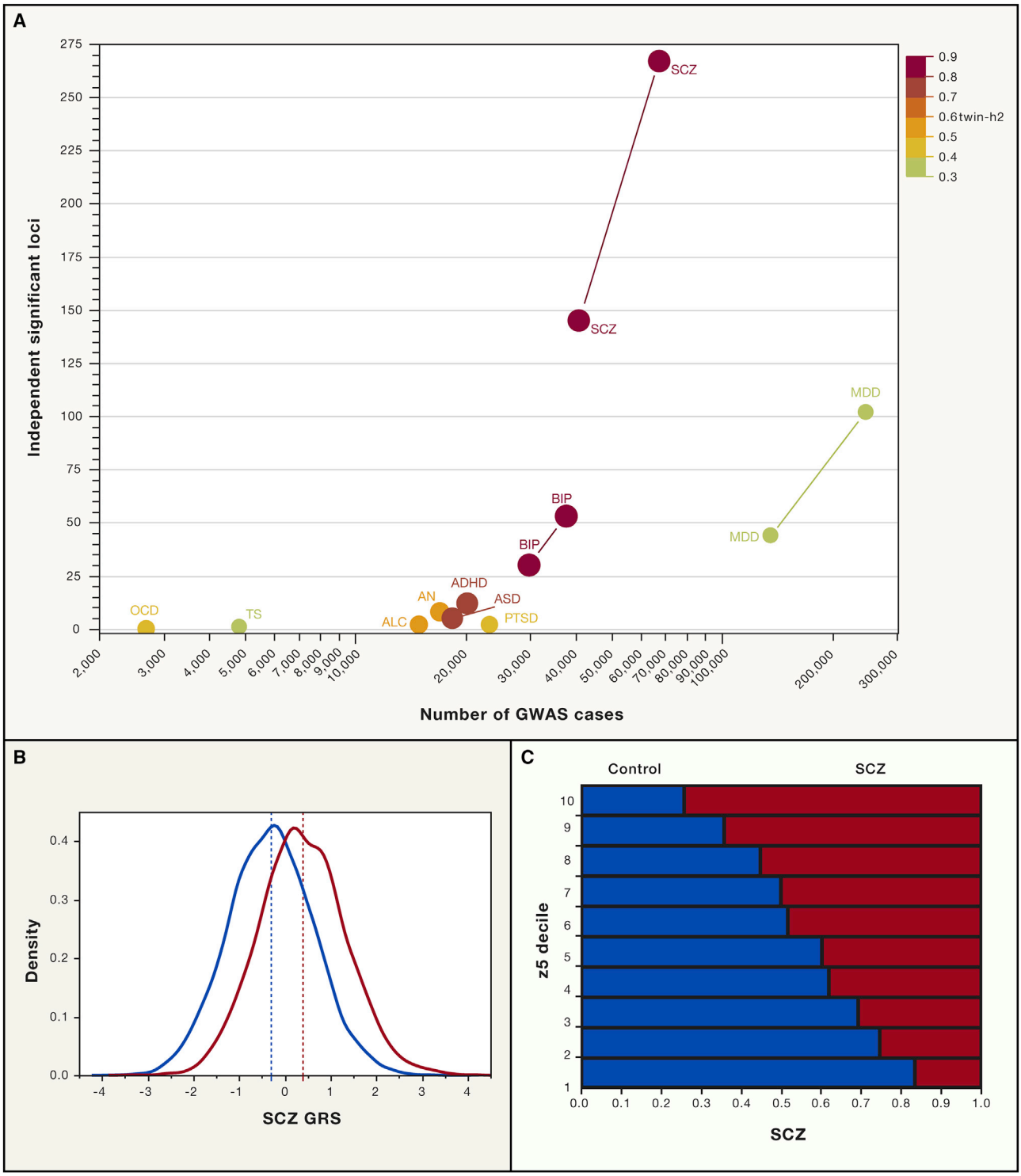

Figure 3. The Yields of GWAS

(A) Overview of common-variant gene discovery for the psychiatric disorders in Table 1. Sources and label definitions are in Table 1. The x axis is the $\log_{10}$ of the number of cases in the largest current GWAS. The y axis is the number of genome-wide significant and LD-independent loci. The color of each point reflects twin heritability per the scale on the right. For BIP, MDD, and SCZ, the graph includes published and in preparation/in press results (connected by a line). Sample size is the major determinant of discovery. We thank PGC colleagues for allowing us to present pre-publication results.

(B) Density plot of genetic risk scores (GRSs) in 4,932 SCZ cases (red) and 6,210 controls (blue) from Sweden (training set is from the PGC 2014 SCZ paper excluding Swedish samples; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The x axis shows the standardized GRS and the

(legend continued on next page)

identification of *de novo* variation (i.e., present in an affected child but absent in parents), which can improve power to detect high-impact variants. Other resequencing technologies can focus on the less-accessible parts of the genome (repetitive regions or regions with variable structure and gene content). Although very expensive and technically complex, single-cell resequencing of nuclei from a tissue can identify somatic mutations that arose during development (these changes are not heritable but may contribute to illness in some individuals) (Evrony et al., 2016; McConnell et al., 2017). The largest resequencing studies of psychiatric disorders have fewer than 25,000 cases, but this will change in the next few years.

SNP arrays commonly include 700,000 or more readily genotyped biallelic genetic variants. These SNPs are preselected for reliability and capacity to capture 90% or more of common genetic variation in a population either directly or indirectly by capitalizing on linkage disequilibrium (LD, the strong tendency for nearby genetic variants to be co-inherited). In effect, direct assessment of <1 million SNPs can be leveraged to accurately estimate genotypes for 5–10 million or more common, uncommon, and even rare genetic variants. SNP arrays are inexpensive ($35 per sample) and have been applied to very large numbers of people. Array technology can also identify large, rare CNVs (Luo et al., 2012; Marshall et al., 2017; Sanders et al., 2011; Sebat et al., 2007). WGS provides substantially more genome coverage and resolution, especially with regard to certain forms of chromosomal structural variation (Redin et al., 2017), but at an order of magnitude cost more than SNP arrays. SNP-array studies of readily measured human traits (e.g., height, educational attainment, lipid levels) now routinely exceed sample sizes of 1 million, and studies of psychiatric disorders have 10,000–130,000 cases. These studies do not directly capture causal genetic variation necessitating substantial follow-up to identify the causal variants and genes affected (Gusev et al., 2018; Sekar et al., 2016; Wang et al., 2018a).

Key issues in all of these studies are rigorous quality control, careful assessment and control for multiple types of bias, and correction for multiple comparisons. A large number of statistical tests are conducted, requiring correction for multiple comparisons. For example, for SNP array studies, an accepted threshold is $p < 5 \times 10^{-8}$, akin to correcting α =0.05 for 1 million comparisons.

Common-Variant Association Studies of Psychiatric Disorders

Most genetic studies of psychiatric disorders in the past decade have used SNP arrays to assess the role of accessible common variation (also known as genome-wide association studies [GWASs]). The common-variant findings for psychiatric disorders are summarized in Figure 3A. Studies in SCZ and MDD have yielded >100 loci; bipolar disorder [BIP] has 53 loci; and ADHD, AN, and ASD have 5–12 loci. The crucial determinant of the number of loci discovered is the number of cases; as sample sizes increase, more loci will be identified (Geschwind and Flint, 2015; Sullivan et al., 2018). As a common disorder with relatively low twin heritability (Levinson et al., 2014), MDD has had notable difficulties with genetic discovery, but focusing on severe cases (CONVERGE consortium, 2015) and increasing sample sizes has been particularly fruitful (Wray et al., 2018).

Across all disorders, 241 loci have a significant association with the 10 psychiatric disorders in Table 1 with 22 loci associated with $\geq$2 psychiatric disorders. Although most loci are disease specific, many loci increase risk for multiple disorders. These loci together implicate ~76 Mb of the genome, as containing common genetic variants involved in the etiology of these disorders. We speculate that many loci contain multiple functional elements that contribute to risk. Around 400 protein-coding genes lie in these loci. Traditionally, genomic location is used to assign SNPs to genes; however, as discussed more fully below, this practice yields an incomplete portrait. If we overlay functional genomic data from human brain (e.g., expression quantitative trait locus [eQTL], regulatory chromatin interactions), about 50% of the time, genes located in loci are also implicated by functional data. Crucially, recent studies have shown that genes located far outside of a locus are often implicated (see Functional Architecture section below) (Wang et al., 2018a; Won et al., 2016).

Although the effects of any individual variant may be small, they can nonetheless point to biological processes that may be highly relevant to therapeutics. For example, GWAS results for SCZ (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and MDD (Wray et al., 2018) are enriched for genes that encode proteins known to interact with pharmacological targets of antipsychotics and antidepressants.

Genetic Risk Scores, SNP Heritability, and Genetic Correlations

In the past decade, GWASs provided the impetus for several methodological developments. These methods were partly motivated by the failure of early genetic studies to identify common-variant associations with SCZ (sample sizes, 250–1000 cases).

First, based on ideas from animal breeding genetics, genetic risk scores (GRSs) initially appeared as part of a SCZ GWAS (Purcell et al., 2009). A GRS captures the number of inherited common-risk variants as a normally distributed number and can be compared to a population mean (e.g., a person might have a standardized SCZ GRS of 2, indicating inheritance of SCZ risk alleles in the top 2–3 percentiles). Computing a GRS requires a sizable external training set and can be applied to new individuals of similar ancestry. GRSs can use significant, nearly significant, and non-significant SNP associations and have clearly indicated that more common variants will be discovered as sample sizes increase (Purcell et al., 2009). Indeed, GRS differences between cases and controls are

y axis shows the smoothed density, a prediction of the proportion of cases or controls with a given GRS value. The dashed vertical lines show the means of each group. The group means differ by over 2/3 of a standard deviation (0.686) and are highly significantly different ($p = 1.1 \times 10^{-254}$, controlling for genotyping array and 5 ancestry principal components [PCs]). The two curves overlap substantially, but there are 48 controls with GRS >2 and 24 cases with GRS <−2.
(C) Depiction of GRS described in (B) but showing the proportions of cases (red) and controls (blue) in each SCZ GRS decile (y axis, 1 = lowest 10%, 10 = highest 10% GRS). x axis is the proportion within each decile. The proportions of cases increase steadily from lowest to highest. However, there are substantial numbers of cases in the lowest decile and controls in the highest decile.

now so widely replicated that GRSs are used for quality control (the absence of a difference often indicates a basic problem with a dataset). Inheriting a notably large number of SCZ risk alleles (e.g., being in the top versus bottom 10% for GRSs) carries more than a 10-fold increased risk of SCZ (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

For example, Figure 3B shows the distributions of SCZ GRSs in a set of SCZ cases and controls. There is a highly significant mean difference between groups, but the distributions overlap substantially. Figure 3C depicts the same data but shows the proportions of cases and controls in each GRS decile. Intriguingly, there are many controls in the top decile and many cases in the lowest decile. Detailed investigations of these observations are underway (e.g., do controls in the upper decile have a subclinical form of SCZ or have strong protective factors? are cases in the lower decile phenocopies or more likely to have a strong-effect genetic variants?).

GRSs have emerged as a potentially important output from psychiatric genetics and may help guide future precision-medicine approaches. In other areas of medicine, GRSs provide new ways to evaluate risk and to stratify patients (e.g., for prostate cancer, breast cancer, cardiovascular disease, and type 2 diabetes mellitus) (Grönberg et al., 2015; Khera et al., 2018; McCarthy and Mahajan, 2018; Shieh et al., 2016). For psychiatric disorders, considerable research is in progress; the potential is that, for the cost of an inexpensive SNP array, GRSs could assist in differential diagnosis, therapeutic selection, outcome prediction, and patient stratification. Multiple clinical questions could be addressed: for an individual with multiple comorbidities (ADHD, ASD, OCD), do the three GRSs indicate that one is the logical focus of treatment? Should this person with MDD and a high BIP GRS receive a mood stabilizer, as well as an antidepressant? Can we identify people with post-traumatic stress disorder (PTSD) at first presentation who are at high risk of a pernicious course of illness? Can information from genes in biological pathways be used to develop "mechanistic GRSs" that could then be used to identify an antipsychotic with the greatest chance of clinical response? We would like to add an important caveat: although GRSs are conceptually straightforward, their creation and use requires considerable care and sophistication to derive secure and reproducible findings (Lewis and Vassos, 2017; Torkamani et al., 2018). As just one example, incorrect inference can readily occur if the GRS training and target datasets are from different ancestries (Martin et al., 2017).

Second, several methods can calculate the heritability of a trait using SNP array data (Bulik-Sullivan et al., 2015; Yang et al., 2011). These provide assessments of heritability based on genome-wide genotypes and improve upon traditional heritability measurements given their basis in direct genetic measurements. SNP heritability can be estimated for traits that are difficult or impossible to assess using twins (e.g., antipsychotic adverse drug reactions). Indeed, SNP heritability estimates are available for thousands of traits (Zheng et al., 2017). Table 1 shows SNP-heritability estimates, and these tend to follow traditional heritability. These provide exceptionally strong indications that common genetic variation is important for all complex psychiatric disorders, and more will be discovered with increasing sample sizes.

In almost all instances, SNP heritability is less than twin/pedigree heritability. If reviewed critically, indirect twin/pedigree heritability estimates are often upwardly biased, and the degree to which SNP heritability is different from indirect measures is unclear. For any real difference between SNP and twin/pedigree heritability, the major reasons are (1) imperfect assessment of common variation (i.e., missing common variation in hard-to-genotype or impute regions), (2) complex, non-SNP common genetic variation whose identification requires resequencing or specialized methods, and/or (3) poor measurement of rare genetic variation with current sample sizes and technologies. It is important to note that the goal of genetic studies of psychiatric disorders is to generate clinical and biological insights and not to align different conceptualizations of heritability.

Third, we can now readily estimate the genetic correlations between traits using SNP array data (Bulik-Sullivan et al., 2015; Yang et al., 2011). These methods have provided insights into the fundamental basis of these disorders. A similar construct could be assessed using twin or pedigree data but with lesser power and precision. Notably, the major psychiatric disorders have significant and often sizable genetic correlations (Lee et al., 2013). A more comprehensive effort of 25 psychiatric and neurological disorders showed that most psychiatric disorders had significant genetic intercorrelations, but there were far fewer for neurological conditions (Antilla et al., 2018). Importantly, comparison of SCZ results between European and East Asian samples indicated that the genetic correlation was indistinguishable from one, strongly indicating that the common-variant genetic basis of SCZ is highly similar across these global populations (Lam et al., 2018). Under a set of specific assumptions, we can also apply Mendelian randomization (MR) to suggest causality; for two traits with sufficient numbers of significant associations, MR can assess the plausibility of whether one trait has a causal relation with another (e.g., lower educational attainment and higher body mass were putatively causal for MDD) (Wray et al., 2018).

Rare-Variant Association Studies of Psychiatric Disorders

Resequencing studies that implicate ultra-rare and *de novo* variation have the major advantage of pinpointing risk variants in specific genes. Compelling results can leverage the extensive neuroscience toolkit for experimental modeling of specific genes. Until relatively recently, identifying rare variants for psychiatric disorders was mainly limited to large structural variants (De Rubeis et al., 2014; Iossifov et al., 2012; Marshall et al., 2017; Sebat et al., 2007). As noted above, resequencing technologies enable rare-variant discovery in ever-larger samples, and we know now that ultra-rare and *de novo* single-nucleotide variants contribute to risk (Genovese et al., 2016; Sanders et al., 2015; Satterstrom et al., 2018a; Singh et al., 2016; Wang et al., 2018b; Willsey et al., 2017). Rare-variant association tests require the aggregation of rare, deleterious mutations at a particular locus (usually in protein-coding exons or annotated regulatory regions) in cases compared to controls (Zuk et al., 2014).

At present, the largest resequencing efforts are for ASD and SCZ. Rare-variant discovery has been most successful in ASD

where WES for rare, *de novo*, protein-truncating variants (PTVs) in mutation-intolerant genes has identified around 100 high-confidence connections to specific genes (Satterstrom et al., 2018a). Although each gene accounts for only a small fraction of cases, rare *de novo* variation is predicted to account for ~15% of ASD cases (Iossifov et al., 2014). Most of these mutations also decrease IQ, and ID is an important comorbidity of ASD (Buja et al., 2018; Iossifov et al., 2014), which is consistent with previous work identifying dozens of known severe, rare medical genetic syndromes associated with ASD (reviewed in Abrahams and Geschwind, 2008; Geschwind, 2009).

The yield of resequencing in ASD is markedly higher than for other psychiatric disorders. WES has implicated only two genes for SCZ (Singh et al., 2016; Steinberg et al., 2017) at sample sizes that yielded dozens of associations for ASD. In TS, a role for *de novo* gene disrupting and missense variants has been established (Willsey et al., 2017), and two high-confidence genes for TS were recently identified (Wang et al., 2018b). Sizable WES of ADHD and BIP are underway. For the other psychiatric disorders in Table 1, major resequencing efforts are at more nascent stages. There is debate in the field as to whether resequencing efforts are worth the 10–15× greater cost, particularly for later-onset disorders that are not associated with ID or neurological impairment. The sobering experiences in SCZ and type 2 diabetes suggest a limited role of large-scale resequencing in adult disorders until the costs decline substantially.

Identification of rare, genic mutations can be extremely informative. They directly implicate specific genes and are amenable to experimental modeling. At the same time, interpretation of these models is a formidable task. While some of these genes are relatively specific to a disorder like ASD, many confer broader phenotype risks (Abrahams and Geschwind, 2008; Ronemus et al., 2014; Satterstrom et al., 2018a). Pleiotropy is more the rule: most mutations increase risk for a range of neurodevelopmental outcomes (e.g., ID, ASD, epilepsy, psychosis). These pleiotropic large-effect mutations may work by disrupting key neurodevelopmental processes rather than specifically causing one defined clinical disorder (Geschwind and Levitt, 2007). Even for a highly significant gene identified from resequencing, precisely which human phenotype is being modeled and with what specificity may be uncertain (i.e., ID and/or ASD). Another question from these findings is whether genes that harbor large-effect mutations causing ASD and ID affect biological processes different from those that cause ASD that are not comorbid with ASD. Indeed, some gene-network analyses suggest the existence of molecular processes that distinguish ASD from ID (Parikshak et al., 2013; Satterstrom et al., 2018a).

The relative contributions of rare *de novo* missense or inherited mutations to psychiatric disorders are not quite as well established as *de novo* PTVs. However, both rare missense and inherited mutations have been shown to contribute to ASD, simply with smaller effect sizes than *de novo* variants (Ruzzo et al., 2018; Sanders et al., 2015). Furthermore, the effects of PTVs can be assessed in a functional and evolutionary context (loss of one copy of the gene and the degree of constraint) (Samocha et al., 2014), while the functional impact of individual missense mutations is harder to determine. One approach to this problem integrates prior information, such as gene or protein-protein interaction (PPI) networks to boost the signal of missense variation (Parikshak et al., 2013). The detection of inherited variation may be further hindered by ascertainment bias from study designs that favor detection of *de novo* variants. It is illustrative that studying families having multiple children with ASD significantly reduced the signal from *de novo* variation compared to singleton families while enhancing that from inherited variation to identify risk genes (Ruzzo et al., 2018). Consistent with a role of rare, inherited variation in risk also comes from a recent WES of ASD and ADHD that excluded cases with ID or comorbidity (Satterstrom et al., 2018b). These investigators found that rare PTVs in mutation-intolerant genes occurred with equal frequency in both ASD and ADHD and that the genes impacted significantly overlapped. Larger samples are needed to determine if genes with statistically significant association with each disorder are shared and whether the mutations have similar molecular impact. For example, even if mutations increasing risk for ASD and ADHD were in the same gene, they might impact different isoforms that could have different functional consequences. Emerging data from RNA sequencing (RNA-seq) from brain show remarkable isoform diversity in parallel with distinct protein interactions and cell-type specificity (Gandal et al., 2018b), further highlighting the importance of understanding mutational consequences in an isoform context.

Copy-Number Variation

CNV refers to structural chromosomal variants greater than 1 kb in size that lead to an increase or decrease in the DNA sequences encompassed by the CNV (e.g., fewer or more than two copies of an autosomal region). Approximately 4% of the genome comprises such structural variation, much of which is common, inherited, and relatively benign with regards to imparting disease risk (Brand et al., 2014; Conrad et al., 2010; Mills et al., 2011; Sebat et al., 2004). Larger *de novo* CNVs, especially ones that disrupt genes or change gene dosages, can carry major risks, particularly for neurodevelopmental disorders (Malhotra and Sebat, 2012; Sebat et al., 2007).

Several dozen rare CNVs are known to confer relatively strong risks for psychiatric disorders, most commonly in ASD and SCZ and less frequently in BIP, TS, and ADHD. Most known pathogenic CNVs increase risk for multiple disorders (de la Torre-Ubieta et al., 2016; Kirov, 2015; Lowther et al., 2017; Malhotra and Sebat, 2012). These recurrent CNVs usually arise *de novo*, mainly via non-allelic homologous recombination in regions flanked by low copy-number repeats.

CNVs associated with psychiatric disorders share several commonalities: (1) they usually contain multiple genes (with a few exceptions; Bucan et al., 2009; Talkowski et al., 2011); (2) they are usually >500 kb in size (although many we expect that many smaller CNVs will be found using WGS), and the major pathogenic mechanism is presumed to be dosage-sensitivity of genes in the CNV, although distal regulatory effects on genes outside of the CNV are also plausible (de la Torre-Ubieta et al., 2018); (3) many CNVs are associated with partial disruption of a range of developmental programs and impact multiple organs (cardiac, gut, immune, and endocrine, as well as brain); (4) most CNVs confer increased risk for multiple psychiatric disorders, including ID, ASD, ADHD, and psychotic disorders (Kirov, 2015; Lowther et al., 2017); and (4) penetrance can be highly

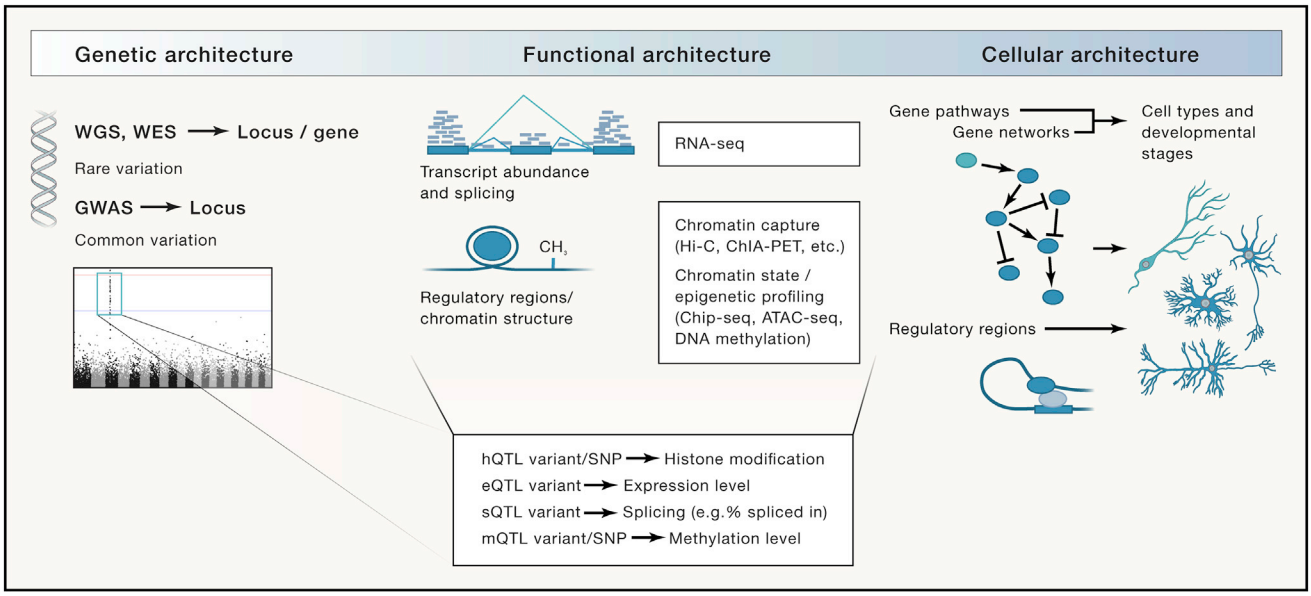

Figure 4. Establishing the Functional and Cellular Architectures Based on Genetic Findings

To begin, genetic analyses identify significant associations with one or more psychiatric disorders. Common variation is usually detected using GWAS and SNP-array technologies. Rare variation capitalizes on CNVs or resequencing via WES or WGS. Some causal variants alter protein structure or function and thereby directly point at specific genes. However, most genetic variation discovered to date is in non-coding regions, which can have highly diverse regulatory functions (e.g., enhancer or repressor activity or regulation of splicing or alternative promotor usage). Assigning non-coding regulatory variants to genes is imprecise, as gene regulation often occurs at a distance and does not necessarily involve the nearest gene. Instead, one can identify candidate target genes impacted by non-coding disease-associated genetic variation using a range of functional genomic data. For example, quantitative mapping approaches can identify how a particular variant affects open chromatin, histone tail modifications, gene expression, splicing, and DNA methylation. These methods integrate DNA-based genetic variation with multi-level "omic" data—RNA sequencing (eQTL or splicing QTL [sQTL]), methylation analysis (methylation QTL [mQTL]), or chromatin immunoprecipitation (ChIP)-seq (histone QTL [hQTL])—to identify the quantitative impact of genetic variation on these molecular phenotypes. Other biochemical methods identify active/open chromatin (ATAC-seq, DNase-seq) or 3D chromatin structures such as enhancer-promotor loops (Hi-C, ChIA-PET), which provide additional information on the relationship between regulatory regions and specific genes with which they interact. Many functional genomic readouts are tissue specific, highlighting the need for comprehensive studies of the human brain across development. When combined, these methods can identify the likely functional impact of disease-associated variation on specific genes, which can then be experimentally validated. Molecular pathways can be identified using pathway or gene-network analysis. Sets of disease-associated candidate genes can be tested for cell-type enrichment to define the cellular architecture. A similar approach can be applied to identified regulatory regions to define functional regulatory networks or the cell types impacted by disease associated regulatory variation.

variable, ranging from subtle effects detectable by neuropsychological tests to mild degrees of anxiety/ADHD to co-occurrence of severe psychiatric disorders (Kendall et al., 2017; Stefansson et al., 2014; Ulfarsson et al., 2017). Emerging evidence suggests that among other factors, some of this pleiotropy may be due to modification GRSs, because even in those with ASD or SCZ carrying large effect *de novo* mutations, there appears to be an additive effect of common variation on phenotypic expression (Tansey et al., 2016; Weiner et al., 2017).

Synthesis

In the past decade, major papers from the PGC and other consortia have conclusively shown that all of the psychiatric disorders in Table 1 have an important contribution from hundreds or thousands of common genetic variants of relatively subtle effect. Exactly how these variants influence gene expression in the context of biological networks is generally unknown but has highlighted critical gaps in our knowledge of gene regulation. Work in progress on the functional architecture and cellular/tissue architecture will, we believe, yield the needed insights. The impact of rare variation is less studied. Empirical data show that rare genetic variation plays a role in some of these psychiatric disorders (ASD and SCZ, in particular, but also TS and ADHD). However, direct comparisons of the contributions of common and rare genetic variation show that common variation dominates heritable risk for SCZ and ASD (Gaugler et al., 2014; Purcell et al., 2014). Still, rare variants that disrupt genes provide a clear starting point for mechanistic studies, and identification of large effect mutations in patients is of substantial clinical utility. Finally, many disorders are early in the discovery process. Consistent with the documented clinical and epidemiological comorbidity, there is also important genetic overlap, including substantial components of genetic variation that increase risk for multiple disorders—both of which necessitate consideration of diagnostic architecture.

Functional Architecture

Moving from common-variant findings to genes, molecular pathways, and cells requires comprehensive genomic analysis. Table 2 contains additional definitions and references to important background that is beyond the scope of this Review. Figure 4 presents a schematic of how we can systematically evaluate the implications and impacts of genetic architecture findings.

Table 3. Many Regulatory Interactions Are Distal

Distance from Regulatory Element to TSS		
eQTL	ATAC-seq	HI-C
127 kb	407 kb	394 kb
Distribution of eQTL Distance from TSS		
<10 kb	>10 kb	>100 kb
24%	76%	29%

Average distance from regulatory elements defined by eQTL, ATAC-seq, and Hi-C in fetal brain is shown, as well as percentage of eQTL in >10 kb (distal) and <10 kb (proximal) bins from the transcription start site (TSS) of genes in fetal brain. Data from de la Torre-Ubieta et al., (2018), Psioudakis et al. (2018), Won et al. (2016), and Walker and Geschwind (Walker et al., 2018). eQTL are generally closer to the TSS than the biochemically defined putative regulatory regions, which is expected, especially given the limited (10 kb) resolution of Hi-C.

From Variant to Gene

Because most genetic variation that contributes to common psychiatric disorders is not in protein-coding regions, a crucial step in understanding disease mechanisms is pinpointing the genes impacted by risk variants (Thurman et al., 2012; Visel et al., 2009). This requires functional annotation of non-coding regions—the goal of consortia like ENCODE (ENCODE Project Consortium, 2011), Roadmap (Kundaje et al., 2015), and GTEx (Battle et al., 2017), which produced genome-wide regulatory maps and transcriptional profiles across spectrum of cells and tissues. However, around half of non-coding regions have regulatory functions that are shared across tissues, meaning that about half of the regulatory elements in a given tissue may be relatively specific to a tissue, cell type, or developmental stage (Liu et al., 2017a; Kundaje et al., 2015; Won et al., 2016). This is particularly important for brain, which has higher cellular heterogeneity and longer developmental trajectories compared to other tissues. The need for brain-specific functional genomic data led to PsychENCODE (PsychENCODE Consortium, 2018) (http://resource.psychencode.org/), which has produced and integrated multiple types of functional genomic data from human brain (Gandal et al., 2018b; Li et al., 2018; Wang et al., 2018a). Its goals are to complement the work of these other consortia by producing accurate regional, cell-type-, and stage-specific annotation of gene regulation and transcription at tissue and cellular levels in brain from healthy individuals and cases with major psychiatric disorders. This effort is complemented by the BRAIN single-cell atlas of cell types and gene expression in human and mouse (Ecker et al., 2017).

These resources essentially provide maps for interpretation of genetic variation implicated in psychiatric disorders in the context of genes, their regulation, and the effects on biological pathways. A complicating factor is that assigning even well-annotated genomic regions to specific genes is not as simple as choosing the closest gene or genes containing variation that is highly correlated with the associated SNPs, which is usually the default approach (Whalen et al., 2016; Won et al., 2016). Rather, as suggested by studies of brain eQTL (Battle et al., 2017; Hauberg et al., 2017) and chromatin structure (de la Torre-Ubieta et al., 2018; Won et al., 2016), nearly half of the target genes of human regulatory variation are not in genomic loci defined by linkage disequilibrium (LD) (Whalen and Pollard, 2018) (Table 3). Thus, ''4D mapping'' of chromatin interactions (i.e., brain regions across developmental time) is critical for understanding the functional relationships of regulatory regions to genes (Dekker et al., 2017).

Functional genomic data include gene expression surveys, open chromatin, eQTLs, chromatin QTLs, methylation QTLs, histone marks, and regulatory chromatin interactions, initially for bulk tissues or sorted types of cells but increasingly at the single-cell level. As illustrated in Figure 4, these data can be combined to define candidate enhancer-promoter interactions (from locus to gene) whose accuracy can then be assessed in a biological system. Most published brain eQTL data have $n < 1,000$ and contain only a fraction of presumed regulatory relationships. Chromatin capture methods such as Hi-C can define chromatin structure in brain nuclei (Dekker et al., 2013) and can predict functional interactions defined by eQTL and enhancer-mRNA relationships (Won et al., 2016). Although integration of functional genomic data from brain yields empirically based hypotheses about regulatory relationships, experimental validation is required. Techniques such as self-transcribing active-regulatory-region sequencing (STARR-seq) permit large-scale validation (which suggests enhancer functionality) (Arnold et al., 2013; Liu et al., 2017b), while analysis in an appropriate cell type with epigenome-editing technologies can confirm target identity (de la Torre-Ubieta et al., 2018; Won et al., 2016). Currently, it is wise to be conservative and rely on regulatory interactions identified by multiple methods (e.g., eQTL/Hi- C, Gusev et al., 2018; or ATAC-seq/Hi-C, de la Torre-Ubieta et al., 2018). These distinct data types—often derived in different laboratories in different samples—show significant overlap in regulatory predictions (Gusev et al., 2018). This is in contrast to comparisons relying on LD blocks or the assignment by the closest gene, where the overlaps with methods that directly assess chromatin are less substantial (Short et al., 2018; Whalen and Pollard, 2018).

Application of functional genomic approaches to define regulatory regions and target genes has yielded important albeit tentative clues as to the developmental and cell type architecture of psychiatric disorders. One example comes from studies that partition disease heritability defined by genome-wide SNP genotyping, or by mapping putative causal variants across the genome, to identify regions of enrichment, and ask in what tissues and what stages are these regions active (de la Torre-Ubieta et al., 2018; Finucane et al., 2018; Skene et al., 2018; Won et al., 2016). As discussed more fully below, these studies have implicated specific development epochs and brain regions in risk for several psychiatric disorders and cognitive phenotypes. These initial studies demonstrate that creation of these gene regulatory maps with multiple methods that address different molecular processes, developmental stages, and brain regions is a critical step in understanding how disease risk biologically unfolds.

From Genes to Networks

To understand how genes contribute to psychiatric disorders, we are faced with the task of measuring and understanding phenotypes across a hierarchically organized complex system,

connecting genes to behavior. Few genes act in isolation but rather affect the function of other genes to influence a particular phenotype via in-cellular networks or pathways (Barabási et al., 2011; Geschwind and Konopka, 2009). This challenge is exacerbated by the polygenic nature of psychiatric disorders. To understand how genes contribute to CNS phenotypes, many groups have applied an analytical framework at a gene-network level involving coordinated regulation of gene expression (Parikshak et al., 2013, 2015). Network analysis can interrogate multiple levels of molecular organization and enable integration with other information, including known pathway annotations. Furthermore, when hundreds of genes are involved, network analysis provides an organizing framework that can divide large gene sets into biologically coherent modules for prioritization (Parikshak et al., 2013, 2015) or add power to GWASs (Horn et al., 2018). Combining network approaches with systems neuroscience permits the methodical connection of heterogeneous genetic risk factors to brain mechanisms (Gandal et al., 2016; Geschwind and Konopka, 2009).

Two general network approaches have been used in psychiatric genomics based on literature-curated pathway databases (e.g., Gene Ontology, KEGG) or data-driven tissue-specific approaches based on transcriptomic, proteomic, or other "omic" data (Parikshak et al., 2015). The former approach has many biases, including weighting highly studied genes, non-CNS functional annotations, or very non-specific annotations (e.g., "synaptic function") and lack of tissue specificity (missing tissue-specific interactions or emphasizing those observed in other tissues). Curated pathway-based studies using combinations of multiple methods and data sources are far more convincing than those using single sources and have yielded evidence for common pathways across psychiatric disorders (Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015) but still do not fully overcome biases inherent in literature curation. This illustrates a weakness in current functional annotations that are broad or biased with regards to neuronal annotation methods. Gene-network approaches can identify presumed functional modules in an unbiased manner, but understanding what these modules mean beyond broad annotations remains a major stumbling block for the field and will require efforts connecting gene expression to neural cell biology and physiology.

Despite these limitations, several studies in ASD and SCZ highlight the power of using transcriptional networks based on normal human brain tissue across development or brain regions or more generalized PPIs (Hormozdiari et al., 2015; Li et al., 2014; Lin et al., 2015) to identify molecular pathways, developmental epochs, or brain circuits enriched for genetic variation. Despite clear genetic heterogeneity, both ASD risk and SCZ risk converge on shared molecular pathways (Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015; Parikshak et al., 2015). In ASD, these pathways involve regulation of transcription and chromatin structure during neurogenesis and subsequent processes of synaptic development and function during early fetal cortical development (Parikshak et al., 2015). A small study implicated similar stages during the developmental of the prefrontal cortex in SCZ risk (Gulsuner et al., 2013), consistent with several decades of neuroanatomical studies (Glausier and Lewis, 2018; Piper et al., 2012). Importantly, these findings emerge from different methods, including PPIs (Lin et al., 2015; O'Roak et al., 2012); integration of protein, gene expression, and phenotype data (Gilman et al., 2011; Hormozdiari et al., 2015); and chromatin marks (Sun et al., 2016). These efforts point at similar pathways and/or convergence of risk loci on similar biological processes (Corominas et al., 2014; Gilman et al., 2012; Li et al., 2014).

One caveat in the interpretation of these studies is that they are based on current knowledge of genetic contributions. In ASD, this is heavily biased toward rare, *de novo* PTVs identified in simplex families, which could impact different pathways than those affected by inherited variation. Although there is likely a role for rare inherited variation in ASD (Krumm et al., 2015), few studies have identified significant signals based on inherited risk variants for specific genes. A recent study of multiplex ASD families found that inherited risk impacts pathways similar to those for *de novo* variation (Ruzzo et al., 2018). Similarly, the developmental trajectories of risk genes implicated by rare and common variation appear to overlap, particularly for the fetal period for ASD risk.

Transcriptomic Networks Define Disorder-Associated Molecular Pathology

Psychiatric disorders are not generally associated with brain pathology on gross or microscopic examination. The development of methods to capture the brain transcriptome led to studies of differential expression in cases versus controls and evaluation of convergent molecular pathology (Parikshak et al., 2015). To organize these data, network/pathway approaches have been applied to brain tissue from subjects with most major psychiatric disorders, including SCZ, MDD, and ASD (Parikshak et al., 2015). However, any changes detected in postmortem brain could be causal or reflect disease consequences. Integration of these data with genetic risk variants provides an opportunity to identify a causal foothold. In ASD, these analyses, replicated using different methods and samples, implicate synaptic and neuronal signaling pathways overlapping with other causal gene-based network methods (Parikshak et al., 2016; Voineagu et al., 2011). Similar network analysis based on gene co-expression identifies transcriptional networks dysregulated in SCZ, including co-expressed neuronal genes enriched for both common and rare SCZ-associated variants (Fromer et al., 2016). Transcriptomic findings for ASD, SCZ, BIP, and MDD suggest shared and disorder-specific gene expression changes (Gandal et al., 2018a). Notably, cross-disorder transcriptome correlations parallel genetic correlations, consistent with common causal biology (Gandal et al., 2018a).

Several genes that cause rare forms of ASD (e.g., *FMR1*, *CACNA1C*, *TCF4*) regulate expression or splicing of many genes associated with psychiatric disorders (Tian et al., 2014; Weyn-Vanhentenryck et al., 2014). *FMR1* in particular interacts with the mRNA of many ASD- and SCZ-risk genes (Iossifov et al., 2014; Parikshak et al., 2013; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Analysis of transcriptional (Cotney et al., 2015; Sugathan et al., 2014), splicing (Berto et al., 2016; Fogel et al., 2012; Weyn-Vanhentenryck et al., 2014), or signaling (Tian et al., 2014) networks indicates that at least some of the rare major gene forms of psychiatric disorders impact pathways that are more generally related to risk in

the population. This further highlights the relevance of rare forms of psychiatric disorders to understanding common genetic variation.

Tissue and Cellular Architecture

As with gene network analyses to identify biological pathways, it is possible to apply similar methods to identify empirically the brain regions and developmental stages in which the genetic findings are enriched. These analyses are important in a general sense—are these disorders rooted in early fetal development, childhood, adolescence, or adulthood?—but also because of neuroscience tools that can manipulate increasingly specific brain cell types in space and time.

Two general approaches are used to determine cell-type or stage specificity. The first assigns genes implicated by risk variants directly to cell types based on transcriptomics (Polioudakis et al., 2018; Skene et al., 2018). The second partitions genetic risk across non-coding regions and compares the predicted activity of these regions across cell types and developmental stages, which to date have been primarily based on tissue-level open chromatin rather than single cells (de la Torre-Ubieta et al., 2018). Development of robust single-cell methods for chromatin analysis promises to be important (Cusanovich et al., 2018a, 2018b). At present, many psychiatric GWASs are under-powered to accomplish these intentions (Skene et al., 2018).

This lack of power for common-variant analyses is certainly the case for ASD, where studies have relied primarily on measuring expression enrichment or *de novo* PTVs. These studies have demonstrated that ASD risk variants are enriched in cortical glutamatergic neurons expressed during neurogenesis and neuronal migration during fetal cortical development in human and mouse (Parikshak et al., 2013; Willsey et al., 2013). Examination of the laminar patterns of expression in primate indicated that ASD risk genes are enriched in upper- relative to lower-layer neurons. This may be important for understanding circuit-level architecture, because upper-layer neurons form the primary direct connections between cerebral hemispheres and cortical regions (Parikshak et al., 2013), and lower-layer neurons primarily, but not exclusively, project to subcortical regions.

A recent study of single-nuclei RNA-seq from human fetal and adult brain has validated the enrichment of genes harboring large-effect *de novo* mutations associated with ASD in fetal glutamatergic neurons (Polioudakis et al., 2018). These detailed transcriptomic profiles provide nuance, especially for individual genes, identifying genes expressed broadly across neurons or with relative specificity for inhibitory neurons, neural progenitors, or non-neural cells (Polioudakis et al., 2018). The importance of the fetal period for ASD is supported by GWAS results integrated with regulatory chromatin interactions and gene expression, which show enrichment of enhancer marks in the fetal brain and higher expression of ASD target genes during fetal corticogenesis (Grove et al., 2019). Comparisons across brain regions, both prenatally and in adult, confirms prenatal cerebral cortical enrichment over other brain regions, both prenatally and relative to adult expression levels.

For SCZ, although earlier developmental stages are important for the action of risk variants (de la Torre-Ubieta et al., 2018), considerable cell-type specificity emerges in the adult brain. The most comprehensive analysis to date used single-cell and single-nuclei RNA-seq from multiple brain regions in mouse and human (Skene et al., 2018). Distinct patterns of enrichment were identified for different disorders, often mirroring known biology (e.g., multiple sclerosis and Alzheimer's disease risk were enriched in microglia). Common-variant genetic findings for SCZ showed enrichment in a limited set of major cell types: pyramidal neurons in cortex and hippocampal CA1, striatal medium spiny neurons, and cortical interneurons. MDD risk was clustered in cortical interneurons and embryonic midbrain neurons (these findings replicate in multiple new datasets, Bryois et al., 2019). Orthogonal functional genomic data are consistent with these findings, as open chromatin in neuronal nuclei (NeuN+) from 14 regions from human adult brain showed significant enrichment of SCZ GWAS findings in cortex and striatum (Fullard et al., 2018), and open chromatin in mouse cortical layers showed SCZ enrichment in excitatory neurons in layer V (Hook and McCallion, 2018).

Although these studies are not yet definitive, we highlight emerging points of consistency. Genetic risk for SCZ appears to be more widespread in 4D (Li et al., 2018) and somewhat more specific to adult brain (particularly pyramidal neurons, striatal medium spiny neurons, and cortical interneurons), but also with strong effects during fetal cortical development (de la Torre-Ubieta et al., 2018; Won et al., 2016). MDD risk is enriched in adult cortical interneurons (Skene et al., 2018), but also with fetal enrichment in midbrain neurons (Skene et al., 2018) (consistent with theories of catecholaminergic cortically projecting brainstem systems in MDD). Genetic risk for ASD appears to act primarily in fetal periods, involving cortical glutamatergic neurogenesis and early development. While ASD risk converges on glutamatergic neuron development, by no means is every risk gene expressed exclusively in these neurons (Polioudakis et al., 2018). These findings broaden and refine the neuronal classes where ASD risk genes act are supported by other analyses (Satterstrom et al., 2018a). The implication of fetal neurogenesis in childhood- and adult-onset disorders may highlight a critical period in early brain development for multiple psychiatric disorders (Geschwind and Rakic, 2013). As knowledge of gene regulation at a single-cell level increases, the precision of assigning of genetic risk to specific cell types will establish a solid framework for the circuit architecture of these disorders.

Diagnostic Architecture

Psychiatry is one of the few areas in medicine that lack of objective biomarkers of illness. Other areas of medicine have frequently updated diagnostic classifications as new biological data and increased understanding of etiopathology emerge. In the absence of objective diagnostic features from laboratory testing, brain imaging, or pathology, the definitions of psychiatric disorders are necessarily based on descriptive data collected via human interactions and organized by expert panels. A long-standing tension is whether psychiatric disorders are better considered as fewer broad categories or more numerous refined categories. In the past 30 years, psychiatric nosology has tended toward the latter position.

For almost all psychiatric disorders, genetic data are the most fundamental biomarker yet discovered (recalling that

humans are exposed to their genomes from conception and given the plausible absence of reverse causation). Given the well-documented and extensive patterns of comorbidity, it is perhaps unsurprising that genetic results show fundamental overlaps between many adult and childhood disorders. For common variation, SCZ has significant positive genetic correlations with BIP, MDD, ADHD, ASD, and AN (Antilla et al., 2018), and MDD has significant positive genetic correlations with anxiety disorders, ASD, ADHD, BIP, and AN (Wray et al., 2018). Neurological conditions, in contrast, have far fewer significant genetic correlations (and largely for clinical subtypes like migraine with/without aura). Moreover, the lifetime presence or absence of many psychiatric disorders have positive genetic correlations with quantitative measures of symptoms—e.g., lifetime MDD has a genetic correlation of 0.98 with depressive symptoms (Wray et al., 2018). Similar results have been reported for ASD, ADHD, and OCD (Martin et al., 2018a). Similarly, for rare variation, as described above, there are pleiotrophic effects for most rare CNVs and exon variants of strong effect, as many such variants increase risk for multiple neurodevelopmental conditions.

Given the emerging genetic findings, one might naturally wonder about clinical genetic testing—what are the standards for technological readiness, and precisely which findings are ready for clinical use in psychiatry? A full treatment of this complex topic is beyond the scope of this Review, and the answers also depend on national laws, local ethical standards, and access to genetic testing technologies. On the scientific side, we think that the available data support three uses in clinical psychiatry. (1) For severe, childhood-onset neurodevelopmental disorders (particularly severe ID and ASD), genetic evaluation of large CNVs and rare mutations that disrupt the protein sequence of genes important to neurodevelopment is indicated. We note that this is now done routinely in many academic centers. The utility is mostly diagnostic for the child and relevant to family planning for the parent; some variants will also be medically important and lead to a change in clinical management. (2) Large CNVs in severe psychotic disorders (SCZ and schizoaffective disorder) will be present in 3%–5% of cases. The utility is diagnostic and in ameliorating medical morbidity given that most CNVs are multi-system disorders carrying additional medical risks. (3) Unusual cases—individuals with a wide range of single-gene disorders can initially present with prominent psychiatric features. Instead of a primary psychiatric disorder, the behavioral features are secondary to a biological process that has been disrupted by a strong-effect mutation. Classic examples include Wilson's disease and Huntington's disease, which can present with psychotic or mood symptoms. The utility here is diagnostic and possibly therapeutic (e.g., copper chelation therapy for Wilson's disease can markedly improve outcomes if not delayed due to a missed diagnosis).

In many countries, genetic tests can be used by consumers without having rigorous evaluation of analytical validity, clinical validity, and clinical utility (again, there are complex and country-dependent issues). However, there are abundant examples of genetic tests that are now being used clinically that have a weak scientific basis. This is problematic, but such testing has been allowed to occur due to failures of regulatory processes.

The fundamental database is not sufficiently complete to draw unambiguous conclusions—research in progress by many groups is combining epidemiological, clinical, and genetic risk factors in historically large samples. However, we posit that the genetic results are consistent with a tentative position: based on significant genetic overlap between most childhood- and adult-onset psychiatric disorders and their intercorrelations with cognitive ability and personality, substantial components of inherited liability are shared by many psychiatric disorders. But with the exception of BIP and SCZ, most liability appears more disease specific. When the scientific database is more mature, revision of psychiatric nosology based on combining clinical with rare- and common-variant genetic results may well be warranted.

Conclusions and Future Directions

Complete Genetic Discovery

In the past decade, genetic approaches to psychiatric disorders have yielded more reproducible insights into etiology than any other prior approach. We now know vastly more about the fundamental causes of these impactful disorders than ever before. What we know now is incomplete and inadequate. We need to complete genetic discovery, and we believe that this should be an international priority in this area. Inexpensive SNP arrays can measure the contributions of the vast majority of common variation and be efficiently assessed in large populations now. To measure the full spectrum of rare variation and less-accessible common variation, we will need resequencing efforts of similar magnitude, but this will likely have to wait for more efficient platforms and improved functional annotations.

Genetic Architecture in Individuals

We have described multiple architectures for psychiatric disorders. The ultimate goal is understanding as fully as possible the etiological process in individuals with a severe psychiatric disorder. How does knowledge derived from large populations contribute to illness in an individual? For example, in those with ASD who harbor a rare *de novo* PTV, is that variant sufficient to cause the disorder, or are additional genetic or environmental risk factors required? The answers will likely vary depending on the gene, but already, there are multiple hints that risk profiles in individuals are likely to be complex, even in those harboring large-effect mutations. For instance, few large-effect mutations are specific to a disorder, suggesting a possible role for additional genetic, environmental, and stochastic factors. Although some large-effect CNVs associated with ASD or SCZ have effects on fecundity, when discovered in population surveys in individuals without regard to disease status, many have relatively modest effects on the ability to have offspring compared with those having the disease diagnosis (Stefansson et al., 2014). In the instances where this has been studied directly, polygenic risk acts additively with major mutational burdens (Gaugler et al., 2014; Niemi et al., 2018; Purcell et al., 2014; Weiner et al., 2017).

The model that we prefer is that many (but not all) large-effect mutations sensitize an individual to manifest a developmental neuropsychiatric disorder. We recognize that there are rare large-effect mutations that show clear preferential effects toward a disorder, as is the case for some CNVs and rare protein-altering mutations. However, the effects on brain development

and function of many *de novo* or Mendelian mutations are so large as to be non-specific with respect to any single disorder (e.g., epilepsy, ASD, SCZ, ID). The resultant phenotype in an individual is dependent on the impact of environmental factors and/or the additive effects of other rare-variation and polygenic risk. This model may also help explain the high unaffected carrier rate for some inherited mutations, if one presumes that the parent carrying the mutation lacks the polygenic risk that has accumulated in the child. However, we are still a long way from being able to confidently predict disorder phenotypes from measurement of genetic risk.

As noted above, the basic data remain incomplete, and further genetic discovery efforts are needed to derive secure and enduring answers to these fundamental questions. We do note that the concept of individual architecture also spans multiple other architectures described in this Review, which will be essential to understanding mechanisms and focused therapeutics in the individual.

Sex Differences

The genetic and pathophysiological explanations for sex differences in psychiatric disorders remain poorly understood, but the advances in gene discovery described here provide a new foundation to fuel studies in this important area. Many psychiatric disorders show a different prevalence or onset in males and females (Seedat et al., 2009). For example, marked sex differences in lifetime risk are apparent for ADHD, AN, ASD, MDD, and SCZ (Hudson et al., 2007; Martin et al., 2018b; Philippe et al., 1999). Whether sex differences are due to differential vulnerability, diverging behavioral/cognitive manifestations, and/or observer bias is not known with clarity but is likely to differ across diagnoses. For example, in ASD, genetic and functional genomic evidence suggests the presence of female protective factors based in brain function and structure (Robinson et al., 2013; Werling and Geschwind, 2013; Werling et al., 2016), whereas in MDD or ALC, social factors likely may have a larger role (Riecher-Rössler, 2017). Understanding the basis of sex differences may provide critical clues for pathophysiology and could inform diagnosis and treatment.

What's the Endgame?

It is essential to consider what is required to improve the diagnosis and treatment of individuals with severe psychiatric disorders. An extreme possibility is that achieving this intention could require a full understanding of the development of the human brain. Achieving this intention is unlikely to occur in the foreseeable future. However, there are indications from other areas of medicine that full understanding of a pathological process is not required to improve therapeutics. For instance, the causes of melanoma are not fully worked out, but the advent of checkpoint inhibitors—based on several key pieces of the melanoma puzzle—has markedly improved outcomes for disseminated disease.

A reasonable, and not overly optimistic, answer is that a solid beachhead is needed—a definite, reproducible, and clear identification of a neurobiological process conferring risk or protection for a psychiatric disorder. With such knowledge, the field changes markedly: beachheads become lodgements, lodgements become full theaters of engagement, and manifest progress becomes achievable. Instead of discovering medicines by accident and happenstance (as with virtually all prototypic medications used in clinical psychiatry), the power of modern rational drug design can be implemented.

To achieve this end, we suggest the need for a concerted global effort. We are far from being able to confidently predict disorder phenotypes from measurement of genetic risk. Given the marked progress to date, we believe it sensible to continue large and comprehensive gene-discovery efforts. Such efforts are now clearly incomplete, but definable stopping points can be articulated (e.g., either where genetic discovery reaches an asymptote or if new discoveries only replicate known functional and cellular architectures). This will require working with groups traditionally underrepresented in psychiatric research to attain an inclusive and complete understanding of the contribution to disease in individuals with non-European ancestries. Discovery efforts across multiple architectures are warranted to understand the individual architecture that underlies disease risk and pathophysiology.

SUPPLEMENTAL INFORMATION

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DECLARATION OF INTERESTS

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WEB RESOURCES

Psychiatric Genomics Consortium, http://www.med.unc.edu/pgc/
PsychENCODE Consortium, https://www.synapse.org//#!Synapse:syn4921369/wiki/235539
Simons Simplex Collection, https://www.sfari.org/resource/sfari-base
Autism Whole-Genome Sequence (AGRE, iHART), http://www.ihart.org/data; https://research.mss.ng

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