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New statistical approaches exploit the polygenic architecture of schizophrenia — implications for the underlying neurobiology

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Schizophrenia is a complex disorder with high heritability. Recent findings from several large genetic studies suggest a large number of risk variants are involved (i.e. schizophrenia is a polygenic disorder) and analytic approaches could be tailored for this scenario. Novel statistical approaches for analyzing GWAS data have recently been developed to be more sensitive to polygenic traits. These approaches have provided intriguing new insights into neurobiological pathways and support for the involvement of regulatory mechanisms, neurotransmission (glutamate, dopamine, GABA), and immune and neurodevelopmental pathways. Integrating the emerging statistical genetics evidence with sound neurobiological experiments will be a crucial, and challenging, next step in deciphering the specific disease mechanisms of schizophrenia.

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Introduction

The etiology of schizophrenia is complex with substantial genetic contributions. Uncovering the perturbed neurobiology by better characterizing the genetic component seems plausible as the heritability, or proportion of variance in disease risk attributable to genetic differences, is estimated to be 60–80% [1]. Although the largest genome-wide association study (GWAS) of schizophrenia identified an unprecedented number of risk loci, a substantial 'missing heritability' remains. Studies of copy number and rare variation not captured by GWAS have added additional insights, but these have revealed few if any Mendelian forms of schizophrenia [2].

The emerging picture is that schizophrenia is a 'pathway disease' [3], where risk is determined by a large number of genetic loci, each with small effect (i.e. it is polygenic) that cluster within particular biological or functional genomic modules. Assuming a large polygenic component, the current low yield of GWAS is expected, as is an opportunity to exploit substantial signal available in genetic variants analyzed in aggregate. Because the heritability is distributed across many loci, individual effects are small. As such, the power for detecting them within a GWAS depends not only on the heritability but also the 'polygenicity' of the phenotype (i.e. with equal heritability a more polygenic phenotype will require larger samples; see Box 1). Here we review advances in statistical approaches aimed at investigating polygenic phenotypes, including to schizophrenia, discussing applications relevant for disease neurobiology.

Main text

Schizophrenia is a polygenic disorder

Since 2011 the Psychiatric Genomics Consortium (PGC; http://www.med.unc.edu/pgc) has performed successive meta-analyses across a growing collection of schizophrenia GWAS. The first [4] used a combined 51 695 participants to identify 7 independent loci (genome-wide significance, $p < 5 \times 10^{-8}$) explaining ~0.5% of variability in schizophrenia risk. Increasing the sample to 61 061 participants [5] identified 22 risk loci that explained ~1% of risk variability. The most recent [6••] combined 150 064 participants to identify 108 loci that explained ~3% of the risk. Given the statistical power of these studies, it is highly unlikely that any single locus with even a moderate effect remains undiscovered. Further, predictive models using collections of

Box 1 Heritability, polygenicity and statistical power

Common SNPs surveyed in GWAS are estimated to account for 33% of the variability in risk for schizophrenia but the total number of contributing loci, while thought to be 'large,' is not known. Estimating bounds on this quantity is important for study design but represents a technically challenging inverse problem. Because the sum of per locus effects necessarily equals the heritability, positing a larger number of causal loci equivalently posits a smaller average effect per locus and, correspondingly, reduced statistical power for discovery.

Box figures A–C demonstrate the relationship between the number of causal variants ($M = 1000$, 10 000, or 100 000) and per locus statistical power for a fixed heritability ($h^2 = 0.33$ on the liability scale). The statistical power at, or probability of detecting, a locus (at $p < 5 \times 10^{-8}$, 'genome-wide significance') explaining a proportion of the variance in liability q^2 with a sample size N and proportion of cases v is a function of the non-centrality parameter from the allelic association chi-square test (Eqns. (1)–(3)). In box figures A–C the power to detect each of the M causal loci (colored lines) at genome-wide significance is shown across a range of sample sizes ($v = 0.25$ as in the latest GWAS). The power curves for the expected mean, 10% and 90% single locus effects are highlighted (black lines) as is the current largest GWAS sample size for schizophrenia (grey vertical bar). For the highlighted effects per locus variance explained and corresponding odds ratio, assuming a causal allele frequency of 0.10, are provided.

As the polygenic component of a trait becomes distributed over more loci, the expected yield of a GWAS is greatly diminished (noted by the shifting to the right of the power density from A to B to C) and increasingly more causal loci will not reach statistical significance. Importantly, the heritability becomes distributed among SNPs at different significance levels, also depending on the number of causal loci and sample size (Supplementary Materials and Figures S7–9). Multivariate enrichment tests, by aggregating across loci, aim to test the hypothesis that heritability is aggregated in some collections of modestly significant variants more abundantly than others. Further, assuming the causal loci are, in fact, not randomly distributed with respect to genomic or biological modules, the power to discover individual loci can be increased by exploiting auxiliary information with advanced statistical models (see *Leveraging enrichment to prioritize schizophrenia loci* section). (See Supplementary Materials for extended simulation background, methods, figures and code) (Box Figure).

Box equations

The mean effect size, $E(q^2)$, as proportion of variance in liability explained by the locus,

$$E(q^2) = \frac{h^2_{chip}}{M} \quad (1)$$

The non-centrality parameter, λ, of the chi-square statistic from the allelic association contingency table can be approximated [25] as,

$$*\lambda \approx \frac{(q^2 N i^2 v(1-v))}{(1-k)^2} \quad (2)$$

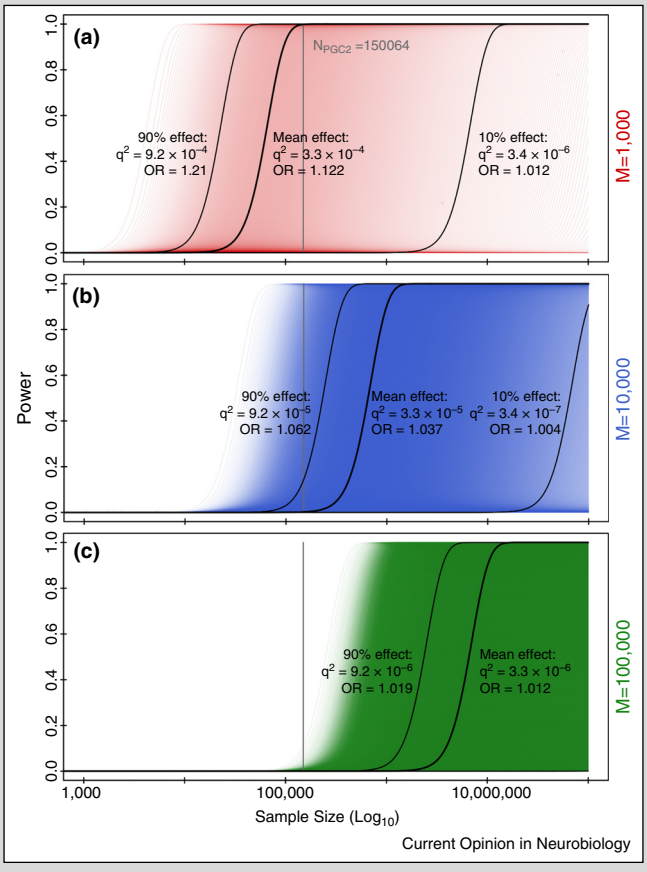
The power, $1-\beta$, to detect an effect of size q^2 is given by the non-central chi-square distribution,

$$1-\beta = P(\chi^2_{d,\lambda} > \chi^2_{d,0;\alpha} | \lambda, d) \quad (3)$$

where k is the population prevalence of disease, $i = (z/k)$, $z = \Phi(\Phi^{-1}(k))$ = height of the standard normal curve at the truncation point (liability threshold) corresponding to a tail probability of k; d the degrees of freedom for the chi-square test (1 for an allelic test); and α the chosen false positive rate = 5×10^{-8} for GWAS; $X^2_{d,\lambda;\alpha}$ = chi-square statistic corresponding to the $1-\alpha$th quantile, assuming d degrees of freedom and a non-centrality parameter λ.

*Approximate formula taken from the reference is appropriate only for small q^2 (confirmed by simulation) and assuming a multiplicative model of genotype relative risk. For precision, simulations are based on an explicit, verbose transformation from q^2 to $\chi^2_{d,\lambda;\alpha}$, also assuming a multiplicative model of relative risk (see supplementary materials), however, the qualitative relationship among parameters holds in both cases.

Box Figure



The relationship between power, sample size, and polygenicity.
The power to detect a causal locus, assuming fixed heritability, depends on both the sample and the number of causal loci. When 1000 causal loci were assumed the power to detect each causal locus was the highest (A). When 10 000 causal loci were assumed, power was intermediate (B), while with 100 000 casual loci were the power to detect each causal locus was greatly diminished (C), even at extreme sample sizes.

thousands of variants not reaching significance in each study explained substantially more, as much as 6%, 8% and 18% of the risk, respectively [4,5,6••]. Similarly, the chip heritability, an estimate of the risk attributable to all of the single nucleotide polymorphisms (SNPs) analyzed in a given GWAS (see below), suggests 33% of the variability could be explained [6••,7]. Taken together this evidence suggests that schizophrenia is highly polygenic, with many individually small effects yet to be localized. Concurrently, several statistical approaches have been used to identify functional modules where these hidden effects may cluster (i.e. are 'enriched' for polygenic effects).

Polygenicity sensitive statistical approaches

Variance components models have been used for nearly a century to partition phenotypic variance into genetic (typically *poly*genic) and environmental components [8]. Traditionally, family or twin populations were used to estimate the contribution of the *expected* genetic covariance (i.e. 1 for monozygotic twins, 0.5 for first degree relatives, 0 for unrelated, among others) to phenotypic similarity as the additive, or narrow-sense, heritability (h^2). More recently this approach has been extended by substituting the *realized* genetic covariance, with additive genetic similarity computed directly from observed SNP data, for its expectation [9]. This approach uses unrelated individuals, who vary slightly about the population mean in realized genetic relatedness. Because observed markers are sampled from a given microarray (or 'chip') it is distinguished from heritability (h^2) as the chip heritability (h^2_{chip}). Importantly, the h^2_{chip} only captures variability at a subset of the genome and is therefore expected to be less than the h^2, but nonetheless, it can be seen as an estimate of the upper bound of variance explainable by discoveries from a GWAS using the same SNPs and adequate sample size (review [10]).

Estimates of h^2_{chip} can also be used to compare the contributions of different classes of SNPs [11–13]. By estimating chip heritability from classes of SNPs separately and contrasting the results, one can partition the heritability among SNP sets, quantifying enrichment. Chip co-heritability extends this approach to multiple phenotypes, estimating the proportion of covariance between two traits explainable by a SNP set, providing a metric for the overlap and directional consistency of SNP effects between the traits [14]. Risk profile scores (RPS) actualize variance explained estimates. For up to hundreds of thousands of SNPs, per allele effects estimated in large GWAS are used to compute effect size weighted total risk alleles carried by individuals in an independent sample (an RPS) [15•]. The RPS can be used to test for associations between aggregate schizophrenia risk and other phenotypes in healthy or patient populations [15•,16]. Note, variance explained by RPS is generally expected to be much less than corresponding chip heritability estimates because it is limited by the precision of the individual SNP effects estimated in the reference GWAS [16].

A diverse class of enrichment methods compares distributions of test statistics, *Z's*, or corresponding *p*-values, *p's*, from a GWAS for SNPs in different categories. These tests measure the abundance of extreme test statistics or low *p*-values relative to that expected under null among the classes. Maurano *et al.* [17] introduced this as 'fold-enrichment,' while Andreassen *et al.* [18••,19,20•,21] and Schork *et al.* [22••] show equivalent 'conditional QQ-plots' (Supplementary Materials). Schork *et al.* [22••] also measured this enrichment as the mean($Z^2 - 1$), a related quantity. These approaches can be applied to SNPs within different genome functions [17,22••,23••] or to detect co-localization of SNP effects across multiple traits [18••,19,20•,21]. Traditionally, genome-wide 'enrichment' of this type was attributed to statistical artifacts from poor study design (population stratification or cryptic relatedness) [24], in part because GWAS were initially predicted to uncover relatively *few* loci of *moderate* effect. Recently, this trend has been shown to be consistent with the many small but real effects expected under a polygenic architecture [25] more or less confirmed for schizophrenia [26]. This polygenic perspective has become the prevailing view among recent schizophrenia GWAS reports [6••,26].

Methods for assessing enrichment of associations in 'pathways' test for co-localization of variants associated with groups of genes or regulatory elements involved in related biological processes that may be defined either by expert knowledge or molecular studies. Briefly, multiple SNP effects are typically combined into a gene-level statistic and then gene-level statistics are aggregated into a pathway statistic to shed insights into biological processes, although many variations have been proposed (reviews of pathway analysis [2,27•,28•]). The dependence on a single approach can be reduced by combing pathway enrichment methods into consensus scores, as with schizophrenia and across psychiatric disorders [29].

Linkage disequilibrium (LD) score regression offers an estimate of chip heritability from GWAS summary statistics alone by regressing SNPs' association statistics (Z^2) on their 'LD scores', the sum of the squared correlations (r^2 LD) between the minor allele count of one SNP and all other SNPs, a measure of the amount of genetic variation the SNP represents (introduced in [26]). The LD score heritability can also be partitioned among functional genomic classes [65], providing a theoretically grounded enrichment test extending the approach of Schork *et al.* [22••]. Bulik-Sullivan *et al.* [66] use the LD score regression to estimate LD score genetic correlations, providing a test for co-localization of associations akin to chip co-heritability.

Mathematically sophisticated multivariate approaches, often Bayesian in formulation, explicitly model the entire distribution of test statistics from a GWAS (e.g. [30–34]). These approaches are diverse in their implementation, but generally include a set of covariates (i.e. functional genome annotations or secondary trait associations) that are trained or fitted to predict the SNP test statistics. Predominantly such models are used to prioritize candidates among suggestive associations on the basis of the covariates. The covariate-modulated mixture model (CM3) method, for example, has been used to identify a number of novel schizophrenia loci (see below). However, hypothesis testing can be performed on estimated weights for each covariate to test enrichment as its predictive power in the context of a particular model.

Regulatory variants play a role in schizophrenia

Regulatory variants may play an especially crucial role in complex trait evolution and etiology [35], a hypothesis well supported for schizophrenia (Table 1). GWAS have particularly implicated variants related to genes expressed in the brain and variance components models show that a significantly larger proportion of the chip heritability is accounted for by variants related to brain-expressed genes [7]. Polygenic enrichment of SNPs representing proximal gene elements (5′UTRs, exons, introns, 3′UTRs, and/or promoters) implicates regulatory elements at least as strongly as coding exons, a trend not unique to schizophrenia [13,22••,65]. In fact, among the 108 loci recently identified, only 10 contained plausibly causal non-synonymous coding variants [6••]. Enrichment for brain tissue eQTLs, which may regulate genes proximally or distally, is shown for schizophrenia [6••,32,36] and cross-disorder [37] associated loci. Enrichment tests using GWAS discoveries [4,5] as well as more inclusive polygenic pathway analyses [4,5,38,39] have confirmed an excess of microRNA (especially mir137) targets within candidate loci. Interestingly, evolutionarily conserved regions [65], thought to represent uncharacterized regulatory elements, were also enriched for schizophrenia associations. Enhancers (distal gene-regulatory elements) active in multiple fetal and adult brain tissues [6••,23••,40,65] are also enriched. An important experimental report demonstrated the distal regulatory mechanism underlying the *CACNA1C* gene loci in human prefrontal cortex tissue and stem-cell derived neurons [23••]. Functionally unannotated variants [13,22••,23••], silenced DNA [65] and enhancers active in schizophrenia irrelevant tissues [6••,65] showed depletions for both loci discovered by GWAS and polygenic enrichment. Together this supports the notion that schizophrenia is a pathway disorder with disruptions perhaps driven by dysregulation. Functional fine-mapping studies experimentally characterizing causal regulatory mechanisms underlying statistical candidate loci are crucially important for understanding the instantiation of schizophrenia susceptibility within the genome. Part and parcel to this is a continued need to characterize gene regulation in cells and tissues relevant for schizophrenia.

Neurobiological pathway perturbations in schizophrenia

Schizophrenia GWAS implicate immunity, neuronal maturation, synaptic plasticity, calcium signaling and neurotransmission with genome-wide significant loci (Table 1) [4,5,6••]. An across psychiatric disorders GWAS [37] also supports calcium signaling. Differential co-expression modules defined in brain tissue from schizophrenia patients and healthy controls give support for GABAergic, Glutamatergic and Oligodenrocyte function by polygenic enrichment [41]. Broader enrichment in calcium signaling may be driven specifically by altered expression of calcium channel subunits [5]. Similarly, synaptic gene enrichment may be driven by gene subsets affecting cell-adhesion, trans-synaptic signaling, structural plasticity and excitability [5]. Consensus analyses implicated previously unreported pathways involved in histone modification and post-synaptic density, in addition to immune response, neuronal and calcium signaling [29]. Although immune response may not intuitively relate to neurobiology, the gene sets associated with schizophrenia may be bound into a larger schizophrenia network through neural microRNA activity [38,42] or play plausible neurodevelopmental roles [43,44]. Transcriptome comparisons of schizophrenia patient and healthy control brain tissue provide additional support as altered expression within synaptic, immune GABAergic and oligodendrocyte pathways.

An on-going challenge in interpreting pathway findings lies in the semantics of the pathway labels. Meaning is dependent on a number of factors including how genes are assigned to pathways, how boundaries among pathways are set, and the cells and tissues considered, among others (general review [27•]; schizophrenia focused review [45•]). Although there is surface level convergence among the findings reported here, very few studies truly replicate pathways defined by identical criteria or taken from the same database (see Table 1). Improving the precision, resolution, consistency and context of 'pathways' is a continued effort, although current findings are uniting previously unconnected neurobiological themes.

Schizophrenia shares genetic loci with other phenotypes

Characterizing co-localized associations among GWAS of disparate phenotypes (i.e. single loci identified in GWAS of different traits) can improve the understanding of disease pathogenesis, classification and risk-profiling while suggesting uncharacterized biological mechanisms. In addition to well-established overlaps with bipolar disorder [4,5,6••,19,32,37,46,47,66], schizophrenia GWAS have revealed numerous other relationships (Table 1). Many loci identified by GWAS overlap with rare, de novo and copy number variants implicated in autism and intellectual disability, although the variant type (rare or

Table 1

Implicated biological and genomic modules.

Class		Module	Enrichment method	Pathway source	Inclusion threshold	Cite
Genome functions	Enriched	Brain expressed genes	Chip h^2 partitioning		$p < 1$	[7]
			Multivariate model parameter		$p < 1$	[32]
		Proximal promoters (across tissues)	Chip h^2 partitioning		$p < 1$	[13]
			LD score h^2 partitioning		$p < 1$	[65]
		Proximal promoters (multiple adult and fetal brain tissues)	Conditional QQ Plots; mean($Z^2 - 1$)		$p < 1$	[22••]
			Custom permutation-based test		$p < 5 \times 10^{-8}$	[40]
		5' untranslated regions (5'UTR)	Conditional QQ Plots; mean($Z^2 - 1$)		$p < 1$	[22••]
			LD score h^2 partitioning		$p < 1$	[65]
			Chip h^2 partitioning		$p < 1$	[13]
		Exons	Conditional QQ Plots; mean($Z^2 - 1$)		$p < 1$	[22••]
			LD score h^2 partitioning		$p < 1$	[65]
			Chip h^2 partitioning		$p < 1$	[13]
		3′ untranslated regions (3'UTR)	Conditional QQ Plots; mean ($Z^2 - 1$)		$p < 1$	[22••]
			LD score h^2 partitioning		$p < 1$	[65]
			Chip h^2 partitioning		$p < 1$	[13]
		eQTLs (brain)	RPS		$p < 0.5$	[36]
			Pathway analysis		$p < 10^{-3}$	[37]
			Multivariate model parameter		$p < 1$	[32]
		Enhancers (multiple brain and fetal tissues)	Conditional QQ Plots; mean($Z^2 - 1$)		$p < 1$	[23••]
			Custom permutation-based test		$p < 5 \times 10^{-8}$	[40]
			LD score h^2 partitioning		$p < 1$	[65]
			Fine-mapping GWAS		$p < 5 \times 10^{-8}$	[6••]
		Enhancers (immune cells)	Fine-mapping GWAS		$p < 5 \times 10^{-8}$	[6••]
		Transcription factor binding sites	Multivariate model parameter		$p < 1$	[32]
		MIR137 targets	GWAS		$p < 5 \times 10^{-8}$	[4]
			GWAS		$p < 5 \times 10^{-8}$	[5]
			Pathway analysis		$p < 10^{-4}$	[4]
			Pathway analysis		$p < 1$	[5]
			Pathway analysis		$p < 0.01$	[38]
		DNAse hypersensitive Regions (DHS)	Chip h^2 partitioning		$p < 1$	[13]
		Conserved DNA	LD score h^2 partitioning		$p < 1$	[65]
	Depleted	Nonsynonymous variants	Fine-mapping GWAS		$p < 5 \times 10^{-8}$	[6••]
		Introns	Chip h^2 partitioning		$p < 1$	[13]
		Functionally unannotated intergenic variants	Conditional QQ Plots; mean($Z^2 - 1$)		$p < 1$	[22••]
			Chip h^2 partitioning		$p < 1$	[13]
		Enhancers (bone, cartilage, kidney and fibroblast)	Fine-mapping GWAS		$p < 5 \times 10^{-8}$	[6••]
		Enhancers (FANTOM5)	LD score h^2 partitioning		$p < 1$	[65]
		Insulators (CTCF silenced DNA)	LD score h^2 partitioning		$p < 1$	[65]
Biological systems	Enriched	Calcium signaling	GWAS	Gene function	$p < 5 \times 10^{-8}$	[4]
			GWAS	Gene function	$p < 5 \times 10^{-8}$	[5]
			GWAS	Gene function	$p < 5 \times 10^{-8}$	[37]
			GWAS	Gene function	$p < 5 \times 10^{-8}$	[6••]
			Pathway Analysis	Gene Ontology (GO)	$p < 10^{-3}$	[37]
			Pathway Analysis	Gene Ontology (GO)	$p < 1$	[29]
		Calcium signaling subprocess (calcium channel subunits)	Pathway Analysis	Custom module	$p < 1$	[5]
		Dopamine	GWAS	Gene function	$p < 5 \times 10^{-8}$	[6••]
		Glutamate	GWAS	Gene function	$p < 5 \times 10^{-8}$	[6••]
		Differential co-expression network (Glutamate)	Pathway	Expression Study	$p < 10^{-3}$	[23••]
		Differential co-expression network (GABA)	Pathway	Expression Study	$p < 10^{-3}$	[23••]
		Neuronal signaling	Pathway Analysis	GO/PANTHER/KEGG	$p < 1$	[29]
		Synaptic plasticity	GWAS	Gene function	$p < 5 \times 10^{-8}$	[6••]
		Synapse subprocess (cell-adhesion)	Pathway Analysis	Custom module	$p < 1$	[5]

Table 1 (*Continued*)

Class		Module	Enrichment method	Pathway source	Inclusion threshold	Cite
		Synapse subprocess (trans-synaptic signaling)	Pathway Analysis	Custom module	$p < 1$	[5]
		Synapse subprocess (structural plasticity)	Pathway Analysis	Custom module	$p < 1$	[5]
		Synapse subprocess (excitability)	Pathway Analysis	Custom module	$p < 1$	[5]
		Post-synaptic density	Pathway Analysis	Gene Ontology (GO)	$p < 1$	[29]
		Neuronal maturation	GWAS	Gene function	$p < 5 \times 10^{-8}$	[4]
		Differential co-expression network (oligodendrocyte function)	Pathway Analysis	Expression Study	$p < 10^{-3}$	[23••]
		Histone modification	Pathway Analysis	GO/PANTHER/KEGG	$p < 1$	[29]
		Immune response	GWAS	Gene function	$p < 5 \times 10^{-8}$	[5]
			GWAS	Gene function	$p < 5 \times 10^{-8}$	[6••]
			Pathway analysis	GO/PANTHER/KEGG	$p < 1$	[29]
Shared associations	Enriched	Healthy with affected first degree relative	RPS		$p < 0.2$	[56]
		Bipolar disorder	GWAS		$p < 5 \times 10^{-8}$	[4]
			GWAS		$p < 5 \times 10^{-8}$	[5]
			GWAS		$p < 5 \times 10^{-8}$	[6••]
			Joint GWAS		$p < 5 \times 10^{-8}$	[37]
			Chip co-h^2		$p < 1$	[46]
			LD Score co-h^2		$p < 1$	[66]
			Conditional QQ plots		$p < 1$	[19]
			Multivariate model parameter		$p < 1$	[32]
			RPS		$p < 0.05$	[47]
		Schizoaffective disorder	RPS		$p < 0.05$	[47]
		Experience of psychosis	RPS		$p < 0.05$	[47]
		Autism	GWAS		$p < 5 \times 10^{-8}$	[5]
			GWAS		$p < 5 \times 10^{-8}$	[6••]
			Joint GWAS		$p < 5 \times 10^{-8}$	[37]
			Multivariate model parameter		$p < 1$	[32]
			Chip co-h^2		$p < 1$	[46]
		Intellectual disability	GWAS		$p < 5 \times 10^{-8}$	[5]
			GWAS		$p < 5 \times 10^{-8}$	[6••]
		Major depressive disorder	Joint GWAS		$p < 5 \times 10^{-8}$	[37]
			Chip co-h^2		$p < 1$	[46]
			Multivariate model parameter		$p < 1$	[32]
			LD Score co-h^2		$p < 1$	[66]
		Anorexia	LD Score co-h^2		$p < 1$	[66]
		ADHD	Joint GWAS		$p < 5 \times 10^{-8}$	[37]
			Multivariate model parameter		$p < 1$	[32]
			RPS		$p < 0.05$	[49]
		Multiple sclerosis	Conditional QQ plots		$p < 1$	[21]
		Cardiovascular disease risk factors	Conditional QQ plots		$p < 1$	[19]
		Creativity	RPS		$p < 1$	[57••]
		Neurocognitive performance	RPS		$p < 0.5$	[52]
		Age related cognitive change	RPS		$p < 0.5$	[53]
		Sensory motor gating	RPS		$p < 0.5$	[54]
		WM related fMRI signal	RPS		$p < 0.05$	[55]

There have been many recent reports of genome, pathway and phenotype modules enriched for schizophrenia GWAS association signal. A method of 'GWAS' means there were genome-wide significant ($p < 5 \times 10^{-8}$) associations in the module. 'Custom module' compiled from [63,64]. 'Gene Function' pathway source denotes inclusion due to the function of single genes within loci implicated by GWAS significance. GO, Gene Ontology (http://geneontology.org/); PANTHER (http://pantherdb.org/); KEGG (http://www.genome.jp/kegg/).

common SNP, copy-number variant, among others) may determine the particular outcome [5,6••,48•]. Chip co-heritability estimates show genetic relationships between schizophrenia and major depressive disorder [66,46], autism [46] and anorexia [66]. Cross disorders GWAS and enrichment tests suggest a link with ADHD [32,37,49]. Andreassen *et al.* showed co-localization of schizophrenia associations with multiple sclerosis [21] and cardiovascular disease risk factors [18••]. These studies are consistent with genetic factors mediating epidemiological comorbidities, although the causal relationships have not been resolved.

Interpreting co-localized GWAS associations can have challenges of ambiguity much like pathway studies. Because any SNP represents ('tags') through LD a genomic region containing many potentially causal SNPs, the observation of associations at the same SNP in multiple GWAS does not necessarily imply the same underlying causal variant or even that causal variants are within the same gene. For this reason, it is difficult to infer the level at which *pleiotropy*, or shared genetic signal, is occurring – causal variant, causal gene or correlated locus – from GWAS statistics (review on GWAS pleiotropy [50]). As such, different methods assessing co-localization among GWAS may produce inconsistencies depending on their assumptions for pleiotropy. Chip co-heritability approaches [14,66] require consistent direction of effects among GWAS, while enrichment methods such as [18••,19,21] do not. Although some argue directional consistency is a stronger test of pleiotropy [66], it is not straightforward to link causal effects to GWAS test statistics across studies [51]. Further, consistent overlap among loci of disparate traits, regardless of direction, may point to interesting, uncharacterized biological mechanisms such as regulatory hubs. Further analytic and functional characterization of co-localized associations is crucial.

Using the GWAS summary statistics made available by the PGC (http://www.med.unc.edu/pgc/downloads), another approach to testing overlap has been to use RPS to test trait associations with for schizophrenia polygenic risk (review [15•]). Notably, variability in phenotypes related to cognitive ability [52,53], sensory motor gating [54], working memory related fMRI signal [55], psychotic experience [47], schizoaffective disorder [47] and affected relatives [56] are associated with schizophrenia RPS. A recent study found and interesting association between schizophrenia RPS and increased creativity in healthy individuals [57••]. These studies confirm the relatively mild risk for schizophrenia induced by any one, or even collection of common risk SNPs, but highlight their involvement with normal variability in other traits. Continuing to investigate the co-localization of genetic effects will provide clues as to how biological networks are connected, informing both our understanding of healthy neurobiological processes as well as those perturbed in schizophrenia.

Leveraging enrichment to prioritize schizophrenia loci

A subset of multivariate models have been applied to schizophrenia GWAS to nominate novel candidate loci [18••,19,20•,21,34]. These methods rely on an Empirical Bayes [58] philosophy well suited to the statistical properties of polygenic phenotypes [20•,58]. The distribution of test statistics from a GWAS is modeled as a mixture of two distributions, a 'null' and 'non-null,' with subtle variations proposed [36,59]. Statistical theory predicates a known shape for the distribution of test statistics under null. 'Statistical significance' is estimated for each SNP as the probability that its test statistic, given the magnitude, was drawn from the null distribution. This significance quantity (the local false discovery rate [58]) is a function of the excess of extreme in the observed mixture distribution relative to that expected under null alone. If the distribution of test statistics varies as a function of category (i.e. genome annotations) these features can be incorporated into the significance estimation [20•,33,34].

One instantiation of this, the conditional FDR [18••,19,21,60], prioritizes SNPs based on statistical relationships across traits. When SNP associations for a second trait systemically co-localize with those of a primary trait of interest, suggestive association with the second trait can be used to prioritize suggestive associations with the primary trait. This method was applied to schizophrenia GWAS results paired with bipolar disorder [19], cardiovascular risk factors [18••] and multiple sclerosis [21] to nominate 74, 25, and 39 novel loci. Andreassen *et al.* [20•] used the covariate-modulated local false discovery rate [33], which incorporated the set of genome-annotations, to prioritize 86 candidates. Wang *et al.* [34] used a covariate-modulated mixture model (CM3) to select 693 independent loci from the most recent PGC schizophrenia GWAS that predicted by the model to replicate at $\geq$80%, although an independent test set is not yet available. Given its emergence as a 'pathway disease,' statistical methods that take advantage of the clustering of effects within modules may effectively identify the next wave of statistical associations for schizophrenia.

Conclusion

Neurobiological inferences from GWAS of schizophrenia are maturing, in large part due to a conceptual focus on polygenic architecture. Formerly a few biologically disparate associations were stretched into cloudy, uncharted territory. Presently, it is becoming possible to aggregate and assimilate extensive polygenic signals into an ever more connected network of neurobiological relevance. Schizophrenia is clearly a 'pathway disorder' [3] and the polygenic component is beginning to coalesce into coherent neurobiological modules. Genetic evidence for traditional, therapeutics-based theories of schizophrenia, including glutamatergic, GABAergic and dompaminergic signaling disruptions, are emerging, as is support for disturbances to brain development, calcium signaling and synaptic functioning. Provocative transcriptional, histological, and neuroscientific studies have begun to demonstrate important connections between these systems and immune pathways [43,44], adding plausibility to the GWAS findings. The relative paucity of large effect and de novo nonsynonymous variants, coupled with extensive enrichment for gene regulatory elements among schizophrenia loci suggest that it may be a specific and perhaps subtle state shift in this emerging network that leads to schizophrenia. An interesting hypothesis along

these lines is that more 'severe' genetic insults to the same neurobiological network may result in more 'severe' phenotypes such as autism or intellectual disability [48•]. Schizophrenia risk variants may need to be considered within this important network context for added interpretability [45•]. The polygenic overlap between schizophrenia and a range of human traits and diseases could implicate pathways across traditional categories, questioning current disease nosology. Further, emerging evolutionary considerations [61,62] suggest we may need to consider variants within a human-specific network background to identify relevant schizophrenia neurobiological perturbations, which may call for novel neuroscientific approaches. The emerging evidence from schizophrenia GWAS emphasizes a need for further refinement and development of analytic approaches, continued mapping of gene regulatory elements within relevant cells, integration of diverse data into pathways and careful thought about how best to functionally characterize the neurobiology associated with genetic risk for schizophrenia in animal and cell models.

Conflict of interest statement

No author reports any conflict of interest regarding the current study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.conb.2015.10.008.

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