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Polygenic risk scores in clinical psychology: Bridging genomic risk to individual differences

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Abstract

Genomewide association studies (GWAS) across psychiatric phenotypes have shown that common genetic variants generally confer risk with small effect sizes (OR<1.1) that additively contribute to polygenic risk. Summary statistics derived from large discovery GWAS can be used to generate polygenic risk scores (PRS) in independent, target datasets to examine correlates of polygenic disorder liability (e.g., does genetic liability to schizophrenia predict cognition). The intuitive appeal and generalizability of PRS have led to their widespread use and new insight into mechanisms of polygenic liability. However, presently, when applied across traits they account for small effects (less than 3% of variance) and are relatively uninformative for clinical treatment and, in isolation, provide no insight into molecular mechanisms. Larger GWAS are needed to increase their precision and novel approaches integrating various data sources (e.g., multi-trait analysis of GWAS) may improve the utility of current PRS.

Keywords

polygenic; PRS; GWAS; candidate; schizophrenia; psychopathology

It has long been recognized that psychiatric phenotypes travel in families (Schulze et al., 2004). By the 1820s, the first dedicated psychiatric hospital in the world, Bethlem, routinely asked whether presenting illnesses were hereditary (Plomin et al., 2013). In the early 20th century, family- and twin-based designs were used to empirically examine the latent genetic architecture of psychiatric phenotypes (Kendler, 2015). For example, in the first large scale systematic modern psychiatric genetics study, Rüdin examined rates of schizophrenia, known as *dementia praecox* at the time, among 2,733 siblings of 725 diagnosed probands (Rudin, 1916). Family and twin studies conducted over the subsequent century have largely confirmed early observations that, much like other complex traits, psychiatric disorders and related phenotypes (e.g., personality, brain volume) are generally moderately to highly heritable with a complex non-Mendelian polygenetic architecture that is importantly moderated by experience (Polderman et al., 2015). Clinically, the results from early family-

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based latent genetic research were initially used to enact eugenics programs (e.g., forced sterilization) in egregious and ill-fated efforts to reduce severe mental illness (Schulze et al., 2004) before informing our understanding of disease etiology, comorbidity, and nosology (Gilbertson et al., 2002, Posthuma and Polderman, 2013). The direct clinical application of latent genetic research is inherently limited; it cannot inform genetic risk beyond simple assessments of familial history, detect actionable therapeutic pathways (e.g., specific molecular pathways through which latent genetic risk is manifested), or lead to generalizable individually tailored treatments.

Advances in molecular genetic knowledge and technology facilitating the examination of specific measured genetic variation generated considerable enthusiasm that clinically-relevant and actionable results would soon be obtained [e.g., mechanistic insight, identification of treatment targets, personalized medicine (Craddock and Owen, 1996)]. Early hypothesis-driven (candidate gene) efforts adopted a bottom-up approach by studying variants with putative functional implications [e.g., *COMT* rs4680 (Egan et al., 2001), *ADH1B* rs1229984 (Thomasson et al., 1991), 5-HTTLR within *SLC6A4* (Lesch et al., 1996, Caspi et al., 2003), *MAOA* promoter variant (Caspi et al., 2002)] within pathways (e.g., serotonin, dopamine, alcohol metabolism) known to be associated with psychiatric expression. Complementary studies probed biological [e.g., neural phenotypes (Hariri et al., 2002, Egan et al., 2001)] and behavioral [e.g., working memory (Goldberg et al., 2003)] mechanisms through which such putative risk may manifest (Bogdan et al., 2017) as well as how genetic variation may impact treatment response (Perlis et al., 2010).

In the past decade, technological advancements and related cost reductions, combined with the realization of the candidate gene research limitations (Duncan and Keller, 2011) and unprecedented collaborative team science have encouraged the transition to genomewide association studies (GWAS) and the use of a top down scientific approach (i.e., from associations with clinical manifestations to more basic biological mechanisms)(Kendler, 2013, Visscher et al., 2017)]. GWAS results have validated the role of some candidate loci [e.g., rs1229984 for alcohol dependence (Gelernter et al., 2014)] and genes [e.g., *SIRT1* (CONVERGE, 2015), *DRD2* (Schizophrenia Working Group of the Psychiatric Genomics, 2014)], but not others [e.g., *COMT* rs4680 and schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics, 2014); but see also meta-analytic work supporting this association with evidence of recessive mode of inheritance (Gonzalez-Castro et al., 2016)], and led to the discovery of replicable associations with novel variants [e.g., *CACNA1C* (Ferreira et al., 2008)]. More broadly, results from GWAS have profoundly reshaped our understanding of the genetic architecture of mental illness in two important ways. First, our hypotheses regarding the nature of biological contributors to disease were inadequate. Not only was our focus on specific pathways (e.g., dopamine for addictions; serotonin for depression) relatively naïve, but our estimates of the effect size associated with single variants was far too optimistic. We now know that, with few exceptions [e.g., *APOE*, rs429358 and rs7412 haplotypes and Alzheimer's Disease (Corder et al., 1993)], individual common variants are associated with small effects [e.g., odds ratios < 1.1 (Schizophrenia Working Group of the Psychiatric Genomics, 2014)]. Our second lesson is more encouraging - the additive effects of independent and commonly occurring variants, when weighted by their association with a disorder or related construct in an adequately powered

GWAS (Figure 1), are reliably predictive of variance in the same and related phenotypes (Figure 2; Tables 1–6). These additive scores, which we refer to as polygenic risk scores (PRS),[1] along with other polygenic approaches (e.g., pathway-based analyses, machine learning, LD score regression) hold tremendous potential to contribute to our etiologic understanding of psychopathology and quantification of individual risk that may ultimately contribute to advances in the characterization and treatment of mental illness.

The Elephant in the Room: Why do Genetic Research

To appreciate achievements in psychiatric genetics and to confront emerging challenges, we must, at the outset, examine whether studies aimed at identifying disease-related genetic variation are worthwhile. In particular, critics have argued that risk-attributable effect sizes are too modest, at least for common variants (e.g., OR < 1.1), to be therapeutically meaningful. From a public health perspective, only a few might argue that highly heritable traits, such as Autism Spectrum Disorders, Schizophrenia, Bipolar Disorder and Late-Onset Alzheimer's Disease should not be interrogated using genetic approaches. However, some may propose that the pursuit of common variant association identification has either not yielded sufficiently new discoveries or, as for Schizophrenia, has reached an asymptote where the clinical relevance of every new discovery may not be as proportionally related to magnitudes of sample size, effort and continued funding, particularly as newly discovered variants are likely to be associated with increasingly smaller effect sizes. Similarly, there has been skepticism regarding investment of resources to gene discovery for disorders such as depression and addictions (Merikangas and Risch, 2003), that are less heritable. The skeptical argument is that such conditions are amenable to environmental intervention and therefore, building a better genetic model is more a source of intellectual self-gratification than of consequence to public health.

We fundamentally disagree with the position that the search for common variants associated with psychopathology is no longer relevant. Gene discovery, for disorders with moderate and high heritability, continues to be essential from two perspectives: *mechanistic insight*, and *treatment improvement*. Indeed, GWAS would be less appealing if research were to cease at gene discovery. This is rarely the case. However, the progress from discovery and replication of a locus to the outline of its etiologic significance takes time, resources, and collaborative interdisciplinary science (International Schizophrenia et al., 2009, Sekar et al., 2016).

Mechanistic insight:

Systematic translational research inspired by genetic association has strengthened our understanding of gene-brain/body-behavior relationships and identified potential therapeutic pathways. We briefly illustrate with two examples:

Immune pathways to schizophrenia: The most strongly linked common genetic variation to schizophrenia was identified through GWAS and resides within the major histocompatibility complex (MHC) region (e.g., rs115329265 OR=1.21, $p \approx 2.48e^{-31}$) (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Seven years following

[1]Scores are also referred to as genetic risk scores (GRS) or polygenic scores (PGS) within the broader literature.

the initial identification of this region for schizophrenia (International Schizophrenia et al., 2009), Sekar and colleagues (2016) distilled the MHC genetic signal, in part, to complex structural variation within the complement component 4 gene (*C4*) (Sekar et al., 2016). C4 is a component of the innate immune system's non-specific defense against foreign pathogens, and cellular debris that has also been implicated in the pruning of synapses. These researchers also showed that *C4* variation altered brain *C4* expression proportional to schizophrenia risk and that C4 mediated synaptic pruning during postnatal development in mice. Collectively, these results suggest that the *MHC genetic signal for schizophrenia may be partially attributable to variability in C4-related synaptic pruning*, which ultimately may be leveraged for treatment and/or prevention.

HPA axis regulation and risk for stress-related disease: Genes identified outside of GWAS have also produced promising insights. Work pioneered by Binder, Ressler, and colleagues has linked variation in *FKBP5* to pleiotropic stress-related health effects (e.g., PTSD, depression, Alzheimer's disease, and aging) and related biological correlates (e.g., cortisol response, amygdala function) (Zannas et al., 2016). FKBP5 is a critical regulator of the hypothalamic-pituitary-adrenal (HPA) axis; it is a co-chaperone of the glucocorticoid receptor (GR) complex that diminishes GR sensitivity to cortisol resulting in an impaired ability of the HPA axis to return to homeostasis and transcriptionally regulate the genome. Through a series of programmatic experiments, Klengel and colleagues (Klengel et al., 2013) have shown that increased GR-stimulated *FKBP5* expression observed among individuals with at least one T allele at rs1360780 may arise from alterations in the 3D structure of *FKBP5*. The T allele brings a long range enhancer region in intron 2 into physical contact with the transcription start site (TSS) thereby allowing it to affect expression. Effects of these conformation changes can be further compounded by T-allele specific childhood stress-related demethylation of a functional glucocorticoid response element within intron 7, which also contacts the TSS. Demethylation here, which some evidence suggests may only be stable following stress exposure early in life, enhances *FKBP5* expression in the context of GR stimulation, resulting in a further reduction of HPA axis negative feedback. *It is thus possible that the 3D conformation changes lead to a prolonged stress response that, when coupled with early life stress exposure, results in lasting epigenetic changes further impairing HPA axis regulation including its ability to influence the transcriptome*. While recent large-scale GWAS of stress-related disorders (e.g., PTSD and depression) have not identified variants in *FKBP5* (Duncan et al., 2017, Stein et al., 2016, Wray and Sullivan, 2017), this is unsurprising given the highly interactional nature of these molecular mechanisms and trauma exposure during early life (i.e., without GWASxE such effects would not be expected).

These two examples demonstrate that analyses of common single genetic variants, from GWAS and other empirical research, remains relevant and incredibly important in our polygenic world by identifying potentially clinically informative and actionable mechanistic pathways. They also underscore the premise that moderately heritable traits (e.g. PTSD h^2 ~40%; (Cornelis et al., 2010)) that impose considerable personal and public health burden (Friedrich, 2017) are worthy of genetic inquiry.

Treatment insights:

Accumulated wisdom cautions against dismissing the potential clinical relevance of loci that are associated with small effects as they may provide flags for potential therapeutic targets. Perhaps the most convincing example of how genetic associations with small or modest effect sizes can have great treatment potential comes when considering statins, the first line drug of choice for the treatment of high cholesterol. Statins, developed in the 1970s, work by competitively inhibiting HMG-CoA reductase within the cholesterol synthesis pathway. Subsequent candidate genetic and GWAS-based investigations linked common genetic variation within the HMG-CoA reductase gene (*HMGCR*) to cholesterol. However, the effect sizes of such common genetic variation on cholesterol and cardiovascular risk are miniscule (i.e., < 20×) when compared to the effect of statins (Willer and Mohlke, 2012, Barrett et al., 2015). For example, the *HMGCR* SNP rs12916 reduces LDL cholesterol levels by 2.5 mg/dl for each copy of the protective allele, with even smaller associations with coronary artery disease, while statins typically decrease LDL by 14–70 mg/dL. This example is not unique. Similar observations of large medication effects targeting proteins in which common genetic variation is more modestly associated with disease expression, have been observed across a host of phenotypes (e.g., bone density and estrogens (Hirschhorn and Gennari, 2008)). Indeed, a recent investigation finds that drug targets with evidence of disease association through GWAS are twice as likely to be met with success (Nelson et al., 2015). These results suggest that common genetic variation linked to intermediate phenotypes (e.g., cholesterol for coronary artery disease), and also with disease risk at modest effect sizes, have the potential for great therapeutic value. Similar expectations for psychiatric disorders are not unrealistic (Breen et al., 2016, Wendland and Ehlers, 2016). GWAS may be a particularly fruitful pathway to such discovery, especially within the field of psychiatry, which has thus far struggled to identify mechanistic pathways that may be leveraged for treatment outside of happenstance [e.g., the observed mood benefits of an agent developed to treat tuberculosis that inhibited monoamine oxidase and led to the development of modern antidepressant medications (Ramachandraih et al., 2011)].

In addition to identifying therapeutic targets, molecular genetic variation may also be used to personalize therapeutic options for patients. Such pharmacogenomics approaches have been extraordinarily successful in personalizing cancer care and elucidating treatment pathways (Wheeler et al., 2013). *The genetic architecture of clinically relevant psychological traits and psychiatric disorders is more complex and any such diagnostic genetic panel for these highly polygenic conditions should be viewed with extreme caution*. Nonetheless, genetic research is currently bearing clinically-applicable fruit - for example, rs16969968 within *CHRNA5*, is a common missense polymorphism strongly associated with tobacco smoking (b=1.03, $p \approx 3 \times 10^{-73}$ (Tobacco and Genetics, 2010). This locus moderates the efficacy of treatment and influence numbers needed to treat [NNT (Bierut et al., 2014)]; one study found that while 4 individuals with the high-risk smoking haplotype needed to be treated to benefit one individual (NNT), the corresponding estimate for those with the low-risk haplotype was >1000 (Chen et al., 2012). Further, inspired by associations between *FKBP5* and stress-related psychopathology, initial trials of FKBP5 inhibitors in rodent models of stress have produced promising results (Gaali et al., 2015).

If we are convinced of the value of genetic research (more specifically, common variant discovery and mechanistic probing), but also cognizant of polygenicity, statistical power, and the inherent limitations of nosological boundaries (e.g., heterogeneity and comorbidity) and prior mechanistic knowledge, how might genetic research be leveraged to inform clinical psychology? Polygenic risk scores (PRS) may usefully contribute to the identification of disorder-related risk factors, our understanding of comorbidity, and begin to provide insights into the developmental trajectory of psychiatric phenotypes as well as their course, treatment, correlates, and underlying pathophysiologies.

Polygenic Risk Scores: A Bridge Between Population Variation and Individual Differences

What are PRS

In simple terms, a polygenic risk score is a cumulative index of measured genetic liability to a disorder. PRS are similar to "heritability" (h^2) in that they represent, to some degree, the aggregate and additive effects of segregating loci of small effect (see also section: *Differences from other Heritability Metrics*). Similar to traditional twin estimates of narrow heritability, PRS are additive in nature, consistent with numerous illustrations that support the widespread role of additivity in complex genetics (Hill et al., 2008). Several excellent reviews, both of a technical/practical and interpretive nature, have been written about the utility of PRS (Wray et al., 2014, Chatterjee et al., 2016, Bogdan et al., 2017, Plenge et al., 2013, Dudbridge, 2016). Here, we provide a brief theoretical and practical overview, before exemplifying how PRS approaches have begun to inform the field of clinical psychology and considering ways forward.

PRS Practicalities

Figure 1 illustrates the basic process of deriving a PRS, the steps to which are briefly described here:

STEP 1: Identify a well-powered discovery GWAS in which your sample is not included and obtain summary statistics from that analysis.—The remarkable popularity of PRS is in part attributable to the increasing availability of full summary statistics from discovery GWAS, a data-sharing approach spearheaded by the PGC (https://www.med.unc.edu/pgc/results-and-downloads), who not only share the summary statistics of their GWAS but also do so prior to formal publication and host results files from other consortia and investigators. PRS are derived by applying the "effect" alleles and their corresponding effect sizes (odds-ratios or beta coefficients) from a discovery GWAS to an independent, target sample (Figure 1). Because the effect size is used to weight allelic risk, its reliability is critically important. Hence, the better powered the discovery GWAS is, which is undoubtedly related to sample size, but also, arguably, to phenotypic relevance and strength of assessment, as well as sample composition (CONVERGE, 2015), the greater the confidence we might have in the resulting effect sizes. In Figure 1, we use the example of the current largest GWAS of Schizophrenia which includes 36,989 cases and 113,075 controls (Schizophrenia Working Group of the Psychiatric Genomics, 2014). While it is not necessary for the discovery GWAS to have identified replicable genomewide significant loci

(i.e., association p-values < 5×10^{-8}), the ability for a GWAS to identify such loci may be seen as evidence for statistical power and its potential utility for PRS analyses.

STEP 2: Establish commonality between your target dataset and the discovery GWAS.—PRS are amenable to differences in SNP content across the discovery and target samples; it is preferable to begin by working with imputed data in both the discovery and target dataset to maximize convergence. First, SNPs in the target dataset that overlap with SNPs in the discovery GWAS are extracted. Second, the target data are aligned to the discovery dataset (i.e., individual genotypes are oriented to the same strand of DNA and strand-ambiguous SNPs - A/T or G/C - are either excluded or closely evaluated). These steps are critical to ensure that effect sizes from the discovery GWAS are being accurately applied to the target sample. Typically, sex chromosomes are also removed. Traditional quality control indices should be applied to the target dataset including minor allele frequency cutoffs, Hardy-Weinberg-equilibrium testing, missingness by individual and marker exclusion, cryptic relatedness exclusion, sex check, ancestral outliers, and imputation quality.

STEP 3: Eliminate SNPs in high LD.—Correlated variants can represent non-independent association signals that, if ignored, could overweight PRS in favor of loci in high LD, by essentially counting a single signal multiple times. Indeed, not thinning a PRS according to LD can reduce their precision (Wu et al., 2013). As a result, it is recommended that variants be clumped so that the LD statistic, r^2, is no greater than 0.10. When there are correlated SNPs, it is recommended to select the SNP in your target dataset based on the strength of association in the discovery GWAS (i.e., p-value-informed clumping). For example, if there are 80 SNPs forming an LD block, the SNP selected to represent this cluster should be the one with the largest effect size in the discovery GWAS. Not clumping data may limit the polygenic interpretability of PRS, especially at more significant p-value thresholds where an entire PRS could be driven by a series of correlated variants; but see *Improvements in PRS estimation* for alternatives. Studies also commonly exclude areas of complex linkage structure (e.g., MHC region) or retain one representative SNP across such regions.

STEP 4: Calculate PRS for each individual in your sample.—For each individual in the target sample, *multiply the effect size (if ORs, the log-transformed allelic OR) observed in the discovery GWAS by the number of effect alleles for that variant that the individual possesses*. In our example (Figure 1), for each polymorphism, this product term represents an individual's liability to schizophrenia that is attributable to the alleles present at that single variant. These individual allele scores can then be averaged across the genome to form an overall polygenomic liability, or PRS, for each individual. Typically, an investigator creates multiple PRS that represent degrees of type II error/alpha (i.e., varying p-value thresholds) in the discovery GWAS. Therefore, one might aggregate all variants that were significant at p<1.0, p < .50, p < 0.30, p < .10, < 0.05, p < 5 × 10–3, p < 5 × 10–5 and p < 5 × 10–8 in the discovery GWAS, generating a person-specific PRS for schizophrenia at each p-value threshold. To limit multiple testing, one could select a p-value threshold that is most predictive of variability of the GWAS phenotype or related phenotype in an

independent sample or use permutation based testing to assess whether the overall pattern of associations across p-value thresholds is more than expected by chance within the target dataset (Carey et al., 2016b). PRS can then be used as continuous variables within traditional analytic settings (e.g., regression). Typical covariates in further analyses include factors that confound gene - outcome analyses, such as ancestry differences, age, and sex.

Software programs including PLINK (Purcell et al., 2007, Chang et al., 2015) and integration with PRSice (Euesden et al., 2015b) facilitate PRS calculation.

Technical Considerations.

Sample size: This review underscores the rational range of effect sizes that should be considered when determining sample sizes that would be amenable to PRS analyses (Figure 2). There are two issues to consider here: how predictive is a PRS, and how large of a target sample will usefully detect the effects of that PRS on an outcome. Several technical papers discuss the predictive utility of PRS - So and Sham (So and Sham, 2017) found that SCZ PRS (Schizophrenia Working Group of the Psychiatric Genomics, 2014) had the greatest predictive power of all psychiatric disorders (max Area Under the Curve, AUC = 0.82), which was even higher than some health-related traits [e.g., Type 2 Diabetes and Coronary Artery Disease max AUC = 0.61 (So and Sham, 2017)]. Predictive power for psychiatric disorder PRS appears to increase at more inclusive p-value thresholds, unlike metabolic traits, which is consistent with a greater degree of expected polygenicity. Further, psychiatric PRS are modestly superior in performance when drawn from studies with greater phenotypic precision. Other expositions on the topic have considered R^2 estimation in the context of discovery GWAS sample size (N), the number of presumed independent causal loci (M~70,000) and SNP-h^2 (Daetwyler et al., 2008, Dudbridge, 2013). Simulations from these studies are sobering. For instance, in their GWAS meta-analysis of educational attainment, Rietveld and colleagues (Rietveld et al., 2013) concluded that a discovery GWAS of 1 million individuals for this phenotype might generate a polygenic score that explained 15% of the variance in the same phenotype in a new sample. The second consideration is whether a target sample size is large enough to rule out false negatives or positives. PRS analyses are often simple regressions, and typically account for 0.01% (conservatively) to 3% (optimistically) of variance in cross-trait prediction (e.g., schizophrenia PRS predicting task performance among healthy individuals; Figure 2, Tables 1–6). As such with optimistic estimates, target data sample sizes of at least 300 are needed to detect 3% of variation with 80% power. Samples of 800, 8,000, and 80,000 would be needed to account for 1%, 0.1%, and 0.01% of variance with 80% power, respectively (computed using GPower; (Faul et al., 2007).

Improvements in PRS estimation: Method improvement for PRS estimation is an active area of research, with several new approaches only recently proposed - here, we briefly highlight two. One approach, LDpred (Vilhjalmsson et al., 2015), takes into account the LD between markers, thus eliminating the need for LD-thinning, which may limit the variance explained by PRS in some cases. LDpred estimates posterior mean effect sizes based on LD patterns from a reference genome, by specifying an LD radius (i.e., number of SNPs that are accounted for on either side of another SNP), and has been found to have better accuracy

and calibration. For example, in the same target sample, LDpred explains 25% of the variance in schizophrenia compared to 18% from traditional PRS. Another approach, MTAG (Multi-Trait Analysis of GWAS; (Turley et al., 2017)), which may be thought of as an extension of traditional meta-analysis, enables the joint analysis of several traits, resulting in improved PRS precision. MTAG takes advantage of the increasing number of publicly-available GWAS summary statistics, and the development of techniques which can estimate trait heritability and genetic correlations from summary statistics [LDSR; (Bulik-Sullivan et al., 2015), see also related user-friendly online interfaces/databases (e.g., LD Hub; http://ldsc.broadinstitute.org/ (Zheng et al., 2017)]. Indeed, early analyses have successfully applied MTAG to the study of several psychiatrically relevant traits, resulting in prediction accuracy improvements of 25–50% and increased numbers of genomewide significant hits ((Hill et al., 2017, Turley et al., 2017). Beyond these two examples, several approaches incorporating Bayesian estimation (Mak et al., 2016, So and Sham, 2017) and machine-learning (Pare et al., 2017, Shi et al., 2016), have also been proposed.

Improvements in Discovery GWAS: In addition to increasing the sample size of discovery GWAS and using new tools to improve the utility of PRS available from current GWAS summary statistics, improving discovery GWAS phenotyping may also produce more reliable, applicable, and precise PRS. Indeed, relying on GWAS of psychiatric disorders may be problematic for refining nosology and mechanistic understanding because many, if not all, psychiatric disorders represent heterogeneous amalgamations of symptoms and their correlates. Such heterogeneity may dilute observed genetic effects or result in the identification of broad and generalized genetic associations that may not be applicable to more specific phenotypes. For example, many patients with MDD do not exhibit the cardinal symptom of anhedonia (Treadway and Zald, 2011). Thus, genetic associations with heterogeneous MDD not predicated on the presence of anhedonia, may not be informative for reward-related neural or behavioral phenotypes (Bogdan et al., 2013). The potential implications of GWAS phenotyping may be observed when contrasting two GWAS of depression. In the larger study, which contained 9,240 MDD cases and 9,519 controls, no genomewide significant loci were detected (Major Depressive Disorder Working Group of the Psychiatric et al., 2013). The second study which consisted of Han Chinese women with recurrent, primarily melancholic, depression (n=5,303) or without MDD (n=5,337), identified 2 genomewide significant loci (CONVERGE, 2015), including one within a candidate gene, *SIRT1*, which has been previously linked to reward-related neural and behavioral phenotypes in non-human animal models, as well as anxiety and age-related disease and mortality (Libert et al., 2011, Kishi et al., 2010, Kuningas et al., 2007). Arguably, the phenotypic and population homogeneity of the CONVERGE effort resulted in relatively improved power (Sullivan, 2015). Notably, however, other large scale GWAS of even more heterogenous phenotypes (e.g., those self-reporting a depression diagnosis through 23andMe) have also been met with success (Hyde et al., 2016). Further, other evidence suggests that traditionally conceptualized intermediate phenotypes (e.g., brain volume), may not be associated with larger effects related to common genetic variation suggesting potential limitations to “deeper” phenotyping (Franke et al., 2016). Going forward it will be important to not only have large studies, but also studies with deep phenotyping so that both heterogenous and more precise phenotypes could be leveraged and

their predictive utility for cross-trait association contrasted. Indeed, the genetic architecture of a disorder may be partially or even fully distinct from the genetic architecture underlying related pathophysiology, its response to current treatment (see also Treatment Relevance), or its interplay with the environment (see also Other Applications). Lastly, for some disorders, which require exposure (e.g., substance use disorders, PTSD), it may be important to restrict controls of discovery GWAS to exposed individuals who have not been diagnosed with the disorder to identify sources of disorder liability. Such an approach was recently successful when considering opioid dependence when contrasting with opioid-exposed controls who did not progress to daily injection (Nelson et al., 2016).

Cross-ancestry PRS prediction: Because they rely on LD patterns, which vary ancestrally, PRS derived from a discovery GWAS of Europeans might not be an informative predictor in another ancestral group. Even within ancestral groups, inclusion of indices of nuanced ancestral variability derived from GWAS data, can significantly improve prediction in PRS analyses by eliminating such spurious admixture effects from the weighted PRS (Chen et al., 2015). Studies have begun to probe whether PRS generated from one ancestral population may be predictive of the same phenotype in another. For example, Bigdeli and colleagues (Bigdeli et al., 2017) combined results from the aforementioned CONVERGE Han Chinese cohort with those from a large GWAS meta-analysis of Europeans to report a trans-ancestry genetic correlation of ~0.30 – 0.40. However, LDpred PRS-based analyses were only predictive of recurrent depression, but not other depression phenotypes, after correction for multiple testing (R^2=0.002). A similar study found that PRS derived from a GWAS of neuroticism in 170,910 individuals participating in the European UK Biobank (Okbay et al., 2016) predicted variance in both depression (R^2=0.001) and neuroticism (R^2=0.083) in Han Chinese women (Docherty et al., 2016). Thus, with caution, one could experiment with projecting effect sizes from population A to population B. Of course, the most valuable resource in this regard would be large well-powered discovery GWAS conducted in homogenous populations from different ancestral origins, which are becoming more common (Duncan et al., 2017, Meyers et al., 2017, Xu et al., 2015). Related approaches combining results from large and readily available European or mixed-ethnicity cohorts with smaller training datasets of another ancestry to produce ancestry-adjusted PRS have also been proposed ((Marquez-Luna and Price, 2016, Coram et al., 2017).

Differences from other heritability metrics: Even though they represent the additive effects of segregating loci, *PRS are distinct from twin-heritability and SNP-heritability*. SCZ-PRS explain ~18% of the variance in the disorder in independent samples (Schizophrenia Working Group of the Psychiatric Genomics, 2014); family/twin-h2 and SNP-h2 are 80% and 41% respectively (Sullivan et al., 2017). Estimates of twin-h2 are based on latent sources of additive (and in some cases, non-additive) genetic factors and assume uniform effects of all segregating loci. Furthermore, they rely on certain assumptions, some of which can be reasonably questioned (e.g., random mating). PRS represent a portion of this genetic variance that is attributable to a set of uncorrelated loci, and are less assumption-laden. In fact, PRS approaches have been used to demonstrate the widespread occurrence of assortative, (*non*-random) mating - for instance, polygenic liability to educational attainment in one spouse accounts for 14–19% of the partner's education

outcomes (Hugh-Jones, Verweij et al. 2016). SNP-h2, calculated with a variety of methods [Genetic Complex Traits Analysis: GCTA (Yang et al., 2011); Linkage Disequilibrium Score Regression: LDScR; (Bulik-Sullivan et al., 2015)], may be used to examine the net effect of all genomewide variants, genotyped and imputed and is related to both twin-h2 and PRS. SNP-h2 is more similar to twin-h2 in that they harness effects of all variants, but only explain a proportion of twin-h2 (especially for behavioral traits), which are typically considered the denominator (perhaps, inaccurately) for such estimation. PRS at a threshold of $p < 1.0$ might reasonably be expected to approximate SNP-h2, however some have noted that the LD pruning step of PRS estimation may diminish its predictive utility (Vilhjalmsson et al., 2015), by removing correlated loci with independent effect. Nonetheless, PRS are only expected to predict variance in the same trait if SNP-h2 > 0, and in other traits if they are significantly genetically correlated (SNP-rg > 0); however, we view them to be philosophically different (although, SNP-h2 has attractive technical characteristics)[2]. Twin-h2 and SNP-h2 represent the total variance accounted for by latent genetic and measured common genomic variation, respectively. On the other hand, the *essence of PRS is "prediction"* in an independent sample, using a metric that is algebraically simple (weighted average), so that it might be viewed to have future generalizable clinical relevance.

PRS Application: The example of Schizophrenia

Undoubtedly, schizophrenia (SCZ), which was subjected to GWAS meta-analysis in 36,989 cases and 113,075 controls by the PGC [(Ripke et al., 2013) for other GWAS by the PGC, see (Sullivan et al., 2017)], is amongst the most frequently analyzed and robustly associated psychiatric PRS. Using these SCZ-PRS, in Figure 2; Tables 1–6, we illustrate the utility of the PRS approach in advancing our understanding of the genetic architecture of SCZ and its relationship with other traits and disorders. Broadly, two observations are immediately apparent. First, unlike GWAS, PRS may be examined in substantially smaller samples. Sample sizes range from <200 for certain clinical traits as well as neuroimaging outcomes (e.g., brain activation during probabilistic learning task) to > 100, 000 for population-based studies of common traits, such as self-rated health; how large a sample is sufficient is addressed above in Technical Considerations. Second, effect sizes are (mostly) modest with PRS explaining <1% of the variance for correlated traits [e.g., R^2 for negative symptoms in the population is 0.007, or 0.7%; (Jones et al., 2016) or 0.3% for cognitive abilities (Riglin et al., 2017). These effect size estimates are sobering; even for highly correlated disorders, such as SCZ and Bipolar Disorder (Charney et al., 2017), PRS rarely account for more than 3% of variance in a trait [e.g., 2.5% for educational attainment PRS predicting cognitive function (Rietveld et al., 2013)]. Thus, studies accounting for >5% of variance in cross-trait prediction, or with fewer than several-hundred participants, should be viewed with some skepticism when using current GWAS summary statistics.

SCZ-PRS have primarily been applied to understand relationships across 6 broad domains: schizophrenia-related phenotypes (e.g., psychosis, treatment), other psychiatric disorders, cognition, brain-related phenotypes, immune and health-related and, finally, other

[2]SNP-h2, especially from LD Score Regression, does not require access to raw genotypes, can be used for quality control and can be automated, with less likelihood of user error. However, it requires large sample sizes (n > 3K).

phenotypes (e.g., urbancity). Effect sizes for these studies are graphically summarized in Figure 2 with individual study summaries provided in Table 1–6, and discussed (briefly) below.

Schizophrenia-related Phenotypes (Table 1):

SCZ-PRS have been repeatedly linked to various measures of psychosis, psychotic symptoms and experiences, within clinical and general population samples. Associations with negative and positive symptoms have also been noted. For instance, Jones et al (2016) report that SCZ-PRS are associated with 0.5–0.7% of the variance in psychotic experiences at ages 12–18. In addition, SCZ-PRS have been linked to chronicity and course of illness with one study finding SCZ-PRS to predict the number of hospital admissions, length of hospital stay and enrollment in supportive housing (Meier et al., 2016). Mixed evidence also exists for an effect of SCZ-PRS on treatment response (Wimberley et al., 2017b, Li et al., 2017). Interestingly, the predictive utility for antipsychotic response is improved by incorporating rare variants into such scores (Ruderfer et al., 2016), although null findings also exist (e.g., (Hettige et al., 2016)). Family history also accentuates risk conferred by SCZ-PRS (Agerbo et al., 2015).

Psychiatric disorders and traits (Table 2):

Genetic liability to SCZ has been linked to numerous other psychiatric conditions, including bipolar disorder, major depression, obsessive compulsive disorder, anorexia nervosa, posttraumatic stress disorder, alcohol dependence and attention deficit hyperactivity disorder (Anttila et al., 2016); however, a preponderance of these studies have calculated genetic correlations (SNP-rg). Nonetheless, studies employing the PRS approach find strong associations with a variety of psychiatric phenotypes. Of particular interest, SCZ-PRS successfully distinguish between clinical subtypes of Bipolar Disorder, with stronger associations with Bipolar I and schizoaffective forms (Charney et al., 2017). Substance use disorders have also been robustly linked to SCZ-PRS e.g., (Carey et al., 2016a). In particular, addressing the controversy regarding the role of cannabis use in the development of psychosis (Hall and Degenhardt, 2008), multiple studies have used SCZ-PRS to clearly demonstrate the role of shared genetic etiologies between these two phenotypes (e.g., R2=.47% for SCZ-PRS and ever using cannabis), thus challenging prior causal assertions and providing a new outlook on this relationship that was not possible to query with twin data (Power et al., 2014, Carey et al., 2016a, Verweij et al., 2017, Reginsson et al., 2017, Aas et al., 2017). Within the longitudinal framework, the correlation between SCZ-PRS and psychiatric traits (ADD, ODD/CD, Anxiety and Depression) increases from 0.10 at age 6–7 to 0.25 by age 16 (Nivard et al., 2017). This application of PRS for a clinically uncommon and severe discovery phenotype (i.e., SCZ) to a general population sample of longitudinally evaluated youth highlights the important role that PRS analyses play in bridging clinical psychiatry with developmental psychology and behavioral genetic research that was largely unattainable using latent genetic models of uncommon disorders (e.g., SCZ). One of the largest studies evaluating SCZ-PRS among other traits shows that it predicts a small amount of variance in neuroticism (0.12%) (Gale et al., 2016).

Cognition (Table 3):

SCZ-PRS have unequivocally established a link between genetic susceptibility to SCZ and cognitive deficits during the lifespan. SCZ-PRS are predictive of IQ at ages 7–9 (Riglin et al., 2017, Hubbard et al., 2016) and also to cognitive decline in later life (Liebers et al., 2016). One study suggests stronger effects on Wechsler IQ at age 70 but not age 11, with SCZ-PRS predicting 0.8% of the variance in this developmental decline. Collectively, this research suggests that cognition deficits observed in schizophrenia are attributable in part to common genetic variation, that can also be observed in the population.

Brain-related (Table 4):

A variety of neuroimaging approaches have been used to evaluate potential neural substrates of schizophrenia (Kahn et al., 2015). However, with the exception of offspring and sibling-based studies (Chung and Cannon, 2015), it has been difficult to disarticulate whether such associations may be a consequence of medication (ubiquitous in most samples) or disorder expression as opposed to a marker of risk (Tost et al., 2010). SCZ-PRS can be leveraged to probe whether such neural metrics, or perhaps even novel ones (masked for example by medication usage), may be associated with genetic liability to schizophrenia within healthy populations unexposed to antipsychotic medication or disease course. Most commonly studied in this context are metrics of brain structure (e.g., cortical thickness, cortical gyrification, and gray matter volume), which have produced mixed evidence that increased schizophrenia genomic liability may be associated with reduced cortical thickness and volume (French et al., 2015, Van der Auwera et al., 2017). Other studies have begun to link SCZ PRS to functional imaging phenotypes such as reward- and working memory-related brain function; however results thus far have been mixed and are often derived from small samples (Lancaster et al., 2016b, Erk et al., 2017, Lancaster et al., 2016a). Overall, this evidence suggests that some neural phenotypes associated with schizophrenia may represent neural mechanisms of common polygenic liability. However, other evidence, drawn from large samples, suggests minimal genomic overlap between subcortical brain volume and schizophrenia (Franke et al., 2016). Lastly, a recent study reports that SCZ-PRS are associated with differentially methylated probes in postmortem tissues from the prefrontal cortex, striatum and cerebellum of schizophrenic and control decedents (Viana et al., 2017). The most significantly associated probe was within *DISC1*, a gene associated with schizophrenia. Such studies provide exciting new opportunities for linking static genomic variation, in their polygenic form, to epigenetic variation.

Immunity and Health (Table 5):

Immune-related vulnerabilities are commonly observed in those with SCZ (Muller et al., 2015). Maternal immune response to infectious agents have been causally implicated in individual risk for SCZ, particularly among individuals with a diathesis (Knuesel et al., 2014). Even ex-utero, exposure to infectious agents, such as *Toxoplasmosis gondii*, primarily transmitted to humans through fecal matter from infected carrier felines, precipitates onset of motor, psychotic, and cognitive symptoms (Torrey and Yolken, 2003, Sutterland et al., 2015). Antithetically, while individuals with schizophrenia are more likely to exhibit a pro-inflammatory phenotype (e.g., higher levels of cytokines), risk for

rheumatoid arthritis, an autoimmune disorder is markedly reduced in those with schizophrenia and corresponds to a small, but significant, negative genetic correlation across the disorders as well (rg=−0.046) (Lee et al., 2015, Stringer et al., 2014, Euesden et al., 2015a). PRS may be particularly informative in studies exploring relationships with the immune system due to the overrepresentation of immune function loci in SCZ GWAS (Schizophrenia Working Group of the Psychiatric Genomics, 2014). For example, SCZ-PRS have been leveraged to test novel immune-related hypotheses with one study finding no evidence that SCZ-PRS moderates the relationship between infection and schizophrenia (Benros et al., 2016). Going forward, system-based PRS composition (i.e., forming a PRS from SNPs within biologically-defined pathways) may be particularly useful in this regard (see Improving PRS section below). Studies on health-related phenotypes also highlight several novel genetic relationships that transform our understanding of the relationship between schizophrenia, health and disease, ranging from self-rated health (Harris et al., 2016) to chronic and debilitating conditions such as migraines (Van der Auwera et al., 2016) and farther, to rare but serious progressive neurodegenerative disorders like Amyotrophic Lateral Sclerosis (ALS, Lou Gehrig's Disease (McLaughlin et al., 2017). Prior to the development of the PRS approach, the notion that the genetic underpinnings of such health-related conditions could overlap with predisposition to psychiatric disorders seemed to be an insurmountable challenge to address, particularly for uncommon conditions (e.g., SCZ, ALS) that make family-based approaches impractical.

Others (Table 6):

The advent of the PRS approach has also led to unique answers to additional age-old questions. We now know that genetic liability to SCZ (i.e., PRS) is related to variance in living in urban environments and in neighborhood deprivation, both leading environmental contributors to schizophrenia. Notably, schizophrenia represents an evolutionary paradox (van Dongen and Boomsma, 2013) in that while risk alleles are at selective advantage, the disease is associated with lower reproductive fitness with older paternal age implicated as a risk factor [potentially, due to de novo mutations in the male germ line (Malaspina et al., 2001)]. Yet, SCZ-PRS when applied to a sample of 150, 656 individuals found no correlation with number of children or age at first birth. However, perhaps most sobering is evidence that individuals with higher SCZ-PRS are more likely to drop out of subsequent waves of longitudinal studies, suggesting that distributions of SCZ-PRS, and consequently, their range of related phenotypes, might not be fully represented in cohort data (Martin et al., 2016).

Other Applications

Gene x Environment Interaction (GxE):

Environmental factors, in particular, chronic and unpredictable stressors during childhood, are among the largest risk factors for the expression of psychopathology (Green et al., 2010). Such factors act independently and in concert with genetic liability through predisposing (i.e., gene - environment correlation, R_{GE}) or moderating (i.e., GxE) mechanisms. PRS are beginning to be used to represent genomic liability in the context of stress. For example, five studies of depression PRS report that stressful life events or childhood trauma, as well as

PRS, are independently associated with depression. However, much like the candidate single variant environment interaction literature (Duncan and Keller, 2011), these initial studies have provided conflicting evidence of their interactive effect (GxE) (Musliner et al., 2015, Mullins et al., 2016, Colodro-Conde et al., 2017). Of the 3 reports evaluating stressful life events, 2 report null interactions (Musliner et al., 2015, Mullins et al., 2016) with 1 (Colodro-Conde et al., 2017) suggesting that elevated PRS potentiates the depressogenic effects of stress. In the study with positive findings, the observed PRS x stressful life event interactions accounted for only 0.12% of variance in depression; however, their estimates suggest that it could potentially account for as much as 20% of variance in depression if PRS were derived from a larger GWAS. While significant PRS interactions with childhood trauma explained up to 1.9% of variance in depression, the shape of these interactions was inconsistent. One study found that childhood trauma was associated with increased depression risk among those with lower polygenic liability to depression while depression PRS were associated with elevated depression risk in the context of no childhood trauma (Mullins et al., 2016). In opposition to these findings, the other report found a significant interaction wherein elevated PRS was associated with increased childhood trauma-related depression (Peyrot et al., 2014). Multiple explanations may be evoked to explain these discrepancies such as the use of PRS derived from different GWAS and differences in phenotypic assessments, and sample composition and size. GWAS x E studies are needed (e.g., (Polimanti et al., 2017) as the genetic architecture supporting the development of psychopathology (e.g., depression) in the context of stress may be distinct from the genetic architecture conferring general disorder risk as assessed in the original GWAS from which PRS were derived.

Disorder Specificity:

It may be tempting to contrast the predictive value of PRS derived from discovery GWAS of different disorders to evaluate disorder specific or shared mechanisms that may ultimately inform nosology (e.g., do SCZ-PRS predict reward-related neural function better than depression-PRS?). We suggest that such comparisons should be interpreted with caution, for 2 reasons. First, much like recent unifactoral models of psychopathology (Lahey et al., 2012) and evidence of shared neural mechanisms (Hariri, 2009, Goodkind et al., 2015), cross-disorder GWAS (Cross-Disorder Group of the Psychiatric Genomics, 2013) suggest that common genetic variation conferring liability to various disorders may be shared. Thus, clear hypotheses are needed for expected disorder specificity which may be present for some psychiatric phenotypes, but not others. Second, the robustness of the discovery GWAS can make it challenging to compare PRS. For example, if a PRS for schizophrenia [derived from GWASs containing 36,989 cases and 113,075 controls and identifying 108 independent loci (Schizophrenia Working Group of the Psychiatric Genomics, 2014)] is associated with reward-related brain function, but a PRS derived for depression (derived from GWASs containing 9,240 cases and 9,519 controls identifying no genomewide significant SNPs (Major Depressive Disorder Working Group of the Psychiatric et al., 2013) is not, whether this is indicative of genetically-conferred disorder specificity or simply a confound of the power of the discovery GWAS cannot be disarticulated. However, as the field continues to advance and more well powered psychiatric GWAS are conducted across disorders,

comparisons of PRS across disorders to detect shared and specific polygenic variability may prove informative.

Mendelian Randomization (MR):

MR is an extension of epidemiological causal models (for review see: (Davey Smith and Hemani, 2014, Holmes et al., 2014)). Assume that two traits are correlated - such as body mass index (A) and cardiovascular disease (B) - and that it is reasonable to hypothesize that A causes B. If one could identify genetic variants, including single loci, or multiple variants that comprise a PRS, that are robustly associated with A, but have no independent effects on B [although, methods that adjust for such pleiotropy exist (Bowden et al., 2015)] or on any covariate (e.g., smoking) related to B, then such a PRS might serve as a "genetic instrument" for MR analyses. If BMI PRS predict cardiovascular disease, indirectly through BMI, then such an association may be viewed as evidence in favor of causation (i.e., higher BMI results in cardiovascular disease) (Holmes et al., 2014). In an empirical test of this hypothesis, one study found that BMI PRS (discovery N = 108, 912) predicted cardiometabolic traits and outcomes, but not coronary artery disease, in an independent cohort of 34, 538 individuals. Each unit increase in the BMI-PRS corresponded to 1.08 kg/m^2 increase in BMI, and was associated with inflammation (e.g., C-Reactive Protein: 12% increase), cardiometabolic traits (e.g., fasting insulin: 8.4% increase) and disorders (e.g., type 2 diabetes, OR = 1.29) suggesting that BMI may cause such outcomes. The use of PRS in the study of clinically relevant psychiatric phenotypes is limited, although some argue that cross-trait PRS predictions may, in some cases, be indicative of MR. Current tests of MR in clinical psychology rely on individual loci, arguing that they are less likely to have pleiotropic effect, or create a noisy instrument (e.g., cannabis initiation loci predicting SCZ (Gage et al., 2017)). However, as better powered GWAS of putative causal factors emerge, one may begin to craft PRS as genetic instruments, that may be used to test the plausibility of causality among phenotypes, as long as the potential of pleiotropic effects remains tractable (from a biological and statistical perspective). Several tools have been developed to facilitate MR analyses [e.g., MR-Base: (Hemani et al., 2016) and for gene expression: Summary-data-based Mendelian Randomization (SMR): (Zhu et al., 2016)]. However, it is unclear whether the assumptions of MR analyses (e.g., lack of assortative mating; no confounding pathways) can truly be overcome, and may become more concerning for PRS analyses in light of extensive shared polygenic pathways (Cross-Disorder Group of the Psychiatric Genomics, 2013) and even potential omnigenic undergirding (Boyle et al., 2017).

Treatment Relevance: A Prognostic and/or Diagnostic Tool?

In our opinion, current PRS are not clinically actionable, even though some studies have proposed to have identified marker sets (using other related approaches) that can be diagnostically implemented (Skafidas et al., 2014, Robinson et al., 2014, Belgard et al., 2014). Pleiotropic effects of PRS are evident from Figure 2 and Tables 1–6. How this overgeneralized liability can be harnessed to refine treatment currently remains unclear. At present, the utility of PRS might lie, not as harbingers of future diagnosis but as indicators of vulnerability, which may be modified by a variety of other mitigating or exacerbating influences (e.g., environment, modifier loci). For example, using traditional PRS analyses, SCZ PRS can account for up to 18% of the variance in liability to schizophrenia in an

independent dataset with the upper decile being associated with an OR of 20. Such information may be leveraged to identify individuals at risk. While this likely would not currently impact the immediate treatment that one would receive, it would be intriguing to evaluate whether those most genomically vulnerable respond better or worse to early interventions, which may eventually have public health implications. Of note, PRS derived from GWAS of other psychopathologies (e.g., depression) do not currently account for nearly as much variance in disorder expression (Levine et al., 2014). However, it is expected that sample sizes for discovery GWAS will continue to increase, and with that, there will be greater precision in the effect sizes that are used as weights, and, consequently, the proportion of variance that they explain. Until then, it is critical that PRS are not construed as diagnostic tools but as ordinary predictors of risk, such as childhood trauma or family history, but with less explanatory power.

The current limited utility of PRS should not be taken to imply that there is no future for precision medicine in psychiatry. For some disorders, such as Autism Spectrum Disorders, highly penetrant mutations, copy number variants and chromosomal rearrangements have been compiled into genetic panels used for prediction (Vorstman et al., 2017). Even for other disorders, certain monogenic origins are routinely ruled out in clinical practice (e.g., a deletion on chromosome 22q that causes a schizophrenia-like syndrome) (Bassett and Chow, 2008). To improve and begin to personalize treatments, particularly for the broader range of psychiatric disorders characterized by such polygenicity and largely unknown mechanisms, it may be important to not rely on markers of genomic risk for disorder expression (which may usefully identify new therapeutic targets), but rather on markers of response to current treatments. Consistent with this speculation, one recent approach found no associations between depression and SCZ PRS and response to antidepressants (Garcia-Gonzalez et al., 2017) among 3756 treatment receiving patients. Further, pharmacogenomics GWAS (i.e., the study of treatment response) have consistently revealed larger effects (OR 2.5) than studies of disorder, even when comparing sample size-matched studies (Maranville and Cox, 2016). Thus, the genetics of treatment response, much like the genetics underlying interaction with the environment, may be, at least partially, distinct from the genetics of disorder liability and require its own PRS to have clinical implications.

A Summary of PRS Strengths and Limitations

Strengths

Consistent with their widespread use, PRS approaches offer many strengths. First, they model psychiatric disease liability within a polygenic framework. Second, they are easy to compute and analyze making them amenable to research extensions. Relatedly, their results are intuitive and readily interpretable by a large audience. Third, while PRS require large discovery samples, they can be *tested within much smaller samples*, making them highly appealing to studies with deeper phenotyping on fewer subjects (e.g., neuroimaging). How small is large enough? This will depend upon the precision of PRS and target sample phenotypes and questions. However, given that current observed effects from cross-trait associations suggest that PRS predict 0.01–3.00% of variance across traits, sample sizes would need to be >300 given optimistic estimates of effect size (3%), and in all likelihood,

much larger (see Technical Considerations; Figure 2). However, the application of novel techniques such as LDpred and MTAG may increase their precision and allow for their application in smaller samples (Vilhjalmsson et al., 2015, Turley et al., 2017). Regardless, research using smaller samples should consider the possibility of false positive and/or negative results. Fourth, PRS can be extremely useful within general population samples. Indeed, the consequences of medication and disease expression are an important confound for identifying factors that confer disease risk, especially for severe conditions such as schizophrenia. By using PRS as tools to uncover genetically-driven individual differences in mechanistic phenotypes, the field can combat confounds of medication and disease expression. Fifth, unlike other measures of cumulative genomic influence (e.g., SNP-h2), PRS approaches can be generalized and applied across samples. For these reasons, PRS have accelerated the incorporation of genomically-informed analyses into various clinical psychology subspecialties.

Limitations

Despite their widespread application, unique strengths, and the formative insight generated by their application, PRS have numerous limitations that require careful consideration. First, PRS are constrained to the sample size and phenotyping of the discovery GWAS. Such phenotyping may have a completely or partially distinct genetic architecture of comorbidity, related pathophysiology, response to current treatment, or interplay with the environment. Thus, GWAS across a variety of phenotypes and attempts to harmonize results is becoming increasing important. Second, traditional PRS are uninformed by system-level knowledge or functional annotation and provide no insight into molecular mechanisms. Alternative approaches, such as biologically informed multilocus profiles (BIMPS) that additively combine candidate variants based on their functionality, or methods that combine SNPs into meaningful pathways or networks by liaising with mRNA expression data, and even more sophisticated machine learning methods may overcome this limitation of PRS, but also have their own challenges (Bogdan et al., 2017). Along these lines, PRS are not currently amenable to direct translational work in nonhuman animals, though multiplex CRISPR/Cas9 approaches are beginning to be employed (Cong et al., 2013, Wang et al., 2013), which may ultimately be used to model polygenic variability. Third, while PRS are more predictive than single common polymorphisms, they are not currently predictive of substantial variance, even in the same phenotype as originally probed (with the exception of schizophrenia; see Technical Considerations). As a result, for adequate power, they still require relatively large samples (>300 for optimistic estimates of cross trait assocaitions using traditional PRS). Fourth, PRS assume additivity. While this assumption has support (Hill et al., 2008), evidence of epistasis is also present (Gibert et al., 2017, Mitra et al., 2017, Hemani et al., 2014).

Improving PRS: Future Directions

How might PRS be improved? In addition to generating larger, well-phenotyped GWAS, and adopting refined approaches for PRS calculation, one potential immediate future pathway is to leverage additional data to enhance and refine meaningful signals. An example of how additional GWAS data may be leveraged in the context of GWAS-based summary statistics to inform PRS construction comes from our multisite study lead by Arloth and Binder

(Arloth et al., 2015). Here, the GR agonist dexamethasone was administered to healthy and depressed participants who were genotyped. RNA expression was measured before and after (+3 h) dexamethasone administration. First, we identified SNPs that were associated with dexamethasone-related changes in gene expression. Second, we found that these SNPs were significantly enriched for nominal associations in GWAS of various psychiatric disorders, including depression. Third, we created a PRS of SNPs that are associated with both dexamethasone-induced gene expression and depression and found in independent samples that this profile was predictive of depression as well as an overgeneralized amygdala response. Thus, it is possible to use GWAS derived summary statistics alongside additional targeted results to prioritize SNPs with both evidence of mechanistic function and disease association that may be more powerfully predictive than disease association alone. In this context, it would be important to show that such biologically-constrained PRS are not merely reflective of global genomic risk and indeed provide greater predictive utility.

Such approaches could also be implemented without one's own independent data using available databases of basal gene expression (e.g., GTEx (Consortium, 2013), Braineac (Hardy et al., 2009), CommonMind (Fromer et al., 2016)) and methylation to prioritize variants across the entire genome. Similar approaches have been used to functionally partition SNP-h2 using functional annotation. (Gusev et al., 2014, Finucane et al., 2015). Such integration may enhance the biological plausibility of disease associated variants and potentially enhance their power. However, such an approach becomes clearly dependent on the quality of data in both contributing datasets and currently available databases of biological phenotypes such as mRNA expression, which are typically composed of small samples with restricted age ranges and tissue types, as well as a lack of detailed phenotypic and exposure characterization. For instance, many psychiatric disorders are precipitated by stress. Given that stress responsive systems can have direct effects on gene transcription it may be important to consider stress-related gene transcription for such phenotypes (Arloth et al., 2015) and basal expression may not be as informative. Consistent with this notion, glucocorticoid-related gene expression outperforms baseline gene expression when predicting depression [though notably such data should be interpreted as preliminary given the relatively small current sample sizes; (Menke et al., 2012)].

As highlighted above (see Improvements in PRS estimation), several techniques can be leveraged to improve PRS in one's own data, most of which do not require any, or only minimal, additional data. While they require additional work to compute, the potential pay-off cannot be overstated, as the improvement in accuracy will result in a substantially better-powered study. Here we describe one hypothetical workflow for how these techniques may be integrated into future analyses. First, MTAG may be used to generate summary statistics for polygenic risk scores by jointly analyzing the trait of interest with genetically-correlated traits (Turley et al., 2017). Instead of relying on summary statistics from a single GWAS study, MTAG may be used to integrate information from genetically-correlated phenotypes to improve the precision of summary statistics that can be leveraged for PRS construction. Importantly, summary statistic files can come from any study, as long as they are all of the same ethnicity - this includes partially or fully overlapping samples. The primary restriction on which studies can be included is that none of them should have substantially greater power than the study of the trait of interest, as this will increase false-positives.

Second, PRS could be generated using MTAG generated summary statistics by LDpred, which As mentioned above, leverages LD structure and results in improved PRS predictive ability relative to traditional PRS computation. Notably, there are several other computational approaches for improving PRS accuracy, both by adjusting effect-sizes and by modeling LD-structure. These approaches all require additional training data, and as yet a single approach which reliably out-performs all others has yet to emerge. Thus, the choice of adjustment algorithm will largely depend on the availability and nature of training data. LDpred (Vilhjalmsson et al., 2015) is the most well-vetted of these algorithms, and is thus the one we can most confidently recommend. It requires a moderately sized reference panel (N≥1,000) and is the most computationally intense, but importantly, only additional genetic reference panel data are required. This may prove to be particularly useful for studies examining less easily-obtained phenotypes. More recently developed approaches also hold great promise, though they need further validation. For example, GraBLD (Pare et al., 2017) is notable for requiring only a small training dataset (N≥200) that includes the trait of interest. It performs an adjustment for LD and updates effect sizes using a simple machine learning algorithm. Similarly, Lassosum (Mak et al., 2017) uses machine learning, penalized regression, to correct for LD structure and to update effect sizes. It is particularly notable as it can use cross-validation to replace an external training dataset.

Conclusions

The widespread use of PRS to represent generalizable polygenic disorder risk is beginning to provide tractable information about how polygenic liability leads to psychiatric expression as well as the structure of and mechanisms underlying psychiatric comorbidity. At present PRS have the most promise to improve our understanding of putative mechanisms of genetic liability. In this context, it is important to conceptualize such measures as indicators of vulnerability, rather than harbingers of future diagnosis. In fact, any current genetic prediction panel for psychiatric disorders that relies on common variation should be evaluated with considerable rigor for its purported clinical utility. Nonetheless, a unique strength to this approach is that PRS may be applied to large general population samples studying deeply phenotyped constructs, extending the range of psychiatric genetics research. Further, it will be important to consider that effect sizes are small and currently can reasonably be expected to account for only 0.01–3% of variance in related phenotypes when designing studies. In this context, it is critical for adequately powered research to be conducted so that false positive and false negative findings do not misguide research efforts.

As GWAS continue to expand and include large-scale studies of treatment response, it is possible that PRS results may be clinically applicable and potentially even usefully guide personalized treatment recommendations in the distant future. Further, as multiplex gene editing in preclinical models advance, it is plausible that polygenic effects across systems can be modeled to identify potentially influential, covarying, or even novel pathways for future treatment development. In addition to using novel analytic tools such as LDPred and MTAG to enhance the predictive utility of PRS, it will be important to increase the size and diversity of GWAS samples alongside the use of refined and diverse phenotyping. For example, it is possible that genetic loci associated with disorder expression are entirely or partially distinct from those associated with mechanistic pathways and treatment response.

Lastly, integrating polygenic GWAS statistics with functional data (Arloth et al., 2015) and pathway analyses may help guide the identification of potential treatment pathways.

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Central Points

Polygenic risk scores (PRS) represent the additive effect of multiple common variants; they explain <5% of cross-trait variability.

Currently studies of polygenic risk require at least 300 participants to achieve adequate power for cross-trait associations, given optimistic estimates.

Clinical utility of PRS might necessitate discovery GWAS of specific traits (e.g., of treatment response).

Incorporating information from biological systems and/or summary statistics from GWAS of genetically-correlated traits (e.g., MTAG) may improve their predictive utility.

Unresolved Issues

Are PRS for disorders or traits useful for predicting treatment response or interactions with the environment?

Are PRS be clinically informative or prognostic?

How can PRS be modified to be informative from a molecular and system-level perspective?

Terms and Definitions

Single nucleotide polymorphism, or **SNP:** Change in single base pair, A, T, G or C.

Linkage Disequilibrium, or LD: Genetic variation that is physically proximal to each other may be correlated. Knowing an individual's genotype at one locus allows us to guess their genotype at a locus in high LD.

Admixture, or population stratification: Variations in allele frequency and LD across ancestral populations that can lead to spurious association signals if cases or controls have different proportions of individuals from each ancestral group.

GenomeWide Association Study, or **GWAS**: estimating the association between disease or behavioral trait and common SNPs across genome. Significance is $p < 5 \times 10^{-8}$, i.e., Bonferroni corrected for 1 million independent tests.

Haplotype: Set of alleles that are observed in a population, likely due to evolutionary selection, more often than expected by chance alone.

Imputation: Probabilistic estimation of an individual's genotype, based on LD with known genotypes and comparison to a reference genome.

Major Histocompatibility Complex, or MHC: Large segment, spanning 4×10^{-6} base pairs on chromosome 6, with complex LD patterns across highly polymorphic SNPs spanning over 200 Human Leukocyte Antigen (HLA) genes involved in immune response.

Pleiotropy: The phenomenon of the same genetic variation contributing to different disorders or conditions.

Pharmacogenomics: Tailoring treatment based on an individual patient's genetic composition.

Reference genome: Comprehensive sequence data of a reference set of individuals of a specific ancestry; freely available to compare with one's study participant data.

Resources

A variety of resources are available to facilitate PRS analyses.

LDHub (Zheng et al., 2017) allows for computation of SNP-h2 and inter-trait genetic correlation (SNP-rg) using summary statistics. Assists with identification of genetically correlated traits for MTAG: http://ldsc.broadinstitute.org/

MRBase (Hemani et al., 2016) run Mendelian Randomization analyses with summary statistics or data upload: http://www.mrbase.org/

PLINK Software (Chang et al., 2015, Purcell et al., 2007)and online user resources provide tools and information for PRS computation:https://www.cog-genomics.org/plink2 & http://zzz.bwh.harvard.edu/plink/

PRSice Software (Euesden et al., 2015b): Software package that works with plink to generate PRS scores: http://prsice.info/

Psychiatric Genomics Consortium Downloads contain summary statistics that can be used to compute PRS for a variety of psychiatric phenotypes for analyses from the PGC and other groups: https://www.med.unc.edu/pgc/results-and-downloads

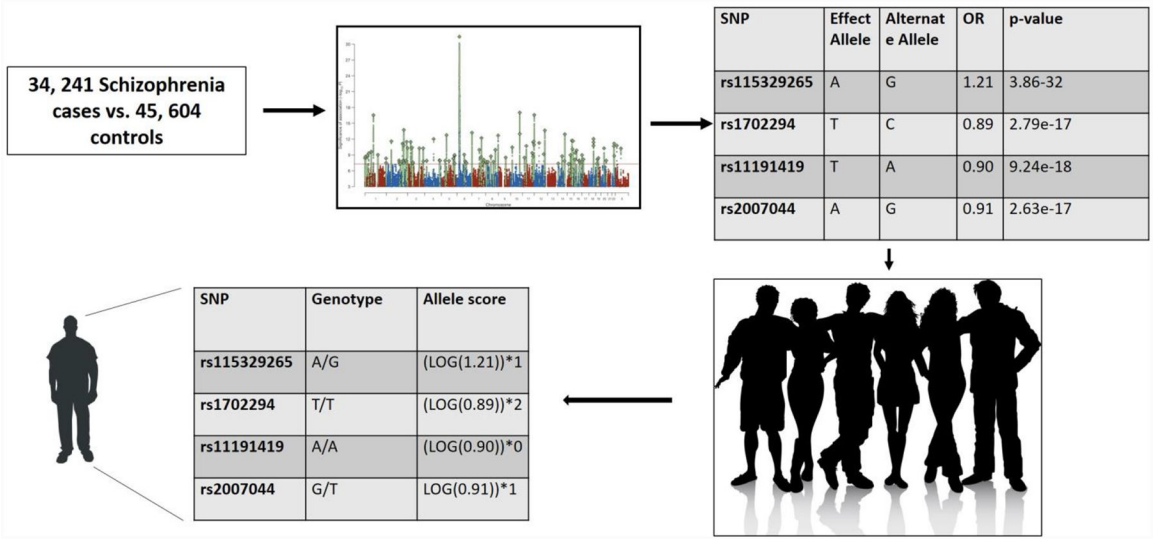

Figure 1. Practicalities of PRS computation.

Here, we exemplify using statistics from the most recent Psychiatric Genetics Consortium GWAS of schizophrenia (Schizophrenia Working Group, 2014) in which a discovery GWAS of 34,241 schizophrenia cases and 45,604 controls (initial discovery not including replication due to shared summary statistics). The effect allele and effect size for each SNP from the discovery GWAS is applied to each individual in a target dataset to create a unique person-specific polygenic risk score. We illustrate the approach using 4 SNPs. Summary statistics may be obtained here: https://www.med.unc.edu/pgc/results-and-downloads

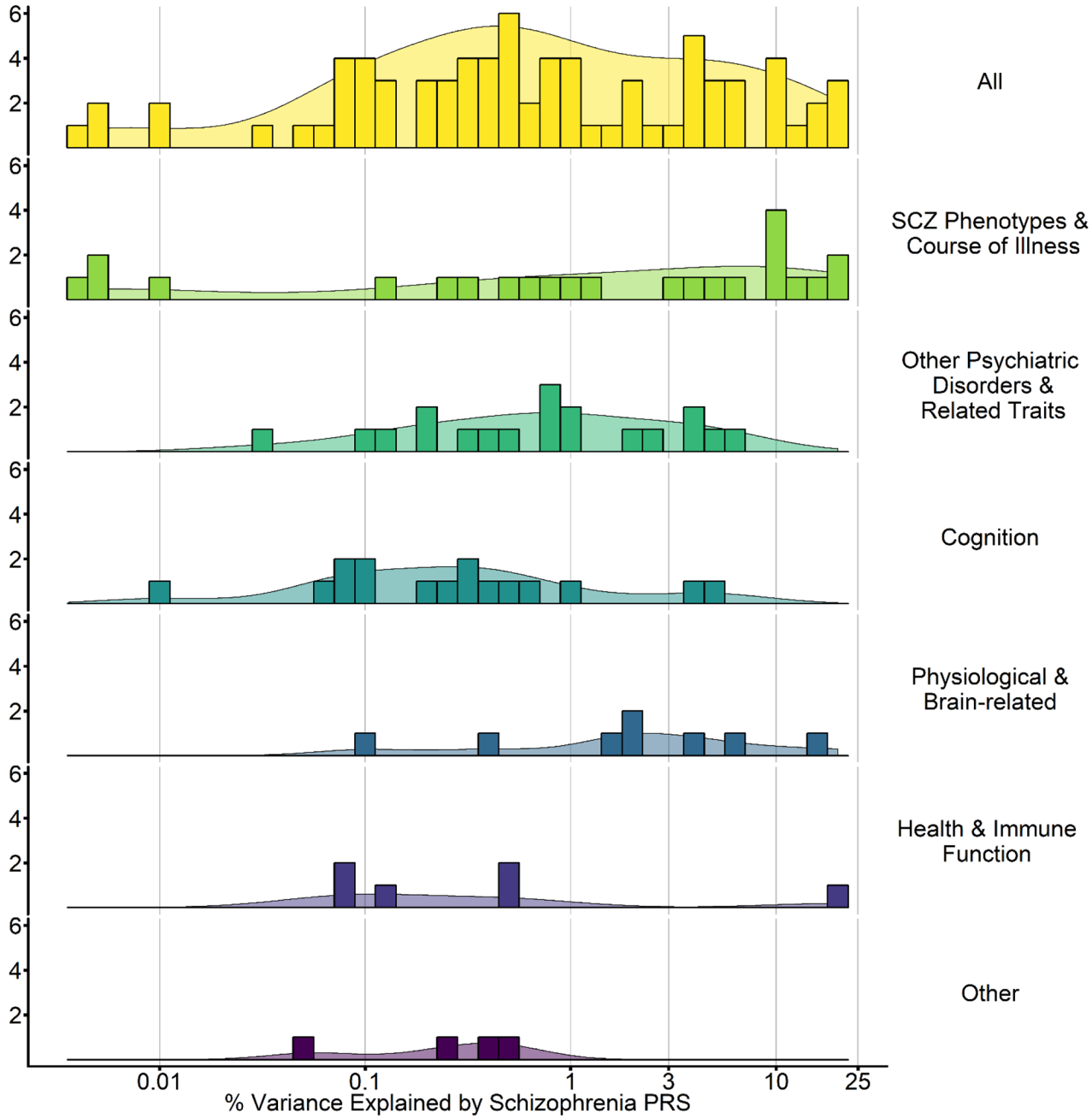

Figure 2. Schizophrenia PRS Effect Sizes Across 6 domains.

Plotted here is the range of the maximal percentage of variance explained by PGC SCZ2 PRS (Schizophrenia Working Group of the Psychiatric Genomics, 2014) in each study. Studies using other summary statistics are not included. Notably, as these are the maximal amount of variance explained and many studies reporting null effects did not report effect sizes, these estimates should be viewed as optimistic. The percentage of variance explained by Schizophrenia PRS in related traits ranges from 0.001 to 40% with 0.5–1.0% being most common. All = all identified Schizophrenia PRS studies. Course of illness = studies assessing course of illness. Psychiatric disorders and traits = studies evaluating other

psychaitic disorders (e.g., bipolar disorder) or traits (e.g., neuroticism). Cognition = cognitive phenotypes (e.g., working memory). Brain-related = imaging phenotypes (e.g., cortical thickness), Health and immune function = immune (CRP levels) and reported health (e.g., physical health). Other = various other phenotypes related to schizophrenia (e.g., urbanicity). Individual studies contributing to this are summarized and * in Tables 1–6.

Table 1.

SCZ PRS and SCZ Phenotypes and Course of Illness.

Domain	Phenotype & References	N	Association and Effect size*
SCZ Diagnosis, Symptoms, and Course	SCZ Diagnosis (Schizophrenia Working Group of the Psychiatric Genomics, 2014) *	2638 SCZ; 2482 CON	Increased in SCZ: 0.184
	SCZ symptoms, age of onset (Stepniak et al., 2014) *	Diagnosis: 1067 SCZ, 1169 CON; other phenotypes: 502 Males.	Increased SCZ risk: 0.14. NS associations with age, symptoms, or suicidality.
	SCZ and x Family History (Agerbo et al., 2015) *	866 SCZ, 871 CON	Increased SCZ: 0.034. Interaction between PRS and family history (p=0.03) - 17.4% of the increased SCZ conferred by family history accounted for by PRS.
	(Goes et al., 2015) *	Sample 1: 592 SCZ, 505 CON Sample 2: 913 SCZ, 1,640 CON Both Ashkenazi	Increased SCZ risk: 0.097
	Childhood-onset SCZ (Ahn et al., 2016) *	120 COS probands, 103 healthy siblings	Increased PRS among COS probands relative to healthy siblings: Up tp 0.1852
	Adolescent symptom expression (Jones et al., 2016) *	3,676–5,444 general population	Psychotic experiences, OR: 0.001, NS. Negative symptoms, age 16.5: 0.007. Anxiety disorder, age 15.5: 0.005. No association with depressive disorder, age 15.5: 0.00005, NS.
	SCZ Diagnosis and Clinical Course Correlates (Meier et al., 2016) *	Sample 1: 876 SCZ, 871 CON Sample 2: 821 SCZ, 832 CON Sample 3: 1773 SCZ, 2161 CON	Increased SCZ: 0.016–0.053; Increased in- or out-patient hospital admissions: rs=0.022–0.113; Longer length of hospital stay: rs=0.069–0.090; More likely to live in supportive housing: 0.006;
	First episode (FE) psychosis *(SCZ-PRS x childhood adversity)* (Trotta et al., 2016)	80 FE SCZ; 110 CON	Increased SCZ, adjusted B = 7.68 (interaction with childhood adversity not significant)
	Symptom dimensions in FE psychosis (Sengupta et al., 2017) *	241 FE SCZ	Baseline: Increased general psychopathology, PANSS total scores, negative symptom scores, and anxiety: 0.0256–0.058. NS: positive symptoms, GAF, depression, social and occupational functioning. Follow-up 1–24 months: lack of association following treatment.
	Psychosis in Alzheimers Disease (AD+P) (DeMichele-Sweet et al., 2017) *	Discovery: 1761 AD + P, 1115 AD-P Replication: 734 AD+P; 1460 AD-P	AD+P: 0.0025 – 0.0032 (101 loci)
	Neurodevelopment, salience attribution, emotion regulation (van Os et al., 2017)	First degree relatives of SCZ: 871 siblings, 812 parents; 523 CON	PRS healthy < PRS relatives. Relatives: Total (negative and positive) and depressive symptoms B=0.11–0.21. NS for positive and negative symptoms independently. Controls: Total (negative and positive) and positive and negative symptoms: B=0.11–0.22.
	First episode (FE) psychosis (Vassos et al., 2017) *	445 FE SCZ, 265 CON (EA), 828 CON (AA)	Increased SCZ risk in EA: 0.094. AA: 0.011 NS. Predicted SCZ development relative to other psychotic disorders among EA: 0.092.
SCZ Treatment Response	(Frank et al., 2015)	434 Clozapine Tx History, 370 Clozapine No History; 78 responders vs. 45 non-responders	Higher PRS among those with a history of Clozapine treatment (P=0.02) Trend for higher PRS among Clozapine nonrsponders relative to those who responded positively (P=0.06); affect potentiated in those with poor premorbid social function.

Domain	Phenotype & References	N	Association and Effect size*
	Dosage (Hettige et al., 2016) *	83 SCZ	No association with antipsychotic dosage: <0.0001
	Response to Lurasidone (Li et al., 2017) *	171 EA, 131 AA	Less responsive to treatment, total symptoms, up to 0.101
	(Wimberley et al., 2017a)	862 SCZ (181 treatment resistant)	No association between PRS and treatment resistence, HR 1.13.

Studies only include those using summary statistics from (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Unless otherwise noted, effect size is represented as Nagelkerke's Pseudo R^2 (multiply by 100 to obtain $\%R^2$); r = correlation, OR = Odds-ration, B = beta coefficient, AUC = Area Under the Curve. EA = European ancestry. AA = African ancestry. NS= non significant. When pearson's r, OR, or d were reported, we estimated r^2.

*indicates study with % of variance explained included in Figure 2.

Table 2.

SCZ PRS and Other Psychiatric Disorders and Related Traits.

Phenotypes	Phenotype & References	N	Effect size*
Development: Childhood Behavior and Psychopathology-related Traits	Early childhood behavioral problems, externalizing and internalizing (Jansen et al., 2017) *	5,100 – 6,952 ages 4–9	Increased internalizing and externalizing: up to ~0.008
	Anxiety, ADHD, and depression during childhood (Nivard et al., 2017)	8,715 ages 6–16	Positive association with childhood psychopathology: b=0.0182. Increasing from childhood to adolescence: r=0.10 to 0.25.
	(St Pourcain et al., 2017) *	4,175–5,553 at ages 8, 11,14,17	Elevated social communication difficulties: up to 0.0043 (increasing in effect size with increasing age).
	Social communication, emotion and conduct problems, (age 4–9) (Riglin et al., 2017) *		Worse communication, increased emotion and conduct problems (increasing from childhood to adolescence): up to 0.001
Depression, Distress, Neuroticism, Loneliness	Distress and Neuroticism *(SCZ-PRS x MDD)* (Whalley et al., 2016) *	Sample 1: 2,587 MDD, 16,764 CON Sample 2: 6,049 MDD, 27,476 CON	PRS x MDD interaction for neuroticism and personal distress (Bs> −0.04). *Neuroticism:* positive assoc in CON: 0.0017–0.0030; NS in MDD: 0.0000090.00003.
		2, 587 – 6,049 MDD cases; 16,764 – 27, 476 controls	*Psych Distress:* positive assoc in CON: .0015–.0022; NS in MDD.
	Neuroticism (Gale et al., 2016) *	108, 038	Positive assoc.: 0.0012
	Treatment response to anti-depressants (Garcia-Gonzalez et al., 2017) *	3,756	NS: 0.0006–0.018
	Loneliness (CITE Gao et al., 2017) *	6,924 ages ≥50	Nominal evidence of a negative association, up to 0.0003
OCD	(Costas et al., 2016) *	370 OCD, 443 CON	Increased OCD, up to: 0.037
	(Sumner et al., 2016) *	1,293 trauma-exposed women	Increased PTSD risk, up to: 0.009
Substance Use	Alcohol, Cannabis, Cocaine Nicotine, Opioid Dependence (Carey et al., 2016a) *	1,160 Alcohol Dependent, 1,413 CON ascertained from studies recruiting for alcohol dependence, cocaine dependence, and nicotine dependence	Surviving multiple test correction: Increased cannabis, cocaine, and nicotine dependence symptoms, up to 0.0109. Nominal positive associations: severe alcohol dependence symptoms, nonproblem cannabis use, nicotine use, opioid use and dependence symptoms.Associations with cannabis and cocaine survive correction for general substance liability.
	Cannabis use prior to onset (Aas et al., 2017) *	Scz Cases: 381 Bipolar Disorder Spectrum: 220 Controls: 415	Patients with Schizophrenia or Bipolar who used cannabis weekly/daily prior to illness had elevated PRS: Cohen's d = 0.3; up to 0.027.
	Substance Use Disorder (Hartz et al., 2017) *	Cases with a substance use disorder Study1: 918 Cases, 988 Controls Study 2: 643 Cases, 384 Controls Study 3: 210 Cases, 317 Controls	SUD cases had elevated Scz PRS: up to 0.037.
	Cannabis use (Verweij et al., 2017) *	6,931	Increased lifetime, regular and quantity of use; up to 0.0049.

Phenotypes	Phenotype & References	N	Effect size*
	Substance Use Disorders (Alcohol, Amphetamine, Cocaine, Cannabis, Opioid, Sedative, Early onset, Ever Smoking (Reginsson et al., 2017) *	144,609 (10,036 admitted for inpatient addiction treatment, 35,754 smokers)	Increased substance use disorder, up to 0.0089.
Suicide	Suicide attempts (Laursen et al., 2017) *	1780 SCZ, 1768 CON	2+ suicide attempts OR = 1.18 in full sample. Up to 0.0021.
	Suicide attempt (Sokolowski et al., 2016) *	660	PRS of neurodevelopmental genes positively associated with suicide attempt: up to 0.052.
Various Traits	50 traits (Krapohl et al., 2016)	3.152 16 year olds	NS. Nominal negative association with autism quotient: attention to detail.
Post-Concussive Symptoms	(Wang et al., 2017a)	845 US Army soldiers who sustained traumatic brain injury	NS: up to 0.0089.

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Table 3.

SCZ PRS and Cognition.

Phenotypes	Phenotypes and Study Reference	N	Association and Effect size*
IQ Metrics and Neurocognitive Function	Neurocognitive Performance (Hatzimanolis et al., 2015)*	1,079	Continuous performance and spatial N-back: ~0.00275. No significant association with IQ or verbal n-back.
	Neurocognition and social cognition (Germine et al., 2016)*	4303 (8 – 21y); Replication: 695 (18 – 35y)	Verbal reasoning and emotion identification speed: 0.003 – 0.005 NS: 36 other accuracy and speed indices.
	Cognitive function and Education (Hagenaars et al., 2016)	36,035–112,067	Negative associations with verbal-numerical reasoning, reaction time, memory: B= −0.006 to-0.062; positive association with educational attainment: B=0.025.
	50 triats - personality, cognition, etc. (Krapohl et al., 2016)		No significant associations following multiple testing. But nominal positive correlations with English and negatively correlated with Autism Quotient: Attention to Detail.
	Cognitive function in older adults (Liebers et al., 2016)*	8, 616	Total Cognitive Function, Attention/Language, Verbal memory: 0.0004–0.0008
	Composite g and subfacets: memory digit, vocabulary, verbal, reaction time *(SCZ-PRS x MDD)* (Whalley et al., 2016)*	Sample 1: 16,764 CON; 2,587 MDD Sample 2: 27,476 CON; 6,049 MDD	Composite g: 0.0032 – 0.0062 (stronger in MDD); G Subfacets 0.0002 – 0.0109
	Cognition and learning, social and communication, emotion and mood regulation, behavior, age 4–9 (Riglin et al., 2017)*	5,100 – 6,952	Lower performance IQ and worse language intelligibility and fluency: up to 0.003
	Executive Function (Benca et al., 2017)*	386	Positive correlation with update specific latent variable: $r < 0.2$ (nom. Sig.). Negatively associated with IQ,: up to 0.01.
	Emotion recognition (Coleman et al., 2017)*	4,097 8 year old children	No association: r2=0.0001 – 0.0011
	Psychosis cognitive and physiological endophenotypes (Ranlund et al., 2017)*	Total: 1,437–3,089 drawn from SCZ: 1,087 SCZ 1st-degree relative: 822 CON: 2,333	SCZ>SCZrelatives>CON. Worse performance on block design: 0.002.. NS: digit span, RAVLT.
	SCZ and Cog performance (Wang et al., 2017b)*	1,130 Taiwanese SCZ	Not associated with SCZ: 0.0008. Lack of association PGC2 not used to test for association with cognitive phenotypes. Cognitive associations reported with PGC1.
Creativity	Creativity (Power et al., 2015)*	86, 292	Increased creativity: up to 0.055

Studies only include those using summary statistics from (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Unless otherwise noted, effect size is represented as Nagelkerke's Pseudo R^2 (multiply by 100 to obtain $\%R^2$); r = correlation, OR = Odds-ration, B = beta coefficient, AUC = Area Under the Curve. EA = European ancestry. AA = African ancestry. NS= non significant. When pearson's r, OR, or d were reported, we estimated r^2.

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Table 4.

SCZ PRS and Physiological and Brain-related Phenotypes.

Phenotypes	Study References	N	Association and Effect size*
Electrophysiology	P300 (Hall et al., 2015) *	271 SCZ or psychotic BIP, 128 CON	Whole group NS: P3 amplitude or latency; ASSR gamma, P50. However, in cases only reduced ASSR: 0.04. nteractions between PRS and case status (P=0.008).
	Prepulse inhibition & baseline startle (Roussos et al., 2016) *	1,493 male	Reduced PPI up to: 0.01175. NS: baseline startle.
	Acoustic startle, affective startle modulation, antisaccade, resting EEG Hz, skin conductance, P300 (Liu et al., 2017b)	4,905	NS after multiple testing correction. Nominal significance for overall startle (p=0,005).
	P300 amplitude and latency (Ranlund et al., 2017) *	515	NS: up to 0.019
Functional Magnetic Resonance Imaging	Probabilistic Learning (Lancaster et al., 2016a)	83	Reduced right frontal pole (whole brain; $P_{FWE(whole\ brain)}$=0.037) and left ventral striatum (ROI: $P_{FWE(ROI)}$=0.036) activation during shift > stay choice behavior, .NS: activation to choice outcome.
	Emotion Processing, Episodic Memory, Reward Processing, Theory of Mind, Working Memory (Erk et al., 2017)	578	*Emo:* NS. *Epi Mem and Theory of Mind:* Increased perigenual anterior cingulate cortex during episodic memory recognition $P_{FWE(ROI)}$<0.047. *Rew:* NS, *ToM:* Posterior cingulate/precuneus $P_{FWE(ROI)}$<0.025. No other significant associations.
Structural Magnetic Resonance Imaging	Hippocampal volume (Harrisberger et al., 2016)	36 First Episode (FE) Psychosis; 42 At Risk Mental State (ARMS)	B = −0.42
	White matter integrity (Alloza et al., 2017)	28 SCZ, 36 CON	SCZ diagnosis: 0.057; NS associations with network.
	Gray matter volume (Van der Auwera et al.,2015, Van der Auwera et al., 2017) *	Sample 1: 1,426 Sample 2: 1,299	NS: whole brain or ROI associations in amygdala, hippocampus, parahippocampus, NS: max ~0.001 from 2015.
	Hippocampus changes with 3 month exercise/cog intervention (Papiol et al., 2017) *	20 cases & 23 con with interv. 21 cases with con interv.	NS: total hippocampus. Less change in CA4/dentate gyrus: 0.358 (not plotted in figure)
	Lateral ventricular volume (Ranlund et al., 2017) *	798	NS: 0.004
	Gray matter volume and white matter integrity (Reus et al., 2017)	Volume: 978 WM: 816	NS.
Cortical Thickness and Gyrification	Cortical thickness in context of cannabis use (French et al., 2015) *	Sample 1: 459 male adolescents Sample 2: 333 adolescents Sample 3: 295 male youth	SCZ-PRS x adolescent cannabis use predicted reduced cortical thickness across all 3 samples. Sample 1: 0.06. Main effects inconsistent.
	Cortical gyrification (Liu et al., 2017a) *	315, Replication: 357	Lower gyrification in inferior parietal cortex, up to 0.021
	(Neilson et al., 2017)	43 SCZ/Bipolar cases; 32 CON	Reduced global cortical thickness in patients (F up to 4.54). NS in CON.

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Table 5.

SCZ PRS and Health and Immune Function.

Phenotypes	Study Reference	N	Association and Effect size*
Self-reported Health	(Harris et al., 2016)	111, 749	Reduced health: B=−0.028
Self-reported Tiredness	(Deary et al., 2017)	108,976	Increased tiredness: B=0.028
Amyotrophic Lateral Sclerosis	(McLaughlin et al., 2017) *	12, 577 patients, 23, 475 CON	ALS have higher PRS: 0.0012
Type 2 Diabetes	(Padmanabhan et al., 2016)	EA: 218 CON, 384 SCZ, SCZA, Psy BIP Probands AA: 104 CON, 257 SCZ, SCZA, Psy BIP Probands	NS: positive association among probands and relatives, OR up to 1.41: 0.20.
Infection and infection-related SCZ	(Benros et al., 2016)	1,692 SCZ, 1,724 CON	NS: infection or evidence or PRS x infection
Psoriasis	(Yin et al., 2016) *	Han Chinese: 1139 psoriasis cases, 1132 controls	AUC = 0.54 [0.51 – 0.58]: 0.0050
Migraine	(Van der Auwera et al., 2016) *	3, 973	OR = 0.78 (based on 108 loci): 0.0047

Studies only include those using summary statistics from (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Unless otherwise noted, effect size is represented as Nagelkerke's Pseudo R^2 (multiply by 100 to obtain $\%R^2$); r = correlation, OR = Odds-ration, B = beta coefficient, AUC = Area Under the Curve. EA = European ancestry. AA = African ancestry. NS= non significant. When pearson's r, OR, or d were reported, we estimated r^2.

* indicates study with % of variance explained included in Figure 2.

Table 6.

SCZ PRS and Other Phenotypes

Phenotypes	Study Reference	N	Association and Effect Size*
Urbanicity	(Paksarian et al., 2017)*	1,549 SCZ, 1,549 CON (matched)	Born urban: OR = 1.09: 0.00056; Living urban (15y): OR 1.19: 0.00229
Reproductive fitness	(Mullins et al., 2017)	631SCZ	No sig. assoc. *(# children, age at 1st child)*
Risky Sexual Behavior	(Wang et al., 2017a)*	2,379	Antagonistically pleiotropic SCZ HIV SNP PRS associated with risky sexual behavior: up to ~ 0.005.
Longitudinal Study Participation	(Martin et al., 2016)*	7,867 children and 7,850 mothers	Nonparticipation/Noncompletion: 0.0014 – 0.0042

Studies only include those using summary statistics from (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Unless otherwise noted, effect size is represented as Nagelkerke's Pseudo R^2 (multiply by 100 to obtain $\%R^2$); r = correlation, OR = Odds-ration, B = beta coefficient, AUC = Area Under the Curve. EA = European ancestry. AA = African ancestry. NS= non significant. When pearson's r, OR, or d were reported, we estimated r^2.

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