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Overlapping genetic effects between suicidal ideation and neurocognitive functioning

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Introduction

Suicide is the second leading cause of death among adolescents and young adults aged 15–29, and the third among 10- to 14-year-olds (Centers for Disease Control and Prevention, 2016). In 2017, approximately 17.2% of adolescents reported seriously considering suicide, 13.6% making a plan, and 7.4% attempting suicide (Centers for Disease Control and Prevention, 2017b). While environmental factors, such as early adversity and social environment, have been found to be strong predictors of suicide phenotypes, converging evidence points to a significant genetic risk for suicide (Mirkovic et al., 2016). Twin, family, and adoption studies reveal that suicide aggregates in families and a wealth of research points to genetic factors as partially responsible for the transmission of suicide behaviors in families (Brent et al., 1996; McGirr et al., 2010; Pedersen and Fiske, 2010; Turecki and Brent, 2016). Several studies have also indicated significant genetic influences on a heterogeneous mix of suicide-related phenotypes (e.g., ideation, attempts, plans, completion, etc.), with heritability estimates ranging from 17–55% (Dwivedi, 2012).

Yet, in the wake of an era of discovery, development, and technology in human genetics (Visscher et al., 2012), most genome-wide association studies (GWAS), which integrate

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molecular data rather than concordance across family members, have failed to identify specific markers that contribute to the liability for suicide phenotypes (see review by Mirkovic et al. (2016)). Large scale molecular genetic studies of suicide pose several challenges, for example: (1) difficulty ascertaining a large enough sample for GWAS and/or estimation of marker-based heritability due to the relatively low prevalence of suicide phenotypes; (2) inconsistent results spread across varying phenotypes of suicidal thoughts and behaviors (STB; e.g., suicidal ideation, attempt, completion, etc.), which may represent distinct psychological constructs and may themselves be driven by multiple unique genetic factors; and (3) few datasets from which to pool results, in part due to the fact that many individuals with suicidal behaviors are excluded from study participation due to safety concerns.

A large GWAS of individuals born in Denmark ($N > 50,000$) identified several single nucleotide polymorphisms (SNPs) associated with having a history of making a suicide attempt and found that SNPs explained a total of 4.6% of the variation in suicide attempts (Erlangsen et al., 2018). After accounting for mental disorders, this estimate decreased to 1.9%, providing evidence for the genetic transmission of suicide attempts that is not solely attributable to mental disorders. In fact, several studies suggest that the genetic liability towards suicidal behavior may be independent of the risk for suicide conferred through psychological disorders such as affective disorder, schizophrenia, and substance dependence (Jimenez-Trevino et al., 2011). For example, Ruderfer et al. (2018) used machine learning to generate the probability of a suicide attempt from a large health record database and compared the clinically predicted phenotype to patient reported suicide attempt. SNP-heritability estimates for suicide phenotypes were significant, with the SNP-heritability of actual suicide attempt at 3.5% ($p < 0.001$) and the machine-learning derived suicide risk variable at 4.5% ($p < 0.001$), as well as a genetic correlation between suicide attempt and suicide risk variables ($r_G = 1.07$, $p = 0.003$). Further, suicide attempt was significantly, but incompletely, genetically correlated with several psychiatric disorders, including insomnia ($r_G = 0.34$, $p < 0.001$), depressive symptoms ($r_G = 0.50$, $p < 0.001$), schizophrenia ($r_G = 0.27$, $p < 0.001$), and neuroticism ($r_G = 0.32$, $p < 0.001$). Altogether, these results point to an independent heritable component of suicide attempts and risk, as well as the incomplete shared genetic variance with several psychiatric phenotypes.

Neurocognitive deficits and risk for suicide

Mounting evidence from neurobiological research links deficits in several neurocognitive abilities to suicide phenotypes that may not be attributed to co-morbid psychopathology (Jollant et al., 2011; Richard-Devantoy et al., 2015). Some of the consistently reported neurocognitive features associated with STB include poorer declarative memory, working memory, cognitive flexibility, and more impulsivity (Glenn et al., 2017; Richard-Devantoy and Courtet, 2016), as well as higher order cognitive functions, i.e., executive function (Bredemeier and Miller, 2015). In a review including several studies of neurocognitive dysfunction, Jollant et al. (2011) found that individuals with a history of suicide attempts demonstrate increased attention to negative emotional stimuli, impaired decision-making, poorer problem-solving skills, and lower verbal fluency. Results from several studies also point to cognitive inflexibility as a significant predictor of suicidal ideation among young

adults (Miranda et al., 2012; Miranda et al., 2013). These trends also generalize to non-civilian populations. A recent study among US army soldiers showed that decreased general neurocognitive functioning (i.e., as indexed by a general factor score using the Army's Automated Neuropsychological Assessment Metrics [ANAM] computerized testing battery) was associated with suicide ideation, attempts, and death from suicide, even after controlling for mental health diagnosis, which may suggest a diathesis for STB among those with neurocognitive deficits (Naifeh et al., 2017). Deficits in memory, working memory, and attentional control have been demonstrated in samples comparing suicide attempters with healthy controls, representing specific mechanisms that may play a role in the liability to STB (Keilp et al., 2013; Keilp et al., 2001; Richard-Devantoy et al., 2015).

While the evidence linking suicidality and executive functioning is steadily increasing, a systematic qualitative review of the literature by Bredemeier and Miller (2015) identified only three studies that utilized adolescent populations. These three studies included adolescents with STB, but did not exclusively focus on individuals with a particular psychiatric disorder (i.e., major depression) and two studies focused exclusively on impulsivity, considered to be one of the markers of executive function (Dougherty et al., 2009; Horeish, 2001). The third study (Dour et al., 2011) provided support for an interaction between emotion reactivity and deficits in problem-solving skills in predicting suicide attempts, such that adolescents with high emotion reactivity and poor problem-solving skills were more likely to make a suicide attempt. Findings across all of the reviewed studies suggest that the link between executive dysfunction and STB were strongest among samples of individuals with mood disorders and mixed diagnoses, with the potential for the seriousness or lethality of suicide attempts to function as a moderator (Bredemeier and Miller, 2015). Given the mixed findings related to specific types of executive function, the researchers concluded that the link between executive function and suicide may be more general in nature; however, they also called for additional inquiries capitalizing on simpler measures of specific dimensions of executive function.

Neurocognitive abilities are commonly investigated as endophenotypes for several psychiatric diseases (Flint and Munafò, 2007) and may help to shed light on our understanding of the etiology of complex traits like suicidality (Courtet et al., 2011; Mann et al., 2009). Although neurocognitive traits are heritable and may be more proximal to the underlying biology of disease (Robinson et al., 2015), no genetic studies have examined if there is shared genetic variance that explains the observed phenotypic association between suicide risk and neurocognitive deficits among adolescents; thus, researchers have recently called for inquiries into neurobiological factors conferring suicide risk (Glenn et al., 2017).

Current Study

To date, most genetic studies have been conducted in adult samples and our understanding of how genetic liability for suicide phenotypes influences young people is vastly understudied. Given that findings from twin research suggest that the heritability of suicidal ideation may be greater in magnitude than other suicide phenotypes (e.g., death by suicide, suicide attempt), additional research examining the genetic contributions to suicide phenotypes is warranted (Pedersen and Fiske, 2010). The current study leveraged data from the

Philadelphia Neurodevelopmental Cohort (PNC), which consists of a large ($N > 9,500$) population-based sample of children and adolescents between the ages of 8–21 who received medical care within the Children's Hospital of Philadelphia (CHOP) network. Participants presented with a wide range of medical conditions and those that went on to participate in the larger study were genotyped and completed a structured interview and computerized neurocognitive battery (CNB). The main goals of the present study were to: (1) determine the extent to which genetic factors contribute to suicidal ideation (SI) in a large sample of children and adolescents by estimating the SNP-based heritability; and (2) examine the covariance between SI and neurocognition by determining the extent to which SI is genetically correlated with different domains of neurocognitive functioning linked to suicide risk (e.g., memory, executive, social cognition, and complex cognition). Based on the extant literature identifying neurocognitive dysfunctions associated with suicide behavior (e.g., review by Jollant et al., 2011), we hypothesized that (i) there would be phenotypic associations between suicidal ideation and each neurocognitive domain and (ii) genetic factors would, in part, explain these associations. Therefore, we hypothesized that the genetic variance underlying SI would overlap with one or more of the neurocognitive domains assessed in the PNC.

Materials and Methods

Sample

Data were drawn from the PNC, a collaboration between CHOP and the University of Pennsylvania, and accessed through Neurodevelopmental Genomics: Trajectories of Complex Phenotypes Study via the National Center for Biotechnology Information's (NCBI) Database for Genotypes and Phenotypes (dbGAP, Study Accession: phs000607.v3.p2). The sample consisted of 9,267 youth within CHOP who agreed to participate in genomic studies of pediatric disorders. Participants completed clinical assessments to measure several domains of psychopathology as well as neurobehavioral measures of cognitive and emotion processing. Youth with severe medical condition ratings based on interview and electronic medical records (see Robinson et al. (2015)) or who could not physically or cognitively participate in the neurocognitive tests were excluded from analyses. Youth were not recruited based on psychiatric needs, therefore this sample represents children and adolescents who are not enriched for psychiatric issues. For a thorough description of the study and sample, please see Calkins et al. (2015).

Measures

Suicidal Ideation.—Participants completed a computerized, structured interview of psychopathology symptoms based on the Kiddie-Schedule for Affective Disorders and Schizophrenia (Merikangas et al., 2009). Suicidal ideation (SI) was operationalized as having endorsed one or more of the following items: (1) "Have you ever thought a lot about death or dying?"; (2) "Have you ever thought about killing yourself?"; or (3) "Are you currently (in the past month) having thoughts about death or dying OR killing yourself?". Thus, participants with a zero for SI are youth who do not have past or current SI.

Neurocognitive function.—Participants completed the Penn Computerized Neurocognitive Battery (CNB) that assessed speed and accuracy across twelve tasks that comprise four theoretically based neurobehavioral domains: executive, episodic memory, complex cognition, and social cognition (Gur et al., 2014; Gur et al., 2012). Tasks in the *Executive* domain included abstraction and mental flexibility (ABF, assessed with the Penn Conditional Exclusion Test), vigilance and visual attention (ATT, assessed with Penn Continuous Performance Test), and working memory (WM, assessed with the Penn Letter N-Back Test). Tasks in the *Episodic Memory* domain included verbal material (VMEM, assessed with the the Penn Word Memory Test), faces (FMEM, assessed with the Penn Facial Memory Test), and shapes (SMEM, assessed with the Visual Object Learning Test). Tasks in the *Complex Cognition* domain included language-mediated complex cognition ability (LAN, assessed with the Penn Verbal Reasoning Tests), nonverbal reasoning ability (NVR, assessed with the Penn Matrix Reasoning Task), and spatial ability (SPA, assessed with the Penn Line Orientation Test). Finally, tasks in the *Social Cognition* domain include facial age differentiation (AGD, assessed with the Penn Age Identification Test), emotional intensity differentiation (EMD, assessed with the Penn Emotion Differentiation Test), and emotion identification (EMI, assessed with the Penn Emotion Identification Test).

For each task, accuracy and median response time values were standardized into z-scores using the sample mean and standard deviation for each measure. Median response time values were multiplied by -1 to represent speed so that higher scores for both speed and accuracy represented better performance. Efficiency scores were computed by summing accuracy and speed. Consistent with factor structure validated by (Moore et al., 2015), we conducted a confirmatory factor analysis (CFA) on the efficiency values for all twelve CNB items and extracted four correlated factors across each of the main domains using Mplus version 8 (Muthén and Muthén, 1998–2017). Age and sex were regressed out of each item and full information maximum likelihood estimation was employed for missing data.

The four factor model, shown in Figure 1, demonstrated adequate model fit ($\chi^2(48) = 1448.29$, $p < 0.001$, confirmatory fit index [CFI] = .926, root mean squared error of approximation [RMSEA] = 0.090 [90% confidence interval [CI]: 0.087, 0.095]) as well as loadings similar to those reported by Moore et al. (2015). Factor scores from this model were extracted and used in subsequent genetic models.

Genotyping, Quality Control, and Genetic Imputation

Genetic data from youth who had previously been genotyped across several Illumina platforms (Illumina Human610 Quad v1, Human Hap550 v1.1, Human Hap550 v3.0, Human 1M-Duo, Human OmniExpress-12 v1.0) were obtained from dbGaP (Study Accession: phs000607.v3.p2). All data management and analysis were performed using SNP & Variation Suite (SNP & Variation Suite (Version 8.4.4)), PLINK version 1.9 (Purcell et al., 2007), and R version 3.4.3. First, we conducted principle components analysis (PCA) within each study sample using the 1000 Genomes Project (1KG) Phase III (Version 5) reference panel (Auton et al., 2015) to determine genetic ancestry and perform strand alignment. A total of 4,296 individuals of European Ancestry (EA; the largest homogenous population) were identified and selected for imputation (for a detailed outline of this

protocol, see Brick et al. (2017)). Markers with genotyping rate >95% and MAF >10% were selected and prepared for imputation (i.e. strand alignment and allele frequencies compared to European Ancestry 1KG reference panel) using a perl script developed by Rayner et al. (2016). Next, each sample was genetically imputed separately using the 1KG reference panel and ShapeIT phasing with Minimac3 via the Michigan Imputation Server (<https://imputationserver.sph.umich.edu/index.html#!pages/home>). Following imputation, markers that were not bi-allelic, were not autosomal, or had poor imputation quality score ($r^2 < 0.30$) were removed. Next, markers that had a call rate < 99%, low minor allele frequency (< 1%), or failed HWE test ($p < 0.0001$) were removed and samples with < 90% missing data were removed, resulting in a total of 5,360,405 SNPs (see Supplemental Table 1). All samples were pooled together and a genetic relationship matrix (GRM) was computed using the GCTA software tool [version 1.25.3] (Yang et al., 2011) to remove genetically related individuals (>.05). A total of 3,991 unrelated individuals of EA were retained for analysis. See supplementary materials for a summary of markers removed at each step of QC.

Estimation of additive genetic variance explained by SNPs

Genome-wide association analyses (GWA) were conducted using PLINK to identify any significant loci associated with suicidal ideation. Genomic-relatedness-matrix restricted maximum likelihood (GREML) estimation, as implemented in the GCTA software tool, was used to determine the proportion of variance in suicide and neurocognitive phenotypes attributable to additive genetic variance (h^2_{SNP}) (Yang et al., 2011, 2013). Bivariate models were used to estimate the genetic correlation (r_G) between suicidal ideation and neurocognitive domains. Standardized residuals for all phenotypes were used to control for the effects of age and self-reported gender in all analyses.

Results

Prevalence and sample demographics

Youth ($N = 3,572$ with genetic data and responses for suicide phenotypes) were 49.7% male and ranged in age from 8–21 with a mean age of 13.7 years (standard deviation = 3.7 years). Nearly 17% of children and adolescents in the sample reported SI, including current (3.21%), lifetime thoughts about death or dying (13.83%), or thoughts about killing themselves (7.54%). Point-biserial phenotypic correlations between SI and neurocognitive factors were small, but significant and ranged from 0.07–0.08. For individual CNB tasks, point-biserial correlations with SI ranged from 0.0–0.08. By and large, efficiency scores on tasks were higher for individuals who endorsed SI. See Table 1 for a summary of descriptive statistics.

Exploratory GWAS

For SI, no single marker was significant at the GWA level of $p < 5 \times 10^{-8}$ and no markers passed false discovery rate (FDR; Benjamini & Hochberg, 1995) threshold of $q < 0.05$ (see Figure 2 for a Manhattan plot of results). Eleven markers reached $p < 1 \times 10^{-7}$ and a total of 621 markers reached $p < 10^{-5}$. The top hits were rs148870214 and rs146826470 on chromosome 7, unadjusted $p = 2.52 \times 10^{-7}$ (FDR corrected $p = 0.2875$). Both SNPs are located in a protein coding gene, *SEMA3A* (semaphorin 3A). Variation in *SEMA3A* has been

associated with comorbid alcohol dependence and major depression (Zhou et al., 2017) and may play a role in regulating immune mediated inflammation, with associations to asthma, celiac disease, multiple sclerosis, and cancer (Cozakov et al., 2017; Hu et al., 2016; Kessel et al., 2017; Rezaeepoor et al., 2017; Wallerius et al., 2016). Summary statistics are available at: <https://scholarblogs.emory.edu/bgalab/research/paper-supplements/>

Phenotypic variance attributable to common SNPs

The SNP-heritability estimate for SI was 11% (SE = 8%, $p = 0.086$). SNP-heritability estimates for the neurocognitive domains ranged from 14–24%, with 14% (SE = 8%, $p = 0.025$) for social cognition, 16% (SE = 8%, $p = 0.018$) for memory, 23% (SE = 8%, $p < 0.001$) for complex cognition, and 24% (SE = 8%, $p < 0.001$) for executive. Among individual CNB items, several demonstrated significant SNP-heritability estimates, including EMD, EMI, ATT, LAN, and SPA (see Table 2).

Bivariate analyses of the association between SI and the four neurocognitive factors suggested little genetic overlap. As the factor scores reflect only shared variance among the neurocognitive tasks included within each factor, we also examined the association between SI and performance on each across the 12 cognitive tasks (see Table 2). These results revealed a statistically significant genetic correlation between SI and emotion identification (EMI) ($r_G = 0.79$, SE = 0.45, $p = 0.006$), which weakly loaded (0.32) unto the Social Cognition factor. Overall, bivariate analyses suffered from large standard errors likely due to dampened power and low endorsement of SI.

Discussion

Endorsement of SI had a small SNP-heritability estimate that was positively genetically correlated with emotion identification. Phenotypic analyses revealed that individuals who endorsed SI responded faster and more accurately to the emotion identification task and the genetic correlation between SI and emotion identification was estimated to be significant and large ($r_G = 0.79$). Overall, estimates of SNP-based heritability for neurocognitive factors were consistent with previous research using the PNC. Robinson et al. (2015) examined the marker-based heritability and genetic correlations across several domains of the CNB among youth in the PNC by constructing a common factor across all items, and then extracted the top principle components with eigenvalues greater than one. Their approach yielded three components representing reasoning and executive function items, social cognition, and memory. Significant estimates were found for additive genetic contributions to a general cognitive factor (36%) and reasoning and executive function (46%). In the present study, we derived scores for four empirically and theoretically based factors consistent with Moore et al. (2015) using CFA. Items corresponding to those that loaded on the reasoning and executive function component from Robinson et al. (2015) were separated into two factors: executive and complex cognition in our study because model fit was good and we preferred to maintain separation of potentially distinct domains. In our study, both executive and complex cognition were significant and heritable (24% and 23%, respectively). Though estimates derived from the social cognition (15%) and memory (12%) components by Robinson et al. (2015) were similar to the estimates from the current paper (14% and 16%,

respectively), they were found statistically significant in our study (likely due to smaller estimates of the standard error).

One particularly noteworthy finding from our work was the genetic correlation between SI and better performance on the emotion identification task. The emotion identification task was designed to measure the ability to understand and correctly identify facial expressions of emotion. Although this finding was just on the cusp of a Bonferroni corrected threshold for post-hoc genetic correlations with the factor indicators (i.e., $p < 4.16 \times 10^{-3}$ for 12 tests for each of the individual items), it appears consistent with preliminary work linking increased sensitivity to angry facial expressions and a history of suicide attempts (Pan, Hassel, Segreti, Nau, Brent, & Phillips, 2013; Jollant et al., 2008). In one study, males with a history of suicide attempts demonstrated neural responses to facial expressions that suggested an increased sensitivity to angry faces, difficulty with attention to positive emotional stimuli, and lower activity in regions linked to control of voluntary actions in situations of conflict (Jollant et al., 2008). The authors proposed that these results reveal that individuals with a history of a suicide attempt may struggle to find positive factors in their environment, that they may be more sensitive to disapproval from others, and that they may be more likely to act in response to negative emotions. In an earlier study, Jollant et al. (2005) found that individuals with suicide attempter histories scored lower on decision making tasks than healthy comparison subjects and that among those who had attempted suicide, performance improved as affective lability increased, suggesting that the link between decision making and suicide may be related to emotion dysfunction. The differences observed in Jollant et al. (2005) could not be accounted for by history of axis I disorder; however, other research suggests that not only do individuals with a history of depression and suicide attempts show greater neural activity to angry faces than those without a history of STB, they also show reduced activity in certain regions of the brain when viewing neutral angry, neutral happy, or intensely happy faces (Pan et al., 2013). Pan and colleagues (2013) conclude that individuals with a suicide attempt history may show greater attention to negative emotional stimuli and actually have reductions in empathic responses to positive responses. In the context of the current study's findings, which examined a mix of suicidal ideation as opposed to suicide attempts, it is possible that youth with more passive forms of STB may be more attentive to both positive and negative emotional stimuli than those without STB. Future research examining the intensity and lethality of STB as a moderator of this relationship may help to elucidate the mechanism between STB and response to emotion.

The link between suicide and memory has been supported through meta-analysis (Richard-Devantour et al, 2015). Specifically, results suggest that impairments in long-term and working memory in multiple samples with histories of suicide attempts may lead to difficulties in using past experiences to solve problems and envision the future. The results from current study, however, did not support an association at the $\alpha = .05$ level between SI and working memory. Large genetic correlations were observed between SI and memory and it is possible that larger studies may yield smaller standard errors that could verify the association. Because the episodic memory factor constituted tasks for verbal memory, face memory, and spatial memory, it is possible that SI is more closely related to the mechanisms underlying other memory processes, such as autobiographic memory. Certainly, more

research is needed to identify specific genetic and neurological links between STB and episodic memory impairments.

Limitations

Results from the current study should be interpreted in light of the following limitations. First, the original study did not include questions surrounding specific suicidal behaviors or attempts, therefore the current study focused on a suicidal ideation phenotype. It is possible that ideation, behavior, attempts, and completion may represent related, but distinct constructs and therefore may be differentially heritable (Mann et al., 2009; Mann and Currier, 2010; Zai et al., 2012). For example, the combining of distinct phenotypic subgroups, such as suicide attempters and completers, may help explain why genetic studies to date have not identified common genetic variants contributing to suicide risk (Clayden et al., 2012). Research has indicated that personality traits like aggression, impulsivity, anger, introversion, and neuroticism may be mediators or intermediate phenotypes of STB and these factors may play a role in the differentiation of suicide phenotypes (Savitz et al., 2006). It is also possible that suicidal ideation itself is a heterogeneous phenotype driven by different factors, such as cognitive reactivity (Antypa et al., 2010) and stress-diathesis (Mann et al., 1999; Rizk et al., 2018), and these factors themselves may differ based on the severity and frequency of STB. With regard to neurocognition, one recent systematic review found that studies comparing individuals with a history of a suicide attempt to those with ideation were comparable in most domains, with the exception of observed differences in decision making and inhibition, though these differences were not observed between ideators and nonsuicidal individuals (Saffer and Klonsky, 2018). Unfortunately, the present study is limited to only questions regarding suicidal ideation (i.e., thoughts of death and dying, thoughts of killing self) and no information about attempts, completion, or other personality traits were available.

In addition, despite the relatively large sample size (i.e. the suggested sample sizes for GREML of quantitative traits is around $N=3,000$ to obtain SE estimates down to .1 (Visscher et al., 2014)), heritability of SI was small and utilizing a larger sample would likely result in smaller standard error estimates and possibly more highly significant univariate and bivariate findings. Although SI endorsement was low, it was representative of the rate of SI among adolescents, which is estimated to be 17% in the United States (Centers for Disease Control and Prevention, 2017a; Evans et al., 2018). However, we restricted all analyses to a homogenous set of individuals with European Ancestry. Given the disproportionate rates of SI across racial/ethnic groups (Curtin et al., 2016), research examining the SNP-heritability of SI among other populations is essential to understanding the genetic architecture of SI.

Further, research suggests that it is possible that heritability for SI may be attributable to psychopathology and other comorbid conditions, such as mood and anxiety disorders; however recent studies have suggested that there is a heritable component of suicidality above and beyond what is conferred through psychopathology (Erlangsen et al., 2018). Our study did not examine whether SI was independent from psychiatric diagnoses, therefore the shared heritability may reflect comorbid psychopathology.

Another limitation is the number of tests when assessing the genetic correlations between indicators of cognitive performance with SI. Given that we conducted several tests (i.e., 4 factors and the 12 individual items that comprise the factors), with an error rate of 5%, it is possible that our significant finding is a false positive (i.e., we would expect at least one of the tests to be a false positive). Thus, these findings should be considered hypothesis generating and additional studies are needed to confirm these results.

Finally, while a significant genetic correlation points to shared genetic factors across two traits, direct causal mechanisms cannot be deduced in this study. A genetic correlation suggests that the same genes implicated in SI also contribute to emotion identification; however, we are unable to determine whether this effect is due to biological pleiotropy (e.g., the same genes influence both traits) or an indirect effect pathway (e.g., genes influence SI risk indirectly through neurocognitive functioning, or vice versa).

Future Directions.

Several genetic studies indicate that heritability estimates can vary across age and development (Bergen et al., 2007). While our study is the first known molecular genetic study of adolescent SI, it remains unknown how the heritability estimate changes across the lifespan or is consistent across different ancestral populations of adults. As suicidal thoughts and behaviors often begin in adolescence (Nock et al., 2008), research that can begin to disentangle critical periods of time when genetic factors exert the greatest influence on liability for SI are needed. It is possible that genetic modulation may influence environmental selection and sensitivity (e.g., whereby individuals seek environments that are protective or predisposing to suicide risk), and that this relationship may change across the course of development, further complicating the connection between genes, the environment, and age (Kendler, 2010). Likewise, differences across ancestral populations may reflect subtle variability in the interplay of genetic and environmental risk in different ethnic groups. Altogether, these two caveats underscore the need for additional work across ages and within ancestral groups.

Future research should also focus on fine-tuning suicide-related phenotypes for genetic, neurocognitive, and biological research. Large scale genetic studies are needed to identify and refine suicide phenotypes themselves (i.e., ideation vs. behavior vs. completion) as well as identification of intermediate phenotypes and/or genetic correlations between suicide-related behaviors and personality traits, such as aggression, impulsivity, or hopelessness. That is, it is possible that intermediate phenotypes that are more easily assessed or more predictive of suicide risk may be more (or equally) informative in finding genes associated with suicide phenotypes. Further, given that several studies have shown an association between general neurocognitive functioning and suicide, more research is needed to identify the genetic basis of specific neurocognitive mechanisms implicated in suicide risk. Considering that much of the literature to date groups SI as a binary variable, i.e., comparing individuals with a history of lifetime SI to those without SI, additional research disentangling the genetic and phenotypic differences based on the frequency and severity of SI and other related STBs is also warranted. Identification of specific mechanisms on a

continuous scale of risk, rather than as a binary trait, could also serve to inform prevention and treatment efforts and act as biomarkers for individuals at higher risk for suicide.

Conclusion.

To our knowledge, this is the first SNP-based study of suicide ideation among children and adolescents. Common heritable factors contribute to variation in neurocognitive functioning and some of these factors have genetic overlap with SI. Most notably, genetic factors influencing emotion identification has significant genetic correlations with SI, which itself demonstrated a small SNP-based heritability. Larger studies, with clearly defined suicide phenotypes, are needed to better understand the genetic architecture across suicide risk phenotypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Correlated-traits model of the computerized neurocognitive battery efficiency scores (adjusted for age, sex).

Figure 2.
Manhattan plot of GWAS results for suicidal ideation.

Table 1.

Descriptive statistics of sociodemographic factors and neurocognitive factors (N=3,584).

Variable	Mean/N	SD/%			
<i>Age (range 8–21)</i>	13.7	3.65			
<i>Male sex</i>	1,771	49.69%			
<i>Endorsed SI</i>	598	16.86%			
Domain	Task	SI– Mean (SD)	SI+ Mean (SD)	r	p
<i>Memory</i>	Factor	–0.03 (0.89)	0.17 (0.83)	0.08	<0.001
	VMEM	–0.04 (1.62)	0.22 (1.53)	0.06	<0.001
	FMEM	–0.04 (1.53)	0.25 (1.50)	0.07	<0.001
	SMEM	–0.02 (1.39)	0.12 (1.37)	0.04	–0.029
<i>Social Cognition</i>	Factor	–0.03 (0.95)	0.16 (0.94)	0.07	<0.001
	EMD	–0.04 (1.48)	0.22 (1.48)	0.07	<0.001
	AGD	–0.04 (1.44)	0.22 (1.45)	0.07	<0.001
	EMI	–0.02 (1.57)	0.15 (1.58)	0.04	0.017
<i>Executive</i>	Factor	–0.03 (0.92)	0.17 (0.84)	0.08	<0.001
	ABF	–0.01 (1.56)	0.06 (1.48)	0.02	0.352
	ATT	–0.05 (1.60)	0.27 (1.50)	0.08	<0.001
	WM	–0.06 (1.65)	0.28 (1.42)	0.08	<0.001
<i>Complex Cognition</i>	Factor	–0.03 (0.92)	0.16 (0.85)	0.08	<0.001
	LAN	–0.04 (1.67)	0.24 (1.51)	0.06	<0.001
	NVR	0.01 (0.81)	0.01 (0.92)	0	0.987
	SPA	0.00 (1.43)	0.06 (1.21)	0.02	0.337

Note: Factor indicates that the factor score was used for analyses; individual items for each factor: abstraction and mental flexibility (ABF), vigilance and visual attention (ATT), working memory (WM), episodic memory for verbal material (VMEM), episodic memory for faces (FMEM), episodic memory for shapes (SMEM), language-mediated complex cognition ability (LAN), nonverbal, reasoning ability (NVR), spatial ability (SPA), facial age differentiation (AGD), emotional intensity differentiation (EMD), emotion identification (EMI). SI–/+ = suicidal ideation (absent/present); SD = standard deviation; r = point biserial correlation; p = p-value. Descriptive statistics do not control for effects of sex/age.

Table 2.Univariate (h^2_{SNP}) and bivariate (r_G) estimates of neurocognitive factors.

Domain	Task	h^2_{SNP}			r_G with SI		
		Estimate (SE)	<i>p</i>	N	Estimate (SE)	<i>p</i>	N
<i>Memory</i>	Factor	0.16 (0.08)	0.018	3563	0.70 (0.62)	0.078	7101
	VMEM	0.12 (0.08)	0.064	3557	0.82 (0.71)	0.071	7095
	FMEM	0.10 (0.08)	0.087	3559	0.90 (0.81)	0.071	7097
	SMEM	0.02 (0.08)	0.402	3548	1.00 (2.83)	0.240	7086
<i>Social Cognition</i>	Factor	0.14 (0.08)	0.025	3563	0.31 (0.43)	0.216	7101
	EMD	0.16 (0.08)	0.009	3540	0.16 (0.43)	0.346	7078
	AGD	0.10 (0.08)	0.071	3543	-0.38 (0.62)	0.251	7081
	EMI	0.28 (0.08)	<0.001	3562	0.79 (0.45)	0.006	7100
<i>Executive</i>	Factor	0.24 (0.08)	<0.001	3563	0.26 (0.40)	0.248	7101
	ABF	0.00 (0.08)	0.500	3549	-1.00 (6.77)	0.500	7087
	ATT	0.25 (0.08)	<0.001	3560	0.16 (0.38)	0.327	7098
	WM	0.12 (0.08)	0.063	3521	0.43 (0.57)	0.207	7059
<i>Complex Cognition</i>	Factor	0.23 (0.08)	<0.001	3563	0.15 (0.47)	0.367	7101
	LAN	0.23 (0.08)	<0.001	3546	0.24 (0.41)	0.268	7084
	NVR	0.12 (0.08)	0.070	3544	-0.18 (0.45)	0.346	7092
	SPA	0.12 (0.08)	0.040	3501	0.29 (0.56)	0.285	7039

Note: Factor indicates that the factor score was used for analyses; individual items for each factor: abstraction and mental flexibility (ABF), vigilance and visual attention (ATT), working memory (WM), episodic memory for verbal material (VMEM), episodic memory for faces (FMEM), episodic memory for shapes (SMEM), language-mediated complex cognition ability (LAN), nonverbal, reasoning ability (NVR), spatial ability (SPA), facial age differentiation (AGD), emotional intensity differentiation (EMD), emotion identification (EMI). SI = suicidal ideation; SE = standard error. All analyses adjust for sex/age.