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The interplay between externalizing disorders polygenic risk scores and contextual factors on the development of marijuana use disorders

Jill A. Rabinowitz[a,*], Rashelle J. Musci[a], Adam J. Milam[a], Kelly Benke[a], George R. Uhl[b, 1], Danielle Y. Sisto[a], Nicholas S. Ialongo[a], Brion S. Maher[a]

[a] Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, 624 N. Broadway, Baltimore, MD 21205, United States
[b] New Mexico VA Healthcare System, 1501 San Pedro Drive, SE, Albuquerque, NM, 87108 United States

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ABSTRACT

Externalizing disorders have been extensively linked to substance use problems. However, less is known about whether genetic factors underpinning externalizing disorders and environmental features interact to predict substance use disorders (i.e., marijuana abuse and dependence) among urban African Americans. We examined whether polygenic risk scores (PRS) for conduct disorder (CD) and attention-deficit hyperactivity disorder (ADHD) interacted with contextual factors (i.e., parental monitoring, community disadvantage) to influence risk for marijuana use disorders in a sample of African American youth. Participants ($N = 1,050$; 44.2% male) were initially recruited for an elementary school-based universal prevention trial in a Mid-Atlantic city and followed through age 20. Participants reported on their parental monitoring in sixth grade and whether they were diagnosed with marijuana abuse or dependence at age 20. Blood or saliva samples were genotyped using the Affymetrix 6.0 microarrays. The CD and ADHD PRS were created based on genome-wide association studies conducted by Dick et al. (2010) and Demontis et al. (2017), respectively. Community disadvantage was calculated based on census data when participants were in sixth grade. There was an interaction between the CD PRS and community disadvantage such that a higher CD PRS was associated with greater risk for a marijuana use disorder at higher levels of neighborhood disadvantage. This finding should be interpreted with caution owing to the number of significance tests performed. Implications for etiological models and future research directions are presented.

1. Introduction

Marijuana abuse and dependence have been associated with a number of negative sequelae, including psychiatric disorders (e.g., major depression), reduced educational attainment, and unemployment (Kosty et al., 2017; Pacek et al., 2012). As of 2013, marijuana use disorders have disproportionately affected African American adults, with 4.6% meeting diagnostic criteria for a marijuana use disorder compared to 2.7% and 2.8% of Caucasian and Hispanic adults, respectively (Hasin et al., 2015). Substantial changes in policy and public opinion surrounding marijuana use have prompted several states to legalize marijuana, resulting in African American young adults having greater access to this substance. This is a source of concern given that about a third of people who use marijuana will develop a marijuana use disorder (Hasin et al., 2015). Given the negative outcomes associated with marijuana use disorders, an examination of individual and

environmental factors that are associated with marijuana use disorders may serve to inform preventive and early interventions among African Americans.

Externalizing symptoms and disorders have been positively predictive of more frequent marijuana use (Chabrol and Saint-Martin, 2009; McAdams et al., 2012) and disorders (Farmer et al., 2014). Two externalizing disorders that have been predictive of marijuana use disorders are conduct disorder (CD), defined as a consistent pattern of antisocial and disruptive behaviors that often violate social norms, and attention-deficit hyperactivity disorder (ADHD), a syndrome characterized by marked inattention, impulsivity, and hyperactivity (American Psychiatric Association, 2000; Bidwell et al., 2014; Fergusson and Boden, 2008; Grant et al., 2015). Youth with higher CD symptoms tend to be higher in novelty seeking, less responsive to punishment socialization techniques, and may be more likely to affiliate with deviant peers, all of which may predispose these youth to using

* Corresponding author.
  E-mail address: Jrabino3@jhu.edu (J.A. Rabinowitz).
[1] Tel.: +1 505 265 1711x5372.

marijuana more heavily (Lahey and Waldman, 2012). Moreover, youth with higher ADHD symptoms may exhibit lower levels of executive functioning, higher levels of disinhibition, and elevated risk taking; these characteristics may similarly confer risk for more frequent marijuana use and potentially the development of marijuana abuse and dependence (Du Rietz et al., 2018; Miranda et al., 2016).

Studies examining the relationship between CD and ADHD symptoms and marijuana use disorders have typically examined CD and ADHD symptoms phenotypically. However, genetic factors associated with CD and ADHD symptoms may also play a role in the development of marijuana use disorders. CD, ADHD, and marijuana use disorders may be a part of a larger externalizing syndrome, which is supported by work indicating strong, positive correlations between these conditions (Carragher et al., 2014; Harty et al., 2015; Korhonen et al., 2010; Krueger et al., 2005; Miles et al., 2002). For example, using a twin study paradigm, Korhonen et al. (2010) found that 49% of the covariance between externalizing behaviors and drug use initiation (e.g., cannabis use) was attributed to common genetic features. Thus, it is possible that the genetic architecture of CD and ADHD symptoms is associated with risk for marijuana use disorders, although it is unclear whether this is the case based on extant research.

Molecular genetics studies represent an effort to identify genes that account for the heritability estimates generated by quantitative genetic studies. Knowledge obtained from molecular genetics work may shed light on neurobiological mechanisms underlying phenotypes. The polygenic risk score (PRS) approach represents one of the more common molecular genetics strategies to understand the genetic architecture underlying substance use and disorders (Dick et al., 2010). A PRS is created by aggregating multiple genetic variants, identified through genome-wide association (GWA) scans, to produce a genetic score reflective of a particular phenotype (Dick et al., 2010). The consideration of polygenic influences that are associated with marijuana use disorders is consistent with substantial evidence that numerous genetic variants associated with psychiatric outcomes (i.e., CD and ADHD) likely influence liability for substance use problems (Hines et al., 2014). In terms of studies that have examined the association between CD and ADHD polygenic factors and marijuana use disorders, no studies to our knowledge have examined these relations. Available work indicates that higher polygenic loading for (a) CD was associated with increased risk for alcohol dependence; and (b) ADHD was associated with higher levels of alcohol and tobacco use in samples of individuals of predominantly European ancestry (Dick et al., 2010; Du Rietz et al., 2018). However, it is unclear whether these PRS are related to other substance use problems, such as marijuana use disorders, among African American adults.

Although polygenic influences of CD and ADHD may influence risk for marijuana use disorders, not all individuals higher in these PRS will develop a disorder. Indeed, the development of substance use disorders is often dependent on both individual and contextual factors (Burdzovic Andreas and Watson, 2016; Hill et al., 2011). This is supported by a number of psychiatric and molecular genetics studies indicating that genetic loading for different disorders interacts with environmental factors to influence heterogeneity in risk for psychopathology (Bronfenbrenner, 1994; Caspi and Moffitt, 2006; Dodge, 2009). Proximal environmental factors, such as parental monitoring, may influence risk for marijuana use disorders among individuals with different genetic loading for CD and ADHD. Parents higher in monitoring may structure their children's time and encourage youth disclosure, which may attenuate youth's risk for engaging in illicit drug use, especially during middle childhood when youth often have greater unsupervised time in new settings (Dishion and McMahon, 1998). Higher levels of parental supervision have been linked to youth being offered marijuana less frequently, and less subsequent marijuana use (Lakon et al., 2015; Siegel et al., 2014). Although parental monitoring may reduce risk for marijuana use disorders, it is unclear whether this parenting behavior influences African American youth with different CD and ADHD genetic

loading. Among African American youth with higher genetic loading for CD and ADHD, parental monitoring may inhibit these youth from seeking out high-risk environments and/or affiliating with substance-using peers, which may set youth on a trajectory towards reduced risk for a marijuana use disorder in adulthood.

The consideration of distal contextual factors (i.e., community disadvantage) in conjunction with polygenic influences is also paramount when considering risk for marijuana use disorders. Indeed, higher levels of neighborhood disadvantage are positively predictive of more frequent marijuana use (Furr-Holden et al., 2014; Reboussin et al., 2015). In more impoverished communities, youth may have greater exposure to illicit drugs, may be more likely to be offered drugs, and perceive drug use as normative (Gilliard-Matthews et al., 2015; Wallace et al., 2017). Minimal informal social controls, less resident consensus regarding appropriate standards for youth behavior, and prevalent availability of substances may enable the development of a marijuana use disorder. This may be particularly true among youth higher in CD symptoms who are more likely to be offered drugs, and less likely to refuse drugs upon being offered them (Burdzovic Andreas et al., 2016; Burdzovic Andreas and Pape, 2015; Rosenberg and Anthony, 2001). Exposure to communities higher in disadvantage characterized by greater sales and rates of drug use may also facilitate heavy marijuana use among individuals higher in ADHD symptoms, given their propensity for risk taking and poorer impulse control (Wallace and Muroff, 2002). However, it is uncertain whether community disadvantage exacerbates risk for marijuana use disorders among African American youth with a higher CD and ADHD PRS. Consistent with diathesis-stress and G x E triggering models, contextual stressors, such as community disadvantage, may promote the expression of a genetic diathesis (i.e., higher genetic loading for CD and ADHD) (Shanahan and Hofer, 2005), though research is wanting.

An additional limitation of extant work is the failure to consider sex differences in the relations between environmental factors, genetic influences of externalizing disorders, and marijuana use disorders. Among urban, African American adolescents, lower levels of parental knowledge of youth's whereabouts predicted more frequent marijuana use among adolescent males, but not females (Tebes et al., 2011). In addition, differences in the base rates of marijuana abuse and dependence have been observed in predominantly European samples, with male adolescents displaying greater rates of marijuana use disorders relative to females (Young et al., 2002). Differences in the incidence rates of marijuana use disorders and the possibility that contextual effects operate differently among males compared to females underscore the importance of examining sex differences to assist in the development of interventions aimed at attenuating problematic marijuana use.

In the present study, we sought to address a number of gaps in the literature. First, we examined whether externalizing disorders PRS (i.e., CD and ADHD) were associated with marijuana abuse and dependence among young adults. Second, we examined whether proximal (i.e., parental monitoring) and distal (i.e., community disadvantage) contextual factors moderated the relation between CD and ADHD polygenic influences and marijuana use disorders. Third, we examined whether there were sex differences in the effects of contextual factors and polygenic influences on marijuana abuse and dependence. Fourth, we examined relations between PRS, contextual factors, and marijuana use disorders in a sample of African American young adults, a population that may experience a number of contextual stressors that may exacerbate risk for heavy marijuana use (Galea et al., 2005).

2. Method

2.1. Participants

The study's analytic sample was drawn from three cohorts of participants in a series of randomized controlled trials of elementary-school-based universal prevention interventions. The trials were