

Familial Aggregation of Suicide Explained by Cluster B Traits: A Three-Group Family Study of Suicide Controlling for Major Depressive Disorder

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Objective: There is substantial evidence suggesting that suicide aggregates in families. However, the extent of overlap between the liability to suicide and psychiatric disorders, particularly major depressive disorder, remains an important issue. Similarly, factors that account for the familial transmission of suicidal behavior remain unclear. Thus, through direct and blind assessment of first-degree relatives, the authors conducted a family study of suicide by examining three proband groups: probands who committed suicide in the context of major depressive disorder, living depressed probands with no history of suicidal behavior, and psychiatrically normal community comparison probands.

Method: Participants were 718 first-degree relatives from 120 families: 296 relatives of 51 depressed probands who committed suicide, 185 relatives of 34 nonsuicidal depressed probands, and 237 relatives of 35 community comparison subjects. Psychopathology, suicidal behavior, and behavioral measures were assessed via interviews.

Results: The relatives of probands who committed suicide had higher levels of suicidal behavior (10.8%) than the relatives of nonsuicidal depressed probands (6.5%) and community comparison probands (3.4%). Testing cluster B traits as intermediate phenotypes of suicide showed that the relatives of depressed probands who committed suicide had elevated levels of cluster B traits; familial predisposition to suicide was associated with increased levels of cluster B traits; cluster B traits demonstrated familial aggregation and were associated with suicide attempts among relatives; and cluster B traits mediated, at least in part, the relationship between familial predisposition and suicide attempts among relatives. Analyses were repeated for severity of attempts, where cluster B traits also met criteria for endophenotypes of suicide.

Conclusions: Familial transmission of suicide and major depression, while partially overlapping, are distinct. Cluster B traits and impulsive-aggressive behavior represent intermediate phenotypes of suicide.

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Suicide is a major health problem. Research efforts have made clear that it is a complex behavior that is the result of several interacting factors (1). Suicide aggregates in families, as indicated by both family history (2–6) and family studies with direct interviews of relatives (7–10), suggesting an approximately fivefold risk increase for suicidal behavior among relatives (8, 10, 11).

Suicide is almost exclusively manifested in the context of a psychiatric illness (12, 13), particularly mood disorders (12, 13). One central question has been regarding the extent of overlap between the liability to suicide and psychiatric disorders. A qualitative family study in the Old Order Amish (14) was the first to suggest independent liabilities, since mood disorders aggregated in a number of families in this population, but cosegregation with suicide was found in only a few cases. Subsequent studies (7, 8, 10) have supported the independence of liabilities by statisti-

cally controlling for psychiatric disorders. However, to our knowledge, no study has yet been designed to definitively address the extent to which the susceptibility to suicide is independent of the susceptibility to mental illness.

People who commit suicide have a predisposition (15, 16) that is believed to be transmitted via intermediate phenotypes between genes and suicidal outcomes. Several lines of evidence suggest that cluster B personality disorders and associated traits may act as intermediate phenotypes of suicidal behavior (17–29). Accordingly, suicide completers have higher levels of these behaviors (7, 8, 18), violent suicide methods are related to aggressive behavior (21), and an individual's age at the time of suicide is associated with levels of impulsive-aggressive behavior (26). However, most importantly, levels of impulsive-aggressive behavior appear to be related to increased suicide risk among patients with the same psychiatric diagnosis,

This article is featured in this month's AJP **Audio** and is discussed in an editorial by Dr. Brent (p. 1087).

TABLE 1. Sociodemographic Characteristics of Probands

| Characteristic | Group | | | | | | Analysis | | |
|----------------------|---|------|---------------------------------------|------|--------------------------------------|------|----------|----|--------|
| | Depressed Probands Who Committed Suicide (N=51) | | Nonsuicidal Depressed Probands (N=34) | | Community Comparison Probands (N=35) | | χ^2 | df | p |
| | N | % | N | % | N | % | | | |
| Gender | | | | | | | | | |
| Female | 15 | 29.4 | 17 | 50.0 | 16 | 45.7 | 4.27 | 2 | 0.118 |
| Male | 36 | 70.6 | 17 | 50.0 | 19 | 54.3 | | | |
| University education | 7 | 14.3 | 16 | 46.9 | 21 | 60.6 | 20.18 | 2 | ≤0.001 |
| Married | 18 | 35.3 | 13 | 37.5 | 12 | 35.3 | 0.04 | 2 | 0.98 |
| Household income | | | | | | | 8.81 | 2 | 0.18 |
| <\$10,000 | 36 | 70.6 | 16 | 47.1 | 18 | 51.4 | | | |
| \$10,000–\$29,999 | 8 | 15.7 | 7 | 20.6 | 9 | 25.7 | | | |
| \$30,000–\$50,000 | 4 | 7.8 | 3 | 8.8 | 4 | 11.4 | | | |
| >\$50,000 | 3 | 5.9 | 8 | 23.5 | 4 | 11.4 | | | |

such as a diagnosis of major depression (20) or borderline personality disorder (25), and can differentiate those who die early as opposed to later in the course of illness (27).

In the present study, we sought to directly address these important issues by testing the independence of liability to depression and suicide using a three-group family-study design. Specifically, rates of recurrence of suicidal behavior in relatives of suicide probands who died during an episode of major depressive disorder were compared with recurrence rates of suicidal behavior in relatives of 1) living depressed probands with major depressive disorder but no history of suicidal behavior and 2) living comparison probands without major depressive disorder or suicidal behavior. In addition, we formally tested the hypothesis that cluster B disorders and impulsive-aggressive behavior are intermediate phenotypes of suicide. Although we have previously published a family study (10), the present study was based on a different sample investigated using a different study design and different research instruments.

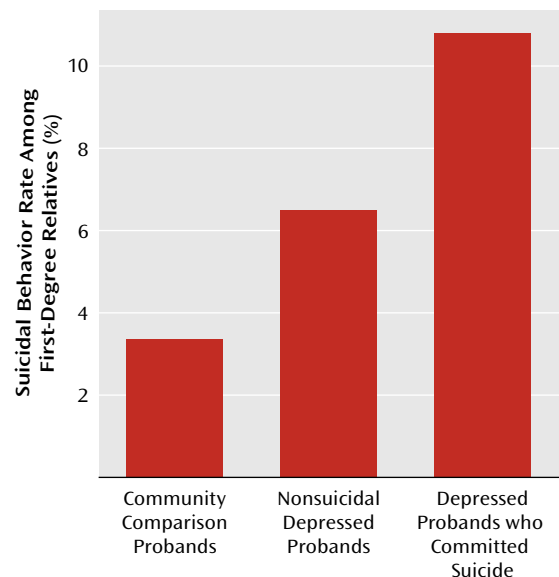
Method

Proband Groups

We recruited the family members of 51 individuals (mean age=40.47 years [SD=12.78]; men, 70.6%) who died by suicide in the context of major depressive disorder, as identified by psychological autopsy. This method (20, 25, 30–32) involved proxy-based interviews with the person best acquainted with the deceased. Participants were consecutively recruited from the Greater Montreal region in collaboration with Quebec's Coroner's Office. Participation was in excess of 60%. Families recruited were likely to be representative of depressed suicide probands who had comparable demographic, clinical, and comorbid characteristics with other samples of individuals who died by suicide in the context of major depression (20, 33, 34).

Thirty-four individuals who met criteria for major depressive disorder and a negative history of suicide attempts (mean age=39.61 years [SD=10.36]; men, 50.0%) were recruited from McGill University-affiliated outpatient clinics. Our definition of negative history also included the absence of ambiguous (unclear whether death was desired) or interrupted (stopped by a third party) suicide attempts. Participation acceptance was ≥90%, and the clinical profile of these probands was similar to that of other samples of depressed outpatients screened for the absence of suicidal behavior (20).

FIGURE 1. Suicidal Behavior Among First-Degree Relatives



Thirty-five individuals (mean age=38.28 years [SD=15.63]; men, 54.3%) with a negative history of both depressive disorders and suicidal behavior were recruited using the acquaintanceship method (selection among family friends) and via advertisement in local newspapers. Excluding their preselection for the absence of depressive disorder and suicidal behavior, their rates of psychopathology were consistent with prevalence rates in the general population (35).

Proband Comparability and Family Ascertainment

Although the three groups of probands were not directly matched, group comparisons suggested comparable age, sex, marital status, and income (Table 1). Depressed probands who committed suicide were less likely to have received a university education ($p \leq 0.001$).

To facilitate logistic effort and improve group comparability, we focused on first-degree relatives. Relatives were directly and blindly assessed and scored for demographic characteristics, axis I and II disorders, suicidal behavior, and personality traits. In total, 231 relatives (out of 718) underwent assessment. We obtained data from 101 relatives (out of 296) of the depressed probands who committed suicide (mean age=46.67 years [SD=15.03]; women, 73.0%); 59 relatives (out of 185) of the nonsuicidal depressed probands (mean age=47.20 years [SD=16.67]; women, 74.6%); and 71 relatives (out of 237) of the community comparison probands (mean age=45.14 years [SD=15.63]; women, 54.3%).

TABLE 2. Psychiatric and Behavioral Characteristics of Probands

| Characteristic | Group | | | | | | Analysis |
|--|--|----------------|--|----------------|---|----------------|----------------|
| | 1: Depressed Probands Who Committed Suicide (N=51) | | 2: Nonsuicidal Depressed Probands (N=34) | | 3: Community Comparison Probands (N=35) | | |
| | N | % ^a | N | % ^a | N | % ^a | χ ² |
| Axis I disorders (last 6 months) | | | | | | | |
| Alcohol abuse | 17 | 34.7 | 3 | 8.8 | 1 | 2.9 | 16.77*** |
| Substance abuse | 9 | 17.6 | 1 | 2.9 | 0 | 0.0 | 10.26** |
| Psychotic disorder | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | |
| Axis I disorders (lifetime) | | | | | | | |
| Alcohol abuse | 20 | 40.8 | 7 | 21.2 | 1 | 2.9 | 16.34*** |
| Substance abuse | 12 | 23.5 | 4 | 11.8 | 1 | 2.9 | 7.52* |
| Axis II disorders | | | | | | | |
| Cluster A | 2 | 4.0 | 0 | 0.0 | 0 | 0.0 | 2.52 |
| Cluster B | 9 | 18.0 | 1 | 3.2 | 1 | 3.2 | 6.82* |
| Cluster C | 6 | 12.0 | 5 | 16.1 | 2 | 6.5 | 1.42 |
| | Mean | SD | Mean | SD | Mean | SD | F |
| Number of lifetime axis I disorders | 1.58 | 1.11 | 1.70 | 1.11 | 0.31 | 0.58 | 21.77 |
| Barratt Impulsiveness Scale II score | 65.59 | 14.26 | 64.52 | 10.18 | 53.37 | 9.96 | 12.96*** |
| Brown-Goodwin History of Aggression score | 7.80 | 8.86 | 5.06 | 6.50 | 2.09 | 2.26 | 6.67** |
| Buss-Durkee Hostility Inventory score | 33.42 | 13.86 | 27.76 | 11.50 | 18.51 | 9.67 | 14.81*** |
| Temperament and Character Inventory scores | | | | | | | |
| Novelty seeking | 21.21 | 6.77 | 19.11 | 6.38 | 17.98 | 6.69 | 2.42 |
| Harm avoidance | 16.74 | 7.31 | 19.62 | 7.04 | 11.53 | 6.04 | 12.11*** |
| Persistence | 5.41 | 2.37 | 4.43 | 2.11 | 4.90 | 2.06 | 1.88 |

^a Total number on which percentages are based varies because of missing data for some variables.

^b $\chi^2=3.86$, $p=0.049$. The confidence interval is large because of the small number of cases in groups 2 and 3.

* $p \leq 0.05$. ** $p \leq 0.01$. *** $p \leq 0.001$.

son probands (mean age=39.78 years [SD=18.29]; women; 69.0%). Groups were comparable with respect to sex ($\chi^2=0.55$, $df=2$, $p \geq 0.05$) but not age ($F=4.52$, $df=2$, 229, $p < 0.05$). Relatives who were unavailable for direct interview were assessed using the Family Interview for Genetic Studies (36). This yielded an additional 487 indirectly assessed relatives (N=195, 126, and 166, respectively). Family density for directly assessed relatives was comparable among the three groups.

The study was approved by our local institutional review board. Living probands, next of kin of deceased probands, and family members signed written informed consent.

Assessments

For proband comparability, we used proxy-based interviews to characterize living probands. DSM-IV (37) psychiatric diagnoses were obtained using the SCID-I (38) and SCID-II (39) interviews. Kappa coefficients for key diagnoses ranged from very good to excellent as follows: depressive disorders, kappa=0.87; substance abuse, kappa=0.87; schizophrenia, kappa=1.0; cluster B personality disorders, kappa=0.80; and generalized anxiety disorder and panic disorder, kappa=0.78.

History of suicidal behavior was assessed with the semistructured Mental Health Clinical Research Center Suicide History Form (40). Suicide attempts were defined as behavior causing or having the potential to cause self-injury with the intention to die as a result of the behavior. The Mental Health Clinical Research Center Suicide History Form also characterizes the medical severity of suicide attempts and codifies them along an 8-point Likert scale, with a score of 8 representing death.

We utilized the following impulsive aggression questionnaires: Brown-Goodwin History of Aggression (41), Barratt Impulsiveness Scale (42), Buss-Durkee Hostility Inventory (43), and Temperament and Character Inventory (44). The Temperament and Character Inventory reward dependence subscale was excluded as a result of reliability concerns (26). Internal consistency estimates for informant versions were overall excellent for the Brown-Goodwin History of Aggression ($\alpha=0.91$), Barrett Im-

pulsiveness Scale ($\alpha=0.89$), Buss-Durkee Hostility Inventory ($\alpha=0.86$), and Temperament and Character Inventory ($\alpha=0.95$). As related to self-report versions, these estimates were overall very good for the Brown-Goodwin History of Aggression ($\alpha=0.80$), Barratt Impulsiveness Scale ($\alpha=0.80$), Buss-Durkee Hostility Inventory ($\alpha=0.81$), and Temperament and Character Inventory ($\alpha=0.90$).

Previous studies conducted by our investigator group (20, 25, 45–47), as well as other researchers (30–32), on the validity of the proxy-based behavioral assessments used in the present study demonstrate the similarity between information obtained from an informant and information obtained from the subject.

Statistical Analyses

We performed analyses using the SPSS Statistical Package version 14 (SPSS Inc., Chicago).

For categorical variables in group analyses, we used chi-square tests, with odds ratios and 95% confidence intervals (CIs) reported for paired-group comparisons, t tests or one-way analysis of variance (ANOVA), and Tukey's post hoc tests for continuous variables.

Additional analyses were conducted to examine familial aggregation of suicidal behavior and cluster B traits as intermediate phenotypes of suicide, using linear models (restricted maximum likelihood). In these analyses, we used the term "random effect" to account for the nonindependence of data obtained from individuals within the same family. Continuous variables were included in the model as covariates, and categorical variables were included as fixed effects. Pairwise comparisons of group-estimated marginal means are reported.

We hypothesized that cluster B traits would serve as intermediate phenotypes of suicide. We sought to test this hypothesis according to the criteria for endophenotypes as described by Gottesman and Gould (48). Specifically, we evaluated whether cluster B traits would 1) be more common among depressed probands who committed suicide, 2) be more prevalent among the predisposed group (relatives of depressed probands who com-

| Comparison | | | | | | | | |
|-------------------|--------------------------|-------------------------|---------------------|---------------------------|-------------------------|------------------|-------------------------|-------------------------|
| 1 Versus 2 | | | 1 Versus 3 | | | 2 Versus 3 | | |
| Odds Ratio | 95% CI | Fisher's Exact Test (p) | Odds Ratio | 95% CI | Fisher's Exact Test (p) | Odds Ratio | 95% CI | Fisher's Exact Test (p) |
| 5.49** 7.07* | 1.46–20.61 0.85–58.66 | | 18.06*** | 2.27–143.68 | 0.009 | 3.29 | 0.32–33.31 | 0.49 |
| 2.56 2.30 | 0.93–7.03 0.67–7.87 | | 23.44*** 10.46** | 2.96–185.55 1.29–84.68 | | 9.15* 4.53 | 1.05–79.1 0.48–42.82 | |
| 6.58 ^b | 0.79–54.80 | | 6.58 ^b | 0.79–54.80 | | 1.00 | 0.06–16.73 | |
| Tukey's Test (p) | | | Tukey's Test (p) | | | Tukey's Test (p) | | |
| 0.85 | | | <0.001 | | | <0.001 | | |
| ≤0.001 | | | 0.92 | | | ≤0.001 | | |
| 0.20 | | | 0.001 | | | 0.21 | | |
| 0.11 | | | 0.006 | | | ≤0.001 | | |
| 0.17 | | | 0.003 | | | ≤0.001 | | |

mitted suicide), 3) be familial, 4) be associated with the measured outcome (suicidal behavior), and 5) mediate the effect between vulnerability and outcome.

Mediation testing was conducted as proposed by Baron and Kenny (49). Applied to cluster B traits as mediators of familial predisposition to suicide, the criteria were 1) an association between familial predisposition and recurrence of suicidal behavior in relatives of suicide subjects, 2) an association between familial predisposition and the proposed endophenotype, 3) an association between the endophenotype and recurrence of suicidal behavior in relatives, and, finally, 4) a decrease in significance between family history and recurrence of suicidal behavior in relatives when controlling for cluster B traits. The first and second criteria overlap with the criteria described by Gottesman and Gould, and thus we focused on the fourth criterion, for which there is evidence of mediation when there is a decrease in the total effect when controlling for the mediator.

Results

With respect to current (past 6 months) axis I psychopathology, as expected (12, 13), depressed probands who committed suicide were more likely to have met criteria for alcohol abuse and illicit substance abuse than nonsuicidal depressed probands and community comparison probands (Table 2). Depressed probands who committed suicide were also more likely than community comparison probands, but not nonsuicidal depressed probands, to have met criteria for lifetime alcohol abuse and illicit substance abuse. Further, comorbidity with cluster B personality pathology was more common among depressed probands who committed suicide.

Personality trait comparisons revealed differences in scores for the Barratt Impulsiveness Scale, Brown-Goodwin History of Aggression, Buss-Durkee Hostility Inventory, and

harm avoidance subscale of the Temperament and Character Inventory. Tukey's post hoc comparisons showed that depressed probands who committed suicide and nonsuicidal depressed probands had higher scores than community comparison probands on the Barratt Impulsiveness Scale, Buss-Durkee Hostility Inventory, and harm avoidance subscale of the Temperament and Character Inventory, but no significant differences were found between depressed probands who committed suicide and nonsuicidal depressed probands. Post hoc tests also revealed higher scores for the Brown-Goodwin History of Aggression among depressed probands who committed suicide relative to community comparison probands. No other group differences were seen.

Suicidal Behavior Among Relatives

With respect to lethal suicidal behavior, among first-degree relatives of depressed probands who committed suicide, nonsuicidal depressed probands, and community comparison probands, 1.6%, 0.6%, and 0.0%, respectively, died by suicide. When lethal and nonlethal suicidal behaviors were combined, the respective rates rose to 10.8%, 6.5%, and 3.4% ($\chi^2=11.57$, $df=2$, $p\leq 0.01$ [Figure 1]).

We tested the relationship between family history (three-group definition) and recurrence of suicidal behavior among directly assessed relatives. We also examined random effects for members of the same family and controlled for age. This model received significant contributions from family history ($F=4.24$, $df=2$, 71.14 , $p<0.05$) and the intercept ($F=9.73$, $df=1$, 170.10 , $p<0.01$) and a tendency for age ($F=3.63$, $df=1$, 171.33 , $p=0.06$), suggesting independence of liability after accounting for the nonindependence

TABLE 3. Characteristics of First-Degree Relatives

| Characteristic | Proband Group From Which Relatives Were Recruited | | | | | | Analysis |
|--|---|----------------|--|----------------|---|----------------|----------|
| | 1: Depressed Probands Who Committed Suicide (N=101 relatives) | | 2: Nonsuicidal Depressed Probands (N=59 relatives) | | 3: Community Comparison Probands (N=71 relatives) | | |
| | N | % ^a | N | % ^a | N | % ^a | |
| | | | | | | | χ^2 |
| Axis I disorder (last 6 months) | | | | | | | |
| Major depression | 16 | 16.3 | 8 | 14.3 | 2 | 3.0 | 7.28* |
| Minor depressive disorder | 3 | 3.1 | 2 | 3.8 | 0 | 0.0 | 2.29 |
| Alcohol abuse | 3 | 3.1 | 3 | 5.4 | 0 | 0.0 | 3.39 |
| Substance abuse | 1 | 1.0 | 0 | 0.0 | 1 | 1.5 | 0.78 |
| Panic disorder | 4 | 4.1 | 1 | 1.8 | 2 | 3.0 | 0.59 |
| Axis I disorder (lifetime) | | | | | | | |
| Major depression | 45 | 45.9 | 2 | 4.1 | 11 | 16.4 | 16.00*** |
| Minor depressive disorder | 13 | 13.3 | 5 | 8.9 | 3 | 4.5 | 3.57 |
| Bipolar disorder | 1 | 1.0 | 0 | 0.0 | 1 | 1.5 | 0.78 |
| Alcohol abuse | 13 | 13.3 | 7 | 12.7 | 6 | 9.0 | 0.76 |
| Substance abuse | 10 | 10.2 | 2 | 3.6 | 4 | 6.0 | 2.56 |
| Panic disorder | 7 | 7.1 | 5 | 9.1 | 4 | 6.0 | 0.44 |
| Psychotic disorder | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | |
| Axis II disorders | | | | | | | |
| Cluster A | 1 | 1.0 | 0 | 0.0 | 1 | 1.5 | 0.79 |
| Cluster B | 5 | 5.2 | 2 | 3.6 | 1 | 1.5 | 1.46 |
| Cluster C | 6 | 6.3 | 7 | 12.7 | 2 | 3.1 | 4.42 |
| | Mean | SD | Mean | SD | Mean | SD | F |
| Barratt Impulsiveness Scale II score | 59.15 | 10.8 | 58.09 | 9.10 | 57.57 | 9.44 | 0.45 |
| Brown-Goodwin History of Aggression score | 4.92 | 6.95 | 5.50 | 8.22 | 3.58 | 5.15 | 1.30 |
| Buss-Durkee Hostility Inventory score | 24.33 | 9.65 | 26.36 | 11.7 | 20.79 | 8.72 | 4.25* |
| Temperament and Character Inventory scores | | | | | | | |
| Novelty seeking | 19.87 | 5.16 | 17.23 | 5.02 | 18.68 | 5.48 | 3.68* |
| Harm avoidance | 14.15 | 6.56 | 16.74 | 6.28 | 13.64 | 6.09 | 3.39* |
| Persistence | 3.98 | 1.86 | 5.25 | 1.94 | 4.81 | 1.92 | 7.05*** |

^a Total number on which percentages are based varies because of missing data for some variables.

* $p \leq 0.05$. ** $p \leq 0.01$. *** $p \leq 0.001$.

dence of data. Pairwise least significant difference group-estimate comparisons revealed significant differences between relatives of depressed probands who committed suicide and relatives of nonsuicidal depressed probands ($p=0.03$) as well as between relatives of depressed probands who committed suicide and community comparison probands ($p=0.01$), but not between relatives of nonsuicidal depressed probands and community comparison probands ($p=0.88$).

Similarly, we tested this relationship with respect to the medical severity of suicide attempts and found contributions from family history ($F=3.37$, $df=2$, 209 , $p<0.05$) and the intercept ($F=4.18$, $df=1$, 209 , $p<0.05$) but not age. Pairwise least significant difference group-estimate comparisons revealed significant differences for severity of suicidal behavior between relatives of depressed probands who committed suicide and relatives of nonsuicidal depressed probands (mean difference=4.00 [SD=2.02], $p \leq 0.05$) as well as between relatives of depressed probands who committed suicide and community comparison probands (mean difference=4.48 [SD=1.94], $p<0.05$), but not between relatives of nonsuicidal depressed and community comparison probands (mean difference=0.48 [SD=2.21]).

Relatives of depressed probands who committed suicide and nonsuicidal depressed probands were more likely than relatives of community comparison probands

to meet criteria for current and lifetime major depressive disorder (Table 3). No other axis I or II characteristics significantly differentiated these two groups. Differences between indirectly assessed relatives followed the same pattern (data not shown).

With respect to personality-trait characteristics, significant differences were observed for the Buss-Durkee Hostility Inventory score and the harm avoidance, novelty seeking, and persistence subscale scores from the Temperament and Character Inventory. Tukey's post hoc comparisons revealed that relatives of depressed probands who committed suicide had higher novelty seeking scores than relatives of nonsuicidal depressed probands and lower persistence scores than both nonsuicidal depressed probands and community comparison probands (Table 3). Relatives of nonsuicidal depressed probands had higher Buss-Durkee Hostility Inventory and harm avoidance scores than relatives of community comparison probands ($p<0.05$). No other post hoc comparisons reached significance.

Cluster B Traits as Intermediate Phenotypes of Suicide

Commonly studied aspects of impulsive aggression are impulsivity, hostility, and aggression. Cluster B personality disorders can be considered pathological manifestations of these traits (50). Measures of impulsive aggression re-

| Comparison | | | | | | | | |
|------------------|------------|-------------------------|------------------|------------|-------------------------|------------------|-----------|-------------------------|
| 1 Versus 2 | | | 1 Versus 3 | | | 2 Versus 3 | | |
| Odds Ratio | 95% CI | Fisher's Exact Test (p) | Odds Ratio | 95% CI | Fisher's Exact Test (p) | Odds Ratio | 95% CI | Fisher's Exact Test (p) |
| 1.17 | 0.46–2.93 | | 6.34** | 1.40–28.57 | | 5.41* | 1.10–26.6 | |
| 1.79 | 0.34–9.19 | | | | 0.27 | | | 0.09 |
| 2.29 | 0.25–21.08 | 1.0 | 0.68 | 0.04–11.07 | | | | 1.0 |
| | | | 1.36 | 0.24–7.65 | | 0.59 | 0.05–6.71 | |
| 1.21 | 0.62–2.36 | | 4.32*** | 2.02–9.23 | | 3.54** | 1.53–8.19 | |
| | | 1.0 | 1.47 | 0.09–23.91 | | | | 1.0 |
| 1.04 | 0.39–2.80 | | 1.55 | 0.56–4.31 | | 1.48 | 0.46–4.70 | |
| 3.06 | 0.64–14.53 | | 1.79 | 0.53–5.96 | | 0.58 | 0.10–3.31 | |
| 0.76 | 0.23–2.55 | | 1.21 | 0.34–4.31 | | 1.57 | 0.40–6.17 | |
| Tukey's Test (p) | | | Tukey's Test (p) | | | Tukey's Test (p) | | |
| | | 0.52 | | | 0.11 | | | 0.02 |
| | | 0.02 | | | 0.41 | | | 0.34 |
| | | 0.08 | | | 0.89 | | | 0.04 |
| | | 0.001 | | | 0.04 | | | 0.49 |

late to a superordinate category (51), and, accordingly, twin studies suggest a common genetic effect for cluster B personality disorders (52). Our studies in suicide completion highlight the interaction between impulsive and aggressive traits in increased risk for suicide, even after accounting for main effects (25). To represent the co-occurrence of impulsive and aggressive traits, we created a measure representing the latent construct of impulsive aggression/cluster B traits. Using factor analysis to create an aggregate measure of cluster B traits, a single factor emerged, with an eigenvalue of 2.91 and component loadings of 0.68 (cluster B disorders), 0.74 (Buss-Durkee Hostility Inventory), 0.78 (Brown-Goodwin History of Aggression), and 0.73 (Barratt Impulsiveness Scale).

We hypothesized that impulsive-aggressive behavior and cluster B traits would function as intermediate phenotypes, also called endophenotypes, and mediate familial aggregation of suicide. Our test of cluster B traits as an endophenotype of suicide followed the criteria outlined by Gottesman and Gould (48). The approach and results from these analyses are illustrated in Figure 2.

Prevalence among probands. We used one-way ANOVA to determine whether the aggregate measure differentiated the proband groups (depressed probands who committed suicide: 0.77 [SD=1.43]; nonsuicidal depressed probands: 0.16 [SD=0.79]; community comparison probands: -0.57 [SD=0.67]; $F=13.90$, $df=2$, 98, $p\leq 0.001$).

Tukey's post hoc tests revealed a difference between depressed probands who committed suicide and nonsuicidal depressed probands approaching significance ($p=0.06$) and significant differences between community comparison probands and depressed probands who committed suicide ($p\leq 0.001$) and nonsuicidal depressed probands ($p<0.05$). We therefore observed a gradient of cluster B traits, with probands who committed suicide exhibiting higher levels of these traits than community comparison probands.

Association with family predisposition to suicide.

We aimed to determine whether a familial predisposition to suicide was associated with increased levels of cluster B traits in first-degree relatives. In predicting cluster B traits, we found significant contributions from family history ($F=3.56$, $df=2$, 62.50, $p<0.05$), age ($F=15.17$, $df=1$, 174.36, $p\leq 0.001$), and the intercept ($F=8.06$, $df=1$, 166.77, $p<0.01$). Estimated means for cluster B traits were as follows: relatives of depressed probands who committed suicide, 0.03 (95% CI=-0.18 to 0.24); relatives of nonsuicidal depressed probands, -0.09 (95% CI=-0.35 to 0.15); and relatives of community comparison probands, -0.40 (95% CI=-0.65 to -0.15). Pairwise comparisons revealed significant differences between relatives of depressed probands who committed suicide and relatives of community comparison probands ($p=0.01$), but not relatives of depressed probands who committed suicide and

relatives of nonsuicidal depressed probands or relatives of nonsuicidal depressed probands and relatives of community comparison probands.

Re-evaluating the model with relatives of nonsuicidal depressed probands and community comparison probands combined revealed significant contributions from family history ($F=4.03$, $df=1$, 63.82 , $p<0.05$), age ($F=12.75$, $df=1$, 176.75 , $p\leq 0.001$), and the intercept ($F=7.34$, $df=1$, 170.81 , $p<0.01$). Estimated means for cluster B traits were as follows: positive family history, 0.02 (95% CI= -0.18 to 0.24); negative family history, -0.25 (95% CI= -0.43 to -0.07).

Thus, familial predisposition to suicide was associated with increased cluster B traits, although the effect was less pronounced with the three-group definition.

Are cluster B traits familial? We next tested whether cluster B traits were themselves familial by predicting the aggregate cluster B trait measure as a function of diagnostic criteria for cluster B disorders among index subjects. This model did not include familial predisposition to suicide. Significant contributions to the model were from the absence or presence of cluster B disorders among index subjects ($F=131.80$, $df=1$, 171.47 , $p\leq 0.001$), age ($F=14.70$, $df=1$, 176.05 , $p\leq 0.001$), and the intercept ($F=91.55$, $df=1$, 175.74 , $p\leq 0.001$). The estimated trait mean for relatives of probands who met criteria for cluster B personality disorders was 2.67 (95% CI= 2.18 to 3.17), and the estimated trait mean for relatives of probands who did not meet criteria for these disorders was -0.23 (95% CI= -0.34 to -0.13). Thus, cluster B traits demonstrated familial loading.

Association with recurrence of suicidal behavior in relatives. To test whether the cluster B aggregate was associated with recurrence of suicidal behavior in relatives, we evaluated a model predicting recurrence of suicidal behavior among relatives and included the aggregate and age. The intercept did not significantly contribute to the model, and thus it was removed and the model re-evaluated. The final model received contributions from cluster B traits ($F=17.33$, $df=1$, 170 , $p\leq 0.001$) and age ($F=20.39$, $df=1$, 170 , $p\leq 0.001$). Fixed-effects estimates revealed a positive association between the cluster B aggregate and suicide attempts (0.10 , 95% CI= 0.05 – 0.15 ; $t=4.16$, $df=170$, $p\leq 0.001$).

Mediating familial predisposition. To evaluate mediation, we followed Baron and Kenny's (49) criteria. In predicting recurrence of suicidal behavior among relatives, we included family history, the cluster B aggregate, and age. The intercept did not significantly contribute to the model and was removed prior to reporting final effects. The model revealed a significant effect for cluster B traits ($F=13.07$, $df=1$, 167 , $p\leq 0.001$), but not age, and a large decrease in effect for familial predisposition to suicide that no longer significantly contributed to the model was found ($F=1.88$, $df=2$, 167 , $p=0.14$). Estimates revealed that increased cluster B traits were associated with suicidal behavior (0.09 , 95% CI= 0.04 – 0.14 ; $t=3.67$, $df=168$, $p\leq 0.001$), suggesting that cluster B traits act as intermediate pheno-

types accounting for a portion of the familial vulnerability to suicide.

Cluster B Traits and the Severity of Suicidal Behavior

Since cluster B traits act as intermediate phenotypes of suicide, we hypothesized that this would extend to an association between cluster B traits and severity of suicidal behavior. We therefore repeated endophenotype analyses examining the medical severity of suicidal behavior. These models are detailed in the data supplement accompanying the online version of this article, and the approach and results are summarized in Figure 2. Briefly, identical results emerged, with increased severity of suicidal behavior associated with both a family history of suicide and cluster B traits, and, most importantly, cluster B traits mediated the relationship between family history and severity of suicidal behavior.

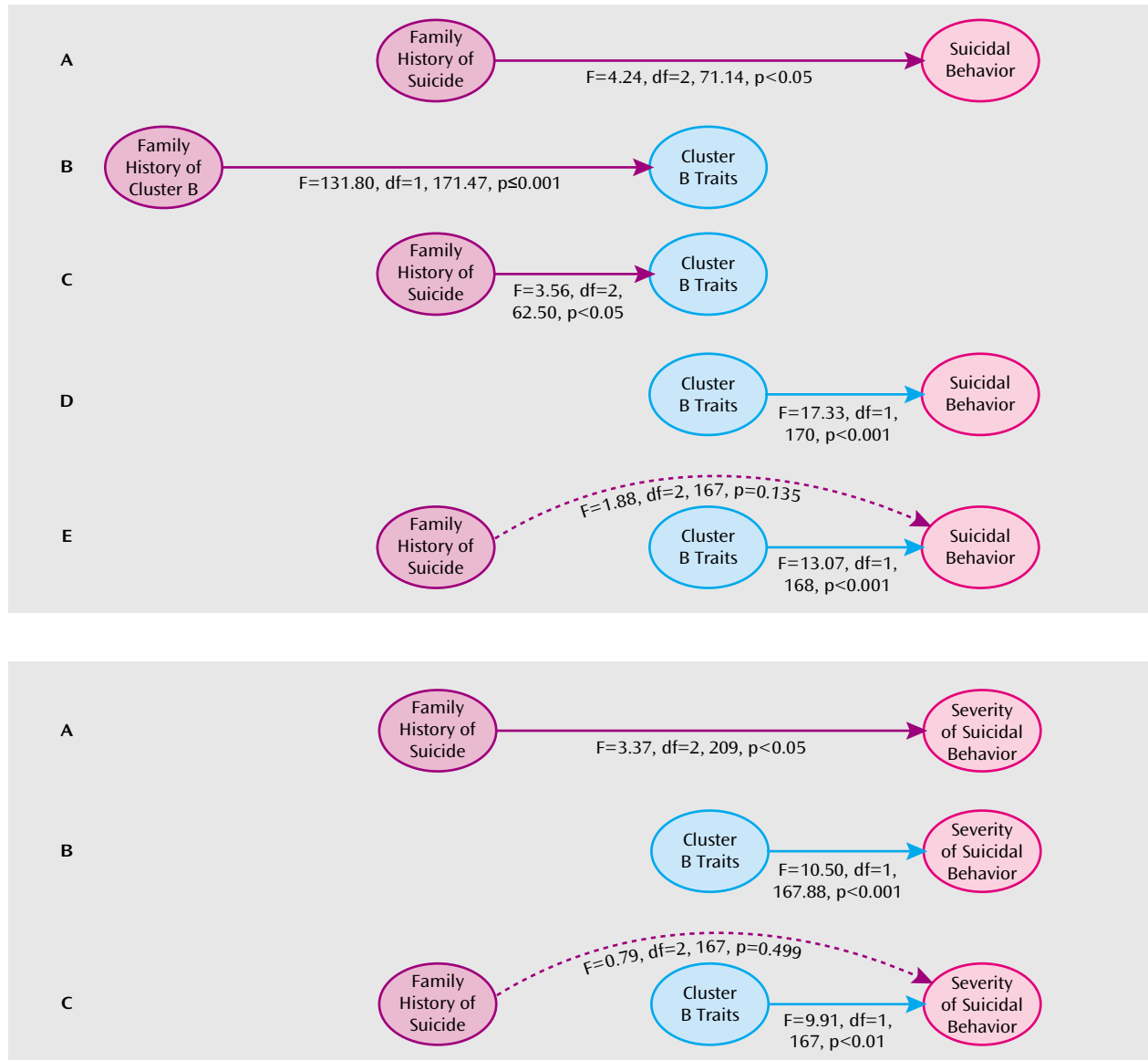
Discussion

The familial aggregation of suicidal behavior has been investigated in previous studies. Although it is clear that suicide has a familial component, an issue that has remained to be addressed more clearly is the amount of overlap between the liabilities for suicide and psychopathology. We addressed this issue in the present study using a three-group family design.

Suicidal Behavior

A well-established observation in suicide studies is that lethal and nonlethal suicidal behaviors, although distinct entities, are partially overlapping (53). In the present study, we were able to examine familial recurrence of both lethal and nonlethal suicidal behaviors, although direct and blind interviews with relatives limited our investigation of cluster B traits as endophenotypes of suicide to nonlethal suicidal behavior.

Our results demonstrate that the familial liabilities to suicide and major depression are distinct. In our sample, a higher proportion of relatives of depressed probands who committed suicide died by suicide (1.6%) compared with relatives of nonsuicidal depressed probands (0.6%) and relatives of community comparison probands (0.0%). With respect to combined lethal and nonlethal suicidal behaviors, a substantially higher proportion of relatives of depressed probands who committed suicide engaged in suicidal behavior (10.8%) compared with relatives of nonsuicidal depressed probands (6.5%) and relatives of community comparison probands (3.4%). This finding is consistent with recurrence rates reported in previous family studies of suicide with probands who committed suicide and comparison probands (7). The gradient in recurrence reported in the present study confirms a degree of overlap in the familial loading of suicide and major depressive disorder and, more importantly, indicates a familial compo-

FIGURE 2. Cluster B Traits as Intermediate Phenotypes of Suicidal Behavior^a

^a Traits co-occurring with impulsive-aggressive behavior are represented.

nent for suicide outside of the domain of liability to psychiatric illness.

Liability to Psychiatric Illness

Families identified by increased risk for major depression were remarkably similar with respect to the loading of psychopathology. Most importantly, by identifying families via a proband with major depressive disorder, similar recurrence rates of major depressive disorder were found. Moreover, the rate of approximately 15%, compared with 3% among the relatives of community comparison probands screened for the absence of this condition, is consistent with the literature on familial loading for affective disorders (54). Although we expected to find differences in the clinical manifestation of the disorder, such as age of

onset (mean age: 35.76 years [SD=13.05] versus 36.26 years [SD=15.00]) or number of depressive episodes (mean number of episodes: 1.34 [SD=0.58] versus 1.45 [SD=0.73]), to contribute to differences in suicidal behavior, analyses from our sample suggest that this is not the case ($p>0.52$).

Impulsivity and Aggression

Support for the role of cluster B personality disorders and impulsive aggression in the familial transmission of suicidal behavior has been obtained from studies with suicide attempters (3, 8) and completers (7, 10). It has also been reported that the offspring of suicide attempters score higher on measures of impulsive aggression, in addition to attempting suicide at a younger age (55), and im-

pulsivity and aggression appear to serve as intermediate phenotypes of suicide, principally among younger individuals (26).

An important contribution of the present study is the formal testing of cluster B traits as intermediate phenotypes of suicide. Using an aggregate measure of cluster B traits consisting of commonly used measures of impulsive aggression and cluster B personality psychopathology, our study clearly indicates that familial aggregation of suicide is partly and significantly explained by the transmission of cluster B traits. The relatives of probands who committed suicide had elevated levels of cluster B traits and were more likely to engage in suicidal behavior, and these variables were of greater severity in this group. Moreover, cluster B traits showed evidence of familial loading and were strongly associated with suicidal behavior. Last, the relationship between family history and suicidal behavior was accounted for, at least in part, by levels of cluster B traits. Thus, our study indicates that impulsive-aggressive traits act as intermediate phenotypes.

Recent research has highlighted the role of abuse in the familial transmission and elicitation of impulsive-aggressive behavior in suicide (3). A possible proposition is that life events (56), particularly childhood adversity (57, 58), exacerbate pre-existing vulnerabilities and, in their presence, are conducive to a range of psychiatric conditions and suicide. An alternative interpretation is that vulnerability to cluster B traits may concomitantly increase and/or influence the risk for childhood adversity, a phenomenon known as gene-environment correlations.

Strengths and Limitations

A strength of the present study is the cross-generational, three-group design decorticating familial liability to major depression and suicide. Moreover, the study benefits from direct and blind assessment of relatives as opposed to proxy-based familial assessment.

A limitation to the study is the cross-sectional, retrospective assessment of psychopathology and suicidal behavior. The necessary postmortem assessment of probands who committed suicide using proxy-based interviews was counterbalanced by similar methods for all probands, thereby avoiding any artifacts related to postmortem characterization. We were limited in our ability to examine suicide completion among relatives. Thus, future investigation in larger samples is warranted.

Conclusions

The present study investigated, by design, the extent of overlap between familial liability to major depressive disorder and suicide. We found that the liability to suicide is overlapping with, yet distinct from, liability to major depressive disorder. A marked gradient emerged consistent with this distinct and overlapping liability. Moreover, our analyses indicate that cluster B traits are endophenotypes

of suicide and account for, in part, familial aggregation of suicidal behavior.

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