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A Primer on the Genetics of Comorbid Eating Disorders and Substance Use Disorders

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Abstract

Eating disorders (EDs) and substance use disorders (SUDs) frequently co-occur; however, the reasons for this are unclear. We review the current literature on genetic risk for EDs and SUDs, as well as preliminary findings exploring whether these classes of disorders have overlapping genetic risk. Overall, genetic factors contribute to individual differences in liability to multiple EDs and SUDs. Although initial family studies concluded that no shared familial (which includes genetic) risk between EDs and SUDs exists, twin studies suggest a moderate proportion of shared variance is attributable to overlapping genetic factors, particularly for those EDs characterized by binge eating and/or inappropriate compensatory behaviors. No adoption or molecular genetic studies have examined shared genetic risk between these classes of disorders. Research investigating binge eating and inappropriate compensatory behaviors using emerging statistical genetic methods, as well as examining gene-environment interplay, will provide important clues into the etiology of comorbid EDs and SUDs.

Keywords

eating disorders; substance use disorders; comorbidity; genetics

Introduction

Epidemiological and clinical studies have reported higher prevalences of substance use disorders (SUDs) among women with eating disorders (EDs) – including anorexia nervosa (AN), bulimia nervosa (BN) (Bulik et al., 2004; Dansky, Brewerton, & Kilpatrick, 2000; Gadalla & Piran, 2007; Holderness, Brooks-Gunn, & Warren, 1994; Hudson, Hiripi, Pope, & Kessler, 2007; Root et al., 2010; Wiederman & Pryor, 1996), and more recently, binge eating disorder (BED) (Hudson et al., 2007; Kessler et al., 2013) – than control women. For instance, in one of the largest epidemiological explorations of this association in the National Comorbidity Survey Replication (NCS-R), Hudson and colleagues (2007) found the prevalences of SUDs to be as high as 27%, 37%, and 23% in individuals with AN, BN, and BED, respectively, indicating elevated odds in the range of 2.00–4.60. In clinical samples, 26% of women seeking treatment for alcohol abuse met diagnostic criteria for a

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probable ED (Peveler & Fairburn, 1990) and as many as 41% of women with illicit drug abuse have reported a lifetime ED, especially BN or BN symptoms (Holderness et al., 1994).

Disentangling the etiology ED and SUD comorbidity is critical for two significant reasons. First, individuals with comorbid EDs and SUDs are susceptible to increased morbidity and mortality. For example, alcohol abuse increases the risk for mortality over two-fold in AN (Franko et al., 2013), and women with comorbid BN and alcohol use disorder are more likely to have drug dependence, major depression, suicidality, and engage in unsafe sex compared with women with only BN or alcohol dependence (Duncan et al., 2006). Second, treatment of EDs that occur in the presence of comorbid SUDs brings unique challenges given the increased likelihood of the presence of additional psychopathology and that improvement in one disorder may cause increased symptoms in the other disorder. A better understanding of the shared etiological mechanisms between these disorders is central to the development of treatment protocols and pharmacotherapies that are more efficacious.

Although the phenotypic association between EDs and SUDs has been well-established and comprehensive reviews suggest that environmental (Center on Addiction and Substance Abuse, 2003) and neurobiological (Kaye et al., 2013) factors influence the etiology of the comorbidity, whether genetic factors play a role in this overlap has been overlooked in recent years despite emerging evidence of a genetic association. Thus, we provide the reader with a concise primer on the genetics of comorbid EDs and SUDs. Here, we review: (1) existing literature on genetic vulnerability in EDs and SUDs (e.g., family, twin, and molecular genetic studies); (2) whether studies should be focusing on the symptom or diagnostic level; and (3) the literature for and against classifying EDs as an addiction. Finally, we provide avenues for future genetics research in ED-SUD comorbidity.

Genetic Vulnerability in Eating and Substance Use Disorders

Excellent reviews on the genetics of EDs (e.g., (Trace, Baker, Penas-Lledo, & Bulik, 2013; Yilmaz, Hardaway, & Bulik, 2015)) and SUDs (e.g., (Agrawal et al., 2012; Kendler et al., 2012; J. C. Wang, Kapoor, & Goate, 2012)) are available elsewhere. Thus, we do not provide an in-depth review here, but rather focus our attention on those genetic factors most likely to play a role in ED-SUD comorbidity. Family, adoption, twin, linkage, and genetic association studies on AN, BN, BED, alcohol use disorder, nicotine dependence, and illicit drug use disorders most relevant to this review were identified through select PubMed searches, as well as a review of references cited in these articles. Studies published through June 1, 2015 were considered. Of note, although genetic studies on SUDs, and to a lesser extent EDs, independently have included men, there is limited information on shared genetic risk between EDs and SUDs in this population. Therefore, we focus our review on women. A glossary of genetics-related terms used throughout this review are bolded in the text and is provided in the Table.

In brief, it has been well-documented in family studies that, assessed independently, EDs and SUDs run in families. For EDs, there is substantial evidence for the familial aggregation of AN, BN, and BED (Hudson et al., 2006; Lilenfeld et al., 1998; Lilenfeld, Ringham,

Kalarchian, & Marcus, 2008; Strober, Freeman, Lampert, Diamond, & Kaye, 2000); likewise, alcohol, nicotine, and illicit drug use disorders are commonly found to cluster in families (Bierut et al., 1998). From twin studies, heritability estimates for EDs range from 28% to 74% for AN, 28% to 83% for BN, and 39% to 45% for BED, with the remaining variance attributable to unique environmental factors (Trace, Baker, et al., 2013). On the other hand, overwhelming evidence from family, twin, and adoption studies indicate that about 50% of the variation in SUDs is attributable to additive genetic factors. Evidence also suggests that the magnitude of genetic influence varies by substance (e.g., as high as 79% for cocaine dependence (Kendler, Karkowski, Neale, & Prescott, 2000)) and developmental period (e.g., as low as 0% in adolescents (Kendler, Schmitt, Aggen, & Prescott, 2008)). Given the significant comorbidity between EDs and SUDs, and the strong familial risk involved in each, it has been hypothesized that the disorders share a familial vulnerability, albeit genetic or environmental (Holderness et al., 1994; Wolfe & Maisto, 2000).

Family Studies of Eating and Substance Use Disorder Comorbidity

Given the higher than expected prevalences of EDs among SUDs and SUDs among EDs, as well as the contribution of genetic risk for these disorders independently, studies have examined their familial co-aggregation. Unfortunately, findings have been mixed. Initial reports observed an increased likelihood of a SUD in first-degree relatives of probands with BN (Holderness et al., 1994). However, when proband SUD was controlled for, findings indicated that the prevalence of SUDs among relatives were accounted for by proband SUD (Kaye et al., 1996; Lilenfeld et al., 1997, 1998; Schuckit et al., 1996). In other words, prevalences of SUDs were not higher among relatives of probands with BN without a comorbid SUD.

In contrast, a study with non-treatment seeking women with BED not recruited by obesity status found that BED and SUDs may share a common familial transmission such that female relatives of probands with BED were significantly more likely to have a SUD, regardless of proband SUD comorbidity status. (Lilenfeld et al., 2008). However, another study reported no familial co-aggregation of BED with alcoholism or drug use disorder among obese treatment seeking individuals (Lee et al., 1999). Still other research (Yanovski, Nelson, Dubbert, & Spitzer, 1993) has reported an increased prevalence of substance abuse among first-degree relatives of obese individuals with BED but not within themselves. To date, limited reports have explored the prevalence of EDs in relatives of those with a SUD or the impact of family history of ED on SUD vulnerability. However, in general, initial family study findings suggested that, with the possible exception of BED which has been less frequently studied, AN, BN, SUDs, and their symptoms may follow independent transmission (Nurnberger et al., 2004; Schuckit et al., 1996; von Ranson, McGue, & Iacono, 2003).

Two critical limitations of these family studies should be considered – principally, their reliance on diagnostic entities or the grouping of several substance classes together. While it is possible that diagnostic EDs and SUDs do not co-aggregate with a pattern consistent with shared genetic etiologies, the study of subthreshold disordered eating behaviors in family members of those with a SUD or the extent of problematic substance use in those with EDs

might support the role of shared genetic vulnerabilities. In addition, there may be disorder specific associations that cannot be detected when multiple disorders are examined jointly and twin studies underscore this. A further complicating factor is that family studies are not able to tease apart genetic and shared environmental factors from each another as twin studies can. One final note worth mentioning is that the lack of significant familial risk from these initial family studies does *not* omit the possibility that genetic factors still contribute to ED-SUD comorbidity since these family studies are often underpowered to detect significant effects given the low prevalence of EDs. Thus, using alternative study designs to understand genetic risk for the comorbidity between EDs and SUDs is warranted.

Twin Studies of Eating and Substance Use Disorder Comorbidity

To date, four twin studies have explored the genetic overlap between aspects of EDs and SUDs, and, in contrast to family studies, support the role of overlapping genetic influences. The first report examined the degree of genetic overlap across lifetime histories of six psychiatric disorders including BN and alcoholism (problem drinking or alcohol dependence) (Kendler et al., 1995). Although findings revealed that a majority of the genetic liability to alcoholism was independent from the other five disorders (including BN), there was evidence of a small amount of genetic overlap with BN (6%). Expanding on this first investigation, Baker and colleagues (2010) explored the genetic correlation (r_g) between a BN symptom count and several SUDs including: alcohol use disorder, regular smoking (defined as ever engaging in an average of at least seven episodes of smoking per month), and illicit drug use disorder. The strongest r_g was observed between BN and an alcohol use disorder, estimated at 0.53 (95% confidence interval (CI): 0.30, 0.80), whereas the r_g between BN and any illicit drug use disorder was estimated at 0.37 (95% CI: 0.15, 0.58) and regular smoking estimated at 0.35 (95% CI: 0.20, 0.51). Finally, significant genetic correlations have also been observed between broad definitions of BN diagnosis and an illicit drug use disorder ($r_g = 0.39$; 95% CI: 0.05, 0.79) (Baker, Mazzeo, & Kendler, 2007) and alcohol use disorder ($r_g = 0.23$; 95% CI: 0.01, 0.44) (Trace, Thornton, et al., 2013). Although the correlation between broadly defined BN and an alcohol use disorder was lower than in previous reports, it was well within the confidence limits of prior correlation estimates.

In addition to BN diagnosis, shared genetic factors also appear to influence the comorbidity between binge eating, inappropriate compensatory behaviors, and alcohol misuse. Specifically, an r_g of 0.31 (95% CI: 0.09, 0.53) and 0.61 (95% CI: 0.34, 1.00) was estimated between problematic alcohol use and binge eating and between problematic alcohol use and inappropriate compensatory behaviors, respectively (Slane, Burt, & Klump, 2012). An independent study also observed significant genetic overlap between alcohol dependence and inappropriate compensatory behaviors ($r_g = 0.32$; 95% CI: 0.19, 0.45), as well as between alcohol dependence and binge eating ($r_g = 0.29$; 95% CI: 0.11, 0.47) (Munn-Chernoff et al., 2013). Finally, a study examining the genetic and environmental overlap between an alcohol use disorder and a combined assessment of binge eating and inappropriate compensatory behaviors in a sample of European American and African American young adult women reported a similar r_g (0.33; 95% CI: 0.18, 0.49) to prior

studies, with no difference between the two racial/ethnic groups (Munn-Chernoff, Grant, Agrawal, et al., 2015).

Taken together, in contrast to family studies that note limited co-aggregation, twin studies implicate shared genetic influences in the relationship between aspects of EDs and SUDs. While this discrepancy can be attributed to the use of diagnoses versus symptoms, it also resounds that intriguing possibility raised earlier that genetic co-aggregation may be salient to some relationships only (e.g., BED and alcohol misuse), whereas for other correlations (e.g., with AN), the contributors may be entirely distinct.

Molecular Genetic Studies of Eating and Substance Use Disorder Comorbidity

No study to date has examined the role of genetic variants in comorbid EDs and SUDs. Perhaps this is because of the relative rarity of ED diagnoses and the contradicting need for extraordinarily large samples. However, independent linkage and candidate gene association studies of each disorder have identified genomic regions and genetic variants of interest. In brief, chromosomes 1 and 14 have been implicated in both EDs and SUDs (Bulik et al., 2003; Devlin et al., 2002; Grice et al., 2002; J. C. Wang et al., 2012), but the precision and reproducibility of these signals are dubious. Candidate gene studies, which use *a priori* information about biological processes, have focused on the dopamine and serotonin systems. Dopamine is involved in reward, food intake, motivation, motor activity, and emotion, whereas serotonin is important for appetite regulation, aggression, sleep, personality, and mood. In line with this, independent candidate gene studies from both the ED and SUD literature suggest that genetic variants from the dopamine (e.g., Taq1A [rs1800497] in the *DRD2/ANKKI* gene, Val58Met [rs4680] in the *COMT* gene) and serotonin (e.g., 5-HTTLPR in the transporter gene *5-HTT*, rs6311 in the receptor gene *HTR2A*) systems (Baker & Munn-Chernoff, 2014) may play a role in ED-SUD comorbidity.

Although these studies provide a first glance on variants that may contribute to this comorbidity, linkage and candidate gene approaches are now considered an outdated methodology in the genetics field because of their limitations (Trace, Baker, et al., 2013). For example, candidate gene studies are generally underpowered, produce false positive associations (Sullivan, 2007), and findings have not been reproduced in genome-wide association studies (GWAS) (Siontis et al., 2010), which do not require *a priori* knowledge about the function of a gene and instead use a hypothesis-free approach. Highlighting these limitations, the dopamine system has been the focus of alcohol research for decades, and numerous candidate gene studies have documented associations between variants in dopamine-related genes and alcohol dependence (e.g., Munafò, Matheson, & Flint, 2007; Smith, Watson, Gates, Ball, & Foxcroft, 2008). However, existing GWAS on alcohol dependence have not replicated candidate gene findings (Olfson & Bierut, 2012) suggesting that these may not be true findings. Similarly, candidate gene findings in EDs have not been consistently replicated (Yilmaz et al., 2015) and have not emerged as significant in GWAS. Taken together, the problems noted above with linkage and candidate gene studies, coupled with a lack of reproducibility in GWAS, show that narrowing in on a particular neurotransmitter system or biological pathway may prohibit the identification of significant

genetic variants for which there may not yet be a known biological function to EDs, SUDs, and their comorbidity.

The rapidly evolving field of statistical genetics has opened new avenues of research outside of the traditional linkage and candidate gene study methodologies that allow for a comprehensive evaluation of millions of genetic variants simultaneously that influence risk for disorders. This approach more closely aligns with our models for understanding psychiatric disorders and SUDs – that these disorders are polygenic in nature. Currently, the focus has been on using GWAS, and extensions thereof, which have been successful in identifying significant single nucleotide polymorphisms (SNPs) that influence risk for psychiatric disorders, such as schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics, 2014). For example, cross-disorder association studies that combine GWAS datasets for two or more traits in aggregate to identify significant ($p < 5 \times 10^{-8}$) SNPs of shared effect have identified SNPs that influence the comorbidity between psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013). Although no study has conducted cross-disorder association analyses of EDs and SUDs, results from their independent GWAS deserve mention.

Five GWAS of EDs have been conducted. These studies have not found GWAS significant results for AN (Boraska et al., 2014; Nakabayashi et al., 2009; K. Wang et al., 2011), BN symptoms (Wade et al., 2013), or general ED symptoms (Boraska et al., 2012; Wade et al., 2013). However, one AN GWAS study did observe that 76% of replication results were in the same direction as the discovery results, suggesting that true findings exist (Boraska et al., 2014). GWAS of SUDs are more common than those of EDs; however, there is no evidence for SNPs that may be common to SUDs and EDs emerging in top signals. For example, as mentioned, the dopamine and serotonin genes suggested as potential candidate variants for overlap have not been replicated as influencing the risk for SUDs in GWAS. The most promising GWAS signals for alcohol use disorder have been in *ADH1C* and *ADH1B* (Frank et al., 2012; Treutlein et al., 2009), genes that are primarily involved in the conversion of alcohol to acetaldehyde. These genes have not been implicated in EDs. For nicotine, variants in the *CHRNA5-CHRNA3-CHRNA4* gene cluster, in particular, rs16969968 and its proxy, rs1051730, have been unequivocally demonstrated to be associated at genome-wide levels. However, GWAS exacts a punishing correction for multiple testing ($p < 5 \times 10^{-8}$). Examination of less significant signals for both EDs and SUDs may, in fact, show some overlap in contents. Regardless, detecting significant variants will require sample sizes in the tens or hundreds of thousands and replication in independent samples.

Should We Be Focusing on Symptoms Instead of Diagnoses?

Based on early family studies and the single twin study showing little to no evidence for shared genetic liability between EDs and SUDs, it has often been concluded that EDs and SUDs are transmitted independently in families and do not share overlapping genetic risk factors. Thus, it was often frequently determined that research should focus on exploring other avenues to explain the ED-SUD comorbidity. However, as mentioned previously, the lack of strong association in family studies does not definitively exclude the possibility that the same genetic risk factors influence both EDs and SUDs. The twin studies discussed in

this review also challenge this viewpoint and indeed suggest that there are overlapping genetic factors at play in this comorbidity. Further, this evidence indicates that we should be drilling down to the symptom level and should not focus on diagnosis, especially in regard to EDs. These results corroborate epidemiological studies showing higher rates of SUDs among individuals with a lifetime history of binge eating or inappropriate compensatory behaviors compared to individuals with pure restricting AN (Dansky et al., 2000; Gadalla & Piran, 2007; Root et al., 2010).

On a related note, examining earlier stages of SUDs (or EDs), which may eventually lead to a clinical diagnosis, and their association with EDs (or SUDs), has not been frequently examined. The few phenotypic studies that have been conducted show inconsistent results. For example, studies have revealed that cigarette experimentation was associated with using weight control behaviors in early- and mid-adolescence (Tomeo, Field, Berkey, Colditz, & Frazier, 1999), dieting was associated with ever using alcohol in adolescence (Krahn et al., 1996), and individuals who reported binge eating or inappropriate compensatory behaviors had significantly elevated odds (1.37–1.91) of reporting early alcohol or nicotine experimentation (before age 15) and early regular alcohol use (before age 16), even after controlling for other substance use (Munn-Chernoff, Grant, Bucholz, et al., 2015). Still, others (Zaider, Johnson, & Cockell, 2002) reported that alcohol, cigarette, and illicit drug use in late adolescence were not associated with incident ED symptoms. Interestingly, research incorporating a genetic design reported that early alcohol experimentation (i.e., having the first drink of alcohol before age 15 years) was associated with binge eating and inappropriate compensatory behaviors via unique environmental experiences. In contrast, early regular alcohol use (i.e., having an alcoholic drink on at least six separate days or drinking at least one drink each week for eight weeks in a row before age 16 years) was associated with binge eating and inappropriate compensatory behaviors via genetic mechanisms (Munn-Chernoff, Grant, Bucholz, et al., 2015). Thus, these preliminary findings suggest that the genetic effects on ED-SUD comorbidity may not be present throughout all levels of substance use or age groups. Genetic effects may only be expressed once an individual begins to engage in heavier or more problematic use or during adulthood. This hypothesis is in line with research showing that the genetic effects on disordered eating and substance use are minimal during adolescence, yet substantial in adulthood (Kendler et al., 2008; Klump, Burt, McGue, & Iacono, 2007).

In sum, although additional studies are needed that examine the association between other ED symptoms and SUDs, emerging evidence suggests that one must go beyond the ED diagnostic level to uncover shared genetic mechanisms with alcohol, nicotine, and illicit drug use and misuse and that specific associations may only exist between particular ED symptoms and substances. Similarly, it will be important to investigate how SUD symptoms are genetically related to ED diagnoses and symptoms and how genetic effects change as individuals progress from mere “experimentation” with these behaviors to heavier and more frequent patterns of use. These findings may provide important clues regarding the relationship between EDs and SUDs that can inform prevention efforts when symptoms and other sub-phenotypes of these disorders are examined.

Considering Eating Disorders as Addictions

The increased risk of having a SUD if one has an ED and vice versa has led some to question whether EDs, particularly the symptom of binge eating, should be classified as an addiction (Vandereycken, 1990; Wilson, 2010). In contrast to initial arguments that EDs cannot be classified as an addiction because there are no overlapping genetic risk factors (Wilson, 2010), the twin studies discussed here do indeed suggest that genetic factors are involved in the comorbidity between EDs and SUDs. In addition to having shared genetic risk, classifying EDs as an addiction is based on various other arguments including: relatives of patients with an ED have high prevalences of SUDs, treatment for EDs inspired by current treatments for addictions (e.g., Overeaters Anonymous) occasionally show benefit, and those with an ED and a SUD sometimes show similarities in their symptoms and associated traits (Vandereycken, 1990). Animal studies also suggest potential similarities between binge eating and an addiction. Rats given highly palatable or processed food (e.g., high in sugar and/or fat content) exhibit addictive-like behaviors, such as consuming large quantities of food in short periods of time, seeking out the food despite an electric food shock, and reduced dopamine D2 receptor availability, which is observed in drug addictions and BN (Avena, Rada, & Hoebel, 2008; Johnson & Kenny, 2010; Kaye et al., 2013).

Moreover, some of the DSM-5 (American Psychiatric Association, 2013) criteria for a SUD are applicable to an ED diagnosis if one considers food as the addictive substance. For example, individuals with an ED, specifically those who engage in binge eating, often take the substance [food] in larger amounts or over a longer period of time than was intended; exhibit a persistent desire or unsuccessful effort to cut down or control the binge eating; spend a great deal of time obtaining the substance or experience recurrent problems caused or exacerbated by use; and continue to use the substance despite persistent problems caused by its use (Gearhardt, White, & Potenza, 2011; Meule & Gearhardt, 2014). Less clear SUD criteria include recurrent use of the substance in physically hazardous situations, tolerance, and withdrawal; however, rats show features of tolerance and withdrawal to processed foods (Johnson & Kelly, 2010) and sugar (Avena et al., 2008). Interestingly, support for the applicability of DSM SUD criteria for EDs was shown when a majority of patients with BED received a SUD diagnosis when the term substance was replaced with binge eating in a SUD diagnostic interview (Cassin & von Ranson, 2007).

Despite these parallels, there are valid counterarguments to classifying EDs as a SUD. As described previously, even though relatives of probands with an ED have higher rates of SUDs, this appears to be entirely accounted for by proband SUD. There is also disagreement as to what individuals with an ED are addicted to – are EDs a behavioral addiction or is it a particular type of food, such as highly palatable or processed foods, which is the addictive substance? Indeed, in laboratory studies, the pattern of food consumption of individuals with BN and BED is similar to controls; with the key difference being in the amount, rather than type, of food consumed (Wilson, 2010). An addiction model of EDs also does not explain the food restriction or starvation behaviors that can occur, which are often a trigger for binge eating, or the extreme body image disturbance that accompanies an ED. Finally, despite the observed genetic overlap between these two classes of disorders, twin studies also show that EDs and SUDs are not entirely caused by the same genetic factors, and genetic overlap

alone does not warrant EDs to be classified as an addiction. There are still many important differences between EDs and SUDs and much more research is needed to make a definitive conclusion on this topic.

One final, related note worth commenting briefly on is the debate surrounding food addiction, whereby specific, highly palatable foods (e.g., sugar) may have both behavioral and neurobiological addictive potential similar to that of drugs of abuse (Schulte, Avena, & Gearhardt, 2015; Ziauddeen, Farooqi, & Fletcher, 2012). Proponents for the food addiction model suggest that the same DSM-IV (American Psychiatric Association, 1994) features for SUDs can be applied to individuals who have BED or report binge eating (Gearhardt, Corbin, & Brownell, 2009). Importantly however, food addiction is not seen among all these individuals, but only a subset of individuals with BED or who binge eat (Avena, Gearhardt, Gold, Wang, & Potenza, 2012; Ziauddeen & Fletcher, 2013) – thus, food addiction may denote a distinct, yet overlapping entity from BED (Gearhardt et al., 2011).

Despite the fact that proponents of a food addiction model note that it may only be applicable to a subset of individuals with an ED, those who disagree with this model argue that, among other factors, existing evidence does not provide support for shared genetic effects between eating-related phenotypes and SUDs (Ziauddeen et al., 2012). However, the genetic studies reported in the current review indeed implicate shared risk; specifically, binge eating – an important feature of food addiction – is a key genetic factor between ED and SUD comorbidity. Still, we would urge careful consideration of applying the genetic findings outlined in this review to be a reflection of support for food addiction since these studies do not examine specific, highly palatable foods *per se*. Furthermore, in the absence of more rigorous statistical genetic approaches to understand ED-SUD comorbidity, it is difficult to draw definitive conclusions about whether the genetic research to date supports or refutes the concept of food addiction.

Avenues for Future Research

Despite the surge of evidence supporting a shared genetic liability between EDs and SUDs, much work still needs to be done across multiple genetic domains to provide a more comprehensive picture of the ED-SUD association. This research is in addition to having a continued emphasis on binge eating and inappropriate compensatory behaviors, as well as with a range of substance use involvement. Here, we provide a framework to guide the much anticipated research in this area. The Figure provides a broad overview of how genetic factors may influence the comorbidity between EDs and SUDs, ranging from direct effects of genetic variants on these disorders to gene-environment interplay and epigenetics. First and foremost, we need a better basic understanding of the genetic relation between EDs and SUDs. Once we have a basic understanding of this relation, we can begin to explore larger models that include additional shared psychopathologies, risk factors, and pathways, and how these larger factors may impact the genetic association.

First, future studies should examine substance-specific relationships with ED diagnoses and symptoms since both epidemiologic and genetic research suggest that there may indeed be differences depending on the outcome in question. This would include additional twin

studies that include other SUDs, beyond alcohol use disorder, which has received the most attention to date. It is possible that different ED symptoms could share genetic risk with nicotine dependence, cannabis abuse/dependence, or specific SUD symptoms. Additionally, given the high rates of comorbidity (Falk, Yi, & Hiller-Sturmhofel, 2006; Hasin, Stinson, Ogburn, & Grant, 2007; Stinson et al., 2005) and overlapping genetic factors (Bierut et al., 1998; Nurnberger et al., 2004) among substance classes, it will be critical to assess associations while accounting for other substances in addition to conducting studies that examine polysubstance use. Furthermore, this genetic research should include other addictive behaviors that were recently included in the “Substance Use and Addictive Behaviors” section of the DSM-5 (American Psychiatric Association, 2013). For example, gambling disorder – which is present, albeit at a fairly low prevalence, in men with EDs (Davison, Marshall-Fabien, & Gondara, 2014; Jimenez-Murcia et al., 2013) – shares genetic risk with alcohol use disorder (Slutske, Ellingson, Richmond-Rakerd, Zhu, & Martin, 2013). Including a range of substances will provide additional insights into the specificity of the genetic associations between EDs and addictions.

Second, an important step forward is to conduct cross-disorder association studies, particularly in GWAS. These analyses comprise a key component of the Psychiatric Genomics Consortium (Psychiatric GWAS Consortium Steering Committee, 2009) and have been successful in identifying SNPs that are shared across schizophrenia, bipolar disorder, and major depressive disorder (Smoller et al., 2013). These analyses could not only include specific EDs and SUDs, but also commonly co-occurring disorders (e.g., major depressive disorder; (Grant et al., 2004; Hudson et al., 2007; Kessler et al., 2013)) to determine the specificity of associations. Additionally, two post-GWAS techniques that examine shared genetic variant overlap using the GWAS results – the polygenic risk score (PRS) and LD Score regression – could be used. Employing raw genotypes and phenotypes, the PRS (International Schizophrenia Consortium et al., 2009; Smoller et al., 2013; Wray, Goddard, & Visscher, 2007) is a weighted sum of GWAS SNPs (based on effect sizes for every SNP) created for each individual to represent an individual-specific genetic risk score. Once it is developed and validated in an initial sample, this PRS can then be applied to an independent GWAS sample and used as a predictor variable in subsequent analyses. For example, an alcohol use disorder PRS could be developed from an existing GWAS study in sample 1 and then that PRS could be created in and applied to sample 2 to determine the proportion of variance in binge eating that is due to the alcohol use disorder PRS.

LD Score regression, which captures genetic variance shared between disorders (Bulik-Sullivan et al., 2015), could also prove useful. It is a complementary approach to cross-disorder association analyses that can quantify the genetic variance shared between disorders (i.e., r_g) using summary statistics from existing GWAS datasets. Thus, raw genetic and phenotypic data are not necessary, allowing for the genetic variance shared between multiple disorders to be determined with relative ease. Additionally, unlike previous approaches that require family, twin, or adoption studies to estimate the r_g , case-control samples can be used, which can be easier to ascertain than samples of related individuals. Within the context of ED-SUD comorbidity, this approach could determine whether the r_g is stronger between binge eating and alcohol use disorder than between binge eating and other SUDs. Similarly,

other disorders that are comorbid with both EDs and SUDs could be included in LD Score regression. In sum, by conducting a genome-wide scan, it is possible, if not highly likely, that SNPs outside of the traditional targets (i.e., dopamine and serotonin systems) will be identified to contribute to EDs-SUDs comorbidity. Once genetic findings have been consistently replicated, additional research could include the most significant SNPs with neuroimaging research documenting overlapping biological factors for EDs and SUDs (Kaye et al., 2013).

Third, explicating the gene-environment interplay involved in this comorbidity is essential. While twin studies show that additive genetic factors are clearly important in the etiology of EDs, SUDs, and their comorbidity, the working hypothesis is that genetic and environmental factors work in concert to influence risk, not in isolation. Genes and environment are thought to interact in two ways, through gene-environment correlation (rGE) and gene-by-environment interaction (GxE). Relevant to ED-SUD comorbidity, the risk for this comorbidity may be expressed through exposure to high-risk environments that are influenced by genetic factors. For example, individuals who have a genetic propensity for this comorbidity may be more likely to expose themselves to high-risk environments, such as peer groups that are weight focused and engage in risky behaviors, or to parental treatment – through the effects of the parental genotype on the family environment or the evocation of reactions from parents consistent with offspring genetic predisposition. Despite the relevance of rGE to the etiology of ED-SUD comorbidity, studies have yet to address these questions empirically.

To examine GxE, variables of interest are examined statistically to determine whether genetic propensity is expressed differently in various degrees of the environmental factor. A handful of studies have examined GxE interactions in the genetic diathesis of EDs (see (Trace, Baker, et al., 2013)), with more on SUDs (see (Agrawal et al., 2012; Dick & Kendler, 2012; Enoch, 2012)). For example, a GxE has been observed for alcoholism and major depression comorbidity such that major depression was predicted by a genetic diathesis for alcoholism, but only in combination with a disturbed adoptive environment (Cadoret et al., 1996). Additionally, a significant interaction has been observed between carriers of the 5-HTTLPR short allele and childhood maltreatment in BN, such that these women experience increased psychopathological traits (i.e., sensation seeking, insecure attachment, and dissocial behavior) (Steiger et al., 2007, 2008, 2009), which may in turn increase the risk for SUD comorbidity.

There is only one report (Slane, Klump, McGue, & Iacono, 2014) on the influence of GxE on their comorbidity. This study evaluated whether a dysregulated personality profile, marked by behavioral disinhibition and emotional dysregulation, influenced genetic and environmental correlations between BN and alcohol use disorder symptoms. These authors did not find that a dysregulated personality profile impacted the r_g between these phenotypes during young adulthood. Still, gene-environment interplay such as that described above could account for some of the inconsistent findings observed across previous family and twin studies of this comorbidity. Investigating such interplay would allow for the examination of third-variable moderators of the genetic propensity for this comorbidity. Additional research should incorporate known environmental risk factors for EDs and

SUDs, including abuse/trauma or parental divorce, to better understand the extent to which genetic factors are expressed under varying levels of environmental exposures.

Finally, it is unclear how other psychopathology that is often comorbid with EDs and SUDs effect this association. For example, studies have repeatedly demonstrated high rates of mood and anxiety disorders (Dani & Harris, 2005; Grant et al., 2004; Hasin et al., 2007; Hudson et al., 2007; Kessler et al., 2013) among EDs and SUDs and, like other psychiatric disorders and SUDs, are influenced by genetic factors (Shimada-Sugimoto, Otowa, & Hettema, 2015; Sullivan, Neale, & Kendler, 2000); thus, the inclusion of these disorders will be an important part of our overall understanding of shared genetic risk for ED-SUD comorbidity. Similarly, given literature stating that there may be an addictive personality underlying this comorbidity (Holderness et al., 1994), which is marked by impulsivity and novelty seeking that are common in EDs and SUDs (Dick et al., 2010; Pearson, Riley, Davis, & Smith, 2014), it will be important to investigate how personality features that are themselves influenced by genetic factors (Bouchard & Loehlin, 2001) impact the ED and SUD association. Taken together, once more information is obtained about how other psychopathology and personality traits influence genetic effects on ED-SUD comorbidity from a more basic level and in the context of environmental factors, the novel statistical techniques discussed above (e.g., PRS) can be combined with environmental risk factors to provide important clues into who may be at highest risk for the development of EDs, SUDs, and their comorbidity.

Conclusions and Implications

Accumulating evidence supports the idea that EDs and SUDs share genetic underpinnings. While epidemiologic and genetic studies have primarily focused on clinical diagnoses, the strongest evidence stems from the ED symptom level, with binge eating and inappropriate compensatory behaviors being the key features in the genetic association between EDs and SUDs. Why these specific symptoms rather than other ED symptoms is not entirely clear, although it has been suggested that features of EDs and SUDs transcend diagnostic boundaries (Cassin & von Ranson, 2007; Gearhardt et al., 2011; Meule & Gearhardt, 2014). This can be investigated within the National Institute of Mental Health's Research Domain Criteria (RDoC) framework (Insel et al., 2010). For instance, both the negative and positive valence systems may be involved in ED-SUD comorbidity. Loss of control (negative valence domain) is a core feature of binge eating and is also present among individuals who abuse substances. Studies have suggested that loss of control is influenced in part by dopamine (e.g., (Volkow, Fowler, Wang, Baler, & Telang, 2009)), which in turn is a system involved in reward (e.g., (Volkow & Baler, 2015)) (positive valence domain). Thus, continued investigation of the comorbidity between EDs and individual SUDs at the ED symptom level is required in order to further elucidate the etiology behind these disorders and may provide important clues into specific features that are common in these disorders.

Due to the significant comorbidity between EDs and SUDs and that this comorbidity is, at least in part, genetic in nature, clinicians working with patients who have an ED or SUD should be careful to consistently assess for the other disorder in their patients and via a family history assessment. Only through a more thorough understanding of the genetic

factors underlying the comorbidity between EDs and SUDs, and related symptomatology, will we be better able to develop novel and effective treatments for patients with this dual diagnosis, as well as targeted prevention efforts to decrease the likelihood of the comorbid diagnosis occurring.

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Figure.

How genetic risk may influence the comorbidity between eating disorders and substance use disorders

Table

Glossary

Term	Definition
Family study	Compares the resemblance of biologically related individuals, including parents, siblings, and offspring; cannot distinguish between additive genetic and shared environmental effects
Familial aggregation	When the presence of a given trait is more common among family members than by chance
Twin study	Compares the resemblance of monozygotic (identical) and dizygotic (fraternal) twins for a given trait
Heritability or additive genetic effects	Sum of genetic factors influencing liability to a trait for a particular population at a particular point in time
Unique or non-shared environmental effects	Environmental factors that create dissimilarity between twins for a trait; these estimates also include measurement error
Adoption study	Compares adoptee's resemblance to biological relatives and to adoptive relatives for a given trait
Familial risk	Additive genetic plus shared environmental effects
Familial co-aggregation	Two disorders are transmitted together within family members more often than by chance
Shared environmental effects	Environmental factors that increase similarity between twins for a trait
Genetic correlation (r_g)	Degree of genetic association between two traits, where 0.00 indicates no shared association and 1.00 indicates completely overlapping association
Linkage study	Using family samples, can identify regions in the genome that may contain genetic variants associated with a trait
Candidate gene association study	Using samples of families or unrelated individuals, examines whether the allele frequency of a biologically hypothesized genetic variant in cases is significantly different than in controls
Genome-wide association study (GWAS)	Association study that examines the entire genome
Polygenic	When multiple genes contribute to a given trait, as is the case for psychiatric and substance use disorders
Single nucleotide polymorphism (SNP)	A mutation in a single nucleotide that can produce changes in an amino acid sequence
Cross-disorder association study	Uses raw phenotypic information and GWAS data from two or more traits to identify the specific genetic variants influencing these traits
Epigenetics	Those factors that regulate gene expression independent of DNA sequence
Polygenic risk score (PRS)	Using raw phenotypic information and GWAS data, a weighted sum of all common risk SNPs in each individual is used to predict variance in the same (or different) trait in an independent sample
LD Score regression	Uses GWAS summary statistics to quantify the r_g between two traits with SNP information from case-control GWAS studies, rather than from twin studies
Gene-by-environment correlation (rGE)	Occurs when environmental exposure is influenced by genetic factors
Gene-by-environment interaction (GxE)	Environmental factors enhance or buffer genetic risk; also occurs when genetic factors influence response to an environment