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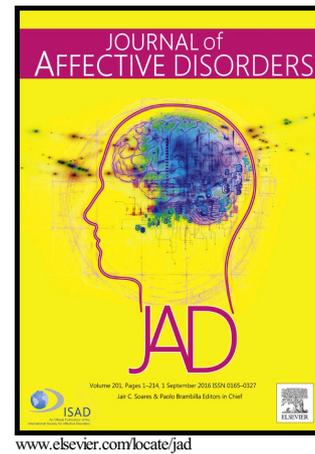
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## Author's Accepted Manuscript

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# Corpus callosum integrity is affected by mood disorders and also by the suicide attempt history: A diffusion tensor imaging study

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## Abstract

### Background

Some MRI studies have noted alterations in the corpus callosum (CC) white matter integrity of individuals with mood disorders and also in patients with suicidal behavior. We investigated the specific impact of suicidal behavior on CC integrity in mood disorders.

### Methods

CC structural changes were assessed by diffusion tensor imaging (DTI) in 121 women (18 to 50-year-old): 41 with bipolar disorder (BD), 50 with major depressive disorder (MDD) and 30 healthy controls (HC). Fractional anisotropy (FA) and DTI metrics were calculated for the genu, body and splenium of CC and compared in the three groups by MANCOVA. Then, they were re-analyzed relative to the suicide attempt history within the MDD and BD groups and to the suicide number/severity.

## Results

FA values for the CC genu and body were lower in non-suicide attempters with BD than with MDD and in HC. Conversely, FA values for all CC regions were significantly lower in suicide attempters with BD than in HC. Finally, higher number of suicide attempts (>2) and elevated Suicidal Intent Scale score were associated with significant splenium alterations.

## Limitations

Limitations include the cross-sectional design (non-causal study), the potential influence of medications and concerns about the generalizability to men. **Conclusion**

Genu and body are altered in non-suicide attempters with BD, while splenium is specifically altered in suicide attempters, independently from their psychiatric status. History of suicide attempts may be a source of heterogeneity in the association between CC alterations and BD and may partially explain the variable results of previous studies.

Keywords: corpus callosum - mood disorders - bipolar disorder - major depressive disorder - suicide - diffusion tensor imaging

## Introduction

Mood disorders are chronic mental diseases associated with significant functional impairment. Major depressive episodes are a common feature of Bipolar Disorder (BD), a serious mental illness that affects approximately 1-4% of the adult population, and of Major Depressive Disorder (MDD), which shows a lifetime prevalence up to 20% (Kessler et al., 2005). The presence/absence of manic or hypomanic episodes, the median age at onset (Kessler et al., 2005), the number of depressive episodes (Perlis et al., 2006) and the prevalence of suicide attempts distinguish these two disorders. Indeed, the lifetime rate of attempted suicide is between 9 and 30% in MDD and up to 61% in BD, compared with 3-5% in the general population (Rihmer, 2005). In recent years, studies using neuroimaging methods have tried to clarify the neurobiology of mood disorders. Earlier studies focused mainly on gray matter alterations. More recently, deep white matter (WM) abnormalities, including anterior cingulum, anterior corona radiata, internal capsule, fronto-occipital lobes and corpus callosum (CC) changes, have been consistently reported in neuroimaging and neuropathological studies of mood disorders (Kemp et al., 2013; Marlinge et al., 2014; Toteja et al., 2014).

CC is the main commissure between the two cerebral hemispheres, traversing the subcortical WM. It contains between 200 and 800 million axon fibers and is of crucial importance for interconnecting associative brain areas that play a pivotal role in the integration of inter-hemispheric information and higher cognitive functions. CC alterations have been increasingly reported in mood disorders (Arnone et al., 2012; Lavagnino et al., 2015; Phillips and Swartz, 2014) and it has been suggested that reduced myelination could underlie these findings (Brambilla et al., 2004). The development of Diffusion Tensor Imaging (DTI) has allowed exploring CC changes in greater detail (Marlinge et al., 2014). For instance, a review of DTI studies on CC

integrity in BD (Bellani et al., 2009) found evidence for decreased fractional anisotropy (FA) values, a metric influenced by various mechanisms, including fiber organization and myelination, in the genu, body and splenium of CC of adult and juvenile patients with BD. Moreover, a recent meta-analysis of DTI studies in patients with MDD emphasized the consistent finding of reduced FA values, particularly for the inter-hemispheric fibers running through the CC genu and body (Liao et al., 2013). However, studies comparing DTI data in CC of patients with BD and MDD are lacking. To our knowledge, only one DTI study reported lower FA values in the CC of patients with late-life BD than in patients with unipolar disorder and healthy controls (Sexton et al., 2012).

Classical MRI studies have described CC abnormalities also in other psychiatric disorders. Particularly, the size of the posterior third of CC is smaller in elderly patients with suicidal behavior compared with healthy controls or with patients with history of depression but without suicidal behavior. This finding, based on structural data, suggests the presence of a specific abnormal inter-hemispheric connectivity in subjects with suicidal behavior, independently from any history of mood disorder (Cyprien et al., 2011). Moreover, it further supports previous reports suggesting that suicidal behavior has a specific underlying biological basis and therefore might constitute a separate nosological entity, now included in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5).

However, to our knowledge, none of the published DTI studies on CC integrated in their analyses the potential confounding effect of suicidal behavior on CC alterations. This omission could partially explain the reported variability in CC regional abnormalities. We hypothesized that CC integrity is affected in BP and in people with suicidal behavior and that different CC areas are altered in these two conditions. This

could represent a possible source of heterogeneity in DTI results in patients with BP with or without suicidal behavior. To test this hypothesis, First CC integrity was assessed using DTI and results were compared in euthymic women with BD or MDD and in healthy control women. Then, the groups of this first analysis were stratified relative to the presence or absence of suicide attempt in the BD and MDD groups to detect a potential specific effect of suicidal behavior on CC integrity in mood disorders. This approach should allow identifying CC areas specifically involved in BP and in suicidal behavior in the same dataset.

## Methods

### Participants / clinical assessment

One hundred and twenty-four non-menopausal right-handed women (age: 18 to 50-year-old) were included in this study. Only women were selected to take into account the current controversy concerning the effects of sex on CC morphology (Predergast et al., 2015). Patients were euthymic on the day of the magnetic resonance examination, as indicated by the scores lower than 7 at the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and Young Mania Rating Scale (YMRS) (Young et al., 1978). Handedness was checked by using the Edinburgh handedness index (Oldfield, 1971). Participants were divided in three groups: 1) women with MDD 2) women with BD, and 3) healthy controls (HC). Patients with MDD and BD were recruited through advertisement with an initial screening by telephone interview, or at the Emergency Psychiatry and Post-Acute Care Departments, Montpellier University Hospital, France. Non-inclusion criteria were any current significant medical problems, including central nervous system disorders, any history of neurological illness or severe head trauma with loss of consciousness, schizophrenia, history of alcohol or drug abuse or dependence within

the past 12 months, pregnancy and lactation, and contraindications to MRI, particularly suicide attempt using firearms. For ethical considerations, euthymic patients were not asked to discontinue their medications for the exam; however, attention was paid to limit the inclusion of heavily medicated subjects. Subjects were considered to be 'heavily medicated' if they were treated with hypnotic drugs or first generation antipsychotics. Taking anxiolytics at the authorized dosage was not considered as an exclusion criterion. Moreover, to ensure that the patients' clinical condition was stable, only women who had a regular follow-up and the same medication regimen for at least 6 months prior to recruitment were included in the study.

HC were recruited in collaboration with the Clinical Investigation Centre 1411 at Montpellier University Hospital using their database of volunteers wishing to take part in biomedical research. Exclusion criteria were the same as for the patients' groups, with the addition of absence of current or past history of DSM-IV Axis I diagnoses, suicidal behavior and current intake of psychotropic drugs.

Written informed consent was obtained from all participants after complete description of the study. Inclusion and non-inclusion criteria were checked, participants were then interviewed in person by a trained psychiatrist. All diagnoses were made according to the DSM-IV criteria using the Mini-International Neuropsychiatric Interview, version 5.0.0. (Sheehan et al., 1998). "Anxiety disorders" included agoraphobia, panic disorder, social phobia, obsessive-compulsive disorder and generalized anxiety. Substance abuse and substance dependence were grouped under "substance use disorders". Suicidal act was defined as any non-fatal, self-directed potentially harmful behavior with the intent to die as a result (Oquendo et al., 2004). The French version of the National Adult Reading Test (NART)

(Beardsall and Brayne, 1990) was used to evaluate the verbal IQ, and the Beck Depression Inventory (BDI) (Beck et al., 1961) to obtain a subjective measure of the current depressive state. The most recent and the most severe suicidal acts were evaluated with the Risk Rescue Rating Scale (RRRS) (Weisman and Worden, 1972) and the Suicide Intent Scale (SIS) (Beck et al., 1974). Computerized versions of all questionnaires were used to avoid missing data. Before MRI acquisition, pregnancy was ruled out with a urine pregnancy test. Most women underwent the clinical and MRI exams on the same day; however, for personal convenience, the clinical evaluation could sometimes be separated from the MRI acquisition. In that case, the participants' euthymic status was systematically re-evaluated (using the HDRS and the YMRS scales), the current use of psychotropic medications was reassessed, and the BDI was re-administered. A clinical interview was also carried out.

Among the 124 participants, two healthy controls were unable to remain in the scanner because of panic attack and were excluded from the study. For technical reasons, data from one woman with BD could not be analyzed. Finally, data from 41 euthymic women with BD (32 BD type I and 9 BD II), 50 with MDD, and 30 HC were retained for the analysis (n=121).

The study was approved by the local ethics committee (People Protection Committee "Sud-Méditerranée IV"). Participants were paid 150€ after completion of the study protocol.

### **Image acquisition**

Brain images were acquired using a 1.5T whole-body MRI system (MAGNETON AVANTO, VB17 version, Siemens, Erlangen, Germany) equipped with a standard 12-channel receive-only head coil, in the Neuroradiology Department of the Montpellier University Hospital, France.

DTI data were acquired by single-shot spin-echo planar imaging and included diffusion gradients applied in 64 non-collinear directions and  $b = 1000 \text{ s/mm}^2$ . Eight  $b = 0$  images were acquired, but only the first one was used for data processing. Whole brain coverage was obtained (55 slices, no gap), oblique to the axial plane, that covered a region extending from the vertex to lower parts of the cerebellum. Slice thickness was 2.5mm and voxels were isotropic. The field of view was 240mm and the size of the acquisition matrix was 96x96, with echo time = 82ms, repetition time = 6700ms and bandwidth 1488Hz/Px.

A 3D T1, magnetization-prepared, rapid acquisition gradient echo (MP-RAGE) sequence with the following parameters (TR/TE/IR 2100/4.1ms/1100ms, 15° flip angle, PAT=2) and aligned with the corpus callosum, (voxel-size 0.98 x 0.98 x 1mm, 160 transversal slices) was also obtained for each participant.

### **Image processing**

DTI measures the diffusion characteristics of water molecules in vivo to identify the direction and integrity of fibers within the WM (Taylor et al., 2004). Water movement is characterized by FA, which is the fraction of directional diffusion in WM and reflects the integrity of the WM tracts (Beaulieu, 2002). FA is influenced by various factors, including fiber organization and myelination, but it does not distinguish between them (Beaulieu and Allen, 1994). Conversely, axial and radial diffusivity (AD and RD) are complementary DTI metrics that describe water diffusion along (AD) or across (RD) axons, thus providing information on the mechanisms of WM organization disruption. For instance, axonal damage leads to a marked AD decrease and only a modest RD reduction. Conversely, demyelination leads to an increase in RD without AD changes (Song et al., 2005). The mean diffusivity (MD), also expressed as the apparent diffusion coefficient (ADC), is another DTI metric to quantify the degree of water

molecule motion. FA and MD can be used to characterize the microstructural properties and integrity of brain WM. High FA and low MD are assumed to be associated with intact WM (Beaulieu and Allen, 1994).

Image processing was performed using MATLAB (MathWorks, Natick, MA) and FSL 5 (Jenkinson et al., 2012), following the standard DTI pipeline that includes brain extraction, eddy current correction, linear regression of the diffusion tensor model, parameters estimation (FA/AD/MD/RD), linear image registration (FLIRT) between diffusion images and 3DT1, followed by non-linear normalization (FNIRT) to estimate the deformation parameters between patient and the Montreal Neurological Institute (MNI) space. Using these parameters, the JHU-ICBM-labels-1 FSL WM labels atlas (Mori, 2005) was warped onto the patient space. Finally, the mean values of the CC genu, body and splenium were extracted from each map.

### **Statistical analysis**

Demographic and clinical variables between groups (HC vs. MDD vs. BD) were compared by univariate analysis of variance (ANOVA) for continuous variables and with the chi-square test for categorical variables. Non-parametric tests (Kruskal-Wallis or Mann-Whitney U) were used for non-normally distributed variables, based on the Shapiro-Wilk test. CC measurement differences between groups were assessed by multivariate analysis of covariance (MANCOVA) that allows the composite evaluation of the entire set of CC measures (genu, body, splenium and total) that are correlated, but not fully independent. This analysis was adjusted for age and NART score (as an indicator of crystallized intelligence), two potential confounders previously reported in the literature (Navas-Sanchez et al., 2014).

Following an overall significant MANCOVA, group differences for each CC region were also assessed by analysis of covariance (ANCOVA), with the same variables as covariates. First, the BD, MDD and HC groups were compared. Then, to assess the specific effect of SA on CC measurements in BD and MDD, we chose an original approach that differentiates our study from other recently published DTI-based analyses of these disorders. Specifically, patients with BD or MDD were divided in non-SA and SA to discriminate more accurately between the specific effects particularly of BD (due to the high number of patients with BD among SA in our study: 25/45) and of suicide attempts on CC integrity. This approach was supported by preliminary analyses (data not shown, available on request) in which HC (no history of psychiatric disorder) were compared with patients with affective disorders who were divided in SA and non-SA, independently of their diagnosis (MDD or BD). In this analysis, the heterogeneity of the two patients' groups did not allow highlighting any specific effect of SA on CC.

FDR (False Discovery Rate) correction for multiple comparisons at the 0.05 level was applied on the p-values (Benjamini, 1995) with SPSS syntax.

MANCOVA analyses were carried out to further explore the association between the mean FA values of CC regions and the number of suicide attempts, with age and NART score as covariates. To assess the correlation between SIS score and CC integrity, partial correlations were computed between the FA values of the different CC regions and SIS total score with age, NART score and number of suicide attempts as covariates.

Analyses were two-tailed and significance was set at 0.05. Statistical analyses were carried out with IBM SPSS Statistics (SPSS Inc., Chicago, Illinois, USA, version 20).

## Results

### Characteristics of the HC, MDD and BD groups

The demographic and clinical data are summarized in Table 1. Mean age ( $p=.778$ ), educational level ( $p=.291$ ) and NART score ( $p=.823$ ) were comparable in the three groups (HC, MDD and BD). Patients with BD reported more depressive episodes ( $p<.001$ ), more mood episodes with psychotic symptoms ( $p=0.003$ ), a higher number of hospitalizations in psychiatric wards ( $p<.001$ ), more use of lithium ( $p<.001$ ), anticonvulsants ( $p<.001$ ) and antipsychotics ( $p<.001$ ) than women with MDD. Conversely, patients with MDD were more often treated with antidepressant drugs ( $p=.018$ ). The BD and MDD groups were comparable concerning the age at first mood episode ( $p=.360$ ), anxiolytic medication ( $p=.646$ ) and lifetime history of suicide attempts ( $p=.059$ ), of anxiety disorders ( $p=.530$ ) and of substance use disorders ( $p=.281$ ).

Demographic and clinical data were not significantly different between suicide attempters (SA) and non-SA, notably the mean age ( $38.0 \pm 9.9$  and  $36.2 \pm 7.8$ , respectively;  $p=0.324$ ), mean educational level ( $13.9 \pm 2.0$  and  $14.5 \pm 2.1$ ,  $p=0.179$ ) and mean NART score ( $22.3 \pm 3.6$  and  $21.9 \pm 3.1$ ,  $p=0.523$ ). Comparison of the information on suicide attempt history in the BD and MDD groups (Table 2) showed that patients with BD reported more suicide attempts ( $p=.020$ ) and had a trend toward higher RRRS scores for the most severe attempt ( $p=.054$ ). No other significant between-group difference concerning the suicide attempt history was detected. The most severe suicide attempt was also the most recent in 28 of the 45 SA. Mean age (respectively  $39.1 \pm 9.3$ ,  $36.6 \pm 10.7$ ,  $p=0.411$ ), mean educational level ( $14.2 \pm 1.8$ ,  $13.6 \pm 2.1$ ,  $p=0.363$ ) and mean NART score ( $22.4 \pm 3.5$ ,  $22.3 \pm 3.9$ ,  $p=0.881$ ) were comparable among SA in the BD and MDD groups.

**DTI imaging differences between healthy controls and patients with MDD or BD**

Comparison of the DTI values in the three groups (HC, BD and MDD), independently of the suicidal status (N=121) (Table 3), showed the presence of significant differences concerning the mean FA values [MANCOVA Wilks  $\Lambda = .824$ ;  $F(8,226) = 2.872$ ;  $p=.005$ ], after controlling for age and NART score. Analysis of covariance found significantly lower FA values for all CC regions in patients with BD compared with HC (genu  $p = .002$ ; body  $p <.0001$ ; splenium  $p = .001$ ; whole  $p <.0001$ ) and also with patients with MDD, except for the splenium (genu  $p = .004$ ; body  $p .001$ ; splenium  $p = .089$ ; whole  $p <.001$ ). The MDD and HC groups did not differ significantly. The RD [MANCOVA Wilks  $\Lambda = .893$ ;  $F(8,226) = 1.646$ ;  $p=.113$ ], AD [MANCOVA Wilks  $\Lambda = .944$ ;  $F(8,226) = .833$ ;  $p=.575$ ] and MD values [MANCOVA Wilks  $\Lambda = .901$ ;  $F(8,226) = 1.517$ ;  $p=.152$ ] were not significantly different in the three groups.

**DTI imaging differences between non-SA and SA across and within diagnostic groups**

The interaction between psychiatric diagnosis and SA reached significance for all CC parts ( $p < 0.002$ ).

The mean FA, RD, AD and MD values of the three CC regions (genu, body and splenium) and of the whole CC were computed for each group (HC, BD and MDD) after the classification of patients with BD or MDD in non-SA and SA.

When considering exclusively non-SA patients (N=46), the overall MANCOVA analysis indicated that FA [MANCOVA Wilks  $\Lambda = .749$ ;  $F(8, 136) = 2.647$ ;  $p=.010$ ], RD [MANCOVA Wilks  $\Lambda = .738$ ;  $F(8, 136) = 2.784$ ;  $p=.007$ ] and MD [MANCOVA Wilks  $\Lambda = .782$ ;  $F(8, 136) = 2.226$ ;  $p=.029$ ] were significantly different in the three

groups (Table 4). Moreover, the FA, RD and MD values (whole CC and regions) of non-SA with BD (N=16) were significantly different compared with those of non-SA with MDD (N=30) and HC (N=30). No significant difference was observed between non-SA with MDD and HC.

Comparison of the DTI measurements (overall MANCOVA) in HC (N=30) and SA (N=45) showed that only the FA values [MANCOVA Wilks  $\Lambda = .688$ ;  $F(8, 134) = 3.446$ ;  $p=.001$ ] were significantly different in the three groups. Specifically, SA with BD (N=25) showed the highest mean FA variations for all CC regions compared with HC (N=30) (genu  $p = .002$ ; body  $p <.0001$ ; splenium  $p = .001$ ; whole  $p<.0001$ ). Conversely, only the FA values for the CC body ( $p = .046$ ) and the whole CC ( $p = .036$ ) were significantly lower in SA with MDD (N=20) than in HC. However, these significant values (alpha level=0.05) did not survive FDR correction (corrected significance level,  $q^*=0.025$ ). No significant difference was found between SA with BD and SA with MDD (Table 4, Figure 1).

### **Association between CC integrity and number of suicide attempts**

To investigate the relationship between suicidal behavior and CC integrity, the association between the FA values of the different CC regions and the number of suicide attempts was assessed, after controlling for age and NART score. This analysis revealed a significant difference in the FA values of the genu ( $p = .020$ ), body ( $p = .030$ ) and whole CC ( $p = .013$ ) between groups, when SA (independently from the diagnosis of MDD or BD) were subdivided in patients with 1 (N=11) and >1 (N=34) suicide attempt. When SA were grouped in patients with 1-2 (N=25) and >2 (N=20) suicide attempts, the FA values of all CC regions were significantly different

between groups (genu  $p = .002$ ; body  $p = .014$ ; splenium  $p = .010$ ; whole  $p = 0.002$ ) (Table 5).

### **Correlation between CC integrity and Suicidal Intent Scale score**

To investigate the correlation between intent to die of the most recent suicide attempt and CC integrity, partial correlations were performed between the FA values of the different CC regions and SIS total score after controlling for age, NART score and number of suicide attempts. This analysis revealed only a significant negative correlation between the splenium FA values and SIS total score (splenium  $r=-0.345$ ,  $p = 0.025$ ; genu  $r=-0.243$ ,  $p=0.121$ ; body  $r= -0.136$ ,  $p=0.390$ ; whole  $r=-0.261$ ,  $p=0.095$ ) (Table 6).

Finally, to identify variables that may have affected the diffusion measures, sensitivity analyses were conducted to exclude 1) people with a lifetime history of psychotic symptoms (N=7 patients with BD) during mood episodes, 2) people with a history of alcohol abuse/dependence (N=6 patients with BD, N=4 patients with MDD). No significant difference was found when comparing again the groups after the exclusion of these patients (data not shown).

### **Discussion**

The present study suggests a specific alteration of CC integrity in female SA, particularly a significant lower FA value of the splenium. As in previous studies, anomalies of all CC regions were observed among patients with BD compared with the MDD and HC groups, but not between patients with MDD and HC. CC anomalies, including with DTI techniques, have been consistently reported in patients with BD (Arnone et al., 2008; Bellani et al., 2009; Walterfang et al., 2009), but the affected CC regions can widely vary (Bellani et al., 2009). Conversely, the presence

of specific CC alterations in patients with MDD is still a matter of debate (Kempton et al., 2011). Moreover, suicidal behavior has never been evoked before as a possible modulating factor of CC integrity in subjects with mood disorders. Our study shows different profiles of CC alterations when patients with and without history of suicide attempts are analyzed separately. Specifically, among non-SA, significant alterations in the CC genu and body were observed only in BD patients compared with both MDD and HC groups whose values were, on the other hand, comparable. When only SA were considered, results were quite different, with specific CC alterations (FA decreases) detected, including the splenium, in SA with BD compared with HC. Moreover, differences (a trend after FDR correction) in the body FA values were found between SA with MDD and HC, while the significant differences in FA values observed between non-SA with BD or MDD disappeared. Finally, an elevated number of suicide attempts (>2) and an elevated SIS total score (strong intent to die) were associated with a significant loss of splenium integrity, suggesting a specific implication of this CC region in the severity of the suicidal behavior. These findings are consistent with our previous structural MRI results reporting a link between a reduced posterior third of the mid-sagittal CC area and suicidal behavior in an elderly general population (Cyprien et al., 2011).

In addition, while the FA, RD and MD values showed overall group differences between non-SA patients and HC, no AD difference was observed. Consistent with our results, a recent DTI study in adult euthymic patients with BD found decreased FA and increased RD and MD, but not AD values in all CC regions compared with control subjects (Emsell et al., 2013b). Previous works suggest that the combination of higher RD and MD with lower FA values is a plausible non-invasive biomarker of poor myelination, as opposed to axonal injury (Alexander et al., 2011; Song et al.,

2002). These findings support the hypothesis that BD is a connectivity disorder, leading to impaired myelination (Marlinge et al., 2014), but in the present study, we could not draw conclusions on the direction of the association between BD and the CC alterations observed by DTI. In contrast, the reduced FA values found in SA with BD or MDD compared with controls were not associated with significant alterations in RD, AD or MD, although RD and MD, but not AD, values tended to be slightly higher in patients than in controls. Similar results were found for MD (ADC) in a recent DTI study on SA (Olvet et al., 2014). Nevertheless, findings about ADC are still inconclusive because ADC is a relatively non-specific marker of diffusivity, and further investigations are required to clarify the role of diffusivity in suicidal behavior (Olvet et al., 2014).

Among women with BD, 17 (41.5%) were taking lithium and 24 (58.5%) were not. Due to the high proportion of patients taking lithium, sensitivity analyses were not possible and consequently the association between decreased CC FA values and mood disorders with/without suicide attempt could not be re-examined after exclusion of the patients currently on lithium medication. However, analysis of the literature data did not bring evidence for an effect of lithium therapy on CC imaging with the DTI technique (Marlinge et al., 2014). For instance, Benedetti et al., reported that lithium intake was associated with increased AD measurements in several WM fiber tracts, including CC, but did not find significant effect on FA and RD values (Benedetti et al., 2013). Likewise, in another study on patients with BD type I (BD-I), no significant association was found between lithium intake and DTI measures (Emsell et al., 2013a). Consequently, as no formal evidence of an effect of lithium therapy on the CC FA values is currently available, we did not control for lithium intake in our analyses. Concerning other mood stabilizers, particularly antipsychotics,

the current literature data do not bring formal proof for a role in connectivity patterns, and suggest that the effects of psychotropic medications, when present, are predominantly normalizing. Therefore, they do not seem to provide an alternative explanation for the CC differences observed between patients with BD and HC. On the contrary, the normalizing effects of such drugs should rather reduce differences between the BD and HC groups and thus lead to type II, instead of type I errors (Hafeman et al., Effects of medication on neuroimaging findings in bipolar disorder: an updated review, bipolar disorders, 2012).

Among patients with BD, seven had a lifetime history of psychotic symptoms during mania or depression according to the MINI criteria. It has been reported that inter-hemispheric pathways are more disrupted in BD-I patients with psychosis than in those without psychotic symptoms, underscoring a potential role for inter-hemispheric disconnectivity in the pathophysiological features of psychosis in BD-I (Sarrazin et al., 2014). Consequently, the history of psychotic symptoms could have interfered with the results of the BD group. However, results were not significantly changed when these seven patients were removed from the sample, suggesting that an effect of psychotic features can be excluded.

Interestingly, in a previous DTI-based study in SA, Olvet et al. (Olvet et al., 2014) found that low FA in the dorsomedial prefrontal cortex was associated with history of suicide attempts, suggesting a role for anterior alterations in suicidal behavior. It is difficult to correlate these findings with our results on the CC. However, this work highlights the need to better investigate the neural correlates of self-referential processing that are located in medial anterior and posterior regions and that may play a role in suicidal behavior, which could represent an attempt to escape from negative self-awareness (Baumeister, 1990).

Another hypothesis for the importance of CC in suicidal symptoms, is environmental. The CC is a structure growing from childhood to early adulthood. It may therefore be sensitive to environmental stimuli for many years. It is known that a very early experience can influence CC morphometry: in nonhuman species, CC development has been reported to be affected by environmental stimuli or insults (Denenberg VH, 1985). In humans, relationships have been found between CC size and history of neglect, parental verbal abuse, and sexual abuse during childhood and adolescence (Andersen et al., 2008; Denenberg VH, 1985; Teicher et al., 2004; Teicher et al., 2010). However, in our sample, history of abuse and/or maltreatment were not collected.

### **Limitations**

This study should however be considered with the following limitations. First, we could not examine the correlations between CC alterations and key features of suicidal behavior, such as attempt method or seriousness of the medical consequences, due to lack of statistical power. Indeed, violent and serious SA seem to present a profile close to that of suicide completers, compared to other SA. Common features between SA and suicide completers might include family history of suicidal behavior, higher medical lethality of the previous attempts and male gender (Giner et al., 2014). As our study included only women, this may partly explain the relative small number of severe (N=9; 20%) and violent (N=3; 6.7%) suicide attempts in this sample. Nevertheless, we could detect FA differences in the CC related to suicidal behavior. Second, the BD group included both patients with BD-I and BD-II and this could affect our results, although the number of patients with BD-II was very small (9 out of 41). Third, this was a cross-sectional study and therefore it does not allow concluding on the causal direction of the association between suicidal behavior

and CC integrity alterations. Environmental factors, such as childhood trauma or stress (Bucker et al., 2014; Li et al., 2014), could be related to changes in CC integrity, before the onset of mood disorders. On the other hand, factors such as neuroprogression in the course of the disease might also affect CC integrity (Lavagnino et al., 2015).

These results remain to be replicated in further works, especially among men because they are more frequently associated with violent suicide attempts (Giner et al., 2014) and male gender is an acknowledged risk factor for suicide (Hawton and van Heeringen, 2009).

The present study suggests that history of suicide attempts exerts a specific effect on CC integrity, which may partially explain the heterogeneity in the findings observed in previous DTI studies on CC alterations in mood disorders. It also highlights the specific association between splenium alterations and number of suicide attempts. These findings should encourage researchers to systematically take into account the history of suicide attempts in the future analyses of CC in mood disorders.

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Figure 1: Corpus callosum regions of interest (ROI) overlaid on the fractional anisotropy map of one study participant.

Legend: The genu, body, and splenium areas were extracted from the JHU-ICBM FSL atlas and warped on the subject's space to prevent any map modification. The resulting ROI are displayed in the (A) axial and (B) sagittal plane. The histograms show the mean fractional anisotropy (FA) values along the corpus callosum regions in patients with (suicidal) or without history of suicide attempts and bipolar disorder (BD) or major depressive disorder (MDD) and in healthy controls (HC); \* <  $p=0.05$  (multivariate covariance analysis with age and NART score as covariates).

Table 1: Comparison of the demographic and clinical characteristics in women with bipolar disorder (BD), major depressive disorder (MDD) and healthy controls (HC).

Characteristics	HC (N=30)	BD (N=41)	MDD (N=50)	$p$	BD vs HC	MDD vs HC	BD vs MDD
<i>Demographic variables</i>							
Age, mean (SD)	37.6 (7.8)	37.7 (9.1)	36.5 (8.8)	.778	NA	NA	NA
Educational level, mean years (SD)	14.6 (2.1)	16.6 (2.0)	14.0 (2.1)	.291	NA	NA	NA
NART score, mean (SD)	22.1 (4.0)	22.3 (3.4)	22.0 (3.3)	.823	NA	NA	NA
<i>Clinical variables</i>							
Age at first mood episode, years, median (IQR)	NA	20.0 (14.5- 25.5)	24.0 (18.5- 29.5)	.360	NA	NA	NA
Number of MDEs, median (IQR)	NA	5 (1.5-	2.0 (1.0-	<.001	NA	NA	<.001

		8.5)	3.0)					
Number of (hypo)manic episodes, median (IQR)	NA	2 (0.5-3.5)	NA	NA	NA	NA	NA	NA
Number of hospitalizations in psychiatry, median (IQR)	NA	3 (0.5-5.5)	0 (0)	<.001	NA	NA	<.001	<.001
Lifetime history of suicide attempt (MINI), N (%)	NA	25 (61.0)	20.0 (40.0)	<.001	<.001	<.001	.059	.059
Lifetime history of anxiety disorders (MINI), N (%)	NA	25 (61.0)	27.0 (54.0)	.503			.503	.503
Lifetime panic disorder and/or agoraphobia		9 (22.0)	6 (12.0)	.203			.203	.203
Lifetime social phobia		7 (17.1)	10 (20.0)	.722			.722	.722
Lifetime obsessive-compulsive disorder		3 (7.3)	3 (6.0)	1			1	1
Lifetime post-traumatic stress disorder		2 (4.9)	3 (6.0)	1			1	1
Lifetime generalized anxiety disorder		6 (14.6)	2 (4.0)	.134			.134	0.134
History of substance use disorders (MINI), N (%)	NA	10 (24.4)	7.0 (14.0)	.004	NA	NA	.281	.281
Past alcohol abuse / dependence		6 (14.6)	4 (8.0)	.337			.337	.337
Past substance abuse / dependence		4 (9.8)	2 (4.0)	.403			.403	.403
Lifetime history of mood disorders with psychotic symptoms (MINI), N (%)	NA	7 (17.1)	0 (0)	0.001	0.018	NA	0.003	0.003
Current antidepressant medications, N (%)	NA	12 (29.3)	27.0 (54.0)	<.001	NA	NA	.018	.018
Current lithium medication, N (%)	NA	17 (41.5)	1.0 (2.0)	<.001	NA	NA	<.001	<.001
Current anticonvulsant medications, N (%)	NA	21 (51.2)	2.0 (4.0)	<.001	NA	NA	<.001	<.001
Current antipsychotic medications, N (%)	NA	13 (31.7)	3.0 (6.0)	<.001	NA	NA	.001	.001
Current anxiolytic medications, N (%)	NA	15 (36.6)	16.0 (32.0)	.001	NA	NA	.646	.646
Hamilton Depression Rating Scale (HDRS), median (IQR)	1.0 (2.0)	3.0 (4.0)	5.0 (3.0)	<.001	<.001	<.001	0.608	0.608
Young Mania Rating Scale (YMRS), median (IQR)	0 (0)	0 (0)	0 (0)	0.017	0.039	0.856	0.021	0.021
Beck Depression Inventory (BDI), median (IQR)	0 (0)	3.0 (8.0)	4.0 (5.0)	<.001	<.001	<.001	0.633	0.633

SD: Standard Deviation, IQR: Inter Quartile Range, NA: Not applicable; MINI: Mini International Neuropsychiatric Interview; NART: National Adult Reading Test; MDE: Mood Disorder Episodes

Table 2: Comparison of the clinical characteristics of suicide attempt history in suicide attempters (SA) with bipolar disorder (BD) or with major depressive disorder (MDD).

Characteristics	Suicide attempters (N=45)			p
	Overall suicide attempters	BD SA (N=25)	MDD SA (N=20)	
Number of suicide attempts, median (IQR)	2 (1-3)	3 (2-4)	2 (1-3)	.020
Age at first suicide attempt, years, median (IQR)	22 (15.5-28.5)	23.0 (15-31)	22.0 (16-28)	.354

History of violent suicide attempt, N (%)	3 (6.7)	3 (6.7)	0 (0)	.242
History of severe suicide attempt, N (%)	9 (20.0)	6 (13.3)	3 (6.7)	.710
More lethal attempt method				
Drug overdose, N (%)	42 (93.3)	23 (56.1)	19 (38.0)	.414
Drowning, N (%)	1 (2.2)	1 (2.4)	0 (0)	
Cutting, N (%)	1 (2.2)	0 (0)	1 (2.0)	
Jumping, N (%)	1 (2.2)	1 (2.4)	0 (0)	
Most severe attempt				
RRRS risk, mean (SD)	8.8 (3.0)	9.1 (2.8)	8.3 (3.5)	.630
RRRS rescue, mean (SD)	12.1 (1.4)	11.8 (1.3)	12.7 (1.5)	.192
Suicide Intent Scale score, mean (SD)	14.5 (4.4)	15 (4.8)	13.7 (4.1)	.611
Most recent attempt				
RRRS risk, mean (SD)	7 (6-8)	7.6 (2.1)	6.8 (1.8)	.054
RRRS rescue, mean (SD)	12 (11-13)	12.0 (1.2)	12.6 (1.6)	.232
Suicide Intent Scale score, mean (SD)	12.4 (4.2)	12.8 (4.7)	12.1 (3.7)	.583

RRRS: Risk Rescue Rating Scale

Table 3: Differences in mean fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD) tractography values of the corpus callosum (CC) regions in women with bipolar disorder (BD), major depressive disorder (MDD) and healthy control (HC).

Regions of Corpus Callosum	Groups			Overall Group Differences	p Values <sup>†</sup>		
	HC (N=30) mean (SD)	BD (N=41) mean (SD)	MDD (N=50) mean (SD)		BD versus HC	BD versus MDD	MDD versus HC
<b>1. FA</b>							
Genu	.6962 (.0245)	.6733 (.0311)	.6911 (.0254)	0.001	<0.000	1	0.004 0.292
Body	.6659 (.0256)	.6358 (.0319)	.6581 (.0305)	<0.0001	<0.000	1	0.001 0.230
Splenium	.7465 (.0251)	.7293 (.0248)	.7384 (.0209)	0.009	0.002	0.089	0.094
Total	.6996 (.0218)	.6755 (.0261)	.6923 (.0206)	<0.0001	<0.000	1	0.001 0.127
MANCOVA $p = .005$							
<b>2. AD (.10<sup>3</sup>)</b>							
Genu	1.4247 (.5853)	1.4261 (.0570)	1.4336 (.0507)	.684	NA	NA	NA
Body	1.4681 (.0609)	1.4930 (.0688)	1.4952 (.0684)	.163	NA	NA	NA
Splenium	1.5405 (.0536)	1.5509 (.0571)	1.5492 (.0551)	.723	NA	NA	NA

Total	1.4825 (.0420)	1.4950 (.0476)	1.4984 (.4356)	.296	NA	NA	NA
				MANCOVA p =			
				.575			
<b>3. RD (.10<sup>4</sup>)</b>							
Genu	5.4960 (.4820)	5.7750 (.5166)	5.5103 (.5691)	.041	NA	NA	NA
Body	5.3981 (.4698)	5.7435 (.5275)	5.4943 (.4900)	.010	NA	NA	NA
Splenium	5.1102 (.4869)	5.3341 (.4126)	.26215 (.4538)	.119	NA	NA	NA
Total	5.3216 (.4343)	5.6105 (.4411)	5.4186 (.4433)	.021	NA	NA	NA
				MANCOVA p =			
				.113			
<b>4. MD (.10<sup>4</sup>)</b>							
Genu	8.4129 (.4051)	8.6035 (.4641)	8.4523 (0.4437)	.169	NA	NA	NA
Body	8.4925 (.4075)	8.8056 (.4397)	8.6468 (.3957)	.008	NA	NA	NA
Splenium	8.5418 (.4087)	8.7258 (.3302)	8.6719 (.3614)	.114	NA	NA	NA
Total	8.4895 (.3467)	8.7236 (.3576)	8.6070 (.3353)	.021	NA	NA	NA
				MANCOVA p =			
				.152			

<sup>†</sup> False Discovery Rate (FDR): Benjamini and Hochberg (Benjamini, 1995) corrected significance level  $q^* = 0.025$

Results of the multivariate analysis of covariance with age and NART score as covariates

Table 4: Mean fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD) values in the corpus callosum (CC) regions according to the suicidal status of patients with bipolar disorder (BD) or major depressive disorder (MDD) compared with healthy controls (HC).

#### PATIENTS WITHOUT HISTORY OF SUICIDE ATTEMPT AND HEALTHY SUBJECTS

Corpus Callosum region	Groups			p Values <sup>†</sup>			
	HC (N=30) mean (SD)	BD (N=16) mean (SD)	MDD (N=30) mean (SD)	Overall Group Differences	BD vers HC	BD vers MD	MD vers HC
<b>1. FA</b>							
Genu	.6962 (.0245)	.6756 (.0372)	.6964 (.0221)	0.009	0.00	0.07	0.809
Body	.6659 (.0256)	.6391 (.0370)	.6652 (.0215)	0.002	0.00	0.02	0.733
Splenium	.7465 (.0251)	.7373 (.0278)	.7395 (.0224)	0.190	0.10	0.65	0.155
Total	.6996 (.0218)	.6801 (.0306)	.6970 (.0174)	0.004	0.00	0.08	0.433

				MANCOVA $p$ = 0.010			
<b>2. AD (<math>\cdot 10^{-3}</math>)</b>							
Genu	1.4247 (.0585)	1.4347 (.0627)	1.4254 (.0498)	.802	NA	NA	NA
Body	1.4681 (.0609)	1.4949 (.0772)	1.4954 (.0681)	.194	NA	NA	NA
Splenium	1.5405 (.0536)	1.5498 (.0652)	1.5502 (.0550)	.828	NA	NA	NA
Total	1.4825 (.0420)	1.4980 (.0517)	1.4964 (.0455)	.391	NA	NA	NA
				MANCOVA $p$ = 0.824			
<b>3. RD (<math>\cdot 10^{-4}</math>)</b>							
Genu	5.4960 (.4820)	5.9038 (.5992)	5.3724 (.4584)	.002	.004	.00	.43
Body	5.3981 (.4698)	5.8524 (.6063)	5.3655 (.3205)	.001	<.001	<.001	.97
Splenium	5.1102 (.4869)	5.3179 (.4457)	5.1526 (.3513)	.146	.052	.15	.51
Total	5.3216 (.4343)	5.6816 (.5089)	5.2949 (.3154)	.002	.001	.00	.99
				MANCOVA $p$ = 0.007			
<b>4. MD (<math>\cdot 10^{-4}</math>)</b>							
Genu	8.4129 (.3310)	8.7183 (.5416)	8.3329 (.3310)	.007	.010	.00	.55
Body	8.4925 (.4075)	8.8846 (.5100)	8.5616 (.3215)	.002	.001	.00	.34
Splenium	8.5418 (.4087)	8.7112 (.3541)	8.6023 (.2925)	.217	.082	.27	.42
Total	8.4895 (.3467)	8.7812 (.4132)	8.5178 (.2554)	.005	.002	.00	.56
				MANCOVA $p$ = 0.029			

**PATIENTS WITH HISTORY OF SUICIDE ATTEMPT AND HEALTHY SUBJECTS**

Corpus Callosum region	Groups			Overall Group Differences	p Values		
	HC (N=30) mean (SD)	BD (N=25) mean (SD)	MDD (N=20) mean (SD)		BD vers us MD HC	BD vers us MD	MD vers us HC
<b>5. FA</b>							
Genu	.6962 (.0245)	.6719 (.0272)	.6831 (.0284)	0.006	0.00	0.2	0.0
Body	.6659 (.0256)	.6337 (.0289)	.6473 (.0387)	0.001	<0.001	0.1	0.0
Splenium	.7465 (.0251)	.7242 (.0218)	.7369 (.0190)	0.003	0.00	0.0	0.1
Total	.6996 (.0218)	.6726 (.0229)	.6854 (.0234)	<0.0001	<0.001	0.0	0.0
				MANCOVA $p$ = 0.001			
<b>6. AD (<math>\cdot 10^{-3}</math>)</b>							

Genu	1.4247 (.0585)	1.4205 (.0535)	1.4460 (.0507)	.259	NA	NA	NA
Body	1.4681 (.0609)	1.4918 (.0645)	1.4950 (.0706)	.265	NA	NA	NA
Splenium	1.5405 (.0536)	1.5517 (.0528)	1.5476 (.0566)	.655	NA	NA	NA
Total	1.4825 (.0420)	1.4930 (.0458)	1.5014 (.0415)	.326	NA	NA	NA
				MANCOVA $p$ = 0.444			
<b>7. RD (<math>\cdot 10^{-4}</math>)</b>							
Genu	5.4960 (.4820)	5.6926 (.4498)	5.7172 (.6629)	.260	NA	NA	NA
Body	5.3981 (.4698)	5.6739 (.4701)	5.6876 (.6300)	.077	NA	NA	NA
Splenium	5.1102 (.4869)	5.3444 (.3991)	5.4263 (.5435)	.058	NA	NA	NA
Total	5.3216 (.4343)	5.5649 (.3960)	5.6040 (.5428)	.058	NA	NA	NA
				MANCOVA $p$ = 0.565			
<b>8. MD (<math>\cdot 10^{-4}</math>)</b>							
Genu	8.4129 (.4052)	8.5301 (.4016)	8.6315 (.5331)	.218	NA	NA	NA
Body	8.4925 (.4075)	8.7551 (.3909)	8.7747 (.4663)	.030	NA	NA	NA
Splenium	8.5418 (.4087)	8.7352 (.3211)	8.7764 (.4326)	.073	NA	NA	NA
Total	8.4895 (.3467)	8.6867 (.3207)	8.7408 (.3987)	.033	NA	NA	NA
				MANCOVA $p$ = 0.234			

Results of the multivariate analysis of covariance with age and NART score as covariates;

<sup>†</sup> False Discovery Rate (FDR): Benjamini and Hochberg (Benjamini, 1995) corrected significance level  $q^* = 0.025$

Table 5: Comparison of the mean fractional anisotropy (FA) values in corpus callosum regions according to the number of suicide attempts (SA) in patients with MDD or BD

Corpus Callosum region	1 SA (N=11) mean (SD)	>1 SA (N=34) mean (SD)	$p$	$\leq 2$ SA (N=25) mean (SD)	>2 SA (N=20) mean (SD)	$p$
Genu	.6933 (.0227)	.6715 (.0277)	.020	.6876 (.0237)	.6634 (.0276)	.002
Body	.6618 (.0291)	.6326 (.0326)	.030	.6497 (.0320)	.6274 (.0328)	.014
Splenium	.7391 (.0253)	.7268 (.0194)	.080	.7372 (.0178)	.7206 (.0222)	.010
Total	.6947 (.0196)	.6729 (.0227)	.013	.6875 (.0206)	.6667 (.0227)	.002

Results of the covariance analysis with age and NART score as covariates.

Table 6: Partial correlations between Suicidal Intent Scale (SIS) total score for the most recent suicide attempt and FA values in the corpus callosum regions.

Correlation coefficient R	$p$ values
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Corpus callosum region (FA)		
Genu	-0.243	0.121
Body	-0.136	0.390
Splenium	-0.345	0.025
Total	-0.261	0.095

Results of the covariance analyses with age, NART score, and number of suicide attempts as covariates;

FA = Fractional Anisotropy; SIS = Suicidal Intent Scale

## Highlights

- Corpus callosum (CC) is altered in bipolar disorders (BD)
- Genu and body CC areas are altered in BD without suicide Attempt (SA)
- History of SA exerts also a specific effect on CC integrity
- Splenium is specifically altered in SA independently from psychiatric status
- Screening for history of SA is crucial in future analyses of CC in affective disorders

Fig. 1

