HAL
archives-ouvertes.fr

Suicidal behavior is associated with reduced corpus callosum area.

Fabienne Cyprien, Philippe Courtet, Alain Malafosse, Jerome Maller, Chantal Meslin, Alain Bonafé, Emmanuelle Le Bars, Nicolas Menjot De Champfleur, Karen Ritchie, Sylvaine Artero

▶ To cite this version:

HAL Id: inserm-00841564

http://www.hal.inserm.fr/inserm-00841564

Submitted on 5 Jul 2013

Suicidal behavior is associated with reduced corpus callosum area.

Cyprien Fabienne*[1,2,3], Courtet Philippe*[1,2,3], Malafosse Alain[1,4], Maller Jerome [5],

Meslin Chantal [6], Bonafé Alain [2,3], Le Bars Emmanuelle [2,3], Menjot de Champfleur

Nicolas [2,3] , Ritchie Karen[1,2,7], Artero Sylvaine[1,2].

[1] Inserm, U888, La Colombière Hospital, Montpellier, F-34093, France;
[2] University of Montpellier 1, Montpellier, F-34000, France;
[3] CHRU Montpellier, Montpellier, France;
[4] Department of Psychiatry, University of Geneva, CH-1211, Switzerland;
[5] Monash Alfred Psychiatry Research Centre, The Alfred & Monash University School of Psychology and Psychiatry, Melbourne, Australia;
[6] Centre for Mental Health Research, Australian National University, Canberra, Australia;
[7] Faculty of Medicine, Imperial College, St Mary's Hospital, London, United Kingdom.

*Authors F.Cyprien and P.Courtet contributed equally to this article

Corresponding Author

Sylvaine Artero
Inserm U888, Nervous System Pathologies: Epidemiological and Clinical Research,
La Colombière Hospital,
34093 Montpellier cedex 5, France
Tel: +33 4 99 61 45 68
Fax: +33 4 99 61 45 79
Email: sylvaine.artero@inserm.fr

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

Number of words-Abstract: 239; Text: 3376
Tables :3 ; Figures: 3, Supplementary material: 0

1

ABSTRACT

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 (SA) (n=21), affective controls (AC) (n=180) without history of suicide attempt but with a history of depression, and healthy controls (HC) (n=234). T1-weighted magnetic resonance images were traced to measure the midsagittal areas of the anterior, mid and posterior CC. MANCOVA 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 SA than in AC (p=0.020) and HC (p=0.010) 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 inter-hemispheric 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.

INTRODUCTION

Corpus callosum (CC) is the main commissure between the two cerebral hemispheres, traversing the subcortical white matter. CC 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 inter-hemispherical information and higher cognitive functions. CC shows considerable inter-individual 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, since 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 inter-hemispheric connectivity and may underlie functional abnormalities of brain regions that are involved in the pathophysiology of mood disorders, such as the dorso-lateral pre-frontal cortex, anterior cingulate, amygdala and hippocampus (20, 21). Furthermore, CC alterations may lead to cognitive and emotional deficits (22). Vulnerability to suicidal behavior (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 alterations 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 suicidal behavior has never been studied in the general population. Researchers in the field have long advocated considering suicidal behavior (SB), 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 etiological 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.

MATERIALS AND METHOD

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, multi-site 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 due to 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 pre-selected based on the following criteria: age ≤80 years and availability of MRI imaging 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 in order to eliminate people with missing information or who did not match the group criteria (see below).

(Figure 1 here)

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

5

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 cut-off score of >16 indicating a high level of symptomatology.

Other measured variables

A standardized interview included questions on demographic characteristics, education level (classified in three groups corresponding to primary, secondary and tertiary level of education) along with a general health questionnaire, including medical history, 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, the global cognitive function was assessed using the Mini-Mental State Examination (MMSE) test (34) and IQ was estimated by the French language adaptation of the National Adult Reading Test (NART) (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 Controls (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 Controls (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 1.5T GE Signa Imaging System (General Electric Medical Systems, Milwaukee, WI) was used to acquire a contiguous AC-PC aligned axial IR-prepared SPGR T1-weighted sequence for volumetric estimations (TR = 12, TE = 2.8, IT = 600, matrix size = 256 x 256, pixel spacing = 0.9375 x 0.9375 mm, NEX = 1, slice thickness = 1.0mm). Slices were then converted to be isotropic (0.9375 mm^3) and re-sliced to 1.00mm^3.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 (ROI) module of Analyze^{TM} 9.0 (Brain Imaging Resource, Mayo Clinic, MN, USA) on a Windows XP Professional workstation. The landmarks based on the midline sagittal slice were: i) no white matter or only minimal white matter in the cortical mantle surrounding the CC; ii) the inter-thalamic adhesion; and iii) the transparent septum and the visibility of the aqueduct of Sylvius (37). Using landmarks adapted from Witelson *et al*. (1989) (2), the manually segmented CC outline was then

7

automatically divided into three or five sub-regions as previously described (13, 38, 39). Specifically, the traced CC was divided in three equal-length parallel horizontal divisions (sub-regions) by using the 'Division' feature within the ROI module of the Analyze^{TM} software and the area within each division was calculated. For three parallel sub-regions, the 'Grid' option was used to divide the object (whole CC) vertically into three sub-regions (CC1 to 3, CC1 incorporates the rostrum and genus and CC3 is the splenium) along the horizontal axis, and areas were then calculated. Figure 2 shows the 3-division CC partitioning scheme. All callosal areas were expressed in mm^2.

Intra-rater and inter-rater reliability

CC outlines were traced by two trained researchers blind to the study hypotheses, group assignment and subjects' identity. The reliability of the CC measurements was assessed using a formula to calculate the intra- and inter-class correlations (intra-CC and inter-CC) that presumes random selection of raters (40). The two researchers (JM, CM) each retraced five MRI images, which were randomly selected among the images they previously traced, and five images which belonged to the group previously traced by the other researcher. Intra-CC was 0.957 for JM and 0.962 for CM. Inter-CC was 0.915. 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, UK). All outputs were manually inspected to ensure accurate and valid data. These data were used as covariables in order to minimize the effect due to global brain size differences.

Statistical analysis

Descriptive analyses were carried out using the chi-square or analysis of variance (ANOVA) tests, based on the variable characteristics. Analyses were two-tailed and significance was set at 0.05. CC measurements were found to be normally distributed based on the Shapiro-Wilks 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 ANCOVA 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, 1999).

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=0.001), but was not statistically different from the AC group (65 %; p=0.30) (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=0.014). The SA and AC groups had comparable rates of lifetime history of anxiety (36.8 % and 36 %, p=0.945), whereas anxiety was much less frequently reported within the HC group (14.1 %; p=0.009 with SA), anxiolytic consumption was higher in the SA group compared to the AC group (33.3 % and 13.3 %,p=0.001). 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).

SA subjects presented a significantly higher rate of childhood abuse (52.4 %) than HC (9.4 %; p<0.001) and AC individuals (16.7 %; p<0.001) In accordance with previous studies, SA subjects reported a significantly (p<0.001) higher rate of head trauma (36.8 %) than people in the HC (9.1 %) and AC (8.9 %) groups.

(Table 1 here)

Analysis of the association between a set of CC measures and suicidal behavior

Table 2 gives the mean values (in mm^2) of the areas of the three midsagittal (anterior, mid and posterior) CC sub-regions 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). MANCOVA 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=0.95; $F_{4,\ 404}$=3.10;

$p=0.002$). There was a robust difference between the SA and HC groups (MANCOVA Wilks $\Lambda=0.92$; $F_{4,\ 179}=3.89$; $p=0.028$) and also between the SA and AC groups (MANCOVA Wilks $\Lambda=0.95$; $F_{4,\ 237}=2.78$; $p=0.005$); however, no significant multivariate difference was observed between the HC and AC groups (MANCOVA Wilks $\Lambda=0.98$; $F_{4,\ 385}=1.34$; $p=0.252$) (Table 2, right panel).

Univariate F tests indicated that the principal differences between the SA and HC groups ($p=0.010$) and between the SA and AC groups ($p=0.020$) concerned the size of the posterior third of CC (Table 2). We then assessed group differences for each CC region by ANCOVA 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 explained by SB of the posterior third of the CC were 1.9 % and 5.6 % when SA was compared to HC and AC respectively. We found no statistical differences for the other CC regions.

MANCOVA also showed a significant overall effect of gender ($p=0.014$), age ($p<0.0001$) and total brain volume ($p<0.0001$) on CC size; conversely no significant effect of history of childhood abuse ($p=0.536$) and head trauma ($p=0.153$) on CC size was observed.

(Table 2 here)

(Figure 3 here)

Finally, the association between smaller CC size and SA group was re-examined after 1) exclusion of men, in order to eliminate completely the gender effect, since 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, in order to eliminate a specific effect of this disorder on CC size; 3) exclusion of cases of anxiety in the HC group, to allow comparison with other studies in which, generally, the healthy control group was free of Axis I psychiatric disorders. Results of these analyses gave similar results and p values (Table 3).

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 healthy controls (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, $p<0.014$), 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) independently of co-occurring psychiatric disorders.

Our findings suggest the presence of abnormal inter-hemispheric connectivity in suicidal behavior. Specifically reduced connectivity that affects CC may underlie functional abnormalities of brain regions involved in the pathophysiology of mood disorders (21). Callosal tracts are organized topographically (2, 41) and this indicates a functional specialization of different CC sub-regions. Callosal fibers that travel

through the posterior body of CC are thought to connect primary motor, primary sensory and parietal association cortices and could be involved in the intelligence network (42-44). Some studies (42-44) have provided evidence that also posterior brain regions (i.e., the parietal lobes) and not only the frontal lobes are involved in problem-solving processes by modulating pathways to (pre)frontal regions or by serving as key locations for the convergence of information. Suicide attempters have been reported to have problem-solving deficits (26) which may in turn be linked to CC atrophy, especially of the posterior third, as found in our study.

There has been little previous research aiming to explain the relationship between SB and CC size, we attempted, nonetheless, to further explore two hypotheses which 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 etiological factor that can affect CC development in non-human 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 males. 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). Since 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 factors, including circadian

13

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, further studies being needed to more precisely describe this mechanism.

The second hypothesis is environmental. 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 non-human species, CC development has been reported to be affected by environmental stimuli or insults (53). CC 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. But, 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 due to the following limitations. Firstly, the sample size of suicide attempters is limited to 21 individuals, however these subjects have been taken from a large group of randomly-selected members of the community, which enhances the generalizability of the findings. Second, our three groups were not optimally matched for gender, which is an important variable

14

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 attempt 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. Finally, given the associational nature of our data we cannot infer a causal relationship between CC area or size and suicidal behavior. However, it is important to note that modifications of CC volume are more likely to be the outcome of events that occurred during developmental windows when the white matter is still maturing rather than to be result of a degenerative effect that occurs in a fully developed system (6).

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 inter-hemispheric communication in suicidal behavior in order to confirm and extend the present findings.

REFERENCES

1.   Witelson SF. The brain connection: the corpus callosum is larger in left-handers. Science 1985;229:665-8.
2.   Witelson SF. Hand and sex differences in the isthmus and genu of the human corpus callosum. A postmortem morphological study. Brain 1989;112 (Pt 3):799-835.
3.   Steinmetz H, Staiger JF, Schlaug G, Huang Y, Jancke L. Corpus callosum and brain volume in women and men. Neuroreport 1995;6:1002-4.
4.   Ryberg C, Rostrup E, Stegmann MB, Barkhof F, Scheltens P, van Straaten EC, Fazekas F, Schmidt R, Ferro JM, Baezner H, Erkinjuntti T, Jokinen H, Wahlund LO, O'Brien J, Basile AM, Pantoni L, Inzitari D, Waldemar G, group Ls. Clinical significance of corpus callosum atrophy in a mixed elderly population. Neurobiol Aging 2007;28:955-63.
5.   Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM. The neurobiological consequences of early stress and childhood maltreatment. Neurosci Biobehav Rev 2003;27:33-44.
6.   Teicher MH, Dumont NL, Ito Y, Vaituzis C, Giedd JN, Andersen SL. Childhood neglect is associated with reduced corpus callosum area. Biol Psychiatry 2004;56:80-5.
7.   Hampel H, Teipel SJ, Alexander GE, Horwitz B, Teichberg D, Schapiro MB, Rapoport SI. Corpus callosum atrophy is a possible indicator of region- and cell type-specific neuronal degeneration in Alzheimer disease: a magnetic resonance imaging analysis. Archives of Neurology 1998;55:193-8.
8.   Teipel SJ, Hampel H, Alexander GE, Schapiro MB, Horwitz B, Teichberg D, Daley E, Hippius H, Moller HJ, Rapoport SI. Dissociation between corpus callosum atrophy and white matter pathology in Alzheimer's disease. Neurology 1998;51:1381-5.
9.   Di Paola M, Di Iulio F, Cherubini A, Blundo C, Casini AR, Sancesario G, Passafiume D, Caltagirone C, Spalletta G. When, where, and how the corpus callosum changes in MCI and AD: a multimodal MRI study. Neurology 2010;74:1136-42.
10.   Frazier TW, Hardan AY. A meta-analysis of the corpus callosum in autism. Biol Psychiatry 2009;66:935-41.
11.   Egaas B, Courchesne E, Saitoh O. Reduced size of corpus callosum in autism. Archives of Neurology 1995;52:794-801.
12.   Hardan AY, Pabalan M, Gupta N, Bansal R, Melhem NM, Fedorov S, Keshavan MS, Minshew NJ. Corpus callosum volume in children with autism. Psychiatry Res 2009;174:57-61.
13.   Sun J, Maller JJ, Daskalakis ZJ, Furtado CC, Fitzgerald PB. Morphology of the corpus callosum in treatment-resistant schizophrenia and major depression. Acta Psychiatrica Scandinavica 2009;120:265-73.
14.   Whitford TJ, Kubicki M, Schneiderman JS, O'Donnell LJ, King R, Alvarado JL, Khan U, Markant D, Nestor PG, Niznikiewicz M, McCarley RW, Westin CF, Shenton ME. Corpus callosum abnormalities and their association with psychotic symptoms in patients with schizophrenia. Biol Psychiatry 2010;68:70-7.
15.   Lacerda AL, Brambilla P, Sassi RB, Nicoletti MA, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC. Anatomical MRI study of corpus callosum in unipolar depression. J Psychiatr Res 2005;39:347-54.
16.   Yang Q, Huang X, Hong N, Yu X. White matter microstructural abnormalities in late-life depression. International Psychogeriatrics 2007;19:757-66.
17.   Arnone D, McIntosh AM, Chandra P, Ebmeier KP. Meta-analysis of magnetic resonance imaging studies of the corpus callosum in bipolar disorder. Acta Psychiatrica Scandinavica 2008;118:357-62.

18. Caetano SC, Silveira CM, Kaur S, Nicoletti M, Hatch JP, Brambilla P, Sassi R, Axelson D, Keshavan MS, Ryan ND, Birmaher B, Soares JC. Abnormal corpus callosum myelination in pediatric bipolar patients. J Affect Disord 2008;108:297-301.

19. Lopez-Larson M, Breeze JL, Kennedy DN, Hodge SM, Tang L, Moore C, Giuliano AJ, Makris N, Caviness VS, Frazier JA. Age-related changes in the corpus callosum in early-onset bipolar disorder assessed using volumetric and cross-sectional measurements. Brain Imaging Behav 2010;4:220-31.

20. Soares JC, Mann JJ. The functional neuroanatomy of mood disorders. J Psychiatr Res 1997;31:393-432.

21. Soares JC, Mann JJ. The anatomy of mood disorders--review of structural neuroimaging studies. Biol Psychiatry 1997;41:86-106.

22. Bellani M, Yeh PH, Tansella M, Balestrieri M, Soares JC, Brambilla P. DTI studies of corpus callosum in bipolar disorder. Biochem Soc Trans 2009;37:1096-8.

23. Mann JJ. Neurobiology of suicidal behaviour. Nat Rev Neurosci 2003;4:819-28.

24. Jollant F, Lawrence NS, Giampietro V, Brammer MJ, Fullana MA, Drapier D, Courtet P, Phillips ML. Orbitofrontal cortex response to angry faces in men with histories of suicide attempts. American Jounal of Psychiatry 2008;165:740-8.

25. Jollant F, Guillaume S, Jaussent I, Castelnau D, Malafosse A, Courtet P. Impaired decision-making in suicide attempters may increase the risk of problems in affective relationships. J Affect Disord 2007;99:59-62.

26. Pollock LR, Williams JM. Problem solving and suicidal behavior. Suicide Life Threat Behav 1998;28:375-87.

27. Matsuo K, Nielsen N, Nicoletti MA, Hatch JP, Monkul ES, Watanabe Y, Zunta-Soares GB, Nery FG, Soares JC. Anterior genu corpus callosum and impulsivity in suicidal patients with bipolar disorder. Neurosci Lett 2010;469:75-80.

28. Oquendo MA, Baca-Garcia E, Mann JJ, Giner J. Issues for DSM-V: suicidal behavior as a separate diagnosis on a separate axis. American Jounal of Psychiatry 2008;165:1383-4.

29. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97-113.

30. Lecrubier Y, Sheehnan D, Weiller E, Amorim P, Bonora I, Janavs J, Dunbar G. The MINI International Neuropsychiatric Interview (MINI), a short diagnostic interview: reliability and validity according to the CIDI. . European Psychiatry 1997;12:232-41.

31. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Washington, DC: American Psychiatric Association; 1994.

32. Radloff L. The CES-D Scale : a self report depression scale for research in the general population. Applied Psychological measurment 1977;1:385-401.

33. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, Stokes J, Handelsman L, Medrano M, Desmond D, Zule W. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse Negl 2003;27:169-90.

34. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.

35. Mackinnon A, Ritchie K, Mulligan R. The measurement properties of a French language adaptation of the National Adult Reading Test. International journal of methods in psychiatric Research 1999;8:27-38.

36. Talairach J, Tourneaux P. Referentially oriented cerebral MRI anatomy: atlas of stereotaxic anatomical correlations for gray and white matter New-York: Thieme Medical Publishers Inc; 1993.

37. Anstey KJ, Mack HA, Christensen H, Li SC, Reglade-Meslin C, Maller J, Kumar R, Dear K, Easteal S, Sachdev P. Corpus callosum size, reaction time speed and variability in mild cognitive disorders and in a normative sample. Neuropsychologia 2007;45:1911-20.

38.	Beauchamp MH, Anderson VA, Catroppa C, Maller JJ, Godfrey C, Rosenfeld JV, Kean M. Implications of reduced callosal area for social skills after severe traumatic brain injury in children. J Neurotrauma 2009;26:1645-54.

39.	Panizzon MS, Hoff AL, Nordahl TE, Kremen WS, Reisman B, Wieneke M, Harris D, Goodman C, Espinoza S, Liu W, Lim K. Sex differences in the corpus callosum of patients with schizophrenia. Schizophr Res 2003;62:115-22.

40.	Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86:420-8.

41.	Zarei M, Johansen-Berg H, Smith S, Ciccarelli O, Thompson AJ, Matthews PM. Functional anatomy of interhemispheric cortical connections in the human brain. J Anat 2006;209:311-20.

42.	Strauss E, Wada J, Hunter M. Callosal morphology and performance on intelligence tests. J Clin Exp Neuropsychol 1994;16:79-83.

43.	Luders E, Narr KL, Bilder RM, Thompson PM, Szeszko PR, Hamilton L, Toga AW. Positive correlations between corpus callosum thickness and intelligence. Neuroimage 2007;37:1457-64.

44.	Jung RE, Haier RJ. The Parieto-Frontal Integration Theory (P-FIT) of intelligence: converging neuroimaging evidence. Behav Brain Sci 2007;30:135-54; discussion 54-87.

45.	Fitch RH, Berrebi AS, Cowell PE, Schrott LM, Denenberg VH. Corpus callosum: effects of neonatal hormones on sexual dimorphism in the rat. Brain Res 1990;515:111-6.

46.	Witelson SF. Neural sexual mosaicism: sexual differentiation of the human temporo-parietal region for functional asymmetry. Psychoneuroendocrinology 1991;16:131-53.

47.	Moffat SD, Hampson E, Wickett JC, Vernon PA, Lee DH. Testosterone is correlated with regional morphology of the human corpus callosum. Brain Res 1997;767:297-304.

48.	Markianos M, Tripodianakis J, Istikoglou C, Rouvali O, Christopoulos M, Papageorgopoulos P, Seretis A. Suicide attempt by jumping: a study of gonadal axis hormones in male suicide attempters versus men who fell by accident. Psychiatry Res 2009;170:82-5.

49.	Gustavsson G, Traskman-Bendz L, Higley JD, Westrin A. CSF testosterone in 43 male suicide attempters. Eur Neuropsychopharmacol 2003;13:105-9.

50.	Perez-Rodriguez MM, Lopez-Castroman J, Martinez-Vigo M, Diaz-Sastre C, Ceverino A, Nunez-Beltran A, Saiz-Ruiz J, de Leon J, Baca-Garcia E. Lack of Association between Testosterone and Suicide Attempts. Neuropsychobiology 2010;63:125-30.

51.	Baca-Garcia E, Diaz-Sastre C, Ceverino A, Perez-Rodriguez MM, Navarro-Jimenez R, Lopez-Castroman J, Saiz-Ruiz J, de Leon J, Oquendo MA. Suicide attempts among women during low estradiol/low progesterone states. J Psychiatr Res 2010;44:209-14.

52.	Bimonte HA, Holly Fitch R, Denenberg VH. Adult ovary transfer counteracts the callosal enlargement resulting from prepubertal ovariectomy. Brain Res 2000;872:254-7.

53.	Denenberg VH, Yutzey DA. Hemispheric laterality, behavioral asymmetry, and the effect of early experience in rats. In Glick SD e editor. Cerebral lateralisation in Nonhuman Species. Orlando, Florida: Academic press; 1985, p. 109-33.

54.	Teicher MH, Samson JA, Sheu YS, Polcari A, McGreenery CE. Hurtful Words: Association of Exposure to Peer Verbal Abuse With Elevated Psychiatric Symptom Scores and Corpus Callosum Abnormalities. American Jounal of Psychiatry 2010.

55.	Andersen SL, Tomada A, Vincow ES, Valente E, Polcari A, Teicher MH. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. J Neuropsychiatry Clin Neurosci 2008;20:292-301.

Table 1. Demographic and clinical characteristics of the three groups.

Variables	Healthy Control group (HC) (n=234)	Suicide Attempt group (SA) (n=21)	Affective Control group (AC) (n=180)	P *	SA vs HC	SA vs AC
Women, % (n)	38 (89)	76.2 (16)	65 (117)	<0.001	0.001	0.300
Age, mean (SD)	71 (3.8)	72.2 (4.3)	71 (3.8)	0.247	n.a	n.a
Education level, % (n)						
low	21.4 (50)	19 (4)	28.3 (51)	0.085	n.a	n.a
medium	45.7 (107)	66.7 (14)	47.2 (85)			
high	32.9 (77)	14.3 (3)	24.4 (44)			
Living alone, % (n)	9.4 (22)	42.9 (9)	25.6 (46)	<0.001	<0.001	0.090
Tobacco use (current or past), % (n)	50.9 (119)	33.7 (7)	41.7 (75)	0.085	n.a	n.a
Alcohol consumption, % (n)	12.4 (29)	28.6 (6)	18.1 (32)	0.071	n.a	n.a
Head trauma, % (n)	9.1 (21)	36.8 (7)	8.9 (16)	0.001	<0.001	<0.001
Mini Mental State Examination (MMSE), mean (SD)	27.7 (1.7)	27.54 (1.9)	27.7 (1.8)	0.722	n.a	n.a
IQ (NART, French version)	21.5 (5.7)	22.6 (5.1)	21.1 (6.2)	0.469	n.a	n.a
High current depressive symptomatology (CES-D >16), n (%)	0 (0)	33.7 (7)	38.3 (69)	<0.001	n.a	0.650
Lifetime major depressive episode (MINI), % (n)	0 (0)	85.7 (18)	59.4 (107)	<0.001	n.a	0.014
Age at first episode, mean (SD)	n.a	41.5 (13.6)	45.3 (16.3)	0.502	n.a	n.a
Age at last episode, mean (SD)	n.a	58.8 (12)	56 (13.7)	0.398	n.a	n.a
Number of episodes, mean (SD)	n.a	1.6 (0.8)	1.6 (1)	0.069	n.a	n.a
Lifetime history of anxiety (MINI), % (n)	14.1 (33)	36.8 (7)	36 (62)	<0.001	0.009	0.945
Lifetime history of bipolar disorders (MINI), % (n)	0 (0)	10.5 (2)	1.2 (2)	<0.000	n.a	<0.000
Lifetime history of mood disorders with psychotic symptoms (MINI), % (n)	0 (0)	0 (0)	2.6 (2)	n.a	n.a	n.a
Age at first suicide attempt, mean (SD)	n.a	44.5 (7)	n.a	n.a	n.a	n.a
Childhood sexual abuse or maltreatment, % (n)	9.4 (22)	52.4 (11)	16.7 (30)	<0.001	<0.001	<0.001
Current anti-depressant medications, % (n)	0 (0)	9.5 (2)	9.4 (17)	<0.001	n.a	0.990
Current anxiolytic medications, % (n)	0 (0)	33.3 (7)	13.3 (24)	<0.001	n.a	0.016

n.a: not applicable

* Chi-square tests, analysis of variance (ANOVA), or Kendall non-parametric test as appropriate

Table 2. Comparison of CC area values in the Suicide Attempt group, Affective Control group and Healthy Control group.

Regions of corpus callosum	Groups			p values			
	Healthy Control (HC) n=234	Suicide Attempt (SA) n=21	Affective Control (AC) n=180	Overall group differences	SA vs HC	SA vs AC	HC vs AC
Anterior third area	224.1 (38.6)	223.3 (34.8)	227 (43)	0.840	0.560	0.660	0.790
Mid third area	137.5 (24.1)	144.2 (33.8)	136.8 (27.6)	0.090	0.221	0.061	0.202
Posterior third area	245.5 (42.6)	219.5 (55.4)	249.7 (46.9)	0.010	0.010	0.020	0.541
Mid-sagittal total area	607.7 (93.3)	596 (85.3)	609.5 (97.7)	0.942	0.913	0.911	0.733
				Mancova $p=0.002$	$p=0.028$	$p=0.005$	$p=0.252$

MANCOVA (multivariate analysis of covariance) with gender, age, childhood abuse, head trauma and total brain volume as covariates.

Table 3. Supplementary analyses. Comparison of CC values (post third area) in the Suicide Attempt group, Affective Control group and Healthy Control group in three different models.

Models	MANCOVA including all CC area	ANCOVA (post third CC) *p values*			
	Post third CC *p values*	Overall group differences	SA vs HC	SA vs AC	HC vs AC
Model 1. Elimination of men	0.030	0.039	0.016	0.013	0.942
Model 2. Elimination of cases of bipolar disorders	0.028	0.024	0.030	0.009	0.218
Model 3. Elimination of cases of lifetime anxiety in the HC group	0.002	0.024	0.020	0.007	0.400

```
                        ┌─────────────────────────────────┐
                        │          ESPRIT STUDY           │
                        │                                 │
                        │            n=1863               │
                        └─────────────────────────────────┘
                                        │
                                        │   Randomly selected subjects
                                        │   from the database (≤80 years
                                        │   of age)
                                        ▼
                        ┌─────────────────────────────────┐
                        │ MRI with Corpus Callosum measurement and │
                        │         brain volume            │
                        │                                 │
                        │             n=710               │
                        └─────────────────────────────────┘
                                        │
                                        ▼
            ┌──────────────────────────────────────────────────┐
            │ - Exclusion of left-handed subjects (n=50) and of │
            │ individuals with dementia (n=15)                 │
            │                                                  │
            │ - Exclusion of subjects with missing data on     │
            │ laterality and with missing variables of interest│
            │ (n=23) or who did not match the groups' criteria │
            │ (n=187)                                          │
            │                    n=435                         │
            └──────────────────────────────────────────────────┘
```

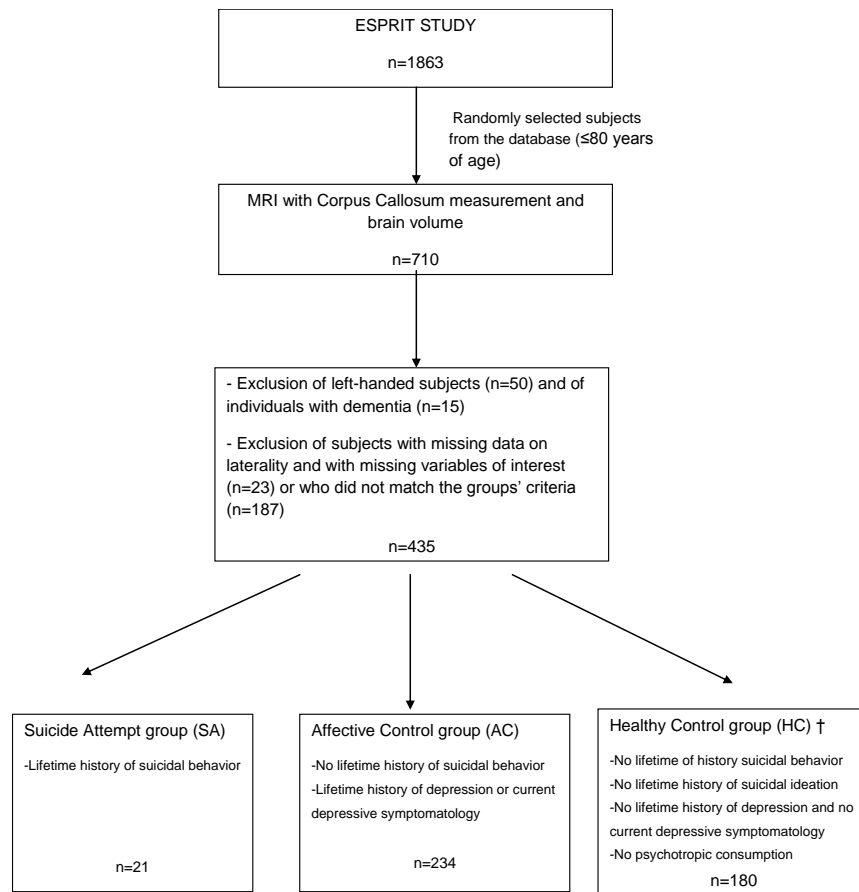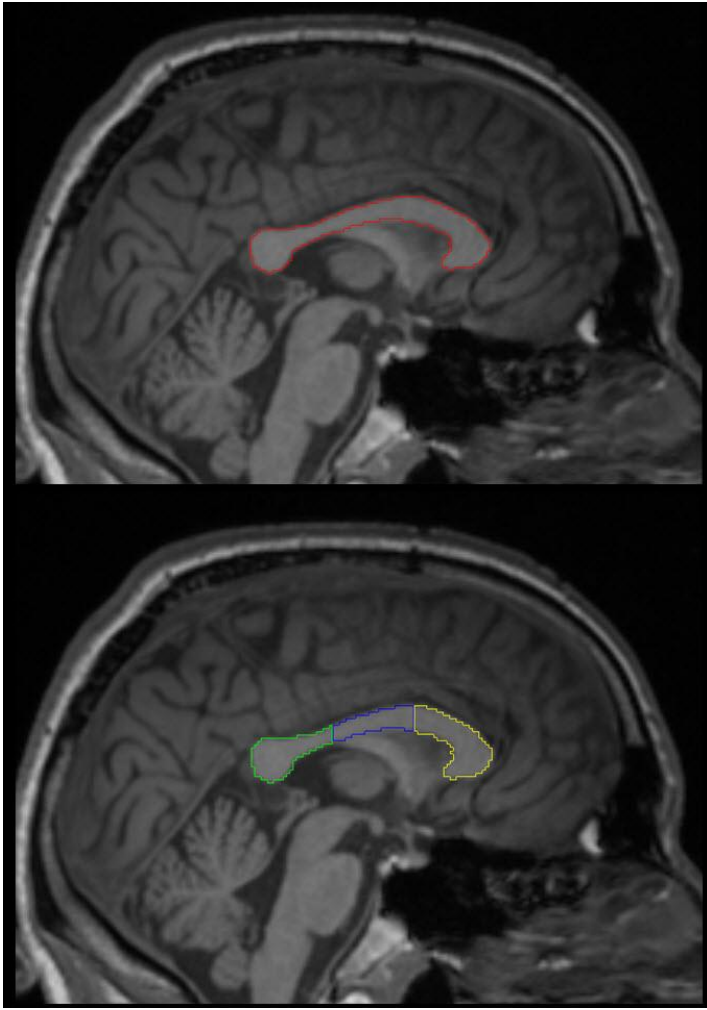| Suicide Attempt group (SA)	Affective Control group (AC)	Healthy Control group (HC) †
-Lifetime history of suicidal behavior	-No lifetime history of suicidal behavior	-No lifetime of history suicidal behavior
	-Lifetime history of depression or current depressive symptomatology	-No lifetime history of suicidal ideation
		-No lifetime history of depression and no current depressive symptomatology
		-No psychotropic consumption
n=21	n=234	n=180

Figure 1: Flow-chart

Figure 2. Example of single (top) and 3-division (bottom) partitioning of the corpus callosum. T1-weighted magnetic resonance images were traced using Analyze[TM] 9.0.
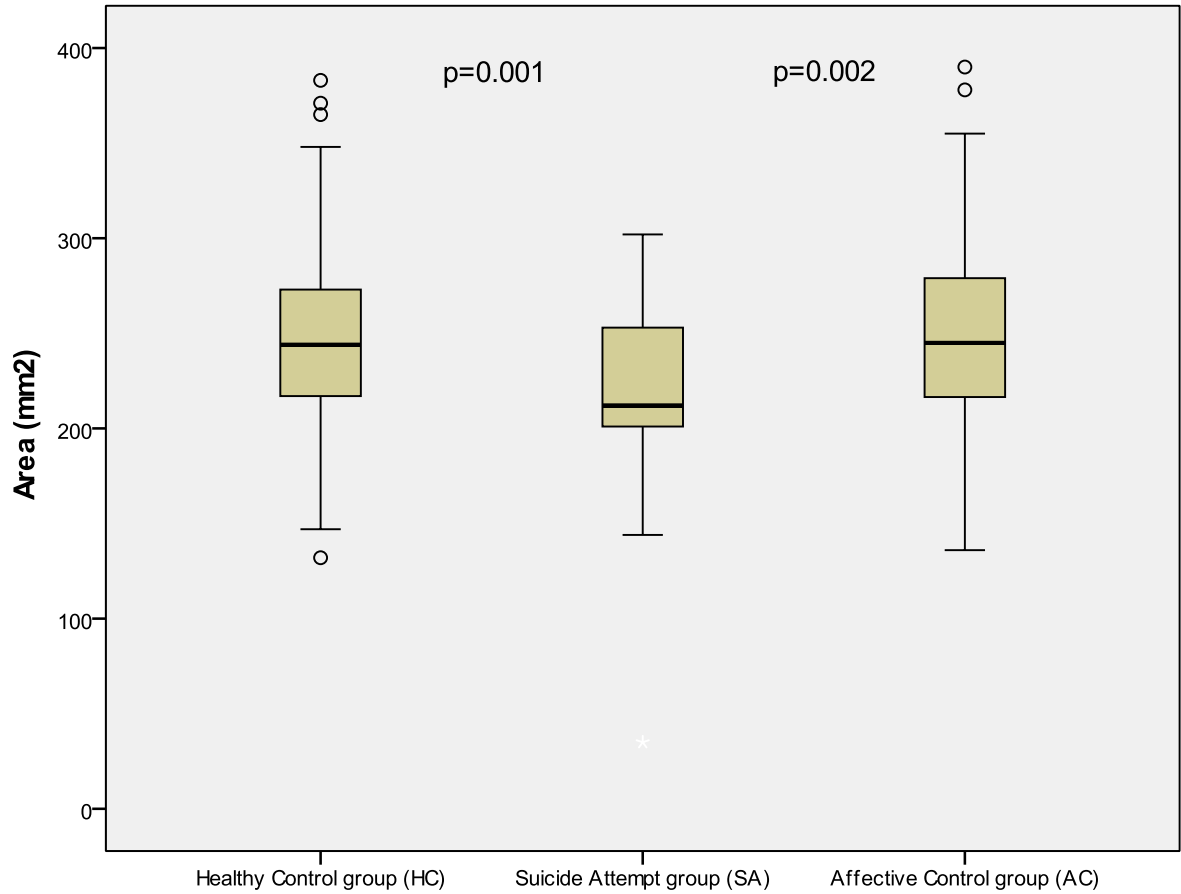
Figure 3. The significant association between smaller volume of the posterior third of corpus callosum (CC) and suicidal behavior (SA group) was confirmed by ANCOVA. Mean values of the areas of CC posterior region for each group are indicated by a horizontal line.