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Associations between Suicidal Thoughts and Behaviors and Genetic Liability for Cognitive Performance, Depression, and Risk-Taking in a High-Risk Sample

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Keywords
Cognitive function · Depression · GWAS · Impulsivity · Polygenic risk scores · Suicide

Abstract
Background: Suicidal thoughts and behaviors (STBs) and nonsuicidal self-injury (NSSI) behaviors are moderately heritable and may reflect an underlying predisposition to depression, impulsivity, and cognitive vulnerabilities to varying degrees. ***Objectives:*** We aimed to estimate the degrees of association between genetic liability to depression, impulsivity, and cognitive performance and STBs and NSSI in a high-risk sample. ***Methods:*** We used data on 7,482 individuals of European ancestry and 3,359 individuals of African ancestry from the Collaborative Study on the Genetics of Alco-

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holism to examine the links between polygenic scores (PGSs) for depression, impulsivity/risk-taking, and cognitive performance with 3 self-reported indices of STBs (suicidal ideation, persistent suicidal ideation defined as ideation occurring on at least 7 consecutive days, and suicide attempt) and with NSSI. ***Results:*** The PGS for depression was significantly associated with all 4 primary self-harm measures, explaining 0.6–2.5% of the variance. The PGS for risk-taking behaviors was also associated with all 4 self-harm behaviors in baseline models, but was no longer associated after controlling for a lifetime measure of DSM-IV alcohol dependence and abuse symptom counts. Polygenic predisposition for cognitive performance was negatively associated with suicide attempts ($q = 3.8e{-}4$) but was not significantly associated with suicidal ideation nor NSSI. We did not find any significant associations in the African ancestry subset, likely due to smaller sample sizes. ***Conclusions:*** Our results encourage the study of STB as transdiagnostic outcomes that show genetic overlap with a range of risk factors.

Introduction

Deaths by suicide increased by 35% [1, 2] between 1999 and 2018 in the USA, becoming the 10th leading contributor to all-cause mortality. Suicidal ideation, or thinking either occasionally or persistently about taking one's own life, is reported by 9.2% of the population during their lifetime, whereas suicide attempts are reported by 2.7% [3]. While suicidal thoughts and behaviors (STBs) comprise portions of the clinical criteria for major depressive disorder (MDD), they are transdiagnostic and often endorsed by individuals with other psychiatric prodromes and syndromes [3].

STBs are heterogeneous, comprised of multiple events that may occur contingently or independently. For instance, 1 study found that 56% of individuals who report premeditation (ideation and a plan) also report making a suicide attempt [3]. The role of impulsivity and aggression in planned versus unplanned suicide attempts remains unresolved, with some studies suggesting greater impulsive aggression associated with unplanned suicides and a more lethal attempt [4], and others documenting more severe and repeated attempts linked to perseveration and planning [5, 6]. Impaired cognitive function may also contribute to the progression from ideation to attempt, regardless of suicidal planning [7], although some studies have documented distributions of higher IQ in children who have died by suicide [8]. It is plausible that susceptibility to both persistent depression and impulsivity, as well as reduced executive functioning, contributes to the transdiagnostic nature of STBs.

While distinct from STB, nonsuicidal self-injury (NSSI) behaviors such as cutting or burning oneself have also become more common, with estimated prevalence ranging from 4.7% in adults [9] to up to 45% in adolescents [10]. While some NSSI serves as a harbinger for future suicide ideation and attempt [11], NSSI is independently related to positive and negative reinforcement of intrapersonal (e.g., management of aversive mood states) and interpersonal (e.g., social signaling) motives [10]. NSSI co-occurs with a variety of psychiatric conditions, particularly borderline personality disorder [12]. Together with STB, they impose substantial personal and societal burden.

Suicidal ideation, attempts, and NSSI are moderately heritable according to twin and family studies ($h^2 \sim 17$–59%) [9, 13], and shared genetic factors contribute to the covariance between STBs and NSSI [9, 14]. Recent genome-wide association studies (GWAS) of self-harm, more broadly [15], and specifically of STB [16–19], have identified genome-wide significant loci, and subsequent polygenic risk scores of these measures have been found to predict modest variance in self-harm behaviors in independent samples. These studies estimate the genome-wide SNP heritability of self-harming behaviors to be 7–10% and also estimate high genetic correlations between self-harming behaviors and MDD ($r_g \sim 0.8$) as well as other psychiatric disorders [15–17, 19]. In addition, modest genetic correlations between self-harming behaviors and risk-taking have been noted ($r_g \sim 0.2$) [16].

In the current study, we examined the genetic contributions to suicidal ideation (sporadic and persistent), suicide attempt, and NSSI in the Collaborative Study on the Genetics of Alcoholism (COGA) – a large, multisite family sample primarily ascertained for alcohol use disorders. Specifically, we conducted the following analyses:

1. First, we examined whether polygenic scores (PGSs) derived from a self-harm GWAS in a large, independent discovery sample predict variance in COGA self-harm behaviors (i.e., are the self-harm behaviors in an independent, population-based sample generalizable to our high-risk sample?).
2. Next, we investigated the role of the 3 most frequently evaluated contributors to the etiology of self-harm by generating PGS from the largest European ancestry GWAS of depression [20], risk-taking behaviors [21], and cognitive performance [22] (and their best available proxies in GWAS of African ancestries). Given

Table 1. Descriptive statistics of STBs in the full COGA sample

Phenotype	Trans-ancestral sample: *N* reporting "yes" (%)	African ancestry sub-sample: *N* reporting "yes" (%)	European ancestry sub-sample: *N* reporting "yes" (%)
Suicidal ideation	4,317 (41.6) (mean age of onset 20.6 [10.0])	1,115 (37.0) (mean age of onset 19.1 [8.7])	3,202 (43.5) (mean age of onset 21.0 [10.3])
Persistent suicidal ideation (among those reporting any ideation)	1,192 (30.8)	249 (28.3)	943 (31.6)
Suicide plan	1,640 (42.5)	437 (27.8)	1,300 (33.0)
Suicide attempt, s	1,120 (10.8) (mean age of onset 21.4 [9.8])	329 (10.9) (mean age of onset 20.1 [8.9])	791 (10.7) (mean age of onset 21.9 [10.0])
More than 1 attempt	418 (39.0)	111 (37.2)	307 (39.7)
Required medical attention	483 (44.9)	141 (47)	342 (44.1)
Wanted to die	655 (70.0)	183 (61.4)	472 (60.8)
NSSI	697 (8.0)	149 (6.0)	548 (8.7)
MDD	2,412 (24.5)	576 (19.2)	1,836 (26.8)

MDD, major depressive disorder; COGA, Collaborative Study on the Genetics of Alcoholism; NSSI, nonsuicidal self-injury; STBs, suicidal thoughts and behaviors.

the ascertainment strategy of the COGA sample, we examined whether any associations remained after controlling for DSM-IV alcohol dependence and abuse symptoms and polygenic liability for problematic alcohol use.

3. Third, in post hoc analyses we examined whether these PGSs relate to severity of suicide attempts (e.g., attempts requiring medical treatment) and STB subtype (i.e., internalizing and externalizing STB).
4. Finally, given prior evidence of sex differences in STBs [23], we tested whether PGS associations with STB differ by sex.

Taken together, our analyses provide a comprehensive evaluation of ideation and self-harming behaviors in this large sample (N = 10,841) which is at heightened risk for alcohol and substance use disorders.

Materials and Methods

Target Sample

COGA was established to examine genetic and environmental underpinnings of alcohol use disorders and related behaviors [24–26]. It includes probands meeting criteria for DSM-IV alcohol dependence, their family members, and community comparison families. Probands with alcohol dependence were ascertained from inpatient or outpatient treatment facilities across 7 sites in the USA. Community-based control families were recruited at the same sites from a variety of sources (e.g., dental clinics). A proportion of the families in COGA are large and have a high density of alcohol use disorders, other substance use disorders, and common psychiatric conditions. There were 10,841 participants (7,482 of European- and 3,359 of African ancestries, based on genetic data) for whom both genotypes and data on self-harm phenotypes were available. The Institutional Review Boards at all sites approved this study, and all participants provided informed consent at every assessment.

Dependent Measures

STBs and NSSI were assessed as an independent module (i.e., not solely nested within the MDD module) in the Semi-Structured Assessment for the Genetics of Alcoholism [27]. Participants had the opportunity to endorse suicidal ideation within the context of a depressive episode in addition to an independent, more detailed examination of suicidal thoughts, behaviors, and their consequences. We examined 4 primary suicide or self-harm-related outcomes in COGA; for each item, a lifetime measure was used (e.g., if an individual reported suicidal ideation at any 1 of several interviews, they were coded as "yes" for suicidal ideation). Ns are provided in Table 1:

- Suicidal ideation: individuals were asked, "Have you ever thought about killing yourself?"
- Persistent suicidal ideation: those reporting any ideation were queried about whether the ideation had persisted for at least 7 consecutive days.
- Suicide attempt: all individuals, regardless of duration of ideation, were asked if they had ever tried to kill themselves. Additional questions also queried number of attempts, whether the individual had a plan to kill themselves, whether they wanted to die, and whether they subsequently required medical attention. In addition, the context of the suicide attempt (e.g., during a depressive episode, while using alcohol or drugs and during a psychotic episode) was recorded.
- NSSI: all individuals, regardless of their STBs, were asked whether they had ever tried to harm/hurt themselves on purpose, without the intention of killing themselves (e.g., cutting and burning).

Covariates

All analyses included age at last interview, biological sex, genotyping array (see below), the first 10 genetic principal components (to control for any residual population stratification), and whether an individual belonged to a case family (i.e., whether an individu-

al was ascertained on account of themselves or a family member having alcohol dependence) or comparison family (i.e., not ascertained for either the presence or the absence of alcohol dependence). We also included Structured Assessment for the Genetics of Alcoholism-derived diagnosis of MDD as a covariate in some analyses, to determine whether PGSs for depression explained variance beyond these clinical diagnoses. Finally, we also controlled for lifetime maximum DSM-IV alcohol dependence and abuse symptom counts or polygenic liability to problematic alcohol use in some analyses to account for the fact that part of the COGA sample was ascertained for alcohol use disorders.

Genotype Data

The COGA sample was genotyped using multiple arrays. Data were combined across arrays using a common set of high-quality variants, and array type was included in all analyses to account for residual differences. Details on genotyping procedures and related quality control can be found in previously published studies [28]. Briefly, analyzed variants were imputed using the 1,000 Genomes Phase 3 [29] reference panel. Imputed SNPs with INFO scores <0.30 or individual genotype probability scores <0.90 were excluded, as were SNPs that did not pass Hardy-Weinberg equilibrium ($p < 1e{-}6$) and SNPs with a minor allele frequency <0.5%. In the PRS creation step, SNPs were further limited to those that were present in the 1,000 Genomes Phase 3 reference panel that matched the ancestry of the discovery GWAS and had MAF >1% in the HapMap3 sample.

Discovery GWAS

We used multiple large-scale GWAS to score polygenic liability for self-harm, depression, risk-taking, and cognitive performance in the COGA sample. For those of European descent, the following GWAS were used to create PGS in the COGA data:

- Self-harm: a measure of self-reported deliberate self-harm from the UK Biobank (N_{cases} = 5,099, $N_{controls}$ = 112,634; summary statistics downloaded from the Neale Lab's UK Biobank GWAS on May 22, 2020: http://www.nealelab.is/uk-biobank, filename = "20,480. gwas.imputed_v3. both_sexes.tsv.bgz." Note that these files are now being hosted on AWS, not Dropbox as they were when these analyses were performed).
- Depression: a meta-analysis of the Psychiatric Genomics Consortium's GWAS of MDD with the "broad depression" phenotype in the UK Biobank from Howard et al. [20]; (N_{cases} = 170,756, $N_{controls}$ = 329,443).
- Risky Behaviors: GWAS of the first principal component of 4 risk-taking behaviors in the UK Biobank: automobile speeding, smoking, number of sexual partners, and drinks per week [21]; (N = 315,894).
- Cognitive Performance: a meta-analysis of a GWAS of general cognitive ability from the COGENT consortium and new GWAS of cognitive performance in the UK Biobank [22] (N = 257,828).
- Problematic Alcohol Use: for some analyses, we covaried for a PGS of problematic alcohol use, to account for the fact that COGA was partially ascertained for alcohol use disorders. To create this PGS, we used a meta-analysis of a GWAS of alcohol dependence from the PGC [30] (excluding the COGA sample), the problem subscale of the Alcohol Use Disorders Identification Test in the UK Biobank [31], and alcohol use disorder from the Million Veteran Program [32].

As noted above, the COGA sample includes many participants of African ancestry. Polygenic prediction is biased when the discovery GWAS and target sample are not of the same ancestries [33, 34]. However, large-scale GWAS of self-harm, depression, impulsivity, and cognitive performance are currently lacking for individuals of African ancestries. Therefore, we approximated polygenic liability to our risk domains using the best currently available data as follows:

- Anxiety: instead of depression, we used a GWAS of generalized anxiety disorder (GAD) scores [35] based on the 2-item GAD-2 scale (N = 24,448) from the Million Veteran Program's African ancestry participants. In the European sub-sample, the genetic correlation between the GAD-2 GWAS and the GWAS of major depression was high (r_g = 0.9) indicating that the GAD-2 GWAS may serve as a reasonable proxy for negative affect, at least in individuals of European ancestry.
- Risk Tolerance: a single item that queried whether someone was a risk-taker was derived from 6,101 individuals (N cases = 2,523) comprising the Pan-UK Biobank sample, which includes GWAS conducted on 6,636 individuals of African descent who were residents of the United Kingdom (https://pan.ukbb.broadinstitute.org). The genetic correlation between the GWAS of this item in the larger sample of European ancestry subjects and our primary GWAS of the first principal component of risk-taking behaviors was moderately high and significant (r_g = 0.50, SE = 0.02).
- Fluid Intelligence: we used a GWAS in the Pan-UK Biobank sample of a sum score of 13 fluid intelligence items (N = 3,280 of African descent). The genetic correlation between the GWAS of cognitive performance and the European ancestry equivalent GWAS of fluid intelligence was high (r_g = 0.99, SE = 0.006).

Statistical Analyses

While we did not preregister these hypotheses, they were formally codified in a funded grant proposal (YIG-0-064-18) to the American Foundation for Suicide Prevention (funder was not involved in any aspect of the study). PGSs were created using a Bayesian prediction method that utilizes continuous shrinkage priors (PRS-CS [36]). This method accounts for linkage disequilibrium between SNPs using an external linkage disequilibrium reference panel that is matched to ancestry. We used the PRS-CS "auto" method, which employs a fully Bayesian approach such that the global shrinkage parameter, ϕ, is automatically learned from the data.

To maximize prediction in the African ancestry subset of COGA, we used a variation of PRS-CS, called PRS-CSx (https://github.com/getian107/PRScsx). This approach uses discovery GWAS summary statistics from both European ancestry and the target ancestry samples and creates meta-analyzed combined weights based on the 2 discovery GWAS and associated regression weights. This method for enhancing prediction in diverse samples aims to capitalize on the information provided from the larger, more well-powered GWAS and the ancestrally matched GWAS. The "score" method in PLINK [37] was used to create final risk scores based on new weights in both PRS-CS and PRS-CSx methods.

First, we tested the association between the PGS for self-harm, depression, risk-taking, and cognitive performance and the 4 primary phenotypes of interest: suicidal ideation, persistent ideation, suicide attempt, and NSSI. We used logistic mixed-effect regression models, controlling for sex, age, array type, case or comparison family assignment, and 10 genetic ancestry principal components as fixed effects, and accounting for family ID as a random effect. Statistical analyses were conducted in R [38]. FDR correc-

Table 2. Associations between self-harm behaviors and PGS for depression, risky behaviors, cognitive performance, and self-harm in the European ancestry subset of COGA

Outcome	PGS	Beta	SE	FDR q value	R^2 (%)
Suicidal ideation	Self-harm	0.097	0.027	5.15E−04*	0.24
Persistent ideation	Self-harm	0.128	0.038	0.001*	0.39
Suicide attempt	Self-harm	0.178	0.041	5.29E−05*	0.68
NSSI	Self-harm	0.162	0.051	0.002*	0.50
Suicidal ideation	Depression	0.278	0.028	3.41E−22*	1.96
Persistent ideation	Depression	0.264	0.040	2.18E−10*	1.73
Suicide attempt	Depression	0.339	0.043	4.38E−14*	2.49
NSSI	Depression	0.167	0.054	0.002*	0.58
Suicidal ideation	Risky behaviors	0.124	0.027	2.00E−05*	0.40
Persistent ideation	Risky behaviors	0.128	0.039	0.002*	0.37
Suicide attempt	Risky behaviors	0.174	0.042	1.01E−04*	0.62
NSSI	Risky behaviors	0.132	0.052	0.014*	0.30
Suicidal ideation	Cognitive performance	0.027	0.027	0.360	0.02
Persistent ideation	Cognitive performance	0.026	0.039	0.545	0.01
Suicide attempt	Cognitive performance	−0.159	0.042	3.76E−04*	0.57
NSSI	Cognitive performance	0.006	0.052	0.911	0.00

Starred rows indicate significance after multiple testing corrections (FDR < 0.05). COGA, Collaborative Study on the Genetics of Alcoholism; NSSI, nonsuicidal self-injury; PGS, polygenic score.

tion was used to account for multiple testing (q values are reported). In secondary analyses, we examined whether the PGSs were associated with number of attempts (1 vs. 2 or more attempts), seriousness of attempt (whether it required medical attention), or whether an individual reported wanting to die.

We also examined the associations between the depression, risk-taking, and cognitive performance PGS and 2 continuous non-orthogonal measures that we created to approximate the degree to which STBs were internalizing-focused and externalizing-focused (extending from previous work by Acion and colleagues [39]):

- STB internalizing features (INT-S): this was a sum of positive responses to 3 yes/no questions: whether an individual experienced persistent suicidal ideation, whether an individual had a plan for suicide attempt, and/or whether they attempted suicide while feeling depressed (scale range: 0–3).
- STB externalizing features (EXT-S): this was a sum of positive responses to 4 yes/no questions: whether an individual attempted suicide while feeling good, after drinking, after using drugs, and/or while having strange thoughts or visions (range: 0–4).

Finally, we also tested whether the associations between PGS and suicidal ideation and attempt varied between males and females by modeling an interaction term between the PGS and biological sex (as well as all other 2-way interactions).

Results

Sample Characteristics

Overall, 41.6% of the sample endorsed lifetime suicidal ideation, with 11.4% of the sample endorsing ideation that persisted for 7 or more consecutive days (Table 1). Suicide attempts were reported by 10.8% of the sample, with a mean age of onset of 21.4 years. Of those reporting suicidal ideation, 46.6% met criteria for a lifetime history of MDD, and 25.6% reported a suicide attempt. Of those reporting suicide attempts, 39% reported >1 attempt, 58.8% met criteria for MDD, and 98.6% reported prior ideation. In addition, 77.8% of those reporting suicide attempts reported making a plan, 61% recalled that they wanted to die, and 44.9% reported subsequently requiring medical attention. Of the individuals who reported a suicide attempt method (n = 159), the most commonly reported method was "taking pills" (50.8%; 57.1% for females, 38.9% for males), with "stabbing or cutting wrists" being the second most endorsed technique (26.2%; 28.6% for females, 22.2% for males). For males, the third most common method of attempt was strangulation (18.5%), while for women, the third most endorsed method was "other or combination" (5.7%). NSSI was endorsed by 8.0% of the sample, 36.0% of whom also endorsed suicide attempts. Of those who reported both NSSI and suicide attempts, 26.3% reported that they did not want to die during their suicide attempt, 7.2% said they "maybe" wanted to die, and the remaining 66.5% reported wanting to die. Suicidal ideation, persistent ideation, and NSSI were more commonly reported by individuals of European ancestries than those of African ancestries (χ^2 test p

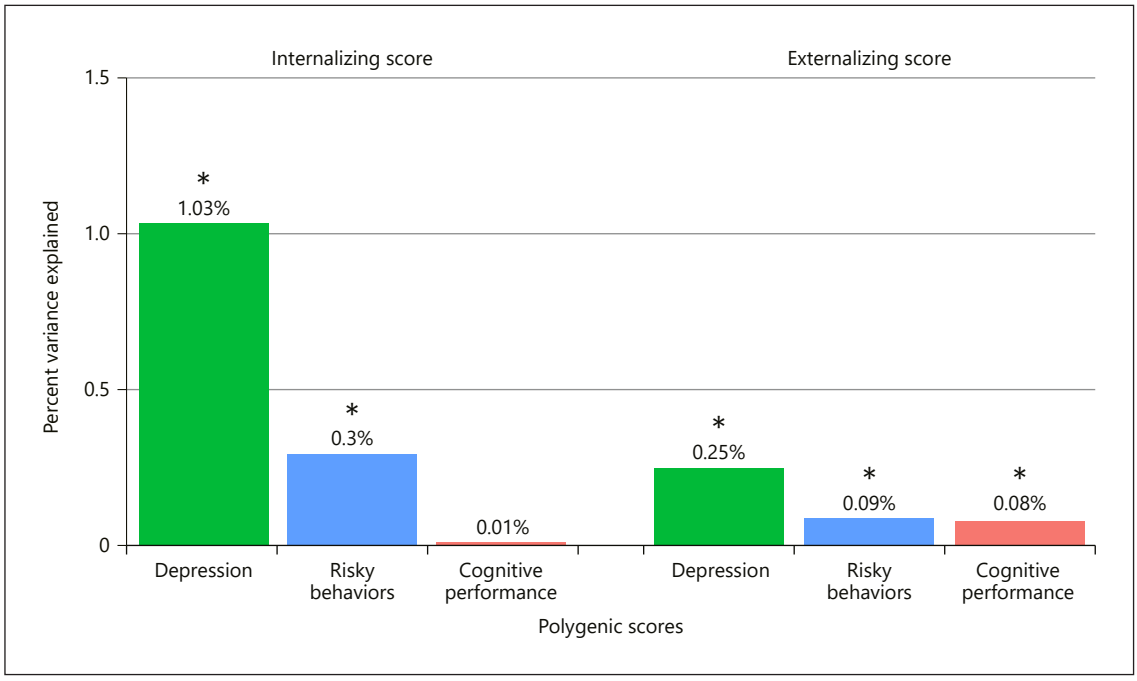

Fig. 1. Variance in the INT-S and EXT-S scores in the European ancestry subset of COGA explained by PGS. Significant associations (FDR *q* value <0.05) are starred. INT-S, STB internalizing features; EXT-S, STB externalizing features; COGA, Collaborative Study on the Genetics of Alcoholism; PGS, polygenic score.

values <3.5e−5), while the prevalence of suicide attempts was similar across ancestral groups ($p = 0.83$). All 4 self-harm behaviors (ideation, persistent ideation, attempt, and NSSI) were significantly more prevalent in females relative to males in our sample (χ^2 test p values <0.003). Mean scores of INT-S and EXT-S were 0.40 (SD = 0.83) and 0.08 (SD = 0.37), respectively (correlation = 0.50).

European Ancestry Sub-Sample

PGS intercorrelations: the depression PGS showed modest but significant correlations with the risky behavior PGS ($r = 0.13$, $p < 2.2e{-}16$) and the cognitive performance PGS ($r = -0.13$, $p < 2.2e{-}16$), but the risky behaviors and cognitive performance PGS were not significantly correlated ($r = -0.02$, $p = 0.13$). The self-harm PGS was modestly but significantly correlated with both the depression ($r = 0.21$, $p < 2.2e{-}16$) and risky behavior PGSs ($r = 0.08$, $p = 6.5e{-}11$) and showed a weaker correlation with the cognitive performance PGS ($r = -0.03$, $p = 0.01$).

PGS associations with self-harm measures: distributions of the PGS (and corresponding Kolmogorov-Smirnov tests) are shown in online suppl. Figures 1–4; for all online suppl. material, see www.karger.com/doi/10.1159/000517169. In the European ancestry subsample of COGA, the self-harm PGS was significantly associated with all 3 STBs and NSSI in the hypothesized direction (q value = 5.3e−5–0.002; Table 2) but explained a very small proportion of variance ($\Delta R^2 = 0.24$–0.68%; online suppl. Fig. 5). Of the 3 hypothesized traits of depression, impulsivity, and cognitive performance that undergird STBs and NSSI, the strongest cross-cutting effect was observed for the PGS of depression, which explained between 0.58 and 2.49% of the variance in these phenotypes. The depression PGS was also predictive of MDD diagnosis in COGA (although the percent variance explained was small: $\%\Delta R^2 = 1.39$). Even after controlling for a lifetime MDD diagnosis, the PGS for depression continued to explain 0.38–2.02% of the variance in the 3 STBs and NSSI. The risky behavior PGS was also significantly associated with all 4 STBs but explained less variance (ΔR^2 ranging from 0.30 to 0.62%). The PGS for cognitive performance was only significantly associated with suicide attempt ($\%\Delta R^2 = 0.57$and q value = 3.8e−4). When all 3 PGSs were simultaneously entered into the model as predictors for suicide attempt, all 3 PGSs remained significantly associated even after FDR correction.

Given the ascertainment strategy of the COGA sample, we tested whether associations remained after accounting for DSM-IV alcohol dependence and abuse

Table 3. Associations between self-harm behaviors and PRS-CSx (multi-ancestry) PGS for negative effect, impulsivity, and cognitive performance in the African ancestry subset of COGA

Outcome	PGS	Beta	SE	FDR *q* value	R^2 (%)
Suicidal ideation	Negative affect	0.203	0.088	0.127	0.29
Persistent ideation	Negative affect	0.104	0.154	0.750	0.11
Suicide attempt	Negative affect	0.040	0.133	0.873	0.04
NSSI	Negative affect	0.326	0.206	0.285	0.15
Suicidal ideation	Impulsivity	0.064	0.041	0.285	0.12
Persistent ideation	Impulsivity	0.057	0.072	0.739	0.11
Suicide attempt	Impulsivity	0.156	0.064	0.127	0.77
NSSI	Impulsivity	−0.151	0.095	0.285	0.81
Suicidal ideation	Cognitive performance	0.009	0.042	0.873	0.002
Persistent ideation	Cognitive performance	0.012	0.073	0.873	0.004
Suicide attempt	Cognitive performance	0.054	0.064	0.739	0.08
NSSI	Cognitive performance	−0.048	0.093	0.807	0.13

The PGS in these models combined discovery GWAS across ancestries (i.e., for negative effect, the European ancestry depression GWAS were combined with the African ancestry GAD-2 GWAS). COGA, Collaborative Study on the Genetics of Alcoholism; NSSI, nonsuicidal self-injury; PGS, polygenic score; GAD, generalized anxiety disorder.

symptom count, or a PGS for problematic alcohol use. The symptom count variable was positively associated with the depression and risky behavior PGS (p = 2e−9 and 3e−24, respectively) and negatively associated with the cognitive performance PGS (p = 0.01). After controlling for alcohol dependence and abuse symptom count, the depression PGS remained significantly associated with all 3 STBs and NSSI (online suppl. Table 1), and the cognitive performance PGS remained significantly associated with suicide attempt. The risky behavior PGS was no longer associated with any of the self-harm behaviors. When controlling for polygenic liability to problematic alcohol use, the depression PGS remained associated with all 3 STBs and NSSI, the risky behavior PGS remained associated with suicidal ideation and suicide attempt, and the cognitive performance PGS remained associated with suicide attempt (online suppl. Table 2).

Post hoc analyses: in post hoc analyses limited to the European ancestry subset, we found that all 3 PGSs (depression, risky behaviors, and cognitive performance) were significantly associated with the EXT-S (score of suicide attempts with externalizing features; q values = 6.5e−5 to 0.02), while only the depression and risky behavior PGSs were associated with the INT-S (score of persistent suicidal ideation or attempt with internalizing features; q values = 4.6e−17 to 5.9e−6; Fig. 1). We did not find any significant associations between the PGS and reporting multiple suicide attempts, wanting to die, or severity of attempt. There were no significant sex-by-PGS interactions, for either ideation or attempt.

African Ancestry Sub-Sample

PGS intercorrelations: similar to PGS correlations in the European ancestry sub-sample, the GAD PGS (representing negative affect) was significantly positively correlated with the risk tolerance PGS (representing impulsivity; r = 0.05, p = 0.002) and negatively correlated with the fluid intelligence PGS (proxy for cognitive performance; r = −0.11, p = 9.6e−11) in the African ancestry subset of COGA. The risk tolerance PGS was negatively correlated with the fluid intelligence PGS (r = −0.09, p = 4.0e−7).

PGS associations with self-harm measures: even when combining discovery GWAS of multiple ancestries using PRS-CSx, no associations survived FDR correction. The strongest association was between the impulsivity PGS and suicide attempt (%ΔR^2 = 0.77, p value = 0.01, q value = 0.13; Table 3).

Discussion

In this study, we show that polygenic liabilities for depression, risk-taking behaviors, and cognitive performance are significantly associated with STBs in a sample ascertained for alcohol use disorders, although they explain only a small portion of the variance in these out-

comes. Relative to national trends [3], self-harm behaviors (suicidal ideation, persistent ideation, suicide attempt, and NSSI) were much more common in this sample, ranging from 8% for NSSI to 42% for suicidal ideation. Prior cross-national estimates suggest that up to 56% of individuals who report premeditation subsequently attempt suicide [3] – this estimate was comparable to what we found (49.7%). Females were more likely to endorse self-harm behaviors (in line with previous findings [3]), and while suicide attempts were similar in prevalence across both ancestry groups, the European ancestry subset of COGA was more likely to endorse NSSI and suicidal ideation. The latter is surprising given a recent study showing escalations in ideation, plans, and attempts in black high school students [40]. The higher level of endorsement of self-harm behaviors by females relative to males in our sample may be partially due to the fact that, although some self-harm behaviors are more common in females than males, males are more likely to die by suicide than females [23, 41] (i.e., survivor bias).

In the European ancestry subset, the PGS for depression was the most robust predictor across all of our measures, explaining up to 2.5% of the variance in suicide attempt. This is consistent with phenotypic correlations and with other genetically informed studies. For instance, Lim et al. [42] found that a PGS for MDD was the most robust predictor of self-harm in the UK Biobank, while a recent GWAS of suicide attempt reported a genetic correlation of $r_g = 0.78$ (SE = 0.03) with MDD [19]. The PGS for risky behaviors was also significantly associated with all 4 self-harm measures, although it explained considerably less variance in all 4 phenotypes (<1%). A recent preprint has similarly found that PGSs for externalizing behaviors are associated with liability to suicidal ideation or attempt [43]. Furthermore, the depression PGS remained statistically significantly associated with all 3 STBs and NSSI after accounting for DSM-IV alcohol dependence and abuse symptom counts, suggesting that associations between the depression PGS and the self-harm behaviors were not solely due to the relationship between depression and problematic alcohol use. Interestingly, the risky behavior PGS retained significant associations with both suicidal ideation and suicide attempts after accounting for polygenic liability to problematic alcohol use, but not in the models controlling for alcohol dependence and abuse symptom counts. This suggests that the variance in these self-harm behaviors explained by polygenic predisposition to risky behaviors is largely shared with lifetime endorsement of alcohol dependence and abuse symptoms.

In contrast to depression and risk-taking, polygenic predisposition for decreased cognitive performance was only significantly associated with increased risk of suicide attempt and modestly so ($\Delta R^2 = 0.57$). The small percent variance explained by the PGS is consistent with other findings in the psychiatric genetics literature [19], and these results support the hypothesis that risk of suicide attempts may involve genetic susceptibility to deficits in executive functioning. Still, future studies should seek to replicate these findings and examine whether these deficits in cognitive function are especially relevant in individuals with certain psychiatric disorders. For example, 1 systematic qualitative review of the literature suggests that deficits in cognitive performance may be more pronounced risk factors in suicide attempts in the context of major depression rather than psychotic illness [44]. However, another study of individuals with psychiatric illnesses found better problem-solving skills in those reporting attempts relative to those with ideation alone [45]. In addition, future studies should examine whether cognitive function differs in its association with suicide attempt compared to death by suicide, given previous findings that children who die by suicide may tend to have higher IQ [8].

Suicide attempts have been frequently studied in the context of concomitant behaviors, such as acute exposure to alcohol and drugs [46]. We broadly classified STBs as "externalizing" and "internalizing," where the former was characterized by elevated mood or psychosis and the latter by perseveration, premeditation, and depressed mood. A previous COGA analysis that compared individuals with "pre-contemplated" (i.e., persistent suicidal ideation) and "impulsive" (no history of persistent ideation) suicide attempts [4] found that a history of depression was associated with pre-contemplated attempts, while alcohol-related aggression was associated with impulsive attempts. We find that while depression and risk-taking PGSs are related to both EXT-S and INT-S, cognitive performance PGSs are related to EXT-S alone. This is somewhat counter to the prior studies that suggest a more prominent role of executive functioning deficits in those with MDD-related suicide attempts than with psychosis, where paradoxical increases in working memory have been observed in those reporting attempts [44, 47]. It is worth noting that INT-S was far more a common feature of STB in COGA than EXT-S; therefore, the latter may have represented unique etiological pathways in this sample, including liability to poorer cognitive performance.

Of those reporting NSSI in our sample, 36% also endorsed suicide attempts. Reporting "wanting to die"

during a suicide attempt was retrospectively recalled with similar likelihood, regardless of lifetime comorbid NSSI (60 vs. 67% in those with NSSI). Of the 4 PGSs tested, the self-harm PGS predicted the most (albeit still very modest) variance in NSSI (0.5%). The overall weak characterization of NSSI by our PGS could be partly attributable to the lower sample size available for this trait, which was not assessed in the earliest interview schedules, but is also plausibly due to the lack of appropriate GWAS available for study. In particular, the low amount of variance in NSSI explained by the self-harm PGS may be due to the relatively small number of cases (and thus, lower statistical power) in the self-harm GWAS (*N* cases = 5,099, relative to 170,756 for depression) or qualitative differences in the NSSI and self-harm phenotypes measured in COGA and the UK Biobank. Most existing biobank-based analyses have relied on composite indices that amalgamate NSSI with suicide attempts – genetic studies of NSSI as a distinct construct are needed.

We did not find any significant associations in the African ancestry sample after correcting for multiple testing. Our null results are possibly due to the smaller sample sizes of both the African ancestry discovery GWAS and the African ancestry target sample in COGA (see online suppl. Material) which was further restricted by the prevalence of suicidal ideation. While the multi-ancestry PRS-CSx method improved upon the single-ancestry PRS approach (online suppl. Table 3), these results highlight the need for larger discovery GWAS of non-European ancestries. It is also possible that the discovery GWAS that we used for African ancestry individuals were not well suited to the analysis (e.g., there was a relative lack of proxies for cognitive performance). Likewise, despite well-documented sex differences in prevalence of STBs [23], sex was not a moderator of genetic liability in our analyses. The effect sizes associated with these interactions may be too small to be detected in a sample of this size, or the effect of PGS on STBs may be sex-invariant in this sample.

There are numerous limitations to the current analyses. First, as noted above, some analyses were likely underpowered (particularly the discovery GWAS of non-European ancestries). Second, recall bias is a concern, particularly in studies of STBs. Third, some characterizations of severity of attempt and our inability to separate passive and active ideation – both at-risk states – may have contributed to heterogeneity in analyses. Finally, it is uncertain whether findings from a large family-based and ascertained sample such as COGA would generalize to other populations. However, a strength of the current sample was its deep characterization of aspects of STBs.

In conclusion, our findings show that polygenic liability for depression and risk-taking is associated with suicidal ideation (both occasional and persistent), suicide attempts, and NSSI, while polygenic predisposition for decreased cognitive performance is only associated with increased risk of suicide attempts in the COGA sample. These results provide supporting evidence that self-harm behaviors are associated with a range of heritable risk factors that shape their transdiagnostic placement in psychiatry.

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Statement of Ethics

This research was conducted at Washington University in St. Louis under approved IRB protocol # 201906072. All participants in the COGA sample provided written informed consent.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

E.C.J., A.A., D.M.D., J.K., and V.H. contributed to the study design. E.C.J., F.A., and R.T. performed analyses. A.A. and J.K. supervised the study. E.C.J. and A.A. wrote the manuscript, J.L.M., J.E.S., Y.C., D.B.C., C.K., M.H.P., H.J.E., and D.M.D. contributed statistical and analytical input, while A.D., R.B., L.A., G.C., S.K., A.P., M.S., J.T., K.B., J.N., B.P., V.H., and J.K. provided phenotypic and clinical input. All the authors contributed to editing and rewriting of the manuscript.

References

1 Hedegaard H, Curtin SC, Warner M. Suicide rates in the United States continue to increase. NCHS Data Brief. 2018 Jun;(309):1–8.
2 Hedegaard H, Curtin SC, Warner M. Suicide mortality in the United States, 1999–2017; 2018.
3 Nock MK, Borges G, Bromet EJ, Alonso J, Angermeyer M, Beautrais A, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. Br J Psychiatry. 2008;192(2):98–105.
4 Conner KR, Hesselbrock VM, Schuckit MA, Hirsch JK, Knox KL, Meldrum S, et al. Precontemplated and impulsive suicide attempts among individuals with alcohol dependence. J Stud Alcohol. 2006;67(1):95–101.
5 Chaudhury SR, Singh T, Burke A, Stanley B, Mann JJ, Grunebaum M, et al. Clinical correlates of planned and unplanned suicide attempts. J Nerv Ment Dis. 2016;204(11):806.
6 Conner KR, Hesselbrock VM, Meldrum SC, Schuckit MA, Bucholz KK, Gamble SA, et al. Transitions to, and correlates of, suicidal ideation, plans, and unplanned and planned suicide attempts among 3,729 men and women with alcohol dependence. J Stud Alcohol Drugs. Sep. 2007;68(5):654–62.
7 Saffer BY, Klonsky ED. Do neurocognitive abilities distinguish suicide attempters from suicide ideators? A systematic review of an emerging research area. Clin Psychol Sci Pract. 2018 Mar;25(1):e12227.
8 Shaffer D. Suicide in childhood and early adolescence. J Child Psychol Psychiatry. 1974; 15(4):275–91.
9 Maciejewski DF, Creemers HE, Lynskey MT, Madden PA, Heath AC, Statham DJ, et al. Overlapping genetic and environmental influences on nonsuicidal self-injury and suicidal ideation: different outcomes, same etiology? JAMA Psychiatry. 2014;71(6):699–705.
10 Nock MK. Self-Injury. Annu Rev Clin Psychol. 2010;6(1):339–63.
11 Kiekens G, Hasking P, Boyes M, Claes L, Mortier P, Auerbach RP, et al. The associations between non-suicidal self-injury and first onset suicidal thoughts and behaviors. J Affect Disord. 2018;239:171–9.
12 Cipriano A, Cella S, Cotrufo P. Nonsuicidal self-injury: a systematic review. Front Psychol. 1946;8:1946.2017
13 Pedersen NL, Fiske A. Genetic influences on suicide and nonfatal suicidal behavior: twin study findings. Eur Psychiatry. 2010;25(5):264–7.
14 Richmond-Rakerd LS, Trull TJ, Gizer IR, McLaughlin K, Scheiderer EM, Nelson EC, et al. Common genetic contributions to high-risk trauma exposure and self-injurious thoughts and behaviors. Psychol Med. 2019; 49(3):421–30.
15 Campos AI, Verweij KJH, Statham DJ, Madden PAF, Maciejewski DF, Davis KAS, et al. Genetic aetiology of self-harm ideation and behaviour. Sci Rep. 2020;10(1):9713.
16 Strawbridge RJ, Ward J, Ferguson A, Graham N, Shaw RJ, Cullen B, et al. Identification of novel genome-wide associations for suicidality in UK Biobank, genetic correlation with psychiatric disorders and polygenic association with completed suicide. EBioMedicine. 2019;41:517–25.
17 Mullins N, Bigdeli TB, Børglum AD, Coleman JRI, Demontis D, Mehta D, et al. GWAS of suicide attempt in psychiatric disorders and association with major depression polygenic risk scores. Am J Psychiatry. 2019;176(8):651–60.
18 Docherty AR, Shabalin AA, DiBlasi E, Monson E, Mullins N, Adkins DE, et al. Genome-wide association study of suicide death and polygenic prediction of clinical antecedents. Am J Psychiatry. 2020;177(10):917–27.
19 Mullins N, Kang J, Campos AI, Coleman JRI, Edwards AC, Galway H, et al. Dissecting the shared genetic architecture of suicide attempt, psychiatric disorders and known risk factors. MedRxiv; 2020.
20 Howard DM, Adams MJ, Clarke TK, Hafferty JD, Gibson J, Shirali M, et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci. 2019;22(3):343–52.
21 Karlsson Linnér R, Biroli P, Kong E, Meddens SFW, Wedow R, Fontana MA, et al. Genome-wide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. Nat Genet. 2019;51(2):245.
22 Lee JJ, Wedow R, Okbay A, Kong E, Maghzian O, Zacher M, et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. Nat Genet. 2018;50(8):1112–21.
23 Fox KR, Millner AJ, Mukerji CE, Nock MK. Examining the role of sex in self-injurious thoughts and behaviors. Clin Psychol Rev. 2018;66:3–11.
24 Begleiter H, Reich T, Hesselbrock V, Porjesz B, Li TK, Schuckit MA, et al. The collaborative study on the genetics of alcoholism. Alcohol Health Res World. 1995;19:228.
25 Schuckit MA, Smith TL, Danko G, Kramer J, Bucholz KK, McCutcheon V, et al. A 22-year follow-up (range 16 to 23) of original subjects with baseline alcohol use disorders from the collaborative study on genetics of alcoholism. Alcohol Clin Exp Res. 2018 Sep;42(9):1704.
26 Nurnberger JIJr, Wiegand R, Bucholz K, O'Connor S, Meyer ET, Reich T, et al. A family study of alcohol dependence: coaggregation of multiple disorders in relatives of alcohol-dependentprobands. Arch. Gen. Psychiatry. 2004;61(12):1246–56.
27 Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JI, et al. A new, semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. J Stud Alcohol. 1994;55(2):149–58.
28 Lai D, Wetherill L, Bertelsen S, Carey CE, Kamarajan C, Kapoor M, et al. Genome-wide association studies of alcohol dependence, DSM-IV criterion count and individual criteria. Genes Brain Behav. 2019;18(6):e12579.
29 1000 Genomes Project Consortium; Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM. "A global reference for human genetic variation. Nature. 2015;526(7571):68–74.
30 Walters RK, Polimanti R, Johnson EC, McClintick JN, Adams MJ, Adkins AE, et al. Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. Nat Neurosci. 2018; 21(12):1656–69.

31 Sanchez-Roige S, Palmer AA, Fontanillas P, Elson SL; 23andMe Research Team, the Substance Use Disorder Working Group of the Psychiatric Genomics Consortium; Adams MJ, et al. Genome-wide association study meta-analysis of the alcohol use disorders identification test (AUDIT) in two population-based cohorts. Am J Psychiatry. 2018;176(2):107.
32 Zhou H, Sealock JM, Sanchez-Roige S, Clarke TK, Levey DF, Cheng Z, et al. Genome-wide meta-analysis of problematic alcohol use in 435,563 individuals yields insights into biology and relationships with other traits. Nat Neurosci. 2020;23(7):809.
33 Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. Nat Genet. 2019;51(4):584.
34 Martin AR, Gignoux CR, Walters RK, Wojcik GL, Neale BM, Gravel S, et al. Human demographic history impacts genetic risk prediction across diverse populations. Am J Hum Genet. 2017;100(4):635–49.
35 Levey DF, Gelernter J, Polimanti R, Zhou H, Cheng Z, Aslan M, et al. "Reproducible genetic risk loci for anxiety: results from ~200,000 participants in the million veteran program. Am J Psychiatry. 2020;177(3):223–32.
36 Ge T, Chen CY, Ni Y, Feng YA, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat Commun. 2019;10(1):1776–10.
37 Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience. 2015;4(1):7.
38 R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2017.
39 Acion L, Kramer J, Liu X, Chan G, Langbehn D, Bucholz K, et al. Reliability and validity of an internalizing symptom scale based on the adolescent and adult semi-structured assessment for the genetics of alcoholism (SSAGA). Am J Drug Alcohol Abuse. 2019;45(2):151–60.
40 Lindsey MA, Sheftall AH, Xiao Y, Joe S. Trends of suicidal behaviors among high school students in the United States: 1991–2017. Pediatrics. 2019;144(5):e20191187
41 Turecki G, Brent DA. Suicide and suicidal behaviour. Lancet. 2016;387(10024):1227–39.
42 Lim KX, Rijsdijk F, Hagenaars SP, Socrates A, Choi SW, Coleman JRI, et al. Studying individual risk factors for self-harm in the UK Biobank: a polygenic scoring and mendelian randomisation study. PLoS Med. 2020;17(6):e1003137.
43 Linnér RK, Mallard TT, Barr PB, Sanchez-Roige S, Madole JW, Driver MN, et al. Multivariate genomic analysis of 1.5 million people identifies genes related to addiction, antisocial behavior, and health. BioRxiv. 2020.
44 Bredemeier K, Miller IW. Executive function and suicidality: a systematic qualitative review. Clin Psychol Rev. 2015;40:170–83.
45 Burton CZ, Vella L, Weller JA, Twamley EW. Differential effects of executive functioning on suicide attempts. J Neuropsychiatry Clin Neurosci. 2011;23(2):173–9.
46 Bagge CL, Borges G. Acute substance use as a warning sign for suicide attempts: a case-crossover examination of the 48 hours prior to a recent suicide attempt. J Clin Psychiatry. 2017;78(6):691–6.
47 Keilp JG, Gorlyn M, Russell M, Oquendo MA, Burke AK, Harkavy-Friedman J, et al. Neuropsychological function and suicidal behavior: attention control, memory and executive dysfunction in suicide attempt. Psychol Med. 2013;43(3):539–51.