Published in final edited form as:

Curr Behav Neurosci Rep. 2016 September ; 3(3): 256–263. doi:10.1007/s40473-016-0084-3.

Cross-Disorder Psychiatric Genomics

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Abstract

Purpose of Review—The following review provides some description of the movement in cross-disorder psychiatric genomics toward addressing both comorbidity and polygenicity.

Recent Findings—We attempt to show how dimensional approaches to the phenotype have led to further addressing the problem of comorbidity of psychiatric diagnoses. And we also attempt to show how a dimensional approach to the genome, with different statistical methods from traditional genome-wide association analyses, has begun to resolve the problem of massive polygenicity.

Summary—Cross-disorder research, of any area in psychiatry, arguably has the most potential to inform clinical diagnosis, early detection and prevention strategies, and pharmacological treatment research. Future research might leverage what we now know to inform developmental studies of risk and resilience.

Keywords

cross-disorder; genetic; GWAS; Psychiatric Genomics Consortium; pleiotropy; co-heritability; comorbidity

Introduction

The field of psychiatry is working toward two objectives. First, we are working to resolve the problem of *excessive comorbidity* of psychiatric diagnoses, which belies a spectrum of latent liability to general psychopathology. Comorbidity, or the observation that having one or more disorders increases the likelihood of additional psychiatric disorders, could be due to the genetic overlap of specific psychiatric disorders, or to the presence of a more general

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Dr. Anna R. Docherty, Dr. Arden A. Moscati, and Dr. Ayman H. Fanous declare that they have no conflict of interest.

polygenic predisposition to psychopathology. By understanding the genetic relationships between highly comorbid disorders, we may be able to better classify, predict, and prevent them.

Second, we are working to address the *massive polygenicity* of psychiatric disorders—that almost all psychiatric disorders are associated with potentially thousands of genes, each conferring very small effect. Comorbidity and polygenicity are not mutually exclusive, and are likely related, due to the frequency of pleiotropy in the human genome (1). Pleiotropy is the genetic overlap of different traits. Locating genetic effects on very polygenic disorders has required genome-wide association studies (GWAS) with tens of thousands of samples (2, 3). In addition to advancing studies that maximize sample size (4), psychiatric genetics has begun to move toward a more dimensional, spectrum-oriented approach to both the trait and to statistical analysis of the genome.

This movement is evidenced in the formation of the Psychiatric Genomic Consortium (PGC) Cross-Disorders Group, the growing participation of the psychiatric genetics community in the Research Domain Criteria (RDoC) Initiative from NIMH, and efforts to improve upon previous genome wide association research (GWAS) via deep phenotyping (5). In the last year, researchers across multiple sites have focused efforts on dimensionalizing 1) phenotypes (i.e., the clinical, cognitive, physiological, personality and neuroimaging trait-based measurement used) and 2) statistical approaches to the genome and genotypic analyses.

While traditional GWAS approaches use univariate tests across millions of common variants along the genome, newer polygenic approaches aggregate effects and quantify risk. In addition, the field is quickly developing and validating strategies to examine the additive effects of genetic variants across genes, pathways, and larger swathes of the genome. These approaches include polygenic profile scoring (6) of traits using GWAS summary statistics, deriving genomic relatedness matrices to calculate heritability estimates from common genetic variants, and modeling the linkage disequilibrium in the sample in order to obtain more accurate estimates of genetic risk (7). This research will be detailed below. Some groups have also begun examination of the entire “phenome” (8) and these efforts are also detailed below. These approaches are more conducive to studying the genetic overlap of disorders and to cross-disorder research in general.

This review will include discussion of recent cross-disorder genetic research on major psychiatric illnesses, as well as novel statistical approaches to such studies. Importantly, the cross-disorder genomics field is relatively new and undeveloped. Studies published thus far rely primarily on European samples. The overwhelming majority of the research presented here comes from molecular genetic association studies, but overlap of this research with previous biometrical (twin and family) structural equation modeling studies of heritability is also discussed. In addition, we draw attention to some studies leveraging deeper phenotyping, RDoC, and empirically-derived symptom dimensions to better understand latent liability across disorders. Finally, as our statistical approaches to examining genetic overlap across disorders are rapidly evolving, we discuss methodological and conceptual considerations moving forward.

Cross-Disorder Molecular Genetics and Genomics

Most psychiatric disorders are at least moderately heritable. Despite moderate to high estimates from twin and family research, and evidence for genetic co-aggregation across disorders, identifying genes with cross-disorder effects has been extremely challenging. Most gene-finding efforts to date have failed to replicate, and research is now examining the degree to which broader-scale, aggregated genetic variation is unique to individual disorders or shared across disorders.

Using two analytic approaches, the International Schizophrenia Consortium (6) measured the extent to which common genetic variation underlies the risk of schizophrenia (SZ). This study implicated the major histocompatibility complex, and provided molecular genetic evidence for a substantial polygenic component to the risk of SZ, involving thousands of common alleles of very small effect, and confirming the hypothesis of polygenicity. In addition, Purcell and colleagues demonstrated that this polygenic component significantly contributes to the risk of bipolar disorder, but not to several important non-psychiatric diseases (6).

To examine shared genetic etiology, the Cross-Disorder Group of the Psychiatric Genomics Consortium (PGC) used genome-wide genotype data from case-control groups for SZ, bipolar disorder (BP), major depressive disorder (MDD), autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD) (9). Using univariate and bivariate methods to examine overlap across disorders, single nucleotide polymorphisms (SNPs) explained 17–29% of the variance in liability. Figure 1 presents SNP-based heritability estimates for each of the major disorders, as well as SNP-based co-heritability estimates for each pair of disorders. This is the most powerful molecular study of cross-disorder genetics to date.¹

The genetic correlations calculated using common SNPs were highest between SZ and BP (0.68 ± 0.04), but were also high in other disorder dyads, in the following order: SZ and major depressive disorder (0.43 ± 0.06), BP and major depressive disorder (0.47 ± 0.06), and ADHD and major depressive disorder (0.32 ± 0.07). They were low and/or non-significant for other pairs of disorders. In addition, the group examined the proportion of SNPs associated with central nervous system function, and found a high proportion of co-heritable SNPs across SZ and BP to be implicated. For other disorders or pairs of disorders, the estimates explained by such SNPs were not significant. However, large standard errors in these data indicate inadequate precision to test this.

This empirical evidence of molecular genetic overlap across psychiatric disorders, and a relationship with CNS-positive genes, indicates some molecular genetic specificity in the relationships between measured disorders. However, it is important to keep in mind that from a dimensional (rather than a categorical diagnostic) standpoint, it is possible that

¹General effects of co-heritability between specific disorders found in these analyses have withstood a recent, more sophisticated statistical approach to controlling for linkage disequilibrium, LD Score Regression (7. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Consortium R, et al. An Atlas of Genetic Correlations across Human Diseases and Traits 2015 2015-01-01 00:00:00.).

genetic susceptibility variants across major psychopathology are simply more likely to overlap when psychopathology in general is more severe (e.g., with SZ and BP). On the other hand, there is some evidence to suggest that neurodevelopmental disorders (such as forms of ASD or social deficits associated with 22q11 deletion, for example) may be etiologically distinct from other more general psychopathology.

Other research of the PGC Cross-Disorder Group's identified risk loci with shared effects across five major psychiatric disorders (3). Focusing on the same five disorders, they analyzed genome-wide single-nucleotide polymorphism (SNP) data in 33,332 cases and 27,888 controls of European ancestry. This work applied multinomial logistic regression to identify the best-fitting model to describe the relations between genotype and phenotype, and examined the cross-disorder effects of loci previously identified to be genome-wide significant for BP and SZ. The study also used polygenic risk-score analysis to examine effects from all common variants measured, and pathway analysis of the genetic overlap for the five disorders. Lastly, the work used enrichment analysis of expression quantitative trait loci. This type of data was used to assess whether SNPs with cross-disorder associations were enriched for regulatory SNPs measured in post-mortem brain samples.

SNPs at four loci met genome-wide significance. These included regions on chromosomes 3p21 and 10q24, and two L-type voltage-gated calcium channel subunits, CACNA1C and CACNB2. Model selection supported the effects of these loci for several disorders, and loci varied with respect to diagnostic specificity for SZ or BP. Polygenic risk scores (also referred to as genetic profile scores) showed cross-disorder associations, particularly between the adult-onset disorders. Importantly, calcium channel signaling pathways were implicated across all five disorders, and SNPs with evidence of cross-disorder association were also enriched for brain eQTL markers. Not only do such large-scale genomic findings show that specific SNPs are associated with the same major psychiatric disorders, but they also suggest that variation in some genes, such as calcium-channel activity genes, have pleiotropic effects.

Broad Overlap of Psychiatric Genomics Consortium Findings with Family and Twin Research

Findings from the recent molecular genomic literature are broadly consistent with twin and family studies of heritability (see (10–15) for examples), with minimal exception. There is a history of biometrical research consistent with the genetic overlap of SZ with BP, and some biometrical evidence consistent with a majority of the PGC findings to date. A general lack of significant overlap between ADHD and ASD found in the Cross Disorder group's data is not consistent with at least one family study of both disorders in children (16), though to date there are few structural equation modeling (non-molecular) studies published about the genetic relationship between ADHD and ASD. This inconsistency might relate to important rare CNVs in both disorders. Lionel and colleagues (17) have explored the overlap of genetic risk in ADHD and ASD by testing for rare CNVs in two independent cohorts of unrelated ASD and ADHD individuals. In these samples, deletions of the neuronal ASTN2 and the ASTN2-intronic TRIM32 genes yielded the strongest association with ADHD and

ASD, but numerous other shared candidate genes (such as CHCHD3, MACROD2, and the 16p11.2 region) were also implicated. Their results have provided evidence for a role of rare CNVs in ADHD risk, and for the existence of susceptibility genes common to ADHD and ASD. It is possible that more PGC Cross-Disorder work over the coming years will explore this genetic relationship further.

Novel Approaches: Dimensional Refinement of the Phenotype

Other methods are deconstructing phenotypes across disorders, and taking a dimensional approach to cross-disorder genomics. In the U.S., the shift toward methods incorporating Research Domain Criteria over the last five years is significant (for reviews of the RDoC approach, see (18–20) and the RDoC website: www.nimh.nih.gov/research-priorities/rdoc). This research approach de-emphasizes dichotomous diagnoses based on operationalized criteria in DSM or ICD classification systems, and emphasizes traits and units of analyses agnostic to diagnosis. This conceptual shift suggests a different flavor of cross-disorder phenotypic research. The RDoC initiative might be valuable not only for promoting investigation of alternative phenotypes that may relate more closely to common neuropathological mechanisms, but also for encouraging the sharing of both phenotypic and genetic data via RDoCdb, the National Institute of Health initiative's online database. For a helpful review of important advances made by the PGC due to this collective approach, see (21).

Taking account of quantitative variation in traits across samples can provide us with critical information about the mode of action at the susceptibility locus (22). By more sensitively measuring cognitive, behavioral, personality, and other types of traits, the biological signals across disorders can be compared and contrasted in a more nuanced fashion. This is important because our current classification system, along with the basic GWAS approach, provides an unformed and somewhat blurry view of psychiatric pleiotropy. While psychiatry and psychology will never have the luxury of modeling etiopathogenesis using Mendelian or infectious disease processes as do other fields of medicine, scenarios that might finally produce results akin to the obesity-diabetes story (23, 24) will require sensitive, continuous and quantitative measurement of traits across disorders, such as psychotic features in BP, reward deficits in SZ, or the prominence of anxiety phenotypes in recurrent depression. RDoC takes a step toward formalizing these scientific pursuits, and the Psychosis Endophenotypes International Consortium also prioritizes this approach.

Schizophrenia and Bipolar Disorder

In addition to the work by the Cross-Disorder Group, some recent genomic research has leveraged a deeper clinical phenotypic profile of symptoms to attempt to parse the genetic etiologies of SZ and BP. In these analyses, patients are genotyped and symptom dimension scores are mapped (with multiple comparison correction) to genes and biological pathways. In one study, our research group (25) detected “modifier loci” previously implicated in the PGC SZ datasets, by using empirically-derived positive and negative symptom scales from the Operational Criteria Checklist (26) in a large Irish meta-analysis. Genes and ontologies/pathways across samples with SZ and BP were significantly associated with negative and

positive symptoms—most notably, *NKAIN2* and *NRG1*, respectively. We observed limited overlap in ontologies/pathways associated with the different symptom profiles, with immune-related categories over-represented for negative symptoms, and addiction-related categories for positive symptoms. This provides evidence that affective symptoms common to both disorders may have common molecular substrates.

A second set of analyses by our group (27) derived factor loadings from the analysis of only narrowly-defined SZ proband cases. When creating SZ-specific factor scores, gene pathway analyses across SZ and BP probands of the primary factor indicated a significant over-representation of three of the primary pathways implicated in the SZ literature: glutamatergic transmission, GABA-A receptor, and cyclic GMP. It is possible that these pathways have differential influences on affective symptom presentation in SZ and BP.

Other research has observed a significant correlation between BP polygenic risk score and the clinical dimension of mania in SZ patients. Ruderfer and colleagues (28) reported a direct comparison of 7,129 SZ cases and 9,252 BP cases, and the creation of a SZ-versus-BP polygenic score that differentiated the two disorders in several independent samples. In addition, they conducted a combined GWAS of 19,779 BP and SZ cases versus 19,423 controls, and in this cross-disorder case-control analysis, they examined associations with symptom dimensions. Results indicated five regions reached genome-wide significance (*CACNA1C*, *IFI44L*, *MHC*, *TRANK1* and *MAD1L1*) and a novel locus near *PIK3C2A* (28). These findings further indicate that examining relationships between clinical symptom dimensions and polygenic signatures can provide informative results about the overlap of major disorders.

Schizophrenia and Obsessive-Compulsive Disorder

The dimensional approach to phenotyping has also informed studies of psychiatric comorbidity where base rates across disorders are very low. One example is the co-morbid presentation of SZ and obsessive-compulsive disorder (OCD). Several studies have examined phenotypic overlap between SZ and OCD symptoms (OCS) due to frequent comorbidity (about ~23%) (29), and low lifetime prevalence for each separately: SZ at 0.48% (30) and OCD at 2% (31). Measurement of OCS in this body of literature generally requires quantitative clinical scoring following clinical interview, and phenotypic evidence for an overlap or a “schizo-obsessive” subtype is mixed (32–34). It is likely that second-generation antipsychotics play a significant role in increasing the risk of OCS and OCD in SZ (see (35) for a review); importantly, despite the frequent and relevant comorbid burden of OCD symptoms in SZ, the incidence of patients with OCD developing psychotic symptoms is only 1.7% (36). With OCS measures and genotyping in larger SZ samples, these phenotypes could be measured well enough to eventually explore pleiotropy in the future.

Schizophrenia and Autism Spectrum Disorders

One of the most developed areas of cross-disorder genomic research to date, aside from the overlap of SZ and BP, is that of SZ and ASDs. Developmental phenotyping with dimensional measures has enhanced our understanding of the relationship of SZ with autism

(AUT). In an early review addressing the putative connection between childhood onset SZ and AUT spectrum disorders by Rapoport et al. (14) both clinical and genetic overlap were highlighted. At that time, two large case–control studies had indicated that parental SZ is a significant risk factor for AUT (37, 38). Rapoport et al. (14) also highlight the growing evidence from linkage and expression studies, and copy number variants that appear to be shared in both AUT and SZ. Of particular note are those regions implicated in the literature on genetically-influenced developmental disabilities, early psychosis, and psychosocial deficits, such as 22q11 deletion, the SHANK3 mutation at 22q13.3, and 16q11. 22q11 deletion syndrome carries a very high, 30% (39), risk of psychosis and is associated with developmental delays and psychosocial and cognitive impairment. At the time, a relevant COMT variant (on 22q11) had also been associated with the level of psychosocial deficits in SZ families (40) and replicated in (41). The association of AUT with abnormalities at the SHANK3 locus has since been replicated several times along with many other genes that impact synaptic function (42).²

The AUT literature has explicitly tested conceptual models of co-heritability. Four types of potential genetic pleiotropy between and across disorders have been illustrated and explored by Crespi and colleagues, see Figure 2 (43), in the tradition of Kendler & Neale’s comparative models of the relationship of endophenotype to disorder (44). We show the models Crespi and colleagues attempted to test, because we believe these should be considered and explicitly tested in future genomic research.

Data from CNVs provided statistical support for the hypothesis that AUT and SZ are differentially associated with the same variants. However, at four of the loci, specific deletions predisposed cases to one disorder while duplications predisposed cases to the other. AUT and SZ shared associated genes more often than expected by chance, suggesting a lack of independence. However, there was limited overlap in the specific genetic markers analyzed in both AUT and SZ, so models C and D (Figure 2) could not be differentiated in this study.

Alternative Applications in Cross-Disorder Genomics

Recent studies have used alternative methods to employ a dimensional approach to cross-disorder genomics. One cross-disorder literature review took a phenotype-based approach, and identified 241 genes involved in multiple brain disorders (45). This cross-disorder approach increased the gene discovery relative to what would be obtained if each disorder, genomic variant, and study were analyzed independently, and results provided some support for shared genomic causes among apparently different developmental disorders. A second application pooled multiple anxiety disorders into “any anxiety”, alongside factor analysis of multiple ordinal anxiety phenotypes, resulting in the first genome-wide significant findings in anxiety disorders (48). Another recent analysis used alternative methods to examine cross-disorder CNVs using a quantitative phenotypic framework: Stefansson et al. targeted

²It is important to note, however, that “synaptic function” is a very broad category in the biological pathway literature, and that psychiatric diagnoses are likely all related to synaptic function to some degree. In addition, there may be unique forms of ASD and psychosis corresponding to earlier onset or increased genetic risk, and these regions could be associated with specific forms of illness that are not broadly generalizable.

cognitive deficits very broadly in an Icelandic sample, predicting specific deficits to be associated with overlapping SZ/AUT CNVs (46). In this approach, CNVs provided an entry point to investigations into the mechanisms of brain dysfunction.

In the last two years there has been a spate of new research reporting relationships between polygenic risk scores for psychiatric conditions and relevant phenotypes. In line with a broad polygenic, correlational atlas of general and psychiatric phenotypes published by Bulik-Sullivan and colleagues (7), Krapohl and colleagues (8) have taken a broad approach to polygenic scoring by exploring associations of polygenic scores for 13 phenotypes (from SZ to dementia to height) with multiple clinical, health, and cognitive variables (conceptually constituting a “phenome”) in an independent sample of over 3000 UK teenagers (8). Despite fairly modest effect sizes, their quantile analyses reflected the ability to stratify individuals by risk score. For example, the highest and lowest septiles for the education profile score yielded half of a standard deviation difference in mean math grade, and a quarter difference in mean behavioral problems. While this broad approach to the phenome has not yet been applied specifically to more than just a few of the major psychiatric disorders, and not in clinical samples, the method lends itself to this type of analysis in the future. We are exploring this type of approach currently in a large sample of college students ($N > 8,000$; A.R.D. & A.M., unpublished data).

In the near future, the PsychENCODE project (47) aims to produce a public resource of multidimensional genomic data using tissue- and cell type-specific samples from approximately 1,000 phenotypically well-characterized, high-quality healthy and disease-affected human post-mortem brains, and functionally characterize disease-associated regulatory elements and variants in model systems. This research begins with a focus on ASD, BP, and SZ, and to examine the heritability of these disorders. These highly anticipated analyses could further elucidate biological mechanisms underlying pleiotropy in psychiatric illness.

Methodological Developments and Considerations for Future Research

The area of cross-disorder genomics is rapidly evolving thanks to methodological advances from, for example, Lee and colleagues (48, 49), Andreassen, Thompson & Dale (50), and Bulik-Sullivan and colleagues (7, 51). Several methodological considerations are worth mentioning here. Lazzeroni, Lu, & Belitskaya-Levy suggest that an over-interpretation of very significant, but highly variable, P-values is an important factor contributing to the unexpectedly high incidence of non-replication in psychiatric genetics (52). They have provided a calculator (52), and show that formal prediction intervals can provide more realistic interpretations of P-values, and comparisons of P-values associated with different estimated effect sizes.

While the opportunity to look across the genome and the phenome using exploratory methods is exciting, it is important to test *a priori* hypotheses whenever possible. To increase the signal-to-noise ratio, measurement should be consistent across data waves and samples, and quantitative measures tested for reliability and validity. Particular limitations of this

research could relate to measurement invariance, and the often diverse methods and measures used across discovery and test samples.

A cautionary note about categorical diagnostic phenotypes for complex traits lies in an analysis of the influence of misdiagnosis on co-heritability estimates (53). Analyses show similar results for levels of misdiagnosis in both genomic and biometrical/family studies. In both scenarios, Wray and colleagues have shown that genetic variances and heritabilities are slightly underestimated, but genetic correlations are overestimated, sometimes substantially so. With just a 10% reciprocal misdiagnosis rate, two genetically distinct but equally heritable disorders with prevalence 1% can generate false-positive estimates of genetic correlations of greater than .2.

Conclusion

These studies provide some overview of cross disorders psychiatric genomics. Much of the work to date on genetic signature across disorders has relied on studies collected to address the genetics of one disorder, and not the overlap across disorders. Future studies addressing the use of study design to distinguish the models presented in Figure 2, for example, will allow for more refinement of genetic signature. In this review, we emphasized the movement in psychiatric genomics toward addressing both comorbidity and polygenicity. We have attempted to show how dimensional approaches to the phenotype have shed light on the observed comorbidity of psychiatric diagnoses. And we have also attempted to show how a dimensional approach to both the genome and phenome, via alternative statistical methods, has begun to address the problem of polygenicity. Future research might leverage these advances further to inform developmental studies of risk and resilience.

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Figure 1.

SNP-Based heritabilities (dark green) and coheritabilities (light green) reported by the Cross Disorder Group of the Psychiatric Genomics Consortium, 2013 (9). ADHD = Attention Deficit-Hyperactivity Disorder, BPD = Bipolar Disorder, SCZ = Schizophrenia, MDD = Major Depressive Disorder, ASD = Autism Spectrum Disorder. SNP-based coheritabilities are greatest for schizophrenia spectrum disorders, but significant across many pairs of disorders. Reprinted by permission from Macmillan Publishers Ltd: Nature Genetics (Cross-Disorder Group of the Psychiatric Genomics C, Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nature genetics. 2013;45(9):984–94.), copyright 2013

Figure 2.

Crespi and colleagues used data from studies of copy-number variants (CNVs), single gene associations, growth-signaling pathways, and intermediate phenotypes associated with brain growth to evaluate four alternative hypotheses for the genomic and developmental relationships between autism and schizophrenia: **(A)** autism subsumed in schizophrenia, **(B)** separateness/independence, **(C)** diametric, and **(D)** partial overlap of disorders. Figure reproduced from Crespi et al. (43).