Original Investigation

Overlapping Genetic and Environmental Influences on Nonsuicidal Self-injury and Suicidal Ideation
Different Outcomes, Same Etiology?

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IMPORTANCE Nonsuicidal self-injury (NSSI) and suicidal self-injury are very harmful behaviors and are associated with several psychiatric disorders. In the recently developed fifth edition of the *DSM*, NSSI and suicidal behavior disorder are for the first time introduced as conditions in their own right instead of symptoms of other psychiatric disorders. It is unclear to what extent NSSI and suicidal self-injury share the same underlying biological mechanisms and are influenced by the same environmental factors.

OBJECTIVE To determine the relative importance of genetic and environmental influences on the variation in NSSI and suicidal ideation and their covariation.

DESIGN, SETTING, AND PARTICIPANTS Classical twin design using a sample of 10 678 male and female adult twins (mean [SD] age, 32.76 [6.99] years) from the Australian Twin Registry, a population-based twin registry. Between 1996 and 2009, the twins participated in semistructured telephone interviews that primarily focused on psychiatric disorders.

MAIN OUTCOMES AND MEASURES Lifetime presence of self-reported NSSI and suicidal ideation.

RESULTS The prevalences of NSSI and suicidal ideation were 4.7% and 26.5%, respectively, and individuals who engaged in self-harm were much more likely to report suicidal ideation (odds ratio = 8.39; 95% CI, 6.84-10.29). Results from a bivariate genetic model indicated that genetic factors explain a substantial part of the variance in both NSSI (37% for men and 59% for women) and suicidal ideation (41% for men and 55% for women), while residual influences (including nonshared environmental influences and measurement error) explain the remainder of the variance. Shared (family) environment did not seem to play a role. Moreover, both behaviors were strongly correlated (r = 0.49 for men and 0.61 for women), and this correlation was largely explained by overlapping genetic influences (76% for men and 62% for women), whereas residual influences accounted for the remainder of the phenotypic correlation.

CONCLUSIONS AND RELEVANCE Results indicated that the substantial correlation between NSSI and suicidal ideation is largely driven by overlapping genetic factors, suggesting that the 2 behaviors share similar biological underpinnings. Overlapping residual influences also explain part of the covariance between the 2 traits. Future research should further investigate which genetic and environmental influences underlie the vulnerability to NSSI and suicidal ideation.

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Self-injurious behaviors are behaviors performed intentionally with the goal to injure oneself and include nonsuicidal and suicidal behaviors (ie, without vs with the intention to die).[1] Lifetime prevalences in adult community samples are estimated to be 4% to 6% for nonsuicidal self-injury (NSSI; including self-cutting, biting, or burning),[2,3] while they are substantially higher in adolescent (14%-47%)[4-6] and clinical (21%-61%)[3,7] samples. Lifetime prevalences for suicidal behaviors are estimated to be 9.2% for suicidal ideation, 3.1% for suicidal plans, and 2.7% for suicide attempts.[8] Nonsuicidal and suicidal self-injurious behaviors are very impairing and are associated with an increased risk of psychiatric disorders such as depression and borderline personality disorder.[9-12] In *DSM-IV-TR*,[13] NSSI and suicidal self-injury were included only as symptoms of certain mental disorders. For instance, NSSI was included as a symptom of borderline personality disorder, although research indicates it also occurs in individuals without borderline personality disorder.[14,15] In the recently developed *DSM-5*,[16] NSSI and suicidal behavior disorder are introduced as conditions in their own right. The American Psychiatric Association indicates that further research is needed to guide decisions for future editions of the *DSM* as to whether these conditions should be considered as formal disorders.

Currently, there is debate about the relationship between NSSI and suicidal self-injury, with some researchers highlighting that both behaviors are distinct[17] and others being more cautious in clearly differentiating these 2 behaviors.[18] Numerous studies have noted that NSSI and suicidal self-injurious behaviors co-occur frequently[14,19,20] and that NSSI longitudinally predicts increased risk of suicidal behaviors.[21-23] However, NSSI and suicidal self-injury can also be distinguished from each other based on the following characteristics[24]: intention (NSSI is not performed with the intention to die, whereas suicidal behaviors are[1,25]), repetition (NSSI has a higher frequency than suicidal behaviors[14,26]), and lethality (NSSI includes methods of low lethality such as burning, whereas suicidal behaviors include methods of higher lethality such as overdose[26]). Moreover, studies have shown that suicidal self-injurious behaviors are associated with greater levels of psychological and psychosocial impairment compared with NSSI alone.[11,27] It is important to investigate whether NSSI and suicidal self-injury have the same underlying biological and environmental mechanisms to determine how distinct or similar both behaviors are. Clarifying this relationship is important for both research and treatment.[24]

Twin studies represent an adequate method to answer this question, as they determine not only the genetic and environmental influences on individual differences in traits but also the extent to which genetic and environmental influences are shared between traits. Studies on suicidal self-injury have found that 30% to 55% of the variance in suicide attempts and 43% to 56% in suicidal ideation could be attributed to genetic factors.[28-31] Studies on NSSI are very rare and findings are inconsistent. For instance, one study showed that thoughts of NSSI were moderately heritable (36%), whereas acts of NSSI were not heritable and were solely explained by environmental influences,[32] although it needs to be noted that this study was limited by a small sample size of 483 twin pairs. Contrastingly, results from an unpublished study[31] among female twins showed that more than half of the variance in self-injury was explained by genes. Moreover, this study is, to our knowledge, the only study that has examined the overlapping genetic and environmental influences on NSSI and suicide attempts. Results showed that both behaviors shared a moderate amount of genetic risk and a very small amount of unique environmental risk. However, because this study is unpublished, results should be interpreted with caution.

Using a large sample of male and female twins, our study determined the relative importance of genetic and environmental influences on NSSI and suicidal ideation as well as on the covariance between both behaviors.

Methods

Participants

The study sample consisted of identical (monozygotic [MZ]) and nonidentical (dizygotic [DZ]) twins from the Australian Twin Registry, a population-based twin registry. Between 1996 and 2009, the twins participated in various semistructured telephone interviews focused on psychiatric disorders.[33-35] In each of these studies, twins completed the same items about NSSI and suicidal ideation. Verbal informed consent was obtained from all participants. Procedures were approved by the Human Studies Committee at Washington University and the Ethics Committee at Queensland Institute of Medical Research.

The combined sample comprised 10 678 twins (4429 men and 6249 women), including 1154 female MZ, 693 male MZ, 932 female DZ, 594 male DZ, and 1038 opposite-sex DZ pairs and 1856 single twins (single twins were retained as they increase precision of the threshold estimates). The participants' age ranged from 19 to 75 years (mean [SD], 32.76 [6.99] years). Zygosity was determined based on standard items about physical similarity, a procedure with high concurrence with DNA typing (≥95%).[36]

Measures

The interview was an adaption of the Semi-Structured Assessment for the Genetics of Alcoholism, which assesses psychiatric disorders in adults and has been shown to be reliable.[37] Nonsuidical self-injury was assessed using the question "Other than when you tried to take your own life, did you ever hurt yourself on purpose, for example, by cutting or burning yourself?" Suicidal ideation was assessed using the question "Have you ever thought about taking your own life?" Answers were coded as yes or no.

Data Analysis

Descriptive statistics were calculated using SPSS version 20.0 statistical software (SPSS Inc). In accordance with standard twin analysis, genetic analyses used maximum-likelihood modeling procedures through the statistical package Mx.[38] Measures were analyzed as raw dichotomous data, assuming that a normally distributed continuum of liability is cut in 2 at a certain threshold, yielding 2 observed categories. In maximum-likelihood modeling, the goodness of fit of a model is distributed as χ^2. By testing the change in χ^2 against the change in *df*, we tested whether dropping or equating specific model para-

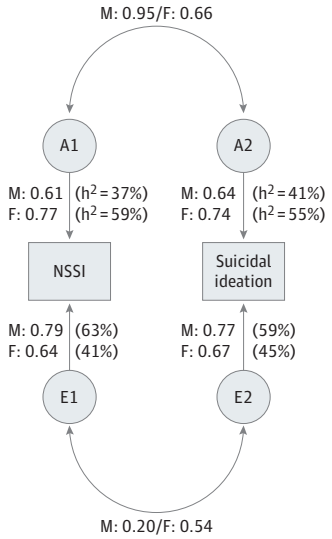
meters significantly worsened the model fit. We used the classical twin design in which the variance in NSSI and suicidal ideation as well as the covariance between them were portioned into genetic (additive [A] and nonadditive [D]) and environmental (shared [C] and residual [E]) influences. Additive genetic variance includes the influence of summed allelic effects on the liability of a trait, whereas nonadditive variance includes dominance (allelic interactions within genes) and epistasis (interaction between multiple genes). Shared environmental variance results from environmental influences shared within twin pairs, making them more similar to each other (eg, family environment), whereas residual environmental variance represents the variance due to unique experiences as well as measurement error.

Portioning of variance into genetic and environmental components can be achieved because MZ twins share 100% of their genes, whereas DZ twins share on average 50% of their segregating genes. Individual differences in phenotypes are the result of a combination of genetic and environmental influences. Structural equation modeling was used to determine which combination fit the observed data best. Moreover, by examining cross-twin cross-trait correlations, we partitioned the covariance between NSSI and suicidal ideation into genetic and environmental parts. Additional information on the classical twin design can be found elsewhere.[39,40]

A limitation of the classical twin design is that C and D are confounded and therefore cannot be tested simultaneously in a model with only twins reared together.[39] The choice of an ACE or ADE model depends on the pattern of MZ and DZ correlations. If the DZ correlation is greater than half the MZ correlation, C is estimated, but if the DZ correlation is smaller than half the MZ correlation, D is estimated.[41]

Prior to genetic modeling, we tested for the effects of age, sex, and zygosity on the thresholds of NSSI and suicidal ideation and then included these as fixed effects in the thresholds model as necessary. Subsequently, we fit models to determine the relative influence of A, C or D, and E. We examined the significance of the genetic and environmental influences by testing whether dropping relevant parameters from the baseline model led to a significant decrease in model fit. For ease of interpretation, the bivariate model was transformed into a correlated factors model[42] (**Figure**).

Figure. Correlated Factor Model



Graphical presentation of the parameter estimates and proportions of variance in nonsuicidal self-injury (NSSI) and suicidal ideation for male (M) and female (F) participants accounted for by additive genetic (A) and residual environmental (E) influences. Heritability (h^2) is the percentage of variance for which genetic factors account. The double-headed arrows represent the genetic and residual correlations, indicating the degree to which the same genetic or residual (including nonshared environmental) factors are influencing the 2 traits. The residual correlation for men is significant at $P = .049$, while all other estimates are significant at $P < .001$.

Results

Descriptive Statistics

Table 1 shows prevalences of and odds ratios between NSSI and suicidal ideation for the overall sample as well as separately for men and women. The overall prevalences of NSSI and suicidal ideation were 4.7% and 26.5%, respectively. Individuals who engaged in self-harm were much more likely to report suicidal ideation (odds ratio = 8.39; 95% CI, 6.84-10.29).

Preliminary Analyses

Before determining the variance components, the effects of sex, age, and zygosity on the thresholds were tested using an α level of .01. We did not find a significant age effect on suicidal ideation, but we did on NSSI (change in $\chi^2_1 = 39.65$; $P < .001$), showing that younger participants reported lifetime NSSI more often. We did not find a significant sex effect on the thresholds for NSSI or suicidal ideation, implying there were no differences in the prevalences between men and women. Moreover, levels of NSSI did not significantly differ between MZ and DZ twins in either sex, nor did the level of suicidal ideation differ between MZ and DZ women. However, men from opposite-sex twin pairs showed a higher prevalence of suicidal ideation than same-sex male twins (change in $\chi^2_1 = 9.10$; $P = .003$), so we did not equate this threshold with the threshold of same-sex male pairs in subsequent modeling. We accounted for sex and age effects in subsequent modeling.

Table 2 displays polychoric twin-pair correlations for each zygosity group. For both variables, the MZ twin-pair correlations were higher than the DZ twin-pair correlations, suggesting genetic influences on both traits. Given that the DZ twin-pair correlations for both variables were less than half the MZ twin-pair correlations, nonadditive genetic influences could be expected for both NSSI and suicidal ideation. Therefore, D (and not C) was estimated in the univariate genetic models.

Genetic Model Fitting

Table 3 depicts the A, D, and E estimates as obtained from the univariate model. While the estimates of broad-sense heritability (H^2; including additive and nonadditive genetic influences) were significant for both men and women for either trait, the separate A and D estimates were not significant for NSSI, and for men the D estimate was not significant for suicidal ideation. It should be noted that separate A and D estimates should

Table 1. Frequencies of and Odds Ratios Between Lifetime Nonsuicidal Self-injury and Suicidal Ideation

Participants	NSSI, No. (%) (n = 10 674)	Suicidal Ideation, No. (%) (n = 10 668)	OR (95% CI)[a] (n = 10 664)
Men	206 (4.7)	1175 (26.5)	5.97 (4.43-8.06)
Women	300 (4.8)	1650 (26.4)	10.91 (8.23-14.47)
Total	506 (4.7)	2825 (26.5)	8.39 (6.84-10.29)

Abbreviations: NSSI, nonsuicidal self-injury; OR, odds ratio.

[a] The ORs were obtained from Mplus version 6 software (Muthén and Muthén) accounting for sample nonindependence.

Table 2. Polychoric Twin-Pair Correlations for Lifetime Nonsuicidal Self-injury and Suicidal Ideation for Each Zygosity Group[a]

Zygosity	Pairs, No.	*r* (95% CI)	
		NSSI	Suicidal Ideation
MZ			
Female	1154	0.62 (0.47 to 0.75)	0.59 (0.51 to 0.66)
Male	693	0.49 (0.22 to 0.70)	0.42 (0.29 to 0.54)
DZ			
Female	932	0.12 (−0.18 to 0.39)	0.14 (0.02 to 0.25)
Male	594	−0.10 (−0.47 to 0.26)	0.22 (0.08 to 0.35)
Opposite sex	1038	0.18 (−0.10 to 0.43)	0.14 (0.03 to 0.24)

Abbreviations: DZ, dizygotic; MZ, monozygotic; NSSI, nonsuicidal self-injury.

[a] Estimated in the Mx statistical package[38] and corrected for age and sex effects.

Table 3. Estimates of the Proportion of Variance in Nonsuicidal Self-injury and Suicidal Ideation[a]

Variance Component	Estimate (95% CI)			
	NSSI		Suicidal Ideation	
	Men	Women	Men	Women
A	0.11 (0.00-0.61)	0.19 (0.00-0.71)	0.43 (0.33-0.53)	0.13 (0.01-0.38)
D	0.35 (0.00-0.67)	0.43 (0.00-0.74)	0.00 (0.00-0.38)	0.45 (0.15-0.61)
H^2 (A + D)	**0.46 (0.18-0.68)**	**0.62 (0.47-0.74)**	**0.43 (0.31-0.53)**	**0.58 (0.50-0.66)**
E	0.54 (0.32-0.82)	0.38 (0.26-0.53)	0.57 (0.47-0.69)	0.42 (0.34-0.50)

Abbreviations: A, additive genetic influences; D, nonadditive genetic influences; E, residual environmental influences; H^2 (A + D), broad-sense heritability; NSSI, nonsuicidal self-injury.

[a] Bold indicates broad-sense heritability.

be treated with caution; A and D are highly confounded as they predict similar (but not identical) patterns of twin-pair correlations. Therefore, when A and D are estimated simultaneously in 1 model, the estimates are imprecise and their relative magnitude can be biased depending on the extent of nonadditive genetic effects (dominance and epistasis). However, H^2 is quite robustly estimated with a classical twin design using only twins reared together.[39,43] For this reason, we only estimated A and E in the bivariate model, where A will have captured both the additive and nonadditive genetic influences.

The Figure depicts the parameter estimates of the bivariate model, separately for men and women. Specifically, the Figure shows proportions of variance in NSSI and suicidal ideation accounted for by genetic (heritability [h^2]) and residual influences as well as the genetic and residual correlations. Parameter estimates could not be equated between men and women (change in $\chi^2_3 = 15.84$; $P = .001$). To test the significance of each path in the Figure, genetic and environmental parameters were dropped from the bivariate AE model (separately for men and women) and model fit was compared using an α level of .05 (**Table 4**). Results showed that the genetic influences on NSSI (A = 0.37 for men and 0.59 for women) and suicidal ideation (A = 0.41 for men and 0.55 for women) were significant (see models 5 and 6 in Table 4). Moreover, the phenotypic correlation between NSSI and suicidal ideation ($r = 0.49$ for men and 0.61 for women) as well as the genetic and residual correlations were significant (see models 2, 3, and 4, respectively, in Table 4).

From the estimates in the Figure, we calculated the extent to which the phenotypic correlation could be attributed to genetic factors.[44] For men, this calculation is (0.61 × 0.95 × 0.64)/(0.61 × 0.95 × 0.64 + 0.79 × 0.20 × 0.77) = 0.76, showing that overlapping genetic factors accounted for 76% of the phenotypic correlation between NSSI and suicidal ideation, with overlapping residual influences accounting for the remaining 24%. For women, 62% of the phenotypic variance was due to common genetic factors and 38% to residual influences.

Discussion

We examined genetic and environmental influences on NSSI and suicidal ideation as well as on the covariance between both behaviors using data from 10 678 twins. Lifetime prevalences of NSSI and suicidal ideation were 4.7% and 26.5%, respectively, and endorsing NSSI was related to an increased risk of suicidal ideation (odds ratio = 8.39; 95% CI, 6.84-10.29). Results of the genetic analyses showed that NSSI and suicidal ideation were moderately heritable. Moreover, both behaviors were highly correlated ($r = 0.49$ for men and 0.61 for women) and most of the phenotypic correlations were due to overlapping genetic influences (76% for men and 62% for women), while overlapping residual influences (including nonshared environmental influences and measurement error) accounted for the remainder. This implies that NSSI and suicidal ideation are partly influenced by the same biological mechanisms.

Table 4. Goodness-of-Fit Statistics for Bivariate Models of Nonsuicidal Self-injury and Suicidal Ideation

Model No.	Model	Men				Women			
		vs Model No.	Change in *df*	Change in χ^2	*P* Value	vs Model No.	Change in *df*	Change in χ^2	*P* Value
1	Full model								
2	Test significance of phenotypic correlation between NSSI and suicidal ideation; drop genetic and residual environmental cross-paths	1	2	160.53	<.001	1	2	352.71	<.001
3	Test significance of genetic correlation between NSSI and suicidal ideation; drop genetic cross-path	1	1	27.72	<.001	1	1	58.76	<.001
4	Test significance of residual correlation between NSSI and suicidal ideation; drop residual environmental cross-path	1	1	3.87	.049	1	1	28.81	<.001
5	Test significance of genetic influences on NSSI; drop genetic influence on NSSI	1	1	29.74	<.001	1	1	77.19	<.001
6	Test significance of genetic influences on suicidal ideation; drop genetic influence on suicidal ideation	1	2	65.21	<.001	1	2	165.90	<.001

Abbreviation: NSSI, nonsuicidal self-injury.

These findings are consistent with prior findings of suicidal self-injury, indicating that approximately half of the variance in suicidality is explained by genes and the other half by residual environmental influences, whereas shared (family) environmental influences do not play a substantial role.[29-31] Previous twin studies on NSSI were based on a small sample size[32] or only examined women[31] and showed inconsistent results; Jang et al[32] did not find significant genetic influences on NSSI acts, while Durrett[31] found that genetic factors largely accounted for the variance in NSSI, consistent with our findings.

Most importantly, we examined the overlap in genetic and environmental influences on NSSI and suicidal ideation. Consistent with previous studies,[21,22] we found a high phenotypic correlation between both behaviors. Furthermore, this comorbidity was largely driven by overlapping genetic factors and to a smaller degree by overlapping residual influences, which is in accordance with the findings from an unpublished study by Durrett.[31]

More generally, our results are consistent with other studies that also found high phenotypic correlations between disorders from the same spectrum (eg, depression and anxiety) as well as high genetic, considerably lower unique environmental, and very low or absent shared environmental correlations between these highly comorbid disorders.[45-48] On the other hand, disorders from different spectra show substantially lower phenotypic correlations and a much lower genetic correlation.[35,46]

Findings from these studies indicate that genetic influences that are overlapping between NSSI and suicidal ideation may also partly underlie vulnerability to other mental disorders such as depression and anxiety. Liability to NSSI and suicidal ideation as well as other highly correlated disorders from the same spectrum may be influenced largely by the same underlying genetic or biological factors, but the exact disorder that develops among vulnerable individuals within the spectrum may be more dependent on unique environmental influences.

Future research should further investigate which genetic and environmental influences underlie vulnerability in NSSI and suicidal ideation. Previous research has identified some potential biological influences. For instance, meta-analyses of molecular genetic studies have shown that polymorphisms in the tryptophan hydroxylase gene (*TPH*)[49] and the serotonin transporter gene promoter (5-HTTLPR),[50] which both play important roles in serotonin functioning, are linked to suicidal self-injurious behaviors. Studies on the molecular underpinnings of NSSI are rare, but they also implicate dysfunctions in the serotonin system.[51,52] Serotonin may play a role because it is linked to impaired emotion regulation and impulsivity,[53] which are in turn associated with self-injurious behaviors.[54-56] Other studies point to a possible influence of endogenous opioids, which play a role in disordered pain and reward, for both suicide and NSSI.[57]

Previous studies have also identified some potential unique environmental influences. For instance, studies have shown that early traumatic childhood experiences (ie, abuse and neglect),[58-62] peer victimization and bullying,[63-66] and intimate partner violence and abuse[67-70] are associated with an increased risk of self-injurious behaviors. Studies that directly compare NSSI and suicidal behaviors to investigate the differential effect of unique environmental contributions are rare, although studies suggest that compared with NSSI, suicidal behaviors are associated with more stressful life events[71] and greater sexual and emotional abuse.[72]

This study is not without limitations, most of which are concerned with the classical twin design. For instance, one assumption of the classical twin design is that there are no effects of gene-environment correlation or interaction; not modeling these influences may lead to biased estimates. Another limitation is that C and D cannot be modeled simultaneously and that simultaneously estimating A and D influences leads to imprecise estimates. Lastly, an important limitation is that we only used single-item responses to determine lifetime NSSI and suicidal ideation, which could have led to incorrect estimations of the prevalences. However, the prevalence of NSSI in our sample (4.7%) is consistent with prevalences reported in previous adult population samples.[2,3] Furthermore, for a subsample of the individuals who endorsed the NSSI item (n = 240), data were available regarding the specific self-injurious behaviors they had endorsed, showing that severer forms of self-injurious behaviors (eg, cutting was endorsed by 64%, burning by 23%) were reported more frequently than moderate forms (eg, scratching oneself, punching oneself, and punching a hard object were endorsed by about 10% each). Note that owing to a lack of power, we were unable to run analyses on this subgroup only. Our prevalence for suicidal ideation is relatively high potentially because the question did not distinguish between brief and sustained suicidal ideation. Given

our crude assessment, it is likely that some of the nonshared environmental variance in and covariance between our measures is due to measurement error, which could have resulted in an overestimation of E and underestimation of A influences.

Conclusions

This study makes an important contribution to the current debate about the relationship between NSSI and suicidal ideation. We have shown that both behaviors are substantially influenced by genetic and residual environmental factors. Furthermore, we found that the substantial correlation between NSSI and suicidal ideation is largely driven by overlapping genetic factors, suggesting that the 2 behaviors share similar biological underpinnings. Overlapping residual influences also explain part of the covariance between the 2 traits. An important goal for future research is to investigate which overlapping and specific genetic and environmental influences underlie the vulnerability in NSSI and suicidal ideation.

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Drafting of the manuscript: Maciejewski, Verweij.
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