Analysis

Genetic cross-disorder analysis in psychiatry: from methodology to clinical utility
Dick Schijven, Jan H. Veldink and Jurjen J. Luykx

Summary
Genome-wide association studies have uncovered hundreds of loci associated with psychiatric disorders. Cross-disorder studies are among the prime ramifications of such research. Here, we discuss the methodology of the most widespread methods and their clinical utility with regard to diagnosis, prediction, disease aetiology and treatment in psychiatry.

Declaration of interest
None.

Keywords
Genetics; pleiotropy; genetic correlation; genome-wide association studies (GWAS); cross-disorder.

In the field of psychiatric genetics, thousands of affected and healthy individuals have been included in genome-wide association studies (GWASs) to test disease associations at common genetic variants, of which single-nucleotide polymorphisms (SNPs) are the most abundant. These occur throughout the genome, on average once every couple of hundreds of base pairs, and have minor allele frequencies >1% in the general population. Currently, arrays are available to genotype over two-million SNPs simultaneously. Genotypes of SNPs that lie close together in the genome are highly likely to be co-inherited and therefore show high correlation, resulting in blocks of SNPs that are in linkage disequilibrium. Linkage disequilibrium can be exploited to impute SNPs that were not directly genotyped on an array, which at present increases the number of SNPs in GWAS data-sets to up to 10–15 million variants. Moreover, an association signal usually covers a genomic region of variable size, called a locus, wherein the associated variants can be in linkage disequilibrium with one or more causal variants. Most SNPs are known to have small effect sizes in mental illness (odds ratios between 1.03 and 1.10), but they collectively account for about 20–30% of the heritability within psychiatric disorders as well as for psychiatric disorders related but essentially different concepts. Pleiotropy defines a single genetic variant affecting more than one phenotype, whereas genetic correlation describes the sharing of polygenic disease architectures at a genome-wide level. Cross-disorder studies can be used in several clinical domains, namely: (a) diagnostics (disorder classification and patient stratification), (b) prognosis (prediction of clinical course and outcome of a disorder) and (c) treatment (discovery of drug targets and treatment tailoring through new insights into disease aetiology). Here, we outline the current and potential future contributions of widely applied approaches in genetic cross-disorder studies for the field of psychiatry, ordered by the clinical domain they target (also see Table 1).

Diagnostics

Genetic correlations are the most widely used estimate to describe the extent to which variance in liability for two disorders is attributable to additive genetic effects and thus expresses the proportion of shared SNP-based heritability between two traits. Initially, methods to estimate genetic correlation from GWAS data relied on individual-level genotype data (e.g. bivariate restricted maximum likelihood, REML), using a genetic relationship matrix that captures genetic similarity between distant relatives. Such analyses can be correlated to phenotypic similarities for two diseases. This was followed by methods which use summary-level data, where linkage disequilibrium score regression (LDSC) is widely applied and genetic correlations are based on similarities in effect sizes and effect directions of SNPs that are shared between GWAS summary statistics of two phenotypes. Bivariate REML and especially LDSC are most accurate for traits with a polygenic architecture, rendering both well applicable to psychiatric disorders. The genetic correlation estimate falls within the range of −1 and 1, where 1 represents the unlikely scenario that shared liability is caused by exactly the same risk SNPs and −1 by the similarly implausible situation where exactly identical SNPs increase risk for one disease while decreasing risk for another. A null correlation indicates absence of shared disease liability due to overlapping genetic architecture. Genetic correlation estimates are based on all SNPs present in two GWAS data-sets or summary-level results regardless of their strength of association with a disease (as sub-threshold variants capture a substantial amount of the SNP-based heritability). The ability to test these correlations at large scale has provided insights into the landscape of disease classifications both within psychiatric disorders as well as for psychiatric disorders relative to other disease groups. Significant genetic correlations are often observed between psychiatric disorders, with schizophrenia and bipolar disorder peaking at approximately 0.8. Surprising
genetic correlations between psychiatric traits and other phenotypes presumed to be aetiologically unrelated have been described, suggesting that biological mechanisms involved in psychiatric disorders overlap with those of phenotypes that are clinically distinct. Examples include significant positive genetic correlations between body mass index on the one hand and major depressive disorder (MDD) (0.11) and attention-deficit hyperactivity disorder (ADHD) (0.21) on the other.6 The positive genetic correlation between schizophrenia and amytrophic lateral sclerosis (ALS) of 0.14 is the first described genome-wide correlation between a psychiatric and a neurological disorder.8

Polygenic risk score (PRS) analysis is another widely applied method to assess polygenic overlap between diseases. This technique uses estimates of SNPs derived from summary-level data of a discovery GWAS to calculate per-individual scores based on the number of effect alleles carried and weighted for the effect sizes at all overlapping SNPs in an individual-level target GWAS data-set. It is possible to calculate these scores on all SNPs tested for association in the discovery GWAS (P ≤ 1), but a selection is often made based on strength of association (e.g. P < 5 × 10-8). These scores thus capture the combined effects of many SNPs and, in cross-disorder studies, PRSs reflecting the polygenic risk for a discovery disease are tested for association with the phenotypic measure of a different target disease.18 For example, schizophrenia PRSs explain up to 2.4% of the phenotypic variance in bipolar disorder.11,18 Strikingly, schizophrenia PRSs were more strongly associated with schizoaffective bipolar disorder, followed by bipolar disorder type I and bipolar disorder type II (risk ratios of 1.37, 1.30 and 1.04, respectively), showing that aetiological differences exist within psychiatric disorders.7 It is furthermore particularly interesting to compare individuals at the extreme ends of the range of PRSs in a study population. For instance, when PRSs calculated using summary-level schizophrenia GWAS data were applied to an independent schizophrenia case-control target GWAS dataset, individuals in the highest PRS decile had up to 20-fold increased odds of schizophrenia compared with individuals in the lowest PRS decile,20 again showing the substantial combined effect of many SNPs. In addition to this within-trait example, the observation of increased odds of disease is to a lesser extent applicable to correlated diseases in between-disorder studies (e.g. highest decile schizophrenia PRSs increasing odds of ALS up to 1.3 compared with lowest decile PRSs in a case-control cohort).8 Explained variances based on PRSs are always much lower than genetic correlation estimates, which has been demonstrated for schizophrenia and bipolar disorder (2.4 vs. 80%). These methods are conceptually different: whereas genetic correlations describe the proportion of shared genetic background based on theoretical full SNP-based heritabilities, PRSs are based on actual SNP effect estimates and applied to explain phenotypic variance that is only partly attributable to genetic factors. PRSs can thus never explain more variance than the heritability of the target disease or, when applied in cross-disorder analysis, the proportion of the heritability shared with other diseases.21

As with genetic correlations, PRSs can be useful to establish genetic links between disorders and define the genetic landscape of psychiatric disorders. In a population of unselected samples and when calculated based on a large number of SNPs, PRSs show a normal distribution. Therefore, the true diagnostic utility

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PRS, polygenic risk score; MDD, major depressive disorder; ADHD, attention-deficit hyperactivity disorder; OCD, obsessive-compulsive disorder; ASD, autism spectrum disorder.
of PRSs as a quantitative phenotype lies in disease classification and the more fine-grained stratification of patients. For example, bipolar disorder with mood-incongruent psychosis shows a stronger correlation to schizophrenia PRSs than bipolar disorder with mood-congruent psychosis and bipolar disorder without psychosis. On a similar note, higher schizophrenia PRSs associate with psychotic features and earlier age at onset in a sample of people with bipolar disorder, whereas bipolar disorder PRSs show a positive correlation with manic symptoms in people with schizophrenia. Future increases in GWAS sample sizes will provide more accurate effect estimates for SNPs, which in turn can further empower PRSs and their specific relation to psychiatric symptoms across the boundaries of DSM-5 (2013) disorder classifications.

### Prognosis

The ability to predict the course of a disorder in psychiatric patients could prove highly valuable as we do not currently have accurate course prediction models for these disorders. For psychotic disorders, the potential of PRSs to predict the conversion from at-risk states to clinical diagnoses has been shown by schizophrenia PRSs being significantly higher in individuals with first-episode psychosis later diagnosed with schizophrenia than in first-episode patients diagnosed with other psychotic disorders, although both groups had higher PRSs than healthy controls. A cross-disorder example includes a population-based sample where PRSs for obsessive-compulsive disorder (OCD), schizophrenia, MDD and combined schizophrenia–bipolar disorder predicted subclinical obsessive-compulsive symptoms, thereby showing the potential of these scores to identify individuals who have increased risk of developing OCD and other psychiatric disorders. With regard to psychiatric conditions where environmental factors play a pivotal role, such as post-trauma psychopathology, PRSs for several disorders (such as post-traumatic stress disorder, depression and anxiety) could ideally be used to screen healthy at-risk groups, e.g. military personnel, and take preventative measures for those with high risk scores. However, their currently low accuracy and sensitivity in clinical phenotypes preclude application of such PRSs to risk prediction at the level of the individual. Therefore, integrating PRSs into a diagnostic workup that includes other data, such as psychiatric signs and symptoms, may in the near future improve prognostic accuracy.

### Treatment

The previously discussed polygenic methods describe the extent to which two disorders correlate, but do not pinpoint specific loci with cross-disorder effects. Information on specific shared disease loci can be obtained by merging individual-level or summary-level data from different disorders in a single association analysis, combining all cases into a single phenotype. Such mega- or meta-analyses increase power to detect pleiotropic loci that were below genome-wide significance thresholds in single-disorder analyses. Combining all cases into a single phenotype precludes application of such PRSs to risk prediction at the level of the individual. Thus, integrating PRSs into a diagnostic workup that includes other data, such as psychiatric signs and symptoms, may in the near future improve prognostic accuracy.

### Caveats in genetic cross-disorder studies

Cross-disorder studies should be interpreted with some caution as observations can be driven by other factors than true overlap at causal variants. First, as opposed to a scenario of true biological genetic overlap, a significant genetic correlation could also be observed if a causal variant directly affects disorder A, whereas disorder B is merely caused by disorder A (mediated pleiotropy). In this scenario, there is no direct effect of the causal variant on disorder B and observed pleiotropy is artificial. Given the differential ages at onset, for psychiatric disorders this would imply that early onset disorders occur first (ASD, ADHD, intellectual disability) and then cause disorders with later onset (MDD, schizophrenia, bipolar disorder), a notion currently lacking support from the scientific literature. In addition, disorder-specific causal variants in different genes might be tagged by the same SNP due to linkage disequilibrium. This SNP could then show an association to both phenotypes although the causal variants are actually different, resulting in spurious pleiotropy.

Second, observed pleiotropy can result from external confounding factors, such as population differences or assortative mating. The latter plays a role in psychiatric disorders, where non-random mating between and within disorders is observed. Third, the above-mentioned cross-disorder analysis approaches only use information on SNPs captured in GWAS data, thus omitting other sources of genetic variation, such as rare variants. Fourth, because of overlap in clinical symptoms, the risk of diagnostic misclassification is particularly pressing in psychiatry and can lead to false positive findings in cross-disorder studies when patient cohorts are not homogenous. Methodology has been developed to identify heterogeneous subgroups of patients in GWAS data-sets (e.g. BUHMBOX) to detect such confounding in cross-disorder analyses. Finally, genotype data of the same healthy controls are often used in multiple GWASs of different disorders. When this overlap is not taken into account in cross-disorder analyses combining these data-sets, a false positive correlation – not reflecting shared genetic risk between diseases but merely a correlation induced by genetically identical people – may arise. It is therefore imperative to identify and exclude duplicate participants in cross-disorder studies using individual-level genotype data. Alternatively, various novel cross-disorder methods have been developed that include correction for inflated test results due to
sample overlap and allow for the use of only summary-level data.\textsuperscript{5,13} Overall, a considerable amount of cross-disorder analyses can now-adays be performed using summary-level data without the require-
ment of access to individual-level genotype data. As new GWAS results are continuously being published, summary-level data are almost always made publicly available in line with many journals’ manuscript acceptance conditions, whereas individual-level data are often available upon request. Sharing of full GWAS results remains essential for cross-disorder analyses by groups and consortia interested in matching genetic data of other studies with their own data-sets.

Conclusion

A range of techniques have been employed to unravel important cross-disorder genetic findings in psychiatry, resulting in intriguing new clinical perspectives at the levels of diagnostics, prognosis and treatment development and prediction.

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