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Post-GWAS in Psychiatric Genetics: A Developmental Perspective on the "Other" Next Steps

Danielle M. Dick, **The EDGE (Examining Development, Genes, and Environment) Laboratory***, **Peter B. Barr**, **Seung Bin Cho**, **Megan E. Cooke**, **Sally I-Chun Kuo**, **Tenesha J. Lewis**, **Zoe Neale**, **Jessica E. Salvatore**, **Jeanne Savage**, and **Jinni Su**

Department of Psychology, Developmental Program, Virginia Commonwealth University

Abstract

As psychiatric genetics enters an era where gene identification is finally yielding robust, replicable genetic associations and polygenic risk scores, it is important to consider next steps and delineate how that knowledge will be applied to ultimately ameliorate suffering associated with substance use and psychiatric disorders. Much of the post-GWAS discussion has focused on the potential of genetic information to elucidate the underlying biology and use this information for the development of more effective pharmaceutical treatments. In this review we focus on additional areas of research that should follow gene identification. By taking genetic findings into longitudinal, developmental studies, we can map the pathways by which genetic risk manifests across development, elucidating the early behavioral manifestations of risk, and studying how various environments and interventions moderate that risk across developmental stages. The delineation of risk across development will advance our understanding of mechanism, sex differences, and risk and resilience processes in different racial/ethnic groups. Here, we review how the extant twin study literature can be used to guide these efforts. Together, these new lines of research will enable us to develop more informed, tailored prevention and intervention efforts.

Keywords

gene environment interaction; pathways of risk; genetics; GWAS; prevention; intervention; twin studies; behavior genetics

The Status of Psychiatric Genetics

Gene identification efforts for substance use and psychiatric outcomes have come a long way over the past decade. For many years gene identification efforts were disappointing, with a history of linkage studies yielding modest lod scores (Agrawal *et al.*, 2008, Dick *et al.*, 2006a, Dick *et al.*, 2004, Foroud *et al.*, 2000, Kim *et al.*, 2005), candidate genes with poor replication records (Allen *et al.*, 2008, Chanock *et al.*, 2007, Lohmueller *et al.*, 2003, Risch *et al.*, 2009), and early genome-wide association studies that produced null findings

Correspondence: Danielle M. Dick, Ph.D., Department of Psychology, Box 842018, Richmond, VA 23284-2018, Phone: (804) 828-8756, Fax: (804) 828-2237, ddick@vcu.edu.

*EDGE Lab contributors listed alphabetically

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(The Wellcome Trust Case Control, 2007). The study of substance use disorders provided rare exceptions, whereby genes encoding nicotinic receptor subunits (Saccone *et al.*, 2007, Hancock *et al.*, 2015, Thorgeirsson *et al.*, 2008), as well as alcohol metabolizing enzyme genes (Gelertner *et al.*, 2014, Bierut *et al.*, 2012), were consistently and robustly associated with nicotine and alcohol dependence, respectively. However, even the considerable body of "failed" studies were quite informative. The expectation that individual genetic variants would be associated with psychiatric disorders at a magnitude that would be small but detectable with hundreds, or a few thousand individuals (Hirschhorn & Daly, 2005) was found to be untenable, and we learned that the risk contributed by any single variant was likely to be tiny rather than just small, with odds ratios on the order of less than 1.1 (O'Donovan, 2015), necessitating much larger sample sizes to be able to detect them. In recognition that the necessary sample sizes would be practically impossible for nearly any single research study to achieve, scientific groups began to collaborate in order to pool resources and participant data into consortia for meta- and mega-analysis (Psychiatric GWAS Consortium Steering Committee, 2009).

The Psychiatric Genomics Consortium (PGC) has led the way in coordinating these efforts for psychiatric disorders. The exemplar for the new, more successful gene identification strategy has been schizophrenia, a rare psychiatric disorder whose high heritability of ~80% (Sullivan *et al.*, 2003) made it a top candidate for gene identification. Results from the first report of the schizophrenia PGC group initially remained disappointing – despite having over 9,000 cases, only 5 genome-wide significant associations were found [The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011]. However, it was subsequently discovered that the return on investment was not linear. Doubling and even tripling the sample size yielded only a handful of additional results; however, 108 significant loci were found when a pooled sample of 37,000 cases and 113,000 controls was analyzed, with polygenic risk scores, calculated by weighting findings across the genome, accounting for 7% of the variance in disorder liability (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). A similar story has been found for other complex, highly heritable traits such as height, where no significant variant associations were detected with 5,000 genomes, but an analysis of 250,000 individuals was able to identify over 400 significant loci and account for up to 29% of the trait variance (Wood *et al.*, 2014). Parallel analyses for multiple disorders indicate there is a "breakthrough point" of sample size after which discovery rates increase exponentially, although this threshold differs across phenotypes (O'Donovan, 2015). Disorders with lower heritability, stronger environmental contributions, and/or greater heterogeneity require larger samples sizes for gene identification. For example, for major depression, a disorder with a heritability of ~35% (Kendler *et al.*, 2003) a recent meta-analysis found one genome-wide significant association in a sample of 70,000 participants (Direk *et al.*, 2016). Other substance use and psychiatric conditions with modest heritability and as-of-yet smaller sample sizes, such as Post-Traumatic Stress Disorder and Alcohol Dependence, have not yet attained the success achieved for Schizophrenia. However, efforts are underway to increase the number of available cases for analysis, with the expectation that once an as-of-yet-unidentified breakpoint is achieved, gene identification efforts for these disorders will follow suit.

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The Potential of Gene Finding for Psychiatric Outcomes

The justification for pursuing these large-scale gene identification efforts, which are costly endeavors that require coordination and collaboration across hundreds of scientific groups [The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011], is often that identifying genes influencing disorder will help advance understanding of the underlying biology (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), and be useful in developing new therapeutic drugs (Sanseau *et al.*, 2012, So *et al.*, 2017). This argument can be found in both the scientific literature (Breen *et al.*, 2016), and in lay descriptions about the importance of genetic studies of psychiatric disorders (Yilmaz, 2016). One of the challenges with drug development for psychiatric outcomes is the limited understanding of underlying biology, and likely complex heterogeneity of etiological factors. GWAS findings can be used to identify genes, and the proteins and networks that interact with identified genes, providing potential targets for drug discovery or drug repositioning (De Jong *et al.*, 2016). The most recent phase of the PGC proposes pathway analyses that integrate data from GWAS findings with information about potential druggable targets to advance the pipeline from gene identification to drug discovery (Sullivan *et al.*, 2017). The official PGC twitter account (@PGCgenetics) recently tweeted “PGC goal: Find genetic risk factors to go beyond to: reveal fundamental biology, inform clinical practice, id new therapeutic targets”.

These are clearly important and laudable goals. Substance use and psychiatric disorders have a tremendous societal and personal cost (Kazdin & Blase, 2011), and the need to understand the underlying etiology of these disorders and develop better treatments cannot be understated. Because many of the large gene-finding efforts in psychiatric genetics are being led by medical professionals, it is not surprising that the implications of gene identification (understanding biology, identifying drug targets, informing clinical practice) is often discussed in the context of a biomedical model. For a disorder like schizophrenia, with a high heritability indicating a strong biological component, effective therapeutic treatments are likely to be critical in controlling disease symptoms. However, even for a highly heritable disorder like schizophrenia, the risk of developing the disorder in a *genetically-identical* co-twin of an affected individual is only about 50% (Gottesman, 1991). Thus, genetics is clearly only part of the story, and the environment plays an important role in disease etiology, even in a highly heritable disorder like schizophrenia. Most psychiatric and behavioral disorders are not nearly as heritable as schizophrenia. Substance use disorders have heritabilities in the range of 50-60% (Verhulst *et al.*, 2015; Kendler *et al.*, 2007; Kendler *et al*, 2003), and depression, anxiety, and eating disorders have heritabilities that are even more modest (Shimada-Sugimoto *et al.*, 2015, Sullivan *et al.*, 2000). Further, twin data also demonstrate that the importance of genetic influences can vary tremendously as a function of the environment (Hicks *et al.*, 2008, Dick & Kendler, 2012). That is to say that point estimates of heritability are a reflection of the importance of genetic variation specific to the population characteristics at the time of study; changing the environmental context can change the relative importance of genetic variation in contributing to the disease outcome. Thus, although there is clearly a biological, genetic component involved in why some individuals are more at risk than others, there is a significant environmental component as

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well, with compelling evidence that substance use and psychiatric disorders result from complex interactions of genetic and environmental factors across development (Litten *et al.*, 2015, O'Donovan, 2015).

We also know that for many psychiatric and substance use disorders, environmental interventions can be effective at both preventing and treating the disorder. For example, cognitive-behavioral therapy has been found to be about as effective as pharmaceutical treatment for depression, with the combination of pharmaceutical treatment with cognitive-behavioral therapy showing significant gains in recovery (Keller *et al.*, 2000). A number of other environmental and social interventions also have been shown prevent or reduce the incidence of depression and anxiety, such as exercise (Hearing *et al.*, 2016), mindfulness (Hofmann *et al.*, 2010), and social engagement (Nagy & Moore, 2017). Smoking also provides a clear example of the impact of environmental intervention, whereby changing laws regarding taxation can alter accessibility and affordability of the product, and subsequently alter rates of tobacco consumption (Chaloupka *et al.*, 2012). Family and school based intervention have also been shown to be effective for altering substance use and conduct problems (Brody *et al.*, 2009b, Dishion *et al.*, 2014). Further, there is suggestion that individuals who are most at risk are also most likely to benefit from intervention (Conrod, 2016; Mun, White, & Morgan, 2009; Savage *et al.*, 2015).

This does not undermine the importance of using gene discovery to develop more effective pharmaceuticals. Rather, it underscores another path for important post-GWAS study that can be useful for reducing the burden of psychiatric and behavioral disorders, namely, as robust genetic variants are identified from GWAS, we have the ability to characterize how measured genetic risk unfolds across development, and in conjunction with the environment, can help guide the development of more effective, targeted prevention programming. This post-GWAS avenue of exploration has not received nearly the attention as the potential for drug development and discovery, but we argue that studying the behavioral and developmental pathways of risk associated with robustly identified genetic variants has the potential to be equally important in terms of future harm reduction. The post-GWAS era[1] will allow us to map manifestation of genetic risk across time in order to address questions such as:

- What phenotypes represent early manifestations of genetic risk that may be intervened upon at an earlier developmental phase to prevent more serious challenges from developing?
- What do these phenotypes tell us about the underlying mechanisms by which risk unfolds, and how do they help us understand the disorder in a developmental framework?
- How is genetic risk moderated by specific environmental factors, and do these differ at different developmental stages?

[1]We note that we do not believe we are in a post-GWAS era yet, as we are still amassing large numbers of subjects to robustly identify genetic variants; however, we believe the examples of schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and complex behavioral outcomes like educational attainment and wellbeing (Okbay, et al., 2016), indicate that most behavioral outcomes are likely to follow suit and be in a similar position of robust gene identification in the near future.

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- Does genetic risk manifest differently in males and females? Do different environments moderate risk for males and females?
- Are there different pathways of risk for individuals from different racial/ethnic backgrounds?
- Can we use information about environments that modify risk to develop more targeted and effective prevention and intervention programming?

We discuss each of these potential areas of post-GWAS study in further detail below, reviewing different types of questions that can be addressed, and studies that provide background rationale for the importance of these areas of investigation, to include how the extant twin literature can be used to guide and inform post-GWAS studies on the effects associated with identified genetic variants. Although not intended to be exhaustive, we provide illustrative examples of studies that have begun to carry out these kinds of tests. Many of our illustrations are drawn from the field of substance use research. Substance use outcomes, the primary area of study of the authors, is a rich area for exploration of these developmental questions for a number of reasons. Substance use outcomes encompass nearly all of the many challenges inherent in studying complex behavioral disorders and outcomes. At the population level, they have a significant genetic component, but are also strongly influenced by the environment (Verhulst *et al.*, 2015; Kendler *et al.*, 2007; Kendler *et al*, 2003), and twin studies provide further evidence that the heritability can vary considerably as a function of the environment (Barr *et al.* 2017, Dick *et al.*, 2001, Dick *et al.*, 2007b, Harden *et al.*, 2008, Heath *et al.* 1989, Li *et al.*, 2017, Miles *et al.*, 2005) An environmental exposure is necessary for the development of disorder (access to and ingestion of a substance), making it a rich area for the study of gene-environment interaction. Substance use disorders are phenotypically heterogeneous, with multiple pathways of risk (Dick *et al.*, 2016) and manifestations of the disorder (Hussong *et al.*, 2011; Zucker, 2008). Alcohol and other drug use are also strongly genetically correlated with other psychiatric disorders, most strongly externalizing disorders (Kendler *et al.*, 2003, Krueger *et al.*, 2002, Young *et al.*, 2000), suggesting that studying core component processes as they relate to behavioral disinhibition and impulsivity are likely to play important roles in the development of the disorder, and potentially represent mechanisms by which genetic risk unfolds. Although we use substance use outcomes as an illustration of the “other” next analytic post-GWAS steps, we believe that this general line of research can and should be applied more widely to psychiatric and substance use outcomes.

Post-GWAS Areas of Exploration from a Developmental Perspective

Mapping Phenotypic Risk Across Development

Most psychiatric gene identification studies are carried out in adult samples, particularly for disorders in which the age of onset occurs midway through or late in life. However, the same genetic variants that are linked to onset of symptoms when a person is 20 or 30 or 40 years old have existed in their DNA since embryogenesis. What have they been doing all that time? One important area of post-GWAS study is to trace the developmental pathways by which these identified genetic variants exert their influence. While focusing post-GWAS research on medication development can work as an approach to treating disorders after their

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onset, understanding their earlier manifestations could allow for early prevention/intervention efforts and a means of identifying at-risk individuals before they experience problems.

Alcohol use disorder (AUD) presents a perfect theoretical example to illustrate this. AUD is a developmentally dynamic disorder, because initiation of alcohol use and increasing patterns of consumption are necessary precursors to developing symptoms. Initiation happens, for most individuals, in adolescence, while age of onset for AUD diagnosis peaks later in young adulthood (Kessler et al., 2005; Substance Abuse and Mental Health Services Administration, 2014). Twin studies indicate that genetic influences on alcohol use behavior also vary both quantitatively and qualitatively across development (Dick *et al.*, 2007a, Edwards & Kendler, 2013, Kendler *et al.*, 2008, Meyers *et al.*, 2014), with genetic influences being less important in adolescence and increasing in adulthood. It will therefore be beneficial to follow-up genetic association studies in younger, longitudinal cohorts to determine when and through what pathways specific genes are associated with behaviors that move individuals towards or away from developing problems. Mapping these risk pathways could provide information about the most effective developmental stages to implement prevention and intervention efforts. For example, Olfson et al. found that the ADH1B variant associated with adult alcohol use disorders was associated with age of first intoxication and age at first DSM-5 symptom in a younger study of adolescents (Olfson *et al.*, 2014).

Further, the developmental link between phenotypes is not always straightforward. Adult expression of symptoms/traits often do not map directly onto their expression in childhood, due to numerous biological, psychological, and social changes that take place throughout development. For example, AUDs in adults are characterized by impairments in social and occupational roles that children and adolescents simply do not have, as well as excessive consumption of alcohol at levels that are almost impossible for a young person to achieve given social and legal restrictions on access. Early initiation and moderate consumption are therefore a better indicator of deviant/problem behavior in young children, though they are normative behaviors in adults (Thompson *et al.*, 2014). Similarly, mood and anxiety disorders in children often manifest with physiological rather than cognitive symptoms before they have developed the ability to interpret complex feelings (Ollendick *et al.*, 1994). Post-GWAS studies can use this knowledge to test how genetic influences on late stage outcomes manifest in the earlier progression of traits and behaviors leading up to them. Such knowledge can point to developmental periods and processes (e.g. neurodevelopment, puberty, shifting social roles) that are most relevant for promoting changes in behavior.

One preliminary example of how genetic markers have been associated with different phenotypes across developmental stages is found in studies of the gamma aminobutyric acid receptor alpha 2 (GABRA2) gene. Markers in this gene have been consistently associated with alcohol use disorder in adults (Edenberg et al., 2004, Bierut et al., 2010) but not in adolescents (Dick et al., 2006, Sakai et al., 2010). Instead, during adolescence these markers have been associated with externalizing disorders such as conduct disorder (Dick *et al.*, 2006; Dick *et al.*, 2009; Sakai *et al.*, 2010; Melroy *et al.*, 2014). This demonstrates the

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heterotypic continuity associated with *GABRA2* and the need to test post-GWAS markers in younger samples to understand how risk unfolds across development.

Understanding Mechanism

Not only can genetic influence change in importance for an outcome across time, genetic associations with outcomes can arise through different mechanisms, reflecting the heterogeneous processes by which genotype can be associated with distal behavioral outcomes. Returning to the example of alcohol use, an association has been demonstrated between alcohol use/problem behaviors and a broader dimension of "externalizing" behaviors, which are socially deviant, "acting out" behaviors ranging from conduct disorder in childhood to illicit substance use and antisocial personality disorder in adulthood (Dick *et al.*, 2006b, Verweij *et al.*, 2016). Externalizing behavior in early childhood is a predictor of adult alcohol use (Dick et al., 2013), and may be an early manifestation of how genetic risk for AUDs unfolds, starting with a childhood temperament rather than a direct alcohol use outcome. However, there is also a link between high sociability in childhood and later alcohol use (Dick *et al.*, 2013), indicative of the multiple potential developmental pathways to problem alcohol use that start from underlying genetic predispositions. Understanding how genetic risk unfolds along these pathways is essential to develop effective prevention and intervention to implement before alcohol use develops into an AUD needing treatment. Three such commonly theorized pathways of risk to AUD are characterized by externalizing behavior, internalizing symptoms, or a low level of response to alcohol (Hussong *et al.*, 2011, Schuckit *et al.*, 2015, Zucker, 2008). Each of these pathways has been shown to benefit from tailored personalized intervention (Conrod *et al.*, 2006, Schuckit *et al.*, 2016, Schuckit *et al.*, 2015). Schuckit et al., 2015 demonstrated that an intervention for college drinking that included information about low level of response to alcohol was most effective for those with a low level of response. Similarly, Conrod et al., 2006 used personality targeted interventions focused on externalizing and internalizing characteristics in high school students and demonstrated a reduction in future alcohol outcomes. These studies (and other work by these groups) demonstrate that individuals are differentially responsive to various interventions based on their underlying etiologies and these interventions can be effective before pharmacological treatment would be considered.

These examples are specific to alcohol, but the idea of heterogeneous genetically-influenced pathways is likely to be broadly applicable to psychiatric/substance use disorders. Heterogeneity in symptoms, course, and etiology of disorders is recognized as a profound challenge in studying psychopathology (Dacquino *et al.*, 2015, Geschwind & Flint, 2015, Hines *et al.*, 2005, Lee *et al.*, 2016, Milaneschi *et al.*, 2016, Wium-Andersen *et al.*, 2017). Although this challenge makes gene identification a particularly difficult undertaking, it is hypothesized to be overcome by "brute force" approaches with large sample sizes, as described above (e.g. Schizophrenia Working Group, 2014; Wood et al. 2014). These methods, however, point only to *which* genetic variants are important but not *why*, so post-gene identification it will be important to test identified variants in a more nuanced and specific way to understand through which of many possible pathways that gene influences the phenotype (Geschwind & Flint, 2015, Mackay *et al.*, 2009). For example, one could test whether genetic markers identified as associated with alcohol dependence influence a

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person's biological or subjective response to alcohol or whether they influence sensitivity to reward more broadly. Understanding the different biological and environmental mechanisms underlying complex behavioral traits should help us refine where personalized prevention/treatment efforts can be developed to target the underlying cause of a disorder, which may differ greatly between two individuals with the same symptoms or diagnosis.

Studies have already begun to use GWAS results to inform our understanding of etiological mechanisms, such as the existence of genetic heterogeneity and subtypes within disease classifications (e.g. Edwards *et al.*, 2016; Traylor *et al.*, 2012), and biological pathways that cross diagnostic boundaries, with genetic risk shared across disorders (Cross Disorder Working Group of the PGC, 2013; Bulik-Sullivan *et al.*, 2015; Andersen *et al.*, 2017). For alcohol phenotypes, investigations of GWAS-identified variants have begun to disentangle which genes directly impact alcohol use (e.g. alcohol metabolism genes) and which have indirect effects through a broader liability towards polysubstance use (Haller et al., 2014) or sensation-seeking tendencies (Aliev *et al.*, 2015; Ashenhurst *et al.*, 2016). For example, preliminary studies suggest that genes such as *GABRA2* and aggregate polygenic risk scores may impact AUDs by influencing one's subjective response to alcohol (Uhart *et al.*, 2013), functional differences in brain reward systems (Heitzeg *et al.*, 2014), and personality traits like impulsivity (Villafuerte et al., 2013; Li *et al.*, 2017). Functional annotation of the genetic and biological processes implicated by GWAS variants (Clark *et al.*, 2017; Edwards *et al.*, 2015a) can also serve to improve our understanding of the many mechanisms leading from genes to complex behaviors.

Characterizing Gene Environment Interplay

There is increasing recognition that genetic and environmental influences for many outcomes are likely to interface in complex ways. Interplay between genes and environment include processes of gene-environment interaction (GxE), or the extent to which measured environmental factors moderate genetic influences on a behavior, as well as gene-environment correlation (rGE), or the degree to which exposure to certain environmental conditions is due to genetic influences (Scarr & Mccartney, 1983). Thus even after all genetic variants with a main effect on AUD have been discovered, it will be important to understand their effects in the context of different environments.

In the area of substance use, twin studies yield consistent evidence for GxE effects associated with environments that differ in the degree to which they offer greater opportunity for substance use or exert social control (Shanahan & Hofer, 2005; Dick, 2011; Kendler, 2011). Additionally, the salience of different environments may also vary across the lifespan. In adolescence, twin studies have demonstrated that genetic influences on alcohol outcomes are higher in environments characterized by low levels of parental monitoring/knowledge (Miles *et al.*, 2005) and higher levels of peer deviance (Dick *et al.*, 2007b, Harden *et al.*, 2008, Li *et al.*, 2017). Neighborhood characteristics that increase opportunity and limit control, such as a higher percentage of young adults in the neighborhood (presumably offering greater access to alcohol and social modeling), and a higher percentage of migration in and out of the community (reflecting neighborhood instability) were associated with greater genetic influences on alcohol outcomes (Dick *et al.*, 2001). As individuals transition

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into adulthood, other aspects of one's environment become more important. For example, involvement in romantic partnerships limits genetic influences on alcohol misuse (Barr *et al.* 2017, Heath *et al.*, 1989). The protective effect of marriage against development of alcohol use disorders is also stronger in those at greatest genetic risk (Kendler *et al.*, 2016).

Genetic liability can also play a role in shaping the individual's environment, in the sense that genetically influenced temperamental and personality characteristics lead individuals to select into particular environments. For example, twin studies indicate that part of the relationship between an individual's substance use and that of their peers is the result of common genetic influences (Edwards *et al.*, 2015b, Harden *et al.*, 2008), suggesting those at heightened risk are more likely to select into environments that will exacerbate any predisposition. This effect is also seen in young adulthood where the effect of marriage on reduction in antisocial behaviors is attenuated after adjusting for common genetic influences (Barnes & Beaver, 2012).

Candidate gene-by-environment research has been controversial (Duncan and Keller, 2011; Dick *et al.*, 2015). Moving forward, focusing on genes with robust GWAS evidence is likely to yield more replicable and reliable results. In addition, the twin literature on gene environment interaction can be used to inform more targeted hypotheses about GxE effects that focus on environments shown to moderate latent genetic effects. For example, the protective effect of alcohol dehydrogenase 1B (*ADH1B*) was negated among individuals whose peer groups consisted of mainly drinkers (Olfson *et al.*, 2014). The association between of the nicotinic receptor gene, *CHRNA5*, and nicotine dependence was stronger under conditions of low parental monitoring (Chen et al., 2009). Additionally, the effect of *CHRNA5* on smoking behavior was found to be stronger among those who initiate cigarette use earlier (Hartz *et al.*, 2012). And while marriage had a stronger protective effect on those with the low-risk genotype of *GABRA2*, those with the high risk genotype were less likely to enter into marriage or stay married, suggesting a process of both GxE and rGE (Dick *et al.* 2006c).

Other studies have focused on aggregate measures of genetic risk, testing for moderation of risk associated with genome-wide, polygenic scores. In line with previous twin studies, polygenic risk scores were more strongly associated with alcohol problems (Salvatore *et al.*, 2014) and externalizing behaviors (Salvatore *et al.*, 2015) under conditions of low parental monitoring and high peer deviance. In another study, the effect of polygenic risk scores on smoking was mitigated in neighborhoods with greater social cohesion (Meyers *et al.*, 2013). These aggregate measures of genetic risk still explain relatively small amounts of variance in AUD, or other substance use outcomes. However, as GWAS sample sizes continue to grow and phenotyping in the discovery samples is further refined, our ability to detect the interplay of genetic risk and environmental influences will increase (Dudbridge, 2013).

Continued exploration of the environmental conditions that moderate genetic influences on substance use at different periods in the life course, as well as the ways that those at high risk may select out of protective or into risky environments will help inform treatment and policy initiatives intended to reduce the harms of substance use. Incorporating GxE into designs currently used to examine genome-wide data may provide insight into the specific

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genetic variants that are influenced by environmental conditions (Mukherjee *et al.*, 2012). Though this approach has proven limited thus far (Boardman *et al.*, 2014), it is likely to be more powerful/successful in a post-GWAS era when the risk variants are known. In addition, extending the rationale of GWAS towards identifying environments (e.g. environmental wide association studies, or EWAS) that are important across developmental periods (Park *et al.*, 2014) may allow us to eventually provide aggregate measures of both environmental and genetic risk, which could prove useful in tailoring prevention or treatment efforts. Additionally, because gene-environment correlation is also important, research designs leveraging information from natural experiments, such as a change in policy or a natural disaster, will increase our ability to differentiate processes of rGE from GxE (Schmitz & Conley, 2017). For example, research on the effect of veteran status, using the Vietnam Draft lottery as an instrumental variable, found that veterans with higher polygenic scores were more likely to initiate tobacco use and smoke more heavily (Schmitz & Conley, 2016).

Mapping Pathways of Risk in Males and Females

There is currently a strong push from the National Institutes of Health to more carefully examine the extent to which pathways of risk may vary across males and females. Genetically informed designs can be used to examine the extent to which there are sex differences in the genetic influences on psychiatric outcomes (Powers *et al.*, 2017; Salvatore *et al.*, 2017). There are two forms of sex-specific genetic differences identified in twin studies (Neale & Cardon, 1992). Quantitative sex differences refer to differences in *the degree* to which additive genetic factors account for variation in an outcome in males and females. Qualitative sex differences refer to differences in *the source* of genetic variation across males and females. In other words, researchers can study whether the relative importance of genetic effects varies between males and females, and whether it is the same or different genes. In view of the challenges associated with gene identification, and the massive sample sizes that would be required for sex-specific gene identification, twin studies of latent genetic influence provide much of the field's current knowledge on whether the pathway from genotype–phenotype is the same across males and females. For example, the most comprehensive test of genetic differences in the heritability of alcohol use disorder (AUD) to date comes from the Verhulst *et al.* (2015) meta-analysis of twin and adoption studies of AUD across clinically-ascertained and registry-based samples. They found that genetic factors account for roughly 50% of the variance in AUD, and this estimate applies to both males and females. Furthermore, there was no evidence of qualitative sex differences in the Verhulst *et al.*'s (2015) meta-analysis. This suggests that the source and magnitude of genetic influences on AUD are likely to be the same across sexes. Recent sex-specific analyses in a sizeable (N = 112,117) GWAS of alcohol consumption in the UKBioBank sample (Clarke *et al.*, 2017) largely replicated this conclusion from the twin and adoption studies: The genetic correlation for alcohol consumption in males and females was +0.90 (indicating overlapping genetic influences), and there was no substantial evidence for sex-specific loci.

Identifying whether GxE effects are sex-specific is a natural extension of this work. In the area of alcohol research, sex-specific G × E effects have not been systematically examined, either in studies of twins or measured genotypes (Salvatore *et al.*, 2017). However, theory

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and evidence regarding sex differences from disciplines such as psychology, sociology, anthropology, neurobiology, and physiology (including evidence from preclinical research in non-human animals) suggests that there are sex differences in exposures to many of the environments that have been examined in G × E twin studies, including parental monitoring (Barnes *et al.*, 1997, Svensson, 2003), stressful life events (Kessler & Mcleod, 1984), and the health protecting benefits of marriage (Kiecolt-Glaser & Newton, 2001). In one example along these lines, Perry *et al.* (2013) examined sex-specific G × E effects for *GABRA2* as a function of daily hassles (problematic experiences at work and with one's spouse, children, and friends) and uplifts (pleasurable experiences across the same categories). They found that males who had the high-risk *GABRA2* genotype, as indicated by having one or more copies of the A-allele at rs279871, and who experienced more daily uplifts had a lower probability of alcohol dependence compared to males who had the high-risk genotype and who experienced fewer daily uplifts. In contrast, the probability of alcohol dependence for females did not differ as a function of either their genotype or the number of uplifts experienced. This suggests that an environment characterized by these types of social support mitigate the alcohol dependence risk associated with the A-allele for this variant for males, but not females.

More broadly, with respect to G × E studies of alcohol use outcomes, there are sex differences in processes including alcohol metabolism (Mancinelli *et al.*, 2009); levels of reproductive- and stress-related hormones (Witt, 2007); subjective and neurobiological responses to alcohol intoxication (Wang *et al.*, 2003); and in the latent genetic influences shared between AUD and endophenotypes such as alcohol sensitivity (Heath *et al.*, 1999). Bringing together theory and evidence about how environments and processes differ across the sexes may help build a cohesive body of knowledge about the pathways from sex-specific genetic effects to clinically significant meaningful outcomes (Short *et al.*, 2013).

Mapping Pathways of Risk Specific to Racial/Ethnic Groups

Genetic studies have been conducted primarily in samples of European ancestry; thus, results will be most applicable to those populations and will not be as predictive among individuals from different racial/ethnic backgrounds (Martin *et al.*, 2017). This underrepresentation is a disservice to non-European populations, as well as to the scientific community tasked with providing information for all, in that it limits our understanding of the underlying etiology of psychiatric and substance use outcomes among individuals from more diverse populations (Dick *et al.*, 2017). Genetically informed studies of racially/ethnically diverse populations can be used to examine how social and genetic environmental factors come together to influence psychiatric outcomes in specific populations, which have their own customs and pressures. It is not expected that the biological pathways through which genotypes affect psychiatric outcomes will differ across racial/ethnic groups; however, differences in disease allele frequency and linkage disequilibrium (LD) patterns may lead to outcome differences in the influence of specific genetic variants among diverse populations (Gelernter *et al.*, 2014).

Understanding the underlying issues regarding recruiting and retaining participants is important to performing research inclusive of various ancestries. Studies have explored

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potential causes for the lack of diversity in health research studies, and findings have repeatedly reflected consequences of institutional racism throughout history, which include provider implicit bias (Cooper *et al.*, 2012, Green *et al.*, 2007), participant socioeconomic status (Corbie-Smith, 2004, Freeman & Payne, 2000, Seto, 2001), and participant mistrust (Corbie-Smith, 2004, Wilets *et al.*, 2003). Deep-seated and erroneous racial perceptions (Branson *et al.*, 2007) have been shown to contribute to the lack of recruitment and retention of some non-European participant populations. Additionally, acknowledgement of the research's importance tends to be missing from the investigator-participant interaction, as there is a higher likelihood of recruitment and retention if participants are made aware of the potential impact a study could have on society, as well as on them as individuals (Ejiogu *et al.*, 2011). Furthermore, educational programs could assist in the resolution of some underlying issues in obtaining diverse genetic samples. It has been shown that non-European Americans, for example, were less likely than European-Americans to be knowledgeable of informed consent regulations, as well as more likely to be distrustful of their physicians, for fear of negative outcomes (Wilets *et al.*, 2003). Particularly regarding African-Americans, other cultural factors, such as religion (Advani *et al.*, 2003) or past history (Brandt, 1978, Truog *et al.*, 2012) at the receiving end of biomedical abuses of power, play large roles in sample underrepresentation. In addition, African-Americans may be more difficult to locate and contact in the community, with higher proportions of African-Americans having incorrect addresses or telephone numbers listed, representing a key barrier for including them in genetic studies (Hartz et al., 2011). Improving racial/ethnic diversity necessitates acknowledgement of the underlying issues, as well as targeted efforts to resolve them through proper study organization and investigator preparation (Branson *et al.*, 2007).

Despite the lack of participation thus far, it has been indicated that persons of African ancestry, for example, are willing to participate in research activities if engaged by investigators (Jones *et al.*, 2016, Wendler *et al.*, 2006); consequently, interventions aimed at addressing the underlying issues faced in recruiting and retaining participants of color during genetic studies could potentially improve participation outcomes among African-Americans and underrepresented populations, in general (Konkel, 2015). Recent consortia efforts of gene identification with pooled resources and participant data have included an increasing number of ethnic populations (of African ancestry in particular), providing more opportunities to understand genetic influences on psychiatric disorders in ethnic groups. Efforts to carry these GWAS findings forward to examine how genetic factors interact with environmental factors, including those that are particularly relevant for specific populations (e.g., racial discrimination, cultural socialization), to influence psychiatric outcomes are warranted. This will be important both to aid in our understanding of etiology across all populations, and to inform prevention and/or intervention of psychiatric disorders and efforts to reduce racial disparities in health outcomes.

Informing Prevention/Intervention Efforts

Information about basic pathways of risk can be used to develop more tailored and personalized prevention intervention efforts (Dick & Hancock, 2015). For example, initial studies of prevention and intervention efforts tailored towards pathways of risk for the development of substance use problems have shown great potential in preventing and

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reducing substance use and problems. School-based prevention programming tailored to personality profiles at risk for alcohol problems (e.g., anxiety sensitivity, sensation seeking, impulsivity) has shown significant effects on reducing adolescent alcohol related behavior (Conrod *et al.*, 2013, Conrod *et al.*, 2006, O'leary-Barrett *et al.*, 2013). Among college students, a tailored prevention program surrounding low level of response to alcohol (LR), a genetically influenced biological risk factor for heavy drinking and alcohol problems (Schuckit *et al.*, 2009), yielded significant reductions in heavy drinking among those who carried the risk factor compared to a standard non-tailored prevention program (Schuckit *et al.*, 2015, Schuckit *et al.*, 2012).

Recent efforts have also begun to incorporate genetic information into prevention/intervention studies to test whether the effectiveness of intervention varies as a function of genetic predisposition (Brody *et al.*, 2013). It is well-known that not all children benefit equally from intervention, and a growing number of studies demonstrate that intervention effectiveness varies as a function of genotype (Albert *et al.*, 2015, Bakermans-Kranenburg & Van Ijzendoorn, 2011, Brody *et al.*, 2013). For example, one study found that children who were more biologically sensitive to stress (as indexed by carriers of one or two copies of A allele of a variant of *NR3C1*, a glucocorticoid receptor gene) had higher rates of externalizing behaviors in the control condition and lower rates of externalizing behaviors in the intervention condition in the Fast Track project (Albert et al., 2015). Many of these studies have focused on candidate genes (e.g., Bakermans-Kranenburg *et al.*, 2008; Beach *et al.*, 2010), and, thus are interesting more from a proof of principle standpoint at this time. However, as we have robust genome-wide polygenic scores and identified genes from large-scale gene identification consortia, developmental scientists can play an active role in mapping the behavioral phenotypes that represent earlier manifestations of genetic predispositions and how these outcomes are moderated by the environment (Carlson *et al.*, 2004, Dick *et al.*, 2008). Characterizing these pathways will inform our understanding of how genetic risk unfolds across time, and the nature of malleability of associated outcomes as a function of intervention. Information about genetic risk, and the intermediary behavioral phenotypes mapped to genetic risk, may prove useful in making decisions about which children are likely to be responsive to which interventions (Dick, 2017).

Limitations and Considerations

We have presented a number of areas of investigation that will be important to test with genes emerging from large-scale GWAS studies. However, we note that these areas of study will present their own set of challenges. We must use the knowledge we have gained from the history of gene identification to inform post-GWAS studies. It will be critical for studies addressing the complex questions delineated in this review, involving how measured genetic risk unfolds across development, in conjunction with the environment, and in different groups, to be well-powered to detect genetic effects of reasonable and justified effect sizes. Fortunately, these studies will not require the sample sizes necessary for original gene identification; however, power should be addressed nonetheless. In addition, as has become routine in genetic studies, it will be key to build in replication samples. As has happened in the field of genetics, this will necessitate researchers who have traditionally worked within their own samples to come together to build collaborations. Many psychologists have

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longitudinal samples with rich phenotypic data, and to which genotypic data collections have been added, that will be incredibly useful for the post-GWAS areas of study delineated here. Now is the time for scientists with shared interests in mapping genetic risk across development, and in conjunction with the environment, to build consortia to conduct large-scale, high impact studies that robustly inform our understanding of how genetic risk unfolds. Initiating these studies within the open science framework (OSF; https://osf.io/) is another way to reduce false positives that may otherwise result from extensive exploratory analyses.

Conclusions

As psychiatric genetics enters an era where gene identification is finally yielding robust, replicable genetic associations and polygenic risk scores (Okbay *et al.*, 2016, Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), it is important to consider next steps and delineate how that knowledge will be applied to ultimately ameliorate suffering associated with substance use and psychiatric disorders. Much of the post-GWAS discussion has focused on the potential of genetic information to understand the underlying biology and use this information for the development of more effective pharmaceutical treatments. While this is clearly an important goal, it is not the only one. By taking genetic findings into longitudinal, developmental studies, we can map the pathways by which genetic risk manifests across development, elucidating the early behavioral manifestations of risk, and how various environments and interventions moderate that risk across developmental stages. Here we have reviewed studies that suggest these are important avenues for exploration, and we provide examples of studies that have begun to address these kinds of questions. We note that these new areas of study will present their own challenges, as well. Like gene identification studies, large sample sizes will be necessary, and replication across studies will be critical. However, ultimately, this information will enable us to develop more informed, tailored prevention and intervention efforts; it is the prevention extension of personalized medicine. In our excitement over the potential of genetics to develop more effective and tailored treatment, we must not forget its potential to also inform the prevention of disorders.

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