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Polygenic liability for schizophrenia predicts shifting-specific executive function deficits and tobacco use in a moderate drinking community sample

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ABSTRACT

Individuals with schizophrenia have higher lifetime rates of substance use disorders than the general population, and research suggests high comorbidity rates may be partially explained by shared genetic influences related to common underlying etiology. Moreover, deficits in executive functions are thought to be central to the diagnosis of schizophrenia and are likewise associated with alcohol and tobacco use. The current study examined the associations between schizophrenia polygenic risk scores and tobacco and alcohol use and the mediation of these associations by executive function sub-domains. Results from the Psychiatric Genomics Consortium's meta-analysis of genome-wide association studies of schizophrenia were used to calculate polygenic risk scores in a sample of moderate drinkers. Schizophrenia risk scores were significantly associated with shifting-specific executive function deficits and tobacco use phenotypes. However, risk scores were not significantly associated with alcohol use and executive functions were not significantly associated with either tobacco or alcohol use. These findings extend previous research by suggesting that genetic risk for schizophrenia may be associated with specific sub-domains of executive function as well as smoking. The lack of a relation with alcohol use suggests genetic factors related to schizophrenia and executive functioning may not influence drinking in a non-disordered, social-drinking sample.

1. Introduction

Schizophrenia is a severe and complex mental disorder characterized by a grouping of positive symptoms (e.g., hallucinations and delusions), negative symptoms (e.g., flat affect and anhedonia), and cognitive dysfunction (e.g., deficits in executive functions and working memory; National Institute of Mental Health, 2016). As is the case for many other psychiatric disorders, high rates of alcohol, nicotine and substance use disorders have been documented among individuals with schizophrenia. While the lifetime prevalence rate of schizophrenia is around 1%, lifetime prevalence rates of alcohol use disorder (AUD; 29%; Grant et al., 2015) and nicotine use disorder (27.9%; Chou et al., 2016) are substantially higher, and in those diagnosed with schizophrenia, these rates are even higher still (de Leon et al., 2002; Regier et al., 1990). A meta-analysis by de Leon and Diaz (2005) concluded that individuals diagnosed with schizophrenia are 5.9 times more likely to be current smokers and 3.1 times more likely to have ever smoked compared to the general population. While diagnoses of AUD are comparable among individuals with and without a diagnosis of schizophrenia, individuals diagnosed with schizophrenia are four times more likely to drink heavily (> 4 drinks/day) compared to the general population (Hartz et al., 2014). Moreover, the interrelations between the development of substance use disorders and other psychiatric disorders, including schizophrenia, are of particular importance from a public health standpoint as alcohol consumption and smoking greatly influence health and life expectancy of individuals with mental disorders (Osborn et al., 2007).

Deficits in executive functions (EF) appear to be central to the diagnosis of schizophrenia (Kahn & Keefe, 2013; Kerns et al., 2008; Lewandowski et al., 2011). Research has also shown that EF deficits may have a modest, albeit complicated, relationship with the development of AUD or regular nicotine use (Glass et al., 2009; Houston

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et al., 2014; Parada et al., 2012). Heavy alcohol consumption has been associated with impairments particularly in cognitive flexibility and response inhibition (Houston et al., 2014; Parada et al., 2012; Smith et al., 2014), though deficits in working memory and processing speeds have also been observed (Finn, 2002; Ellingson et al., 2014). While less widely studied, there is also evidence that tobacco use is related to deficits in processing speeds (Glass et al., 2009), and nicotine dependence may be characterized by poorer inhibition (Flaudias et al., 2016). Together, these findings suggest that individual differences in EF may have a causal role in the etiology of both schizophrenia and substance use disorders

Most psychiatric disorders and related phenotypes, including EF, have strong heritable components (Friedman et al., 2008; Sullivan et al., 2003; Sullivan et al., 2012; Verhulst et al., 2015; Vink et al., 2005). Convergent evidence from quantitative and molecular genetic studies has indicated that shared genetic risk may contribute to the correlations between schizophrenia, EF, and substance use disorders (Hatzimanolis et al., 2015; Kendler, 1985). Based on such evidence, it has been proposed that deficits in EF may act as psychiatric endophenotypes for schizophrenia and disordered substance use (Gottesman & Gould, 2003; Gierski et al., 2013; Snitz et al., 2006), and results from recent genome-wide association studies (GWAS) have provided some preliminary evidence in support of this hypothesis. For example, independent studies have identified single nucleotide polymorphisms (SNPs) in the human *CHRNA5* gene, which encodes the α5 nicotinic acetylcholine receptor subunit, that increase risk for both smoking and schizophrenia (Ripke et al., 2014; Tobacco and Genetics Consortium 2010). Further, recent animal-model studies have shown that mice expressing the 'risk allele' of a human α5 SNP (rs16969968) exhibit neurocognitive deficits in behavioral inhibition tasks (Koukouli et al., 2017).

These preliminary findings are encouraging, but it is important to emphasize that these studies have also revealed that most of the common variants involved in the etiology of psychiatric disorders have very small effect sizes (< 1%). Therefore, methods have been developed to test cumulative genetic risk for psychiatric disorders by aggregating the effect of a subset of variants interrogated in GWAS. Using polygenic risk scores (PRSs) to model genetic liability for specific traits, including schizophrenia, has been moderately successful in explaining variation above and beyond genome-wide significant loci. PRSs have been shown to account for up to 7% of variation in liability to schizophrenia with less than half of this explained variance being accounted for by genome-wide significant loci (Ripke et al., 2014). Recent studies have demonstrated that higher schizophrenia PRSs are significantly associated with AUD diagnoses and smoking status in treatment samples (Reginsson et al., 2018), and neurocognitive ability in both clinical and control populations (Hatzimanolis et al., 2015; Wang et al., 2018), demonstrating the utility of PRSs for examining the shared genetic etiology among these traits.

The current study aims to extend prior research by examining the association between schizophrenia PRSs and tobacco and alcohol use phenotypes as well as the mediation of these associations by EF. Given prior findings demonstrating that particular EF deficits may be shared among AUD, smoking, and schizophrenia, it was hypothesized that cumulative genetic risk for schizophrenia may predict increased alcohol use and smoking behaviors and that this relationship may be partially mediated by deficits in EF. Notably, EF ability has been postulated to reflect separate but related cognitive processes, and as such, is generally measured using multiple distinct but correlated tasks. Because each task necessarily includes systematic variance attributable to non-EF processes associated with that specific task, prior research has established a latent variable approach coalescing individual tasks as indicators for three underlying constructs: inhibition, shifting and updating (Miyake et al., 2000; Miyake & Friedman 2012). Latent EF variables increase measurement reliability and construct validity. Further, because they reflect variance correlated across tasks they are, in principle, free from measurement error (Bollen, 1989). Latent variables also eliminate task-specific variance, thereby achieving more cohesive construct estimations (Miyake & Friedman, 2012). To date, only one prior study has evaluated the association between genetic risk for schizophrenia and EF using this latent variable approach (Benca et al., 2017), and results indicated no significant relations between schizophrenia PRSs and latent EF scores.

2. Methods

2.1. Participants

2.1.1. Discovery sample

GWAS meta-analysis summary statistics (36,989 cases with schizophrenia and 113,075 matched controls) available from the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC-SCZ) were used in the construction of schizophrenia PRSs (see Ripke et al., 2014 for information regarding study-specific sample characteristics, genotyping, quality control, and analytic methods used for the PGC-SCZ meta-analysis: https://media.nature.com/original/nature-assets/nature/journal/v511/n7510/extref/nature13595-s1.pdf). Meta-analysis cases were individuals meeting diagnostic criteria for either schizophrenia or schizoaffective disorder. Diagnoses were obtained using structured psychiatric diagnostic interviews. Assessment protocol and quality control procedures used to establish diagnoses were evaluated using a study questionnaire indexing nine key items (e.g., systematic training of interviewers, review of medical information, MDs or PhDs making final diagnostic determination). Participants were 18 years of age or older and were 57.4% male.

2.1.2. Target sample

Participants were recruited from the community via advertisements, online classifieds, and community message boards to participate in a larger study examining the acute effects of alcohol on EF. Study inclusion criteria required participants to be regular, moderate drinkers (i.e., 2–25 drinks per week on average), thus excluding naïve drinkers and very heavy drinkers (see Fleming et al., 2016 for a detailed description of all inclusion and exclusion criteria). Additionally, interested individuals completed the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) as an exclusionary measure, and individuals scoring 4 or above, indicating a moderate level of nicotine dependence, were excluded from participation. Given the length of lab sessions, this was done to ensure participants would not go into acute nicotine withdrawal (Dawkins et al., 2007; McClernon et al., 2016). Interested individuals self-reporting past 12-month treatment for psychological issues including depression, mood disorder, anxiety disorder, bipolar disorder, and ADHD were also excluded from participation.

As part of the larger study, participants completed a baseline battery of computerized EF tasks and self-report measures. Prior to their scheduled appointments, participants were instructed to abstain from alcohol, tobacco, and other drugs for 24 hours. At the beginning of each laboratory session, a breath sample was taken with a breathalyzer (Intoximeters, Inc., St. Louis, MO) to verify zero breath alcohol concentration, and participants were asked to complete and sign an affidavit indicating the time and date of their last smoked cigarette or use of any other type of tobacco. The sample was further restricted to individuals of European ancestry as determined by genotype given that PRSs were generated using linkage disequilibrium data taken from the European-ancestry cohort of the 1000 Genomes Project (The 1000 Genomes Project Consortium 2015). Thus, individuals for the current study (N = 429) were selected based on availability of genotype and phenotype data assessing alcohol use, tobacco use, and EF. The sample was 51% male (n = 220) and ranged in age from 21 to 34 (M = 23.1; SD = 2.6).

2.2. Measures

2.2.1. Alcohol use

Negative consequences related to drinking and symptoms of AUD were assessed using the 24-item Young Adult Alcohol Problems Screening Test (YAAPST; Hurlbut & Sher, 1992). Participants endorsed items by indicating how often they had experienced each consequence: "Never," "Yes, but not in the past year," "In the past year but not the past 3 months," "Yes, in the past 3 months: once; twice; 3 times; 4 or more times" (scored 0, 0.3, 0.5, 1, 2, 3, and 5, respectively). A "negative consequences" score was calculated as the sum of responses to all items, and a separate "AUD symptoms" score was calculated as the sum of responses to nine items which overlap with the Diagnostic and Statistical Manual of Mental Disorders AUD criteria (5th ed.; *DSM-5*; American Psychiatric Association, 2013). Participants were also asked, "What is the maximum number of drinks you have had in one sitting in your lifetime?" ("max drinks" – M = 15.5; SD = 6.3). Log transformations of all alcohol use phenotypes were performed to adjust for positive skew.

2.2.2. Tobacco use

Tobacco use was assessed using self-report items corresponding to Centers for Disease Control and Prevention general concepts (CDC, 2017). Participants indicated their smoking status and lifetime number of cigarettes smoked using 4-point scales: "No, never smoked," "Yes, have smoked, but only a few times," "Not currently, but used to smoke," "Yes, currently smoke," and "1 to 9," "10 to 99," "100 to 200," "More than 200," respectively. Additionally, participants were asked to endorse their number of cigarettes smoked per day as follows: "I never smoke," "1," "2 or 3," "4 or 5," "10 (half pack)," "20 (pack)," "30 (pack and a half)," "40 (two packs)" (scored 0, 1, 1.5, 2, 3, 4, 5, and 6). Never-smokers were excluded from cigarettes per day analyses. Given that heavy smokers (FTND $\geq$ 4) were excluded from study participation, responses were dichotomized to create the following contrasts: (i) individuals who had either never smoked or smoked only a few times compared to those who used to or currently smoke ("smoking status"); (ii) individuals who had smoked 1 to 99 cigarettes compared to those who had smoked 100 or more ("lifetime cigarettes"); and (iii) individuals who did not smoke at all or usually smoked only one cigarette per day compared to those who usually smoked two or more per day ("cigarettes per day").

2.2.3. Executive function

Participants completed a total of nine computerized EF tasks in a randomized order. Tasks were grouped into three sets of three to assess specific domains of EF described in prior literature: prepotent response inhibition, working memory updating, and mental set shifting (Friedman et al., 2008, 2011; Miyake & Friedman, 2012). Inhibition of prepotent responses was measured using the stop-signal, Stroop color-naming, and antisaccade tasks. Updating was measured using the keep track, letter memory, and spatial 2-back tasks. Shifting between mental sets was measured using the color-shape, category switch, and number-letter tasks (for detailed descriptions of each task and administration, refer to Fleming et al., 2016). Data trimming and transformations used in prior studies incorporating these tasks (e.g., Friedman et al., 2008, 2011) were applied to improve distributions toward normality and reduce the effect of influential outliers. EF variables were coded such that higher scores indicated better performance. Consistent with previous work (e.g., Benca et al., 2017; Gustavson et al., 2017; Miyake & Friedman, 2012), structural equation modeling was used to estimate a bifactor model specifying a common latent variable ("Common EF") and two nested latent variables ("Shifting-Specific" and "Updating-Specific"). The bifactor model approach was chosen to reflect advances in conceptualizations relating the unity and diversity amongst EF tasks (Miyake & Friedman, 2012), to reflect the highly heritable common factor that influences each task (Friedman et al., 2008), and to facilitate direct comparisons with other research examining associations between EF latent variables and similar substance use outcomes. This model was fit using all available phenotypic data (i.e., all individuals with EF task data [N = 768] with or without genetic data) to obtain estimates for latent factor scores, which were utilized as phenotypes in all subsequent analyses.

2.3. Target sample genotyping

Genotype data were obtained using DNA isolated from saliva by the Affymetrix Axiom Biobank Genotyping Array (Affymetrix, Inc., Santa Clara, CA), and genotype calls were made according to Affymetrix protocols. Standard genotyping quality control steps (Anderson et al., 2010) were implemented using PLINK 1.07 (Purcell et al., 2007) to evaluate sample and genotype call quality across all genotyped individuals and 628,679 genotyped variants. Degree-of-relatedness estimations were calculated to ensure that the sample contained only unrelated individuals. Self-reported gender was cross-checked using genotypic information and seven individuals with unresolved discrepant sex codes were excluded as a result. Tests for low genotype call rates (call rates < 95%), monomorphic variants, and deviations from Hardy-Weinberg equilibrium (p-value $< 1 \times 10^{-7}$) resulted in the exclusion of one individual and 212,730 single nucleotide variants. An additional 13,005 duplicate, mitochondrial, and sex chromosome markers were excluded. The 1000 Genomes Project European-ancestry cohort (The 1000 Genomes Project Consortium, 2015) was used as a reference panel for (i) allele frequency cross-reference, (ii) genome-wide imputation, and (iii) calculations of sample ancestry proportions. Imputation was conducted on a final set of 393,812 single nucleotide variants using the SHAPEIT2 and IMPUTE2 pipeline (Howie et al., 2009). Ancestry estimations were calculated from variants with a minor allele frequency $\geq$ 0.01 using principal components analysis (Price et al., 2010) as implemented in the Genomewide Complex Trait Analysis software (GCTA; Yang et al., 2011). A scree test supported the use of the first three principal components as covariates to control for possible population substructure.

2.4. Polygenic risk scores

PRSs were generated from the GWAS meta-analysis results of the PGC-SCZ (Ripke et al., 2014). SNPs with a p-value $\leq$ 0.5 and present in the European-ancestry cohort of the 1000 Genomes Project (The 1000 Genome Project Consortium, 2015; n = 4,775,565) were subjected to linkage disequilibrium-based pruning conducted in PLINK (Purcell et al., 2007). Linkage disequilibrium-based pruning was conducted by filtering SNPs using seven p-value thresholds ($p < .01$, $p < .05$, $p < .1$, $p < .2$, $p < .3$, $p < .4$, $p < .5$). Pruned SNPs were then matched to SNPs in the target sample. PLINK was used to calculate PRSs by summing the number of weighted risk alleles (0, 1, or 2) at each locus for each individual, with weights defined as the natural logarithm of the reported PGC-SCZ odds ratio for each SNP. The resulting PRSs represent an aggregate measure of genetic risk with higher scores indicating higher genetic risk for schizophrenia. This was done for each of the seven p-value thresholds resulting in seven correlated risk scores for each individual.

2.5. Data analyses

The bifactor EF model was specified using Mplus 7.3 (Muthén & Muthén, 1998-2012). To evaluate whether schizophrenia PRSs predicted EF ability and substance use, continuous EF latent variable scores (Common EF, Updating-Specific, and Shifting-Specific) and substance use variables (negative consequences, AUD symptoms, max drinks, smoking status, lifetime cigarettes, and cigarettes per day) were regressed on each of the seven sets of PRSs, along with covariates (sex, age, age-squared, and ancestry estimates), in multiple linear and

logistic regression analyses. Additionally, a general causal mediation analysis approach was used to determine whether EF ability partially or fully mediated the causal effect of polygenic risk for schizophrenia on substance use (Imai et al., 2010a; b). Thus, each of the substance use phenotypes were regressed on continuous EF latent variable scores and covariates using the aforementioned approach. As described below, results from these analyses were non-significant. Therefore, additional mediation analyses were not conducted.

3. Results

3.1. Substance use

PRSs were significantly related to multiple tobacco use phenotypes. Specifically, PRSs were significantly associated with cigarettes per day at two *p*-value thresholds ($p < .01$ and $p < .05$) indicating that individuals with higher cumulative genetic risk for schizophrenia had significantly greater odds of smoking two or more cigarettes per day on days that they smoked. The variance in cigarettes per day (≤ 1 vs. ≥ 2) explained by PRSs was 5.3% and 2.2%, respectively. Additionally, PRSs at the $p < .01$ threshold were associated with both lifetime number of cigarettes and smoking status, such that individuals with higher PRSs were significantly more likely to have smoked 100 or more cigarettes in their lifetime and be former or current smokers. PRSs explained 3.0% and 2.0% of the variance in these tobacco use phenotypes, respectively (see Table 1). Given that smoking-related GWAS have consistently reported significant associations with an intronic variant, rs16969968, in the *CHRNA5* gene (Liu et al., 2010; Tobacco and Genetics Consortium 2010; Chen et al., 2012), potential moderating and mediating influences of genotype at this locus were tested, though no significant results were observed. PRSs were not significantly associated with alcohol use phenotypes at any of the seven *p*-value thresholds.

3.2. Executive function

The bifactor model of EF provided good fit to the data, χ^2 (21) = 39.96, $p = .00075$, CFI = 0.97, TLI = 0.95, RMSEA = 0.034, 90% CI [.017–0.050], SRMR = 0.029 (see Fig. 1) demonstrating measurement validity comparable to prior research using this approach (Benca et al., 2017). However, in contrast to prior studies (e.g., Friedman et al., 2008; Friedman et al., 2011) the stop-signal task did not load significantly onto the Common EF factor. Thus, in this sample, variance in stop-signal performance was not well-described by the commonalities shared with other EF tasks. This non-significant factor loading may be due in part to differences in study procedures and sample ascertainment as described below. Descriptive statistics for all EF tasks can be found in Table 1 of Fleming et al. (2016).

Cumulative genetic risk for schizophrenia was significantly associated with Shifting-Specific latent variable scores such that individuals with higher PRSs at two *p*-value thresholds ($p < .01$ and $p < .05$) displayed poorer ability to flexibly adapt ongoing behaviors distinct from task variance captured by the Common EF factor (Miyake & Friedman, 2012). PRSs explained 1.4% and 0.9% of the variance in shifting-specific ability in the current sample. PRSs were not significantly associated with either Common EF or Updating-Specific latent variable scores (see Table 2 for complete EF results). EF latent variable scores were not significantly associated with substance use phenotypes. Therefore, causal mediation analyses assessing EF mediation of the association between PRSs and substance use phenotypes could not be conducted. However, an examination of individual EF task scores (see Supplementary Table S1) revealed that performance in the stop-signal task was significantly associated with both negative consequences, $b = -0.90$, $SE = 0.35$, $p = .010$, and max drinks, $b = -0.65$, $SE = 0.32$, $p = .043$, indicating that better performance on the stop-signal task, i.e., faster reaction times inhibiting a pre-potent response, predicted both fewer negative consequences ($R^2 = 0.023$) and fewer max drinks ($R^2 = 0.013$).

4. Discussion

To examine the potential mediational role of EF as an endophenotype linking genetic risk for schizophrenia and substance use, the current study utilized the PGC-SCZ discovery data set (Ripke et al., 2014) to generate schizophrenia PRSs at seven significance thresholds in an independent European-ancestry community sample. Each set of PRSs was used to predict alcohol use, tobacco use, and EF outcome variables. Additionally, EF latent variable scores were used to predict alcohol and tobacco use phenotypes with the intention of testing EF mediation of the relation between schizophrenia PRSs and substance use. Study results showed that PRSs were significantly associated with shifting-specific EF deficits and tobacco use phenotypes but not with alcohol use. Further, EF performance was not significantly associated with either tobacco or alcohol use. The implications of these findings and their context within the published literature are discussed, in turn, below.

As described, the present study found that cumulative genetic risk for schizophrenia was associated with EF deficits specific to the set-shifting domain. Notably, the present study employed a latent variable model of EF that included a common factor (Friedman et al., 2008). The Shifting-Specific factor associated with schizophrenia PRSs represents shared variance in the shifting tasks after removing variance attributable to the common factor. Thus, this Shifting-Specific factor has been interpreted as representing cognitive flexibility with a focus on the ability to transition between task requirements and flexibly adapt ongoing behavior (Miyake & Friedman, 2012). Prior research has identified a pattern of pervasive EF deficits, including shifting deficits, in those diagnosed with schizophrenia and associations between these deficits and specific symptoms of the disorder. For example, schizophrenia symptoms characterized by thought and affect disorganization have been shown to be related to shifting-specific task performance

Table 1
Main effect of schizophrenia polygenic risk scores at each significance threshold on tobacco use.

Smoking status					Lifetime cigarettes				Cigarettes per day			
P	*b*	*SE*	*p*	Δ R^2	*b*	*SE*	*p*	Δ R^2	*b*	*SE*	*p*	Δ R^2
0.01	1.93	0.85	0.024*	0.020	2.19	0.91	0.016*	0.030	2.80	0.91	0.002**	0.053
0.05	2.38	1.52	0.117	0.009	2.28	1.58	0.149	0.011	3.10	1.54	0.044*	0.022
0.1	3.13	1.98	0.114	0.010	1.83	2.05	0.371	0.004	3.48	1.99	0.080	0.017
0.2	4.55	2.48	0.067	0.013	2.29	2.58	0.374	0.004	4.61	2.51	0.067	0.018
0.3	4.15	2.68	0.122	0.009	2.11	2.87	0.461	0.003	5.32	2.79	0.057	0.020
0.4	3.95	2.86	0.167	0.007	3.06	3.08	0.320	0.005	4.94	2.99	0.099	0.015
0.5	3.83	2.88	0.183	0.007	3.46	3.11	0.266	0.006	5.53	3.03	0.068	0.018

P = *p*-value threshold. Δ R^2 = Δ Nagelkerke's pseudo-R^2; variance explained above and beyond covariates.
* $p < .05$
** $p < .01$

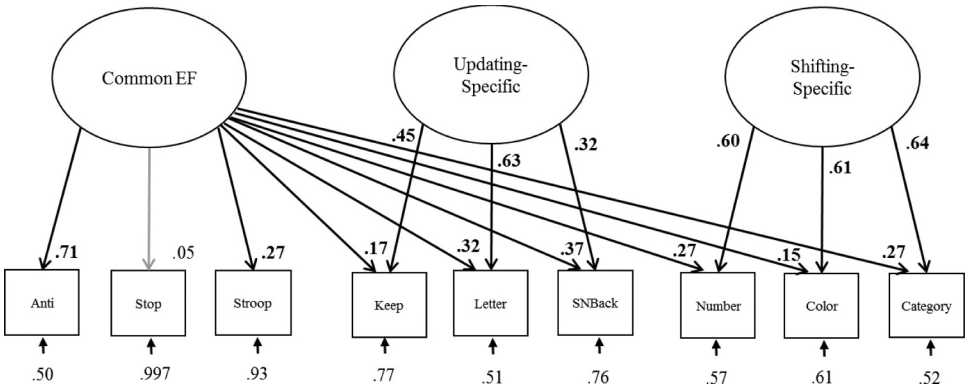

Fig. 1. Bifactor measurement model of executive function (EF): Common EF latent factor accounting for commonalities across all nine manifest EF tasks with nested Updating-Specific and Shifting-Specific latent factors each measured by three manifest EF tasks. All standardized paths are significant at the $p < .01$ level other than the loading of the stop-signal task onto the Common EF latent factor which was non-significant ($p = .340$).

Table 2
Main effect of schizophrenia polygenic risk scores at each significance threshold on executive function.

Common EF					Shifting-Specific				Updating-Specific			
P	*b*	*SE*	*p*	Δ R^2	*b*	*SE*	*p*	Δ R^2	*b*	*SE*	*p*	Δ R^2
0.01	–3.77	2.09	0.071	0.005	–6.11	2.31	0.009**	0.014	2.66	2.19	0.226	0.001
0.05	–3.98	3.69	0.282	0.000	–9.19	4.06	0.024*	0.009	3.16	3.79	0.406	0.000
0.1	–5.85	4.82	0.225	0.001	–9.94	5.16	0.055	0.006	0.81	4.96	0.870	0.000
0.2	–7.14	6.03	0.237	0.001	–1.42	7.07	0.841	0.000	1.49	6.21	0.810	0.000
0.3	–8.57	6.71	0.203	0.001	–0.65	7.87	0.934	0.000	1.80	6.91	0.794	0.000
0.4	–4.41	7.17	0.539	0.000	1.21	8.40	0.886	0.000	0.61	7.37	0.934	0.000
0.5	–4.71	7.23	0.515	0.000	1.02	8.47	0.904	0.000	3.16	7.43	0.671	0.000

P = *p*-value threshold. Δ R^2 = variance explained above and beyond covariates.
* $p < .05$
** $p < .01$

deficits (Leeson et al., 2009; Pantelis et al., 2004). Moreover, working memory is thought to contribute to set-shifting ability generally and working memory deficits may precede the onset of disorganized or other clinical symptoms in those diagnosed with schizophrenia (Kahn & Keefe 2013; Pantelis et al., 2004; Pantelis et al., 2009).

Given substantial genetic contributions to EF ability (Friedman et al., 2008) and higher prevalence of EF deficits found in unaffected first-degree relatives of individuals diagnosed with schizophrenia, it has been hypothesized that these impairments may function as schizophrenia endophenotypes (Snitz et al., 2006). As a result, PRSs created from schizophrenia GWAS results have been utilized in molecular genetics investigations to further understand the relations between the disorder and hypothesized EF endophenotypes. To date, these studies have suggested that there is substantial genetic overlap between cognitive ability and schizophrenia (Lencz et al., 2014). More specifically, other studies have shown that polygenic risk for schizophrenia may be related to diminished working memory accuracy and set-shifting ability (Hatzimanolis et al., 2015; Wang et al., 2018) as well as gene expression in the dorsolateral prefrontal cortex (Fromer et al., 2016), an area of the brain thought to be important for EF generally and for working memory and cognitive flexibility more specifically. However, as mentioned previously, the current study represents only the second genetic investigation of the link between polygenic risk for schizophrenia and EF using latent variable modeling (Benca et al., 2017), and the first to find a significant relation using this approach.

The results of the current study also substantiate prior research suggesting that genetic risk for schizophrenia may explain some of the variance in elevated smoking rates found in individuals diagnosed with schizophrenia. In two recent studies, schizophrenia PRSs were significantly associated with smoking status and cigarettes per day in a mixed community-treatment population (Reginsson et al., 2018) and tobacco use disorders in three large-scale datasets enriched for individuals with substance use disorders (Hartz et al., 2017). In both of these studies, schizophrenia PRSs were also significantly associated with all other substance use disorders tested suggesting a more indiscriminate effect on substance use development. Additionally, other research has focused specifically on the genetic overlap between disordered cannabis use and schizophrenia (Power et al., 2014; Sherva et al., 2016; Verweij et al., 2017). In comparison to these studies, which suggest that shared polygenic liability between schizophrenia and substance use disorders may be characterized by a general risk for engaging in disordered substance use more broadly, the current results indicate that in lower-risk samples (i.e., those not meeting criteria for a substance use disorder) genetic liability for schizophrenia may be more strongly related to smoking behaviors than to heavy drinking.

In addition to deficits in EF, elevated rates of substance use are clinically relevant for individuals diagnosed with schizophrenia. A dual diagnosis of schizophrenia and a substance use disorder often corresponds to an increase in overall disability and poorer outcomes, in terms of both physical and mental health (Mueser et al., 1998; Schmidt et al., 2011) in addition to negative social and economic ramifications (Dixon, 1999). While the relation between schizophrenia and heavy cannabis use has been especially prominent in literatures examining both phenotypes, comorbid heavy tobacco use is also particularly hazardous for individuals with schizophrenia, significantly influencing health and life expectancy. In fact, research suggests that for those diagnosed with schizophrenia, smokers have a two-fold increase in mortality (Kelly et al., 2011), and tobacco-related conditions account for approximately half of all deaths (Ringen et al., 2014).

Contrary to expectations, there were no significant associations between latent EF variable scores and substance use phenotypes in the present study. This is in contrast to prior literature implicating deficits in EF, measured using working memory, response inhibition, and decision-making tasks, as being positively associated with substance use disorder development and maintenance (Glass et al., 2009; Houston et al., 2014; Parada et al., 2012). The nature of the connection between EF ability and substance use or substance dependence appears to be a complicated one, in that prior research suggests that deficits in EF may be more relevant for understanding heavy, disordered substance use in adulthood than for limited substance use or substance use onset (Glass

et al., 2009; Gustavson et al., 2017). Thus, the current sample of moderate drinkers might not have been optimal for observing associations between EF and substance use.

Nevertheless, post hoc analyses indicated that performance on the stop-signal task was negatively associated with number of negative consequences and largest number of maximum drinks consumed in 24 hours. These results supplement an extant literature defining a positive association between poorer performance on tasks of executive behavioral inhibition and disordered alcohol use and related problems (Nigg et al., 2006; Goudriaan et al., 2006; Hu et al., 2016). However, several other studies have found no significant relation between stop-signal reaction time and binge drinking (Bø et al., 2016, 2017; Goudriaan et al., 2011; Henges & Marczinski, 2012; Sanchez-Roige et al., 2014), and less information is available regarding the connection between response inhibition and phenotypes such as maximum number of drinks. Thus, the current study adds to this literature by suggesting that binge episodes resulting in higher maximum drinks may be associated with having a reduced capacity to inhibit conditioned responses. However, as mentioned previously (see Section 3.2), stop-signal was the single EF task that did not load onto the Common EF factor, indicating that variation in stop-signal performance was not captured by the latent variable model approach. Notably, the present study relied on a shorter version of the stop-signal task relative to earlier studies (2 test blocks of 80 trials in the present study vs. 4 test blocks of 96 trials in Friedman et al., 2008). This reduced length could have led to less reliable stop-signal reaction time estimates, which may have negatively impacted the correlations with other test measures given that the relations between EF measures tend to be low (Friedman & Miyake, 2017; Khng & Lee, 2014). Additionally, this could have had a similar effect when estimating the relations between individual EF task indices and substance use phenotypes. Thus, it remains possible that a larger sample or less restricted phenotypes would have yielded additional and/or stronger associations between task-level, and possibly latent, EF deficits and substance use phenotypes.

Findings of the current study should be considered in light of multiple limitations. First, as previously mentioned, participants were drawn from a larger study designed to test the acute effects of alcohol on EF performance, and thus were required to be regular, moderate drinkers. However, given the ethical concerns raised by administration of alcohol to individuals who might have an alcohol use disorder such individuals were excluded from study participation. Additionally, individuals self-reporting symptoms consistent with moderate to high nicotine dependence were excluded from participation. These sampling restrictions have important implications for the hypotheses investigated in the current study, in that the range of values for substance use variables (and, possibly, EF abilities) was restricted. Though it seems unlikely, these selection procedures could have also influenced the correlations between tests, and thus contributed to the non-significant loading of stop-signal performance on the Common EF factor. Similarly, the nature of the sample may have restricted the range of genetic liability for schizophrenia. Such a restricted range may not be found in samples where substance dependence or other psychiatric disorders are more prevalent. Restrictions of these variables may limit the ability to detect predicted associations and generalize these results to more at-risk samples. Second, as the sample was restricted to those of European ancestry, results may not generalize to other samples with more diverse ancestral backgrounds. Finally, the size of the target sample was relatively small which may have affected the ability to detect hypothesized effects across all *p*-value thresholds or possibly led to inflated effect sizes.

Despite these limitations, the present study is the first to examine associations between polygenic liability for schizophrenia, EF, and disordered substance use, attempting to elucidate the role of EF as a plausible endophenotype mediating the relation between genetic risk for schizophrenia and comorbid substance use disorders. While outcomes of the current study prohibited direct testing of this endophenotype mediation hypothesis, taken together, results corroborate prior research findings suggesting important associations between genetic risk for schizophrenia and deficits in particular facets of EF as well as moderate tobacco use. Future investigations might utilize samples including participants from clinical populations where relations between EF measures and substance use phenotypes may be of larger effect.

Conflict of interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.06.025.

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