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Suicidal Behavior Is Associated with Reduced Corpus Callosum Area

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Background: Corpus callosum (CC) size has been associated with cognitive and emotional deficits in a range of neuropsychiatric and mood disorders. As such deficits are also found in suicidal behavior, we investigated specifically the association between CC atrophy and suicidal behavior.

Methods: We studied 435 right-handed individuals without dementia from a cohort of community-dwelling persons aged 65 years and over (the ESPRIT study). They were divided in three groups: suicide attempters (n = 21), affective control subjects (AC) (n = 180) without history of suicide attempt but with a history of depression, and healthy control subjects (HC) (n = 234). T1-weighted magnetic resonance images were traced to measure the midsagittal areas of the anterior, mid, and posterior CC. Multivariate analysis of covariance was used to compare CC areas in the three groups.

Results: Multivariate analyses adjusted for age, gender, childhood trauma, head trauma, and total brain volume showed that the area of the posterior third of CC was significantly smaller in suicide attempters than in AC (p = .020) and HC (p = .010) individuals. No significant differences were found between AC and HC. No differences were found for the anterior and mid thirds of the CC.

Conclusions: Our findings emphasize a reduced size of the posterior third of the CC in subjects with a history of suicide, suggesting a diminished interhemispheric connectivity and a possible role of CC in the pathophysiology of suicidal behavior. Further studies are needed to strengthen these results and clarify the underlying cellular changes leading to these morphometric differences.

Key Words: Corpus callosum, magnetic resonance imaging, suicidal behavior

Corpus callosum (CC) is the main commissure between the two cerebral hemispheres, traversing the subcortical white matter. Corpus callosum contains between 200 and 8000 million axon fibers and is of crucial importance in interconnecting associative brain areas that play a pivotal role in the integration of interhemispheric information and higher cognitive functions. Corpus callosum shows considerable interindividual variability in size and shape, varying furthermore with handedness (1), gender (2,3), and normal aging (4). However, CC size is also susceptible to modification by environmental factors and particularly early life experiences. Indeed, reduced CC size has been linked to early severe stress, such as maltreatment or sexual abuse in childhood (5,6). The pathological and clinical significance of CC atrophy is poorly understood because this structure is relatively understudied in psychiatric disorders, but some links with neuropsychiatric pathologies have been established. Associations with CC abnormalities have been reported in neurodegenerative diseases (7–9) but also in autism (10–12), schizophrenia, (13,14), unipolar depression (15,16), and bipolar disorders (17–19). Thus, CC alterations might contribute to abnormal interhemispheric connectivity and may underlie functional abnormalities of brain regions that are involved in the pathophysiology of mood disorders, such as the dorsolateral prefrontal cortex, anterior cingulate, amygdala, and hippocampus (20,21). Furthermore, CC alterations may lead to cognitive and emotional deficits (22). Vulnerability to suicidal behavior (SB) (i.e., suicide attempt or completion) has been linked with specific neurobiological abnormalities (23), with possible increased sensitivity to negative emotions (24), and with abnormal cognition (25, particularly problem-solving deficits (26); however, to date, there is little evidence about a possible association between CC size and suicidal behavior. To our knowledge, only one clinical study conducted in patients with bipolar disorder has investigated this question and found an inverse correlation between CC size and suicide attempt (27). The association between CC size and SB has never been studied in the general population. Researchers in the field have long advocated considering suicidal behavior, defined as a suicide attempt or completion, as a specific nosological entity (28). This historic turning point in suicidology resulted from the demonstration that psychobiological abnormalities are associated with vulnerability to SB, independently of co-occurring psychiatric disorders. These observations have led to increased interest in identifying further etiologic factors and their effects on brain and psychological functioning for a better understanding of the pathophysiology of suicidal behavior.

The purpose of this study was to examine the association between a set of CC measures and suicidality in a sample of elderly subjects selected from a population-based study.

Methods and Materials

Study Population

Subjects were selected among the individuals who were recruited for the ESPRIT Project (Montpellier, France) (26) between 1999 and 2001. This study is part of a wider, multisite cohort study of...
community-dwelling people aged 65 years and over from the electoral rolls of three French cities (Bordeaux, Dijon, and Montpellier). Subjects were interviewed initially either at one of the study centers or in their own home if disabled. Refusers (among whom 3.3% were excluded because of severe disability) were replaced by other subjects drawn at random from the same electoral division such that each division was equally represented. Refusers were generally slightly older and more likely to live alone than people who accepted to take part in the study. The study protocol was approved by the Ethical Committee of the University-Hospital of Bicêtre (France) and written informed consent was obtained from each participant. The principal aim of this study was to construct a comprehensive database incorporating clinical, biological, genetic, and environmental risk factors of psychiatric diseases, including a neuroimaging component.

For the present study, subjects from the ESPRIT cohort \((n = 1863)\) were randomly preselected based on the following criteria: age \(\leq 80\) years and availability of magnetic resonance imaging (MRI) with estimations of CC areas and total brain volume \((n = 710)\). This group was then further reduced by eliminating people who were left-handed \((n = 50)\) \((29)\) or whose handedness was not specified or with missing variables of interest \((n = 23)\), as well as people who had a diagnosis of dementia \((n = 15)\) (see flow chart, Figure 1). The remaining individuals were then interviewed to collect clinical and demographic data to eliminate people with missing information or who did not match the group criteria (see below).

**Standardized Psychiatric Interview**

The clinical examination consisted of a standardized neurological examination carried out by a neurologist and the administration of the Mini International Neuropsychiatric Interview (MINI) (French version 5.00). The MINI has been previously validated in the general population setting \((30)\) and can be used to identify, based on DSM-IV criteria \((31)\), suicidal behaviors and suicidal ideation, as well as the main Axis I psychiatric disorders. The MINI was administered by trained interviewers (nurses and psychologists) and positive cases were reviewed by a clinical panel of three psychiatrists. Depressive symptomatology at inclusion was also assessed using the Center for Epidemiological Studies-Depression scale (CES-D) \((32)\) with a cutoff score of \(> 16\) indicating a high level of symptomatology.

**Other Measured Variables**

A standardized interview included questions on demographic characteristics and education level (classified in three groups corresponding to primary, secondary, and tertiary level of education), along with a general health questionnaire, including medical his-

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Figure 1. Flow chart. AC, affective control subjects; HC, healthy control subjects; MRI, magnetic resonance imaging; SA, subjects with a history of suicide attempt.
tory, medication, self-reported social isolation, current alcohol consumption, and tobacco use.

A retrospective self-report questionnaire, which examined traumatic experiences during childhood and adolescence based on existing instruments including the Childhood Trauma Questionnaire (33), was also given to the participants. Subjects were asked to respond yes or no to each item. Nine questions about abuse or maltreatment were used in the present study. Finally, global cognitive function was assessed using the Mini-Mental State Examination test (34) and IQ was estimated by the French language adaptation of the National Adult Reading Test (35).

Criteria for Group Assignment
On the basis of the results of the psychiatric interview and clinical history, the remaining participants (n = 435) were divided in three groups: 1) subjects with a history of suicide attempt (SA) (n = 21); 2) affective control subjects (AC) (n = 180) without a history of suicidal behavior (suicide attempt or suicidal ideation) but with lifetime (past or current) history of major depression (MINI) or current high depressive symptomatology (CES-D > 16); and 3) healthy control subjects (HC) (n = 234) without a history of suicidal behavior or of major depression, current low depressive symptomatology (CES-D < 16), and no psychotropic medication use (Figure 1).

MRI Imaging Analysis
Corpus Callosum Measurement. A 1.5 T GE Signa Imaging System (General Electric Medical Systems, Milwaukee, Wisconsin) was used to acquire a contiguous anterior commissure–posterior commissure aligned axial inversion recovery-prepared spoiled gradient recalled T1-weighted sequence for volumetric estimations (repetition time = 12, echo time = 2.8, inversion time = 600, matrix size = 256 × 256, pixel spacing = .9375 × .9375 mm, number of excitations = 1, slice thickness = 1.0 mm). Slices were then converted to isotropic (.9375 mm³) and resliced to 1.00 mm³. The CC outline was manually traced on the midline sagittal slice of the T1 images using anatomical landmarks in a hierarchical order (36) and the region of interest module of Analyze 9.0 (Brain Imaging Resource, Mayo Clinic, Rochester, Minnesota) on a Windows XP Professional workstation (Microsoft, Redmond, Washington). The landmarks based on the midline sagittal slice were 1) no white matter or only minimal white matter in the cortical mantle surrounding the CC; 2) the interhilaramic adhesion; and 3) the transparent septum and the visibility of the aqueduct of Sylvius (37). Using landmarks adapted from Witelson (2), the manually segmented CC outline was then automatically divided into three or five subregions as previously described (13,38,39). Specifically, the traced CC was divided in three equal-length parallel horizontal divisions (subregions) using the division feature within the region of interest module of the Analyze software and the area within each division was calculated. For three parallel subregions, the Grid option was used to divide the object (whole CC) vertically into three subregions (CC1 to CC3, CC1 incorporates the rostrum and genu and CC3 is the splenium) along the horizontal axis, and areas were then calculated. Figure 2 shows the three-division CC partitioning scheme. All callosal areas were expressed in mm³.

Intrarater and Interrater Reliability. The CC outlines were traced by two trained researchers blind to the study hypotheses, group assignments, and subjects’ identities. The reliability of the CC measurements was assessed using a formula to calculate the intraclass and interclass correlations that presumes random selection of raters (40). The two researchers (J.M., C.M.) each retraced five MRI images that were randomly selected among the images they previously traced and five images that belonged to the group previously traced by the other researcher. Intraclass correlation was .957 for J.M. and .962 for C.M. Interclass correlation was .915. All these values are well within acceptable limits.

Brain Volume. Total brain volume (gray plus white matter) was computed for each subject using the segment m-file of the SPM5 software (Wellcome Department of Cognitive Neurology, London, United Kingdom). All outputs were manually inspected to ensure accurate and valid data. These data were used as covariates to minimize the effect because of global brain size differences.

Statistical Analysis
Descriptive analyses were carried out using the chi-square or analysis of variance tests, based on the variable characteristics. Analyses were two-tailed and significance was set at .05. Corpus callosum measurements were found to be normally distributed based on the Shapiro-Wilk test. Differences between groups were calculated with the multivariate analysis of covariance (MANCOVA), which allowed the composite evaluation of the entire set of CC measures (anterior, mid, posterior, and total midsagittal areas) that are correlated and not fully independent. This analysis was performed with gender, age, head trauma, childhood abuse, and total brain volume as covariates. Following an overall significant MANCOVA, group differences for each CC area were also assessed by analysis of covariance with the same variables as covariates.

Finally, we carried out supplementary analyses to assess the reliability of our findings. Specifically, the association between CC
size and suicidal behavior was re-examined after exclusion of men, of cases of bipolar disorder, and of cases of lifetime anxiety in the HC group.

All statistical analyses were conducted using SPSS for Windows version PASW 17.03 (SPSS, Inc., Chicago, Illinois).

Results

Characteristics of the HC, AC, and SA Groups

The SA group had a significantly higher percentage of women than the HC group (76.2% vs. 38%; p = .001) but was not statistically different from the AC group (65%; p = .30) (Table 1). Although SA and AC subjects presented a comparable frequency of current high depressive symptomatology, a higher percentage of SA individuals reported a major depressive episode during their lifetime (85.7% of SA and 59.4% of AC; p = .014). The SA and AC groups had comparable rates of lifetime history of anxiety (36.8% and 36%; p = .945), whereas anxiety was much less frequently reported within the HC group (14.1%; p = .009 with SA), anxiolytic consumption was higher in the SA group compared with the AC group (33.3% and 13.3%; p = .001). Although not statistically significant, we also observed a trend toward increased alcohol consumption in the SA group (28.6% vs. 12.4% and 18.1% for HC and AC, respectively).

The SA subjects presented a significantly higher rate of childhood abuse (52.4%) than HC (9.4%; p < .001) and AC individuals (16.7%; p < .001). In accordance with previous studies, SA subjects reported a significantly (p < .001) higher rate of head trauma (36.8%) than people in the HC (9.1%) and AC (8.9%) groups.

Analysis of the Association Between a Set of CC Measures and Suicidal Behavior

Table 2 gives the mean values (in mm²) of the areas of the three midsagittal (anterior, mid, and posterior) CC subregions, as well as of the total midsagittal area in the three groups (HC, SA, and AC). The major variation among groups was observed for the values of the posterior third area of CC, which appeared to be smaller in the SA group (219.5 ± 55.4 mm²) than in the HC (245.5 ± 42.6 mm²) or AC groups (249.7 ± 46.9 mm²). Multivariate analysis of covariance was then used to assess whether the three groups were statistically different relative to the CC volumes after adjustment for gender, age, head trauma, childhood abuse, and total brain volume. Overall, there were significant differences in the three groups [MANCOVA Wilks Λ = .95; F(4,404) = 3.10; p = .002]. There was a robust difference between the SA and HC groups [MANCOVA Wilks Λ = .92; F(4,179) = 3.89; p = .028] and also between the SA and AC groups [MANCOVA Wilks Λ = .95; F(4,237) = 2.78; p = .055]; however, no significant multivariate difference was observed between the HC and AC groups [MANCOVA Wilks Λ = .98; F(4,385) = 1.34; p = .252] (Table 2, right panel).

Univariate F tests indicated that the principal differences between the SA and HC groups (p = .010) and between the SA and AC groups (p = .020) concerned the size of the posterior third of CC (Table 2). We then assessed group differences for each CC region by analysis of covariance with the same variables as covariates and confirmed that the size of the posterior third area of the CC was significantly smaller in the SA than in the HC or the AC group (Figure 3). Partial eta squared representing the proportion of the variance

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explained by SB of the posterior third of the CC were 1.9% and 5.6% when SA was compared with HC and AC, respectively. We found no statistical differences for the other CC regions.

Multivariate analysis of covariance also showed a significant overall effect of gender (p = .014), age (p < .0001), and total brain volume (p < .0001) on CC size; conversely, no significant effect of history of childhood abuse (p = .536) and head trauma (p = .153) on CC size was observed.

Finally, the association between smaller CC size and SA group was re-examined after 1) exclusion of men, to eliminate completely the gender effect, because the SA group contained a significantly higher percentage of women (76%) than the two other groups (38% in the HC group and 65% in the AC group); 2) exclusion of cases of bipolar disorder, to eliminate a specific effect of this disorder (38% in the HC group and 65% in the AC group); and 3) exclusion of cases of anxiety in the HC group, to allow comparison with other studies in which, generally, the SA group was characterized also by higher rate of lifetime history of major depression than the AC group (85.7 vs. 59.4, p < .014), the fact that statistical analyses did not show any significant difference in CC size between the AC and HC groups is in favor of a specific, depression-independen
t effect of CC size on suicidal behavior. Our observations further support previous reports indicating that suicidal behavior may have a specific underlying biological basis and therefore constitute a separate nosological entity (28) independent of co-occurring psychiatric disorders.

Our findings suggest the presence of abnormal interhemispheric connectivity in suicidal behavior. Specifically, a direct link between testosterone and suicide attempt has not been established in all studies, particularly when confounding factors are involved. Indeed, neonatal injection of testosterone increases the CC size in male rats. In humans, a direct correlation between testosterone level and the posterior part of CC, which is hypothesized to contain testosterone-sensitive fibers (46), has been reported (47). Because some studies have shown a correlation between low levels of testosterone and suicidal behavior (48,49), it may be hypothesized that volume reduction of the posterior third of CC observed in the SA group might be the result of low testosterone levels during the neonatal period. This assumption is, however, questionable, as a direct link between testosterone and suicide attempt has not been established in all studies, particularly when confounding fac-

### Discussion

To our knowledge, this study demonstrates for the first time the existence of structural abnormalities in CC of elderly individuals with suicidal behavior. Specifically, the size of the posterior third of CC was smaller in subjects in the suicidal group (SA) than in HC or the affective control group (AC). Although the SA group was characterized also by higher rate of lifetime history of major depression than the AC group (85.7 vs. 59.4, p < .014), the fact that statistical analyses did not show any significant difference in CC size between the AC and HC groups is in favor of a specific, depression-independent effect of CC size on suicidal behavior. Our observations further support previous reports indicating that suicidal behavior may have a specific underlying biological basis and therefore constitute a separate nosological entity (28) independent of co-occurring psychiatric disorders.

There has been little previous research aiming to explain the relationship between SB and CC size. We attempted, nonetheless, to further explore two hypotheses that have previously been proposed to explain variations in CC size in adulthood. According to the first, CC size is influenced by hormonal stimuli during the neonatal period. Several studies provide direct experimental evidence implicating androgenic hormones (particularly testosterone) as an etiologic factor that can affect CC development in nonhuman species. Indeed, neonatal injection of testosterone increases the CC size of female rats in adulthood (45), while neonatal blockade of androgen receptors followed by neonatal castration reduces adult CC size in male rats. In humans, a direct correlation between testosterone level and the posterior part of CC, which is hypothesized to contain testosterone-sensitive fibers (46), has been reported (47). Because some studies have shown a correlation between low levels of testosterone and suicidal behavior (48,49), it may be hypothesized that volume reduction of the posterior third of CC observed in the SA group might be the result of low testosterone levels during the neonatal period. This assumption is, however, questionable, as a direct link between testosterone and suicide attempt has not been established in all studies, particularly when confounding fac-

### Table 2. Comparison of CC Area Values in the Suicide Attempt Group, Affective Control Group, and Healthy Control Group

<table>
<thead>
<tr>
<th>Groups</th>
<th>Differences</th>
<th>SA Versus HC</th>
<th>SA Versus AC</th>
<th>HC Versus AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Third Area</td>
<td>.840</td>
<td>.560</td>
<td>.660</td>
<td>.790</td>
</tr>
<tr>
<td>Mid Third Area</td>
<td>.090</td>
<td>.221</td>
<td>.061</td>
<td>.202</td>
</tr>
<tr>
<td>Posterior Third Area</td>
<td>.010</td>
<td>.010</td>
<td>.020</td>
<td>.541</td>
</tr>
<tr>
<td>Midsagittal Total Area</td>
<td>.942</td>
<td>.913</td>
<td>.911</td>
<td>.733</td>
</tr>
<tr>
<td>MANCOVA</td>
<td>p = .002</td>
<td>p = .028</td>
<td>p = .005</td>
<td>p = .252</td>
</tr>
</tbody>
</table>

AC, affective control group; CC, corpus callosum; HC, healthy control group; MANCOVA, multivariate analysis of covariance; SA, suicide attempt group.

**Figure 3.** The significant association between smaller volume of the posterior third of corpus callosum and suicidal behavior (suicide attempt group) was confirmed by analysis of covariance. Mean values of the areas of corpus callosum posterior region for each group are indicated by a horizontal line. AC, affective control subjects; HC, healthy control subjects; SA, subjects with a history of suicide attempt.

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tors, including circadian variation, have been taken into consideration (50). Recent findings suggest a role for ovarian hormones in suicidal behavior, (51) with animal studies furthermore suggesting that these hormones may be related to developmental organization and CC size (52). These observations of an association between hormones and CC size are, however, only tentative, with further studies being needed to more precisely describe this mechanism.

The second hypothesis is environmental. The CC is a structure that continues to grow during childhood, adolescence, and early adulthood. This structure may therefore be sensitive to environmental stimuli for many years. It is known that a very early experience can dramatically influence CC morphometry. In nonhuman species, CC development has been reported to be affected by environmental stimuli or insults (53). Corpus callosum size was reduced in male primates that were isolated during early development. In humans, relationships have been found between CC size and history of neglect, parental verbal abuse, and sexual abuse during childhood and adolescence (6,54,55). In our sample, childhood abuse and/or maltreatment were present in 52.4% of subjects with suicidal behavior and could explain the atrophy of CC among suicide attempters. However, we did not find a direct effect of childhood abuse or maltreatment on CC size; in our study, all forms of abuse have been summated, not permitting us to examine the relationship between CC size and type of abuse.

Our findings should be considered preliminary because of the following limitations. First, the sample size of suicide attempters was limited to 21 individuals; however, these subjects were taken from a large group of randomly selected members of the community, which enhanced the generalizability of the findings. Second, our three groups were not optimally matched for gender, which is an important variable affecting CC size (3). However, our results were confirmed also after sex adjustment and after exclusion of men in the supplementary analyses, suggesting that the observed size reduction of the posterior region of CC was probably associated with suicidal behavior rather than gender. Third, the history of suicide attempts and depressive episodes was obtained by directly interviewing the subjects, who were then evaluated retrospectively with a standardized instrument, leading to possible recall bias. While reporting of psychiatric symptoms is open to recall bias, everyday clinical practice depends largely on this method.

This study is the first to report a link between the size of CC and suicidal behavior in an elderly general population. Future structural and diffusion tensor imaging studies to measure white matter integrity would be helpful for exploring the interhemispheric communication in suicidal behavior to confirm and extend the present findings.

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