Journal of Psychiatric Research 61 (2015) 13–18

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Depressed suicide attempters have smaller hippocampus than depressed patients without suicide attempts

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ARTICLE INFO

Article history:
Received 26 August 2014
Received in revised form
11 December 2014
Accepted 15 December 2014

Keywords:
Suicide attempt
Major depressive disorder
Hippocampal volume
Automatic segmentation
MRI
Biomarker

ABSTRACT

Background: Despite known relationship between hippocampal volumes and major depressive episodes (MDE) and the increased suicidality in MDE, the links between hippocampal volumes and suicidality remain unclear in major depressive disorders (MDD). If the hippocampus could be a biomarker of suicide attempts in depression, it could be useful for prevention matters. This study assessed the association between hippocampal volumes and suicide attempts in MDD.
Methods: Hippocampal volumes assessed with automatic segmentation were compared in 63 patients with MDD, with ($n = 24$) or without ($n = 39$) suicide attempts. Acute (<one month) and past (>one month) suicide attempts were studied.
Results: Although not different in terms of socio-demographic, MDD and MDE clinical features, suicide attempters had lower total hippocampus volumes than non-attempters (4.61 (±1.15) cm^3 vs 5.22 (±0.99) cm^3; $w = 625.5$; $p = 0.03$), especially for acute suicide attempts (4.19 (±0.81) cm^3 vs 5.22 (±0.99) cm^3; $w = 334$; $p = 0.005$), even after adjustment on brain volumes, sex, age, Hamilton Depression Rating Scale (HDRS) scores and MDD duration. A ROC analysis showed that a total hippocampal volume threshold of 5.00 cm^3 had a 98.2% negative predictive value for acute suicide attempts.
Conclusion: Depressed suicide attempters have smaller hippocampus than depressed patients without suicide attempts, independently from socio-demographics and MDD characteristics. This difference is related to acute suicide attempts but neither to past suicide attempts nor to duration since the first suicide attempt, suggesting that hippocampal volume could be a suicidal state marker in MDE. Further studies are required to better understand this association.

1. Introduction

Patients with major depressive disorder (MDD) have a 5-fold increased risk of suicide attempt as compared to the general population (Nock et al., 2010) and 4% of MDD inpatients will die by suicide (Bostwick and Pankratz, 2000). Finding a biomarker linked with the risk of suicide attempt would be a major achievement to prevent suicidal behavior in MDD, even if the definition of a reliable and easily assessable one remains a challenge (Lee and Kim, 2011).

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http://dx.doi.org/10.1016/j.jpsychires.2014.12.010
0022-3956/

Nevertheless, an interesting candidate could be hippocampal volume as measured by cerebral MRI (Campbell and Macqueen, 2004; MacQueen and Frodl, 2011). Indeed, the hippocampus is crucial in memory processes and memory alterations have been shown to be associated with suicide attempts (Keilp et al., 2001; Richard-Devantoy et al., 2014b) and with hippocampal volume loss (Van Petten, 2004). Other alterations of cognitive functions, such as executive function, implicated in suicide attempt have been associated with prefrontal cortices (Richard-Devantoy et al., 2014a; Jollant et al., 2011), and this area is known to be regulated by the hippocampus (Jay et al., 1995; Gurden et al., 2000). Furthermore, hippocampus is implicated in the regulation of the hypothalamic-pituitary-adrenal axis, an axis which response is impaired in suicide attempters (Mann et al., 2006).

To the best of our knowledge, only two studies (Monkul et al., 2007; Hwang et al., 2010) assessed the potential of hippocampal volume as a biomarker of suicide attempts in MDD. Both studies failed to show differences in hippocampal volumes in suicide attempters and non-attempters, the first one in MDD women with ($n = 7$) or without ($n = 10$) a history of suicide attempt, and the second one in elderly MDD men, with ($n = 26$) or without ($n = 49$) a history of suicide attempt. The first study assessed hippocampal volume by manually tracing (Monkul et al., 2007) and suffered from a small sample size. The second study (Hwang et al., 2010) benefited from a larger sample size but relied on the standard voxel-based morphometry (VBM) approach. The study of Hwang et al. included elderly patients with an average age of 79 years. In this age group, substantial hippocampal atrophy is present in normal subjects which may confound the detection of suicide-related atrophy. Moreover, the results were obtained using an uncorrected statistical threshold, which, in VBM studies, may produce large numbers of false positives (Henley et al., 2010; Ridgway et al., 2008).

Of note, two other negative studies were published beyond the field of MDD. First, in borderline personality disorder, Soloff et al. (2012) failed to show differences between high- and low-lethality attempters in hippocampus volume using a VBM method. Secund, in schizophrenia, Spoletini et al. (2011) also assessed hippocampal volume using automated model-based segmentation method and found no difference between patients with or without previous suicide attempts. Thus, the relationship between hippocampal volume and suicide attempts in MDD remains unclear.

In this study, we investigated hippocampal volume differences between suicide attempters and non-attempters in patients with MDD, using brain MRI and an automatic hippocampal segmentation technique.

2. Materials and methods

2.1. Design

In a case–control study, the association between suicide attempts and hippocampal volumes was assessed in patients with a current MDE. This study was registered by the Commission Nationale de l'Informatique et des Libertés (CNIL) and was approved by the Ethics Committee of Paris-Boulogne, France, and conformed to international ethical standards.

2.2. Patients

68 in or out-patients aged 18–65 years were included, with a diagnosis of a current MDE in a context of MDD (DSM-IVTR), based on the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Patients were included if their Hamilton Depression Rating Scale 17 items (HDRS) (Hamilton, 1960) score was equal or higher than 18. Patients with organic brain syndromes, unstable medical conditions, bipolar disorders (DSM-IVTR) or current treatment with mood stabilizers, psychotic disorders (DSM-IVTR) or current treatment with antipsychotics, current substance abuse or dependence (DSM-IVTR), as well as pregnancy, breast feeding, and contra-indications to cerebral MRI were not included. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, the study design was reviewed by an appropriate ethical committee, and informed consent of the participants was obtained after the nature of the procedures had been fully explained.

2.3. Major depressive disorder

The HDRS was used to assess the current MDE severity. Presence of previous MDE defining recurrent MDD, MDD duration, presence and duration of prior treatment with antidepressant medication were also assessed.

2.4. Suicide attempts

Suicide attempt assessment was performed by both a psychiatrist and a psychologist, based on patient interviews and medical records. Suicide attempt was defined as a self-destructive act with some intent to end one's life (Institute of Medicine (US) Committee on Pathophysiology and Prevention of Adolescent and Adult Suicide, 2002; O'Carroll et al., 1996). Acute suicide attempts were defined as those which occurred in the month before the evaluation. Past suicide attempts were defined as those which occurred more than one month before. 2 patients who had several suicidal attempts were both acute and past attempters, and they were included in the acute attempter group. Time of the first suicide attempt was also quantified.

2.5. Brain Magnetic Resonance Imaging

Brain MRI acquisitions were performed on 1.5 or 3-T Philips systems with a delay of 8 ($\pm$8) days from the clinical evaluation. All subjects were scanned with a routine whole brain T1-weighted 3D sequence. MRI were acquired with a resolution of either $0.59 \times 0.59 \times 0.29$ or $0.85 \times 0.85 \times 1.10$ in sagittal plan, or with a resolution of $0.94 \times 0.94 \times 1.00$ in axial plan.

The segmentation of the hippocampus was performed using the fully automatic SACHA software (Chupin et al., 2007, 2009; Colliot et al., 2008). This approach segments both the hippocampus and the amygdala simultaneously based on competitive region-growing between these two structures. It includes prior knowledge on the location of the hippocampus and the amygdala derived from a probabilistic atlas and on the relative positions of these structures with respect to anatomical landmarks which are automatically identified. All resulting segmentations were assessed by well-trained raters (R.C and M.C), blind to the clinical data. Automated segmentation was preferred to manual segmentation because it is faster, requires less specific anatomical expertise and does not suffer from high intra- and inter-rater variability. SACHA was previously evaluated in depressed patient (Bergouignan et al., 2009).

Three variables of interest were studied on the basis of previous published papers (Kempton et al., 2011; Sheline et al., 1999; Kronmüller et al., 2008): Total (right + left) hippocampal volume was the main assessment criterion. Right and left hippocampal volumes were also analyzed individually. Total brain volumes were estimated with SPM5 to normalize hippocampal volumes. Five patients were excluded from the analysis because of poor quality of hippocampal segmentations and/or MRI artefacts leading to an unreliable estimation of hippocampal volume.

2.6. Statistical methods

Non-parametric statistics were used. First, bivariate analyses were performed using Chi2 tests for categorical variables and Wilcoxon tests for continuous variables. Second, linear regressions were used to control for potential confounding factors. The a-priori defined confounding factors were brain volumes, MRI acquisition sequence, sex, age, MDD duration and HDRS scores.

A Receiver Operating Characteristic curve was built to determine the optimal hippocampal volume threshold associated with acute suicide attempts. A sensitivity/specificity analysis was performed on all possible total hippocampal volumes. Two thresholds were chosen: a first one to obtain a good sensitivity (to allow a good true positive rate), and the second one to obtain the best compromise between negative specificity and sensibility.

All tests were two-tailed. Significance level was defined as $p < 0.05$.

3. Results

3.1. Sample

63 patients were included in this analysis. Mean age was 46.4 (±12.4) years, 37 (58.7%) were women, 44 (69.8%) had a recurrent MDD, the mean MDD duration was 8.7 (±11.4) years, 77.8% had previous antidepressant medication and the mean duration of previous antidepressant treatment was 2.8 (±4.5) years. 27 patients were treated with antidepressant medication: selective serotonin reuptake inhibitors (n = 14), serotonin and noradrenalin reuptake inhibitors (n = 5), tricyclics (n = 4) or other antidepressants (n = 4).

3.2. Suicide attempts

24 (38.1%) patients were suicide attempters. 13 (54.2%) were past suicide attempters. 11 (45.8%) were acute suicide attempters.

Socio-demographical and clinical characteristics did not differ between suicide attempters (either acute or past) and non-attempters (Table 1). The distribution of MRI sequences did not differ in suicide attempters (X = 1.0; p = 0.6), past attempters (X = 2.2; p = 0.33), acute attempters (x = 0.0; p = 0.99) as compared to non-attempters.

3.3. Hippocampal volumes

Total hippocampal volumes were associated neither with socio-demographic characteristics (Age: r = 0.04, p = 0.74; Sex: t = 1.5, p = 0.13; Educational level: k = 3.1, p = 0.21) nor with clinical characteristics (recurrent MDD: w = 385.5, p = 0.63; MDD duration: r = 0.04, p = 0.73; HAMD-17 score: r = 0.04, p = 0.77; antidepressant naive: w = 403.5; p = 0.32; previous antidepressant duration: r = −0.01; p = 0.94). Similarly, right and left hippocampal volumes were not associated with socio-demographic and clinical characteristics.

3.4. Suicide attempts and hippocampal volumes

Total hippocampal volumes were significantly smaller (p = 0.03) in suicide attempters than in non-attempters (Table 1 and Fig. 1). Similar results were found for right hippocampal volumes (Table 1). After adjusting on brain volume, a trend was still reported remained (p = 0.09 for total hippocampal volume and p = 0.08 for right hippocampal volume) for lower hippocampal volumes in suicide attempters than in non-attempters. After adjusting on gender, age, MDD duration and HDRS score, results were still significant for total hippocampal volumes (HR = 0.68; 95%CI [0.30:0.95], p = 0.03) and right hippocampal volume (HR = 0.68; 95%CI[0.50:0.94], p = 0.02).

After adjusting on MRI acquisition sequences, suicidal attempters again had a lower total hippocampal volume (HR = 0.50, 95%CI [0.30; 0.82], p = 0.007), and a lower right hippocampal volume (HR = 0.67, 95%CI[0.52; 0.88], p = 0.004).

Among the 37 women, 15 were suicide attempters. Socio-demographical and clinical characteristics did not differ for between suicide attempters and non-attempters. Total hippocampal volumes were significantly lower in suicide attempters than in non-attempters (4.36 (±0.90) cm^3 vs 5.12 (±1.06) cm^3, w = 231, p = 0.04). A consistent trend in women suicide attempters is observed for left hippocampal volumes ((2.23 (±0.45) cm^3 vs 2.55 (±0.49) cm^3, w = 216; p = 0.06).

In the 26 men, 9 were suicide attempters. Socio-demographical, clinical characteristics and hippocampal volumes (total, right and left) did not significantly differ for men between suicide attempters and non-attempters. However, even if results were not statistically significant because of the small sample size, total hippocampal

Table 1
Socio-demographical, clinical data and hippocampal volumes in suicide attempters (acute and past) and non-attempters.

	No suicide Attempt (n = 39)	Suicide Attempts (n = 24)	Past suicide Attempts (n = 13)	Acute suicide Attempts (n = 11)	Suicide Attempts (n = 24)	Suicide Attempts vs No suicide Attempt	p	Acute suicide Attempts vs No suicide Attempts	p	Past suicide Attempts vs No suicide Attempt	p	Acute suicide Attempts vs Past suicide Attempts	p
Age (years m (sd))	47.7(12.6)	44.2(11.9)	47.6(13.4)	40.2(13.4)	44.2(11.9)	w = 544	0.28	w = 277.5	0.14	w = 265.5	0.79	w = 92.5	0.23
Women (%)	56.4	62.5	53.8	72.7	62.5	$X^2 = 0.2$	0.63	$X^2 = 1.0$	0.33	$X^2 = 0.0$	0.87	$X^2 = 0.9$	0.34
Low Education Level (%)	7.7	16.7	23.1	9.1	16.7	$X^2 = 1.5$	0.47	$X^2 = 2.4$	0.30	$X^2 = 2.7$	0.26	$X^2 = 4.2$	0.12
Recurrent MDD (%)	66.7	75.0	92.3	54.5	75.0	$X^2 = 0.49$	0.48	$X^2 = 0.5$	0.46	$X^2 = 3.3$	0.07	$X^2 = 4.5$	**0.03**
MDD duration (years m(sd))	9.5(13.4)	7.5(7.3)	9.5(7.3)	5.2(6.9)	7.5(7.3)	w = 421	0.61	w = 236	0.51	w = 185	0.18	w = 102	0.08
HDRS (m(sd))	23.8(4.7)	24.8(4.7)	25.2(7.7)	24.3(5.4)	24.8(4.7)	w = 467	0.99	w = 201.5	0.76	w = 265.5	0.80	w = 73.5	0.93
AD naïve (%)	23.1	20.8	15.4	27.9	20.8	$X^2 = 0.0$	0.84	$X^2 = 0.1$	0.77	$X^2 = 0.3$	0.56	$X^2 = 0.51$	0.47
prior AD duration (years m(sd))	2.9(4.4)	2.6(4.8)	2.7(3.4)	2.5(6.4)	2.6(4.8)	w = 417	0.74	w = 222.5	0.26	w = 194.5	0.61	w = 83	0.14
Total Hippocampus volume (cm^3) m(sd))	5.22(0.99)	4.61(1.15)	5.97(1.30)	4.19(0.81)	4.61(1.15)	w = 625.5	**0.03**	w = 334	**0.005**	w = 291.5	0.43	w = 95	0.18
Right Hippocampus volume (cm$^{3)}$ m(sd))	2.66(0.55)	2.30(0.61)	2.49(0.69)	2.05(0.41)	2.30(0.61)	w = 581	**0.03**	w = 305	**0.003**	w = 276	0.54	w = 95	0.07
Left Hippocampus volume (cm$^{3)}$ m(sd))	2.59(0.54)	2.39(0.54)	2.57(0.54)	2.19(0.45)	2.39(0.54)	w = 520	0.15	w = 285	**0.05**	w = 235	0.77	w = 91	0.13

MDD: major depressive disorder; HDRS: Hamilton Depression Rating Scale 17 items; AD: Antidepressant. Bold: significant p value (<0.05).

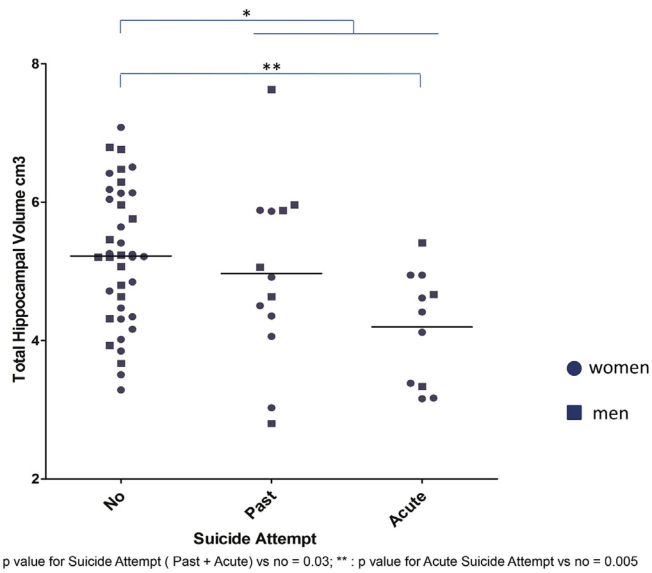

Fig. 1. Hippocampal volume and suicide attempts.

volumes were smaller in suicide attempters than in men non-attempters (5.04 (±1.44) cm^3 vs 5.35 (±0.92) cm^3, w = 89.5; p = 0.50).

3.5. *Acute suicide attempts and hippocampal volumes*

Total hippocampal volumes were significantly smaller in acute suicide attempters than in non-suicide attempters (Fig. 1). The same results were found for right and left hippocampal volumes (Table 1). After adjusting for brain volume, results were still significant for total hippocampal volumes (HR = 0.35, 95%CI [0.15:0.84], p = 0.02), right hippocampal volumes (HR = 0.58, 95%CI[0.39:0.89], p = 0.01) and reported a trend for left hippocampal volumes (HR = 0.69; 95%CI[0.47:1.02], p = 0.06). After adjusting on gender, age, MDD duration and HDRS scores, results were still significant for total hippocampal volumes (HR = 0.36, 95%CI[0.18; 0.73], p = 0.006), right hippocampal volumes (HR = 0.54, 95%CI[0.36:0.81], p = 0.004) and left hippocampal volumes (HR = 0.65; 95%CI[0.44:0.98], p = 0.04). After adjusting on MRI acquisition sequences, results were still significant for total hippocampal volumes (HR = 0.36, 95%CI[0.20; 0.65], p = 0.001), right hippocampal volumes (HR = 0.56, 95%CI [0.40:0.78], p = 0.0009) and left hippocampal volumes (HR = 0.67; 95%CI[0.47:0.95], p = 0.03).

8 women were acute suicide attempters. Socio-demographical and clinical characteristics did not differ for women between acute suicide attempters and non-attempters. Total hippocampal volumes were significantly smaller in acute suicide attempters than in non-attempters (4.09 (±0.76) cm^3 vs 5.12 (±1.06) cm^3, w = 136; p = 0.03). Similar results were found for right hippocampal volumes (2.01 (±0.61) cm^3 vs 2.63 (±0.61) cm^3, w = 113, p = 0.04) and there was a trend for left hippocampal volumes (2.13 (±0.41) cm^3 vs 2.55 (±0.49) cm^3, w = 216, p = 0.07).

Among men, 3 were acute attempters. Socio-demographical, clinical characteristics and hippocampal volumes did not significantly differ for men between acute suicide attempters and non-suicide attempters due to the small size of the sample. However, there was a trend for a smaller right hippocampal volume in acute attempters compared to non-attempters (2.14 (±0.43) cm^3 vs 2.70 (±0.47) cm^3, w = 42, p = 0.09).

3.6. *Past suicide attempts and hippocampal volumes*

Hippocampal volumes did not differ between past suicide attempters and non-attempters, or between acute and past attempters. Only a trend was observed for a smaller hippocampus in acute attempters as compared to past attempters (Table 1).

No significant correlation was observed between hippocampal volumes and duration since the first suicide attempt (total hippocampal volume: r = 0.32, p = 0.15; right hippocampal volume: r = 0.35, p = 0.12; or left hippocampal volume: r = 0.29, p = 0.21).

3.7. *Thresholds of total hippocampal volumes for acute suicide attempts*

The ROC analysis (Fig. S1) showed that the Area Under the Curve (AUC) was 0.75 95%CI[0.61; 0.88].

In this sample, a total hippocampal volume threshold of 5.00 cm^3 (91% sensitivity, 57.7% specificity, 98.3% negative predictive value, 31.2% positive predictive value for acute suicide attempts) is relevant since 98.3% of patients with total hippocampal volumes bigger than 5.00 cm^3 are not acute suicide attempters.

A total hippocampal volume threshold <4.69 cm^3, (72.7% sensitivity, 65.4% specificity, 94.9% negative predictive value, 30.8% positive predictive value) is a compromise for a good specificity and a good sensitivity for acute suicide attempts.

4. Discussion

Suicide attempters have smaller hippocampi than non-attempters in major depression, independently from socio-demographic and MDD or MDE clinical features. Indeed, acute but not past suicide attempts were associated with smaller hippocampi. The ROC analyses showed that a total hippocampal volume threshold of 5.00 cm^3 has a 98.2% negative predictive value for acute suicide attempt. In other words, 98.3% of patients with total hippocampal volumes larger than 5.00 cm^3 are not acute suicide attempters.

Only two previous studies compared hippocampal volumes in MDD depending on the presence or absence of suicide attempts. No difference in hippocampal volumes was shown between 7 women who attempted suicide and 10 women who did not (Monkul et al., 2007). However, this study design differed from ours. First, the time between suicide attempt and MRI was not controlled, and the effect on acute suicide attempt may have been left out. Second, the sample size was relatively small. Third, at the time of study participation, five of the suicidal patients were depressed and two were euthymic. Similarly, seven of the non-suicidal patients were depressed and three were euthymic. On the contrary, all patients of our sample were currently suffering from an MDE. Thus, the HDRS score was lower in the study of Monkul et al. (2007) (13.7 (±10.9) for suicidal attempters and 10.9 (±8.0) for non-attempters) than in our sample (24.8 (±4.7) for suicidal attempters and 23.8 (±4.7) for non-attempters). In the second study (Hwang et al., 2010) (VBM analysis in 70 geriatric male patients with MDD), no gray matter volume difference was found between patients with a suicide attempt history (n = 26) as compared with others. Our results differ for at least three reasons. First, in the previous study, patients were elderly depressed males with no history of depression before the age of 50 years, whereas patients of our study were younger and a majority of women. Second, they used a standard VBM analysis on both gray and white matter, without comparing volumes as we did. Third, as in Monkul et al. (2007), the time between suicide attempt and MRI was not controlled. Our study is thus the first to take into account time between suicide attempt and MRI and to perform hippocampal segmentation.

Our results are in line with those of the powerful meta-analysis of Kempton et al. (2011), showing that there were no significant effect of isolated/recurrent MDD, number of previous depressive episodes, or previous antidepressant drug use on hippocampal volumes in depressed patients.

However, our study has some limitations. Even though cognitive, addictive and psychotic disorders were excluded from this sample, no assessment of axis II disorders or anxiety disorders was available in this study. However, the fact that lower hippocampal volume is associated with recent suicide attempts suggests that this is related to the acute MDE and not to another psychiatric disorder. The number of previous suicide attempts was not available in this study. However, the duration since the first suicide attempt was not correlated with hippocampal volumes, minimizing the possible impact of this parameter. Our sample is relatively small, leading to an insufficient power in sub-groups, especially for the small number of male participants, which may explain the lack of association among them. However, despite a relatively limited sample size, we show significant differences especially in women and in those who attempted suicide within the last month. The use of 3 different MRI acquisition sequence may biases these results. However, these 3 sequences were not differently distributed among the different groups (no suicide attempters, suicide attempters, acute suicide attempters and past suicide attempters). Moreover, adjustment on MRI sequence acquisition did not change the results.

The reason why we evidenced such results remains to be assessed. However, since smaller hippocampus was evidenced only in acute suicide attempters, our result argues for a state but not a trait of suicide attempt risk in MDD. This state status may be related to the plasticity of hippocampus due to neurogenesis (David et al., 2009). However, no causal relationship can be proposed based on our data, since suicide attempts occurred before the MRI acquisition in our sample. Furthermore, we were unable to control for medical consequences of suicide attempts, which may result in structural hippocampal injury, since the hippocampus is sensitive to anoxic injury (Caine and Watson, 2000). Nevertheless, our results may suggest that low hippocampal neurogenesis might be a cause of suicide attempts in MDD. This hypothesis should be investigated in further studies. Regarding the growing literature on the effect of childhood maltreatment on hippocampus volume, structure or function (McGowan et al., 2009), one question is to know if reported volumetric differences may not stem from a higher number of victims of childhood maltreatment in the attempter group. This was not assessed in the present study and is a limitation of this paper.

Finally, we found that hippocampal volume was lower in MDE suicide attempters, particularly acute attempters, as compared to non-attempters. Our results suggest that hippocampus volume could be a good candidate biomarker to help clinicians to predict suicide attempts in MDE. Further studies are required to understand the reasons of this association.

Role of the funding source

This study was funded by the Programme Hospitalier de Recherche Clinique from the French Ministry of Health (AOR10071). Funding was attributed for the data collection.

Contributors

The authors' contributions are the following:

Romain Colle: conception of the work, data management, analysis, drafting, interpretation of data, final approval.

Marie Chupin: volumetry assessment, interpretation of data, revising, final approval.

Claire Cury: interpretation of data, revising, final approval.

Christophe Vandendrie: MRI acquisition, revising, final approval.

Florence Gressier: clinical data acquisition, revising, final approval.

Patrick Hardy: clinical data acquisition, revising, final approval.

Bruno Falissard: analysis, interpretation of data, revising, editing assistance, final approval.

Olivier Colliot: volumetry assessment, interpretation of data, revising, final approval.

Denis Ducreux: MRI acquisition, data collection, revising, final approval.

Emmanuelle Corruble: conception of the work, data collection, data management, drafting, analysis, interpretation of data, final approval.

Romain Colle and Emmanuelle Corruble had full access to all the data of the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

The disclosures of interest are the following: Romain Colle, Marie Chupin, Claire Cury, Christophe Vandendrie have no conflicts of interest. Florence Gressier has given talks for Servier, Lundbeck. Patrick Hardy has no conflicts of interest. Bruno Falissard has been consultant, expert or has given talks for E. Lilly, BMS, Servier, Sanofi, GlaxoSmithKline, HRA, Roche, Boeringer Ingelheim, Bayer, Almirall, Allergan, Stallergene, Genzyme, Pierre Fabre, Astra Zeneca, Novartis, Janssen, Astellas, Biotronik, Daiichi-Sankyo, Gilead, MSD, Lundbeck. Olivier Colliot received lecture fees from Lundbeck and consulting fees from Guerbet. Denis Ducreux have no conflicts of interest. Emmanuelle Corruble received consulting or conference fees from Astra-Zeneca, Bristol Myers Squibb, Eisai, Lundbeck, Otsuka, Sanofi-Aventis, Servier.

Acknowledgments

This study was funded by the Programme Hospitalier de Recherche Clinique from the French Ministry of Health (AOR10071) and the Assistance Publique – Hôpitaux de Paris (P060219).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2014.12.010.

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