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

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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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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.