Trends
in Psychiatry and Psychotherapy

Review Article

Global hippocampal atrophy in major depressive disorder: a meta-analysis of magnetic resonance imaging studies

Atrofia global do hipocampo no transtorno depressivo maior: uma metanálise de estudos com ressonância magnética

Marcelo Antônio Oliveira Santos,[1,2] Lucas Soares Bezerra,[1,2] Ana Rita Marinho Ribeiro Carvalho,[2,3] Alessandra Mertens Brainer-Lima[2,4]

Abstract

Introduction: Major depressive disorder (MDD), an incapacitating mental disorder, is characterized by episodes of at least 2 weeks of apparent changes in mood, cognition, and neurovegetative functions. Many neuroimaging studies using magnetic resonance imaging (MRI) have examined morphometric changes in patients with MDD, but the results are not conclusive. This study aims to review the literature and perform a meta-analysis on hippocampal volume (HcV) in patients with MDD.
Methods: Studies on HcV in patients with MDD diagnosis were identified from major databases (MEDLINE, EMBASE, The Cochrane Library, Scopus, PsycINFO, and SciELO) using the search terms depression, major depressive disorder, MDD, unipolar, magnetic resonance imaging, MRI, and hippocampus.
Results: A meta-analysis of 29 studies fulfilling specific criteria was performed. The sample included 1327 patients and 1004 healthy participants. The studies were highly heterogeneous with respect to age, sex, age of onset, and average illness duration. However, the pooled effect size of depression was significant in both hippocampi. MDD was associated with right (-0.43; 95% confidence interval [95%CI] -0.66 to -0.21) and left (-0.40; 95%CI -0.66 to -0.15) hippocampal atrophy.
Conclusions: MDD seems to be associated with global HcV atrophy. Larger longitudinal follow-up studies designed to analyze the influence of sociodemographic variables on this relationship are required to yield better evidence about this topic.
Keywords: Hippocampal volume, major depressive disorder, MRI, depression.

Resumo

Introdução: O transtorno depressivo maior (TDM) é uma doença mental incapacitante caracterizada por episódios de pelo menos 2 semanas de mudanças claras no afeto, cognição e funções neurovegetativas. Vários estudos de neuroimagem, realizados através de imagem de ressonância magnética (IRM), examinaram mudanças morfométricas em pacientes com TDM, com resultados não conclusivos. Este estudo tem como objetivo revisar a literatura e realizar uma metanálise sobre o volume do hipocampo (VHc) em pacientes com TDM.
Métodos: Estudos de VHc em pacientes com TDM foram identificados a partir dos principais bancos de dados (MEDLINE, EMBASE, The Cochrane Library, Scopus, PsycINFO e SciELO) usando os seguintes termos: depression, major depressive disorder, MDD, unipolar, magnetic resonance imaging, MRI e hippocampus.
Resultados: Foi realizada uma metanálise de 29 estudos que preencheram os critérios específicos. A amostra foi composta por 1327 pacientes e 1004 indivíduos saudáveis. Os estudos foram altamente heterogêneos em relação a idade, gênero, idade do primeiro episódio e duração média da doença, mas o efeito combinado da depressão foi significativo em ambos os hipocampos. O TDM foi associado à atrofia do hipocampo à direita [-0,43; intervalo de confiança de 95% (IC95%) -0,66 a -0,21] e à esquerda (-0,40; IC95% -0,66 a -0,15).
Conclusões: O TDM parece estar associado à atrofia global do VHc. Estudos longitudinais com maior tempo de seguimento, projetados para analisar a influência dos fatores sociodemográficos nessa relação, são necessários para obter evidências mais robustas.
Descritores: Volume hipocampal, transtorno depressivo maior, RM, depressão.

[1] Grupo de Pesquisa em Epidemiologia e Cardiologia, Universidade Federal de Pernambuco, Recife, PE, Brazil. [2] Centro Universitário Maurício de Nassau, Recife, PE, Brazil. [3] Hospital da Restauração, Recife, PE, Brazil. [4] Pronto-Socorro Cardiológico Universitário de Pernambuco (PROCAPE), Universidade de Pernambuco (UPE), Recife, PE, Brazil.

This study was conducted at Departamento de Medicina, Centro Universitário Maurício de Nassau, Recife, PE, Brazil.

Submitted Oct 24 2017, accepted for publication May 06 2018.

Suggested citation: Santos MAO, Bezerra LS, Carvalho ARMR, Brainer-Lima AM. Global hippocampal atrophy in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Trends Psychiatry Psychother. 2018;40(4):369-378. Epub Sep 17 2018. http://dx.doi.org/10.1590/2237-6089-2017-0130

Introduction

Major depressive disorder (MDD) is an incapacitating mental disorder characterized by episodes of at least 2 weeks of apparent changes in affection, cognition, and neurovegetative functions.[1] Patients with MDD present a lower quality of life and higher prevalence of medical conditions. The global prevalence of MDD is approximately 5%. According to the World Health Organization, MDD is estimated to become the second most disabling condition by 2020.[2]

Several neurobiological models have been proposed to explain the pathogenesis of MDD. Because MDD is primarily related to lower affection and humor, many authors have studied and emphasized the role of dysfunctional cortico-limbic networks in MDD.[3] Postmortem and animal model studies have reported lower hippocampal volume (HcV) in participants with depressive disorders. The hippocampus is involved in episodic and declarative memory, as well as in learning, areas that often present deficits in patients with depression.[4] The suggestion that HcV is lower because of depression has been influential in guiding neuroimaging studies on the analysis of the hippocampus.[5]

Many neuroimaging studies using magnetic resonance imaging (MRI) have examined morphometric changes in patients with MDD, but the results are not conclusive. Some studies have reported bilateral,[6] unilateral right,[7] or unilateral left hippocampal hypotrophy in these patients compared with healthy participants,[8,9] whereas others have reported no changes.[10,11] Furthermore, some systematic reviews and meta-analyses have examined studies on HcV in the first depressive episode or in specific groups, such as the elderly (aged ≥ 60 years) with depression.[7,12-14] However, to date, no reviews have systematically examined the macro influence of depression on HcV.

This study aims to examine whether patients with MDD present hippocampal atrophy compared with non-depressive participants. We considered HcV reduction as the primary outcome.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. Details of the study protocol were registered on the International Prospective Register of Systematic Reviews (PROSPERO) and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42018086196.

The electronic databases MEDLINE, EMBASE, The Cochrane Library, Scopus, PsycINFO, and SciELO were searched for papers published between January 1960 and October 2017. The search terminology included the terms depression, major depressive disorder, MDD, unipolar, magnetic resonance imaging, MRI, and hippocampus. Only studies written in English, Portuguese, or Spanish were reviewed. At least two of the authors performed each search. Furthermore, all reference lists of the obtained papers were checked for studies not indexed in electronic databases. The complete search strategy was as follows: Depression; Major depressive disorder; MAJOR DEPRESSIVE DISORDER (MeSH); MDD; (unipolar) AND (depression); Magnetic resonance imaging; MAGNETIC RESONANCE IMAGING (MeSH); MRI; Hippocampus; HIPPOCAMPUS (MeSH); (hippocampal) AND (volume); (1 OR 2 OR 3 OR 4 OR 5) AND (6 OR 7 OR 8) AND (9 OR 10 OR 11).

All observational studies and clinical trials that evaluated the relationship between MDD and HcV measured through MRI were included in this review. Studies with sample groups in which patients presented any other associated neuropsychiatric or metabolic condition were excluded. Inclusion criteria were as follows: patients with a primary diagnosis of MDD assessed using international diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] or International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10]); a healthy comparison group; participants screened for neurological, psychiatric, and other medical disorders that could affect brain structure, including alcohol and substance abuse; MRI as the primary measurement tool; and a continuous measure of HcV as the dependent variable.

Two authors examined the abstracts of the articles retrieved against the defined inclusion criteria. All potentially relevant full-text articles were retrieved for quality and satisfaction assessment of inclusion criteria. Figure 1 summarizes the study inclusion process.

For each data criterion, a data extraction table was pilot-tested on five randomly-selected studies and adjusted accordingly. Two independent reviewers assessed the following data from the patient and control samples: number of participants, HcV means and standard deviations, and mean disease duration. A third author double-checked the extracted data. Disagreements were resolved by consensus between the authors; if no consensus could be reached, a third author made a decision. All volumes were converted to mm^3 before being entered into the meta-analysis.

To certify the quality and validity of the eligible studies, pairs of reviewers working independently

assessed each study using the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) checklist.[16]

Calculations were performed using the STATA software version 13.0 SE. The meta-analyses were performed using a random effects model weighting the studies by the inverse variance and calculating the Hedges' *g* effect size. The random effects model using the DerSimonian-Laird method was selected over the fixed effects approach because previous analyses have indicated considerable between-study heterogeneity.

To assess for between-study heterogeneity, the Cochran Q test was performed and I^2 statistic was recorded and further analyzed by meta-regression. Begg's and Egger's tests were used to determine publication bias.

Results

Twenty-nine studies comprising 1327 patients and 1004 healthy participants fulfilled both inclusion and exclusion criteria and were included in this meta-analysis.[6-9,11-14,17-37] One study that found lower left HcV was excluded because volume measurements were unavailable.[38] A report by Andreescu et al.[39] was also excluded because only global HcV measurements were available. Pantel et al.[40] reported a study in German that was excluded from the analysis because of language limitations.

All studies selected for this review were cross-sectional studies published in English, except one cohort study.[30] The main inclusion criteria entailed adults (≥18 years). The Hamilton Depression Scale was the main

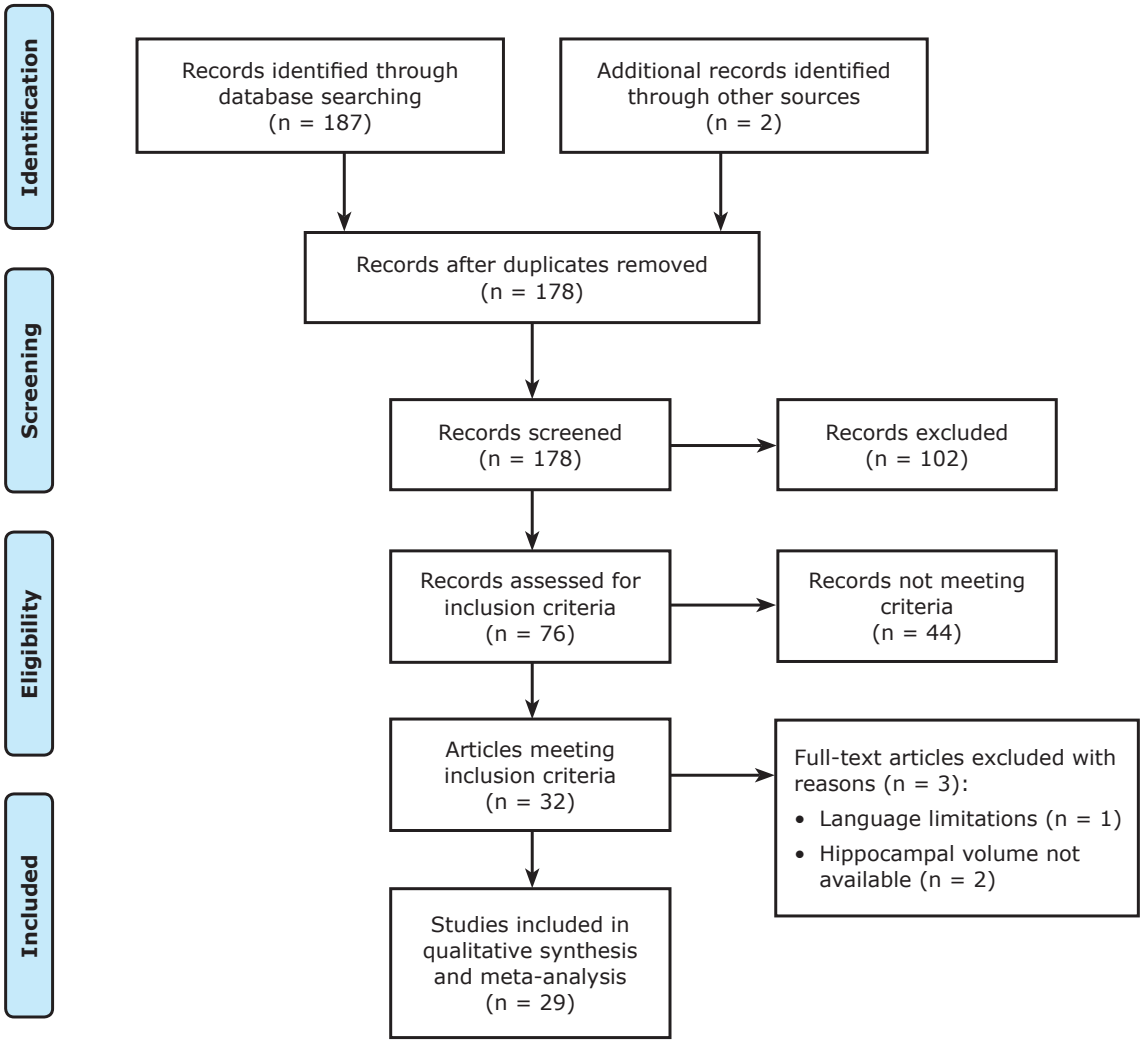

Figure 1 - PRISMA flow diagram for the meta-analysis of hippocampal volume in major depressive disorder. Adapted from Moher et al.[15]

instrument used to assess the severity of depressive symptoms. Mean age of participants in the study groups varied from 16 to 74 years, and the percentage of male participants in each group varied from 0 to 63. The average HcV measured showed slight variations, and two of these measurements markedly deviated from the mean.[9,14] Sample characteristics of the included studies are presented in Table 1. Some of the studies included patients with recurrent depression,[6] first-episode depression,[12,17,26] and late-onset depression.[7,13,21] Eight studies evaluated illness duration, which varied from 7 to 57 months.[6,12,18,25,27,28,33,35] Table 2 shows a summary of the included studies.

Because the study performed by MacQueen et al.[26] analyzed two samples (first-episode versus multiple episodes of depression) that did not overlap, it was considered as having two distinct samples for statistical calculation. Therefore, the degrees of freedom (df), which is typically the number of studies minus 1, was 29 instead of 28.

The Q test of heterogeneity (df = 29) was highly significant, as expected (both right and left hippocampus: $p < 0.00001$). The percentage of heterogeneity given by the I^2 statistic was 84% (95% confidence interval [95%CI] 77.8 to 88.1, $p < 0.00001$) for the right hippocampus and 88% (95%CI 83.4 to 90.7, $p < 0.00001$) for the left hippocampus, which provides high evidence of between-study heterogeneity. Therefore, the effect size was calculated under the assumption of a random effects model. The DerSimonian-Laird pooled effect size revealed bilateral statistical significance: -0.43 (95%CI -0.66 to -0.21) for the right hippocampus (Figure 2) and -0.40 (95%CI -0.66 to -0.15) for the left hippocampus (Figure 3).

Table 1 - Studies of hippocampal volume in patients with major depressive disorder

	Patients with depression				Healthy controls			
Author and year	**Age**	**Right volume**	**Left volume**	**N**	**Age**	**Right volume**	**Left volume**	**N**
Meisenzhal 2010[27]	44 (12.3)	3770 (420)	3670 (410)	92	33.3 (12.2)	3940 (410)	3830 (410)	138
Posener 2003[28]	33 (10.7)	2948.4 (446.7)	2546.00 (392.7)	27	33.2 (10.8)	2993.9 (414.2)	2475 (359.4)	42
Xia 2004[35]	39.5 (12)	3487.2 (62.9)	3109.8 (83.5)	22	35.4 (8.8)	3710.3 (36.6)	3352 (43.5)	13
Sheline 1996[6]	68.5 (10.4)	2283 (324)	2159 (301)	10	68.5 (9.5)	2577 (259)	2544 (333)	10
MacMaster 2004[25]	16.6 (1.8)	2540 (120)	2530 (90)	17	16.2 (1.6)	2880 (110)	3050 (110)	17
Eijndhoven 2009[33]	34.9 (11.5)	3848 (444)	3610 (372.5)	40	37.3 (12.7)	3881 (429)	3716 (364)	20
Saylam 2006[12]	33.4 (9.3)	2696.4 (194.4)	2638.7 (249.2)	24	30.1 (6.1)	2806.3 (256.8)	2786.7 (249.2)	24
Eker 2010[18]	32.1 (9.3)	3310 (420)	3380 (350)	25	29.7 (6.4)	3110 (260)	3330 (300)	22
Vythilingam 2002[34]	33.5 (7)	2884 (120.5)	3235.5 (111)	32	27 (5)	3037 (134)	3179 (123)	14
MacQueen 2003[26]	28.4 (11.8)	2793 (303.8)	2738 (301.1)	20	28.4 (11.5)	2784 (342.2)	2761 (368.4)	20
	35.9 (11.1)	2392 (256.7)	2381 (273.5)	17	36.2 (11.9)	2692 (190.1)	2703 (249)	17
Kaymak 2010[22]	32 (8.5)	2720 (320)	2850 (330)	20	29.3 (5.8)	3400 (250)	3520 (330)	15
Lange 2004[23]	34 (10)	2670 (500)	2790 (410)	17	32 (6)	3190 (370)	2990 (460)	17
Bearden 2009[37]	32.9 (11.9)	1911.1 (280.1)	1885.4 (230.8)	31	36.7 (10.7)	1828.9 (284.2)	1851.9 (326.8)	31
Rusch 2001[29]	33.2 (9.5)	2290 (300)	2170 (260)	25	37.4 (14.4)	2200 (240)	2130 (270)	15
Vakili 2000[10]	38.5 (10)	2610 (580)	2640 (550)	38	40.3 (10.4)	2600 (510)	2460 (380)	20
Mervaala 2000[8]	42.2 (12.2)	3462 (405)	3104 (391)	34	42.1 (14.6)	3700 (467)	3441 (436)	17
Cole 2010[17]	41.9 (8.9)	1860 (220)	1770 (260)	37	42.2 (9)	2080 (280)	1980 (290)	37
Bremner 2000[9]	43 (8)	982 (269)	940 (208)	16	45 (10)	1113 (194)	1166 (248)	16
Frodl 2008[19]	45 (11.1)	3850 (330)	3780 (380)	30	46.3 (13.1)	3830 (420)	3760 (400)	30
Hickie 2005[20]	53.5 (13.5)	3000 (400)	2900 (400)	66	55.8 (10)	3300 (600)	3300 (500)	20
von Gunten 2000[11]	57.6 (13.9)	2597.9 (244)	2498.6 (294.8)	14	58.1 (11.4)	2699.5 (312.7)	2644.4 (409.9)	14
Janssen 2004[21]	64 (10.9)	2840 (390)	3100 (370)	28	62.37 (11.3)	3120 (450)	3200 (520)	41
Steffens 2000[13]	71.4 (8.4)	3300 (440)	3170 (440)	66	67.1 (5)	2980 (390)	2920 (360)	18
Zhao 2008[13]	66 (5.5)	3660 (560)	3435 (550)	61	69 (5.5)	3720 (590)	3510 (620)	43
Taylor 2005[31]	70 (7.3)	3090 (420)	2950 (430)	135	69.4 (6.3)	3120 (440)	2960 (450)	83
Avila 2011[36]	70 (6.67)	3099.3 (489.9)	3439.7 (405.3)	48	70.2 (7.2)	3099.8 (271.6)	3446.5 (334.2)	31
Ballmaier 2008[14]	71.1 (7.6)	1127.5 (231.1)	1116.1 (222)	46	72.3 (6.9)	1308.4 (245.6)	1272.7 (275.6)	34
Lloyd 2004[24]	74 (6.3)	2800 (500)	2700 (400)	51	73.1 (6.7)	3000 (400)	2800 (400)	39
Sawyer 2013[30]	70 (7.5)	3070 (420)	2930 (410)	238	70,4 (6.2)	3110 (430)	2950 (420)	146

Begg's and Egger's tests were performed and showed no evident signs of publication bias (Figure 4). The meta-analysis was repeated, omitting one study at a time, to ensure that the result was not skewed by a single study. This analysis did not change the random-effects estimate, and the results continued to be statistically significant.

Because the studies had significant heterogeneity, the data were analyzed using meta-regression. We assumed that differences in age, sex, duration of illness, and year of publication could explain some of the variation. These variables were analyzed separately and together, but were not significantly correlated with the random-effects estimate in either the right or left hippocampus.

Discussion

The studies included in the analysis yielded highly heterogeneous results. Notably, this heterogeneity was expected because there were marked differences among the patient groups with respect to age and sex distribution, type of MDD (e.g., first episode, dysthymia, refractory, late onset), illness duration, age at the first episode, and factors related to treatment. Moreover, an increase in HcV variation was expected considering various protocols for the scanning and delineation of hippocampal structures.

However, a meta-analysis plays an important role in the analysis of scientific evidence because these possible confounding factors are diluted or neutralize

Table 2 - Summary of included studies evaluating hippocampal atrophy in MDD

Study	MRI tracing method	Condition	Follow-up	Hippocampal atrophy	Symptom assessment	Females in the sample (%)
Meisenzhal 2010[27]	Software	FE, RMD	No	Bilateral	HAM-D	58.3
Posener 2003[28]	Manual	MDD	No	No	HAM-D, CGI	55.8
Xia 2004[35]	Manual	MDD	No	Bilateral	HAM-D	51.4
Sheline 1996[6]	Manual	RMD	No	Bilateral	HAM-D	100.0
MacMaster 2004[25]	Semi-auto	MDD	No	Bilateral	CDRS	52.9
Eijndhoven 2009[33]	Software	FE	No	No	HAM-D	50.0
Saylam 2006[12]	Manual	DF MDD	No	Left	HAM-D	75.0
Eker 2010[18]	Software	FE	No	No	HAM-D	74.4
Vythilingam 2002[34]	Manual	MDD	No	Left	HAM-D, ZDS	100.0
MacQueen 2003[26]	Manual	FE, RMD	No	Bilateral	HAM-D, CGI, BDI-II	51.9
Kaymak 2010[22]	Software	MDD	No	Bilateral	HAM-D	100.0
Lange 2004[23]	Not clear	MDD	No	Not clear	HAM-D, BDI-II	100.0
Bearden 2009[37]	Manual	MDD	No	Left	HAM-D	77.0
Rusch 2001[29]	Software	MDD	No	No	HAM-D	57.5
Vakili 2000[10]	Manual	MDD	No	No	HAM-D	55.3
Mervaala 2000[8]	Manual	DR MDD	No	Left	HAM-D	56.9
Cole 2010[17]	Software	MDD	No	Bilateral	HAM-D	75.7
Bremner 2000[9]	Not clear	MDD	No	Left	Not Clear	37.5
Frodl 2008[19]	Software	MDD	3 years	Left increase*	HAM-D	66.0
Hickie 2005[20]	Manual	LOS, EOS	No	Bilateral	HAM-D	64.0
von Gunten 2000[11]	Manual	MDD	No	No	HADS	57.1
Janssen 2004[21]	Software	MDD	No	Right	MADRS	100.0
Steffens 2000[13]	Software	GD	No	Right	CESD, DDES	71.4
Zhao 2008[13]	Software	MDD	No	No	MADRS	53.7
Taylor 2005[31]	Software	LOS, EOS	No	Right	DDES	70.6
Avila 2011[36]	Manual	LOS, EOS	No	Left	MADRS, HAM-D	72.2
Ballmaier 2008[14]	Manual	LOS, EOS	No	Bilateral	HAM-D	66.3
Lloyd 2004[24]	Software	LOS, EOS	No	Bilateral	MADRS, GDS	75.0
Sawyer 2013[30]	Software	MDD	10 years COHORT	Right	DDES, CESD	69.0

BDI-II = Beck Depression Inventory II; CDRS = Childhood Depression Rating Scale; CESD = Center for Epidemiologic Studies Depression scale; DDES = Duke Depression Evaluation Schedule; DF = drug-free; DR = drug-resistant; EOS = early-onset depression; FE = first episode; GCI = Global Clinical Impression Scale; GD = geriatric depression; GDS = Geriatric Depression Scale; HADS = Hospital Anxiety and Depression Scale; HAM-D = Hamilton Depression Scale; LOS = late-onset depression; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder; MRI = magnetic resonance imaging; RMD = recurrent major depression; ZDS = Zung Depression Scale.
* Left hippocampal volume increased after a 3-year follow-up in use of antidepressants.

each other based on the large number of participants analyzed. Meta-analyses are conducted to determine whether an effect is present, and summarize the data to determine if this effect is positive or negative. This process increases the external validity of the studies as well as the extendibility of results to the general population of patients with MDD.

It is established that HcV losses are expected as a natural process of aging[41]; however, Sheline et al.[42] demonstrated that illness duration, not age, predicted hippocampal loss in women with recurrent MDD. Only eight studies included in our analysis presented information about depression duration. However, in the meta-regression, neither illness duration nor age were significantly correlated with the random-effects estimate.

Seven studies failed to find significant HcV differences in patients with depression compared with healthy participants.[11,18,19,28,29,32,33] Six studies demonstrated significant reduction only in the right hippocampus.[7,20,21,30,31,35] Six other studies showed similar findings in the lower left hippocampus.[8,9,12,13,36,37] Bilateral hippocampal atrophy was reported in 10 studies.[6,14,22-27,34]

MacQueen et al.[26] evaluated one group of patients during their first depressive episode and another during multiple episodes and compared them to healthy matched participants. After the first episode, there were no differences between the depression and comparison groups. However, in the group with multiple depressive episodes, there was bilateral hippocampal atrophy compared with healthy participants.

Vythilingam et al.[34] theorize that HcV is bilaterally reduced in patients with depression who experienced sexual abuse in childhood compared with participants with depression but with no similar experience. Those authors reported 18% smaller volumes for the left hippocampus and 15% smaller ones for the right hippocampus.

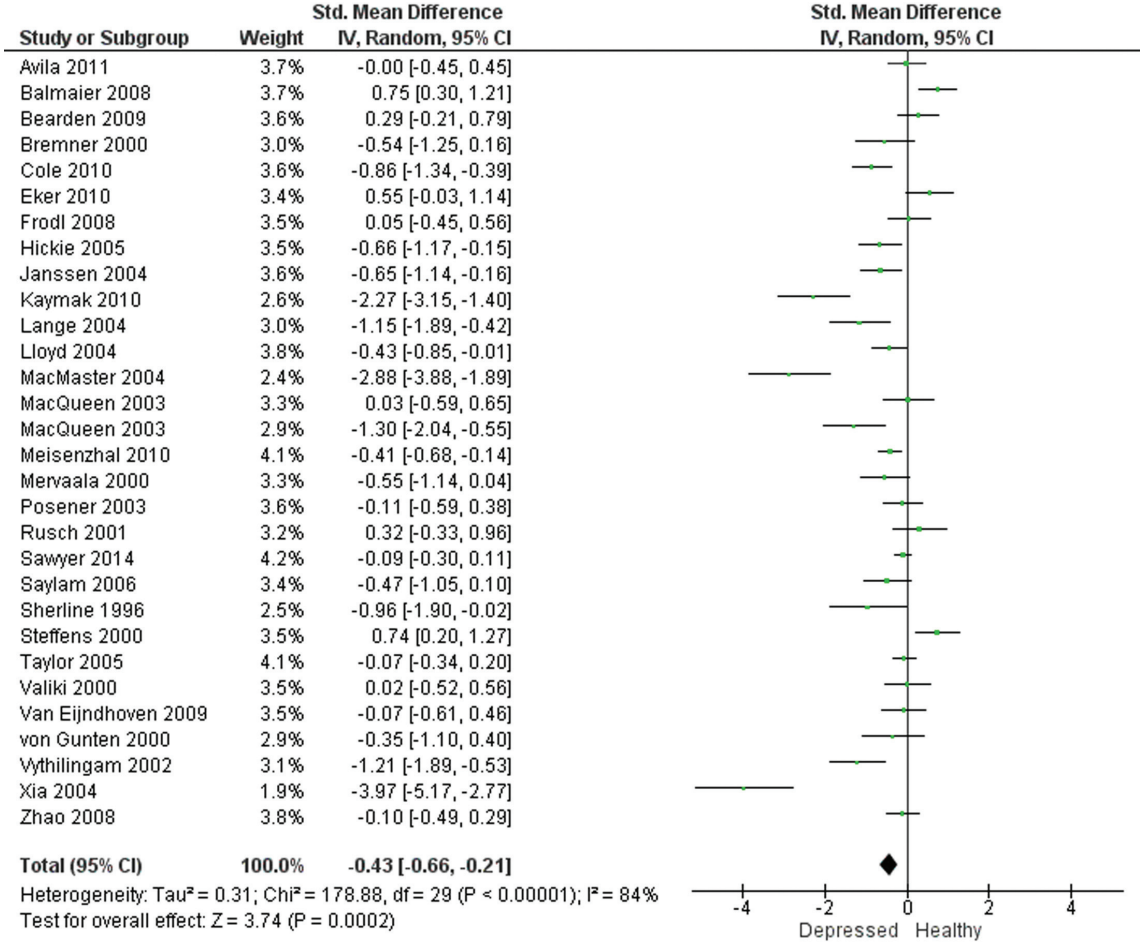

Figure 2 - Standardized mean difference of right hippocampal volume in patients with depression relative to comparison subjects from a meta-analysis of 29 magnetic resonance imaging studies. 95%CI = 95% confidence interval; Std = standard.

According to the results of Vakili et al.,[32] a smaller volume of the right hippocampus was associated with poor responses to antidepressants. This result is incipient, as investigating this association was not the primary objective of the study. However, if confirmed, that finding would be clinically interesting as a potential predictor of treatment response.

The pathophysiological pathways that explain HcV reduction in MDD remain unclear. Some authors theorize that HcV reduction is associated with disturbed hypothalamic pituitary adrenal axis function and adrenal hypersecretion of glucocorticoids, particularly cortisol. According to this hypothesis, cortisol leads to neural atrophy and the inhibition of neurogenesis in the hippocampus.[43] Another important supporting mechanism is the glutamate N-methyl-D-aspartate (NMDA) channel present in inhibitory neurons that comprise this pathway. Subiculum neurons make a synapse with a hypothalamic neuron, inhibiting it through NMDA receptors. The hypothalamic neuron modulates the corticotropic cell, stimulating it through gamma-aminobutyric acid (GAMA) liberation, which culminates in the production and release of the adrenocorticotropic hormone (ACTH). Serum cortisol concentration increases as a product of ACTH, released from the adrenal gland.[44-46]

It is important to address the potential protective properties of selective serotonin reuptake inhibitors (SSRIs) in patients with MDD. As demonstrated by Frodl et al.,[19] after a follow-up of 3 years, patients with MDD who used SSRI antidepressants showed protective effects against hippocampal atrophy as well as an increase in the left HcV. Although this is the only study to demonstrate this association, many studies have indicated that SSRIs reduce functional deficits in inflammatory and ischemic events.[47]

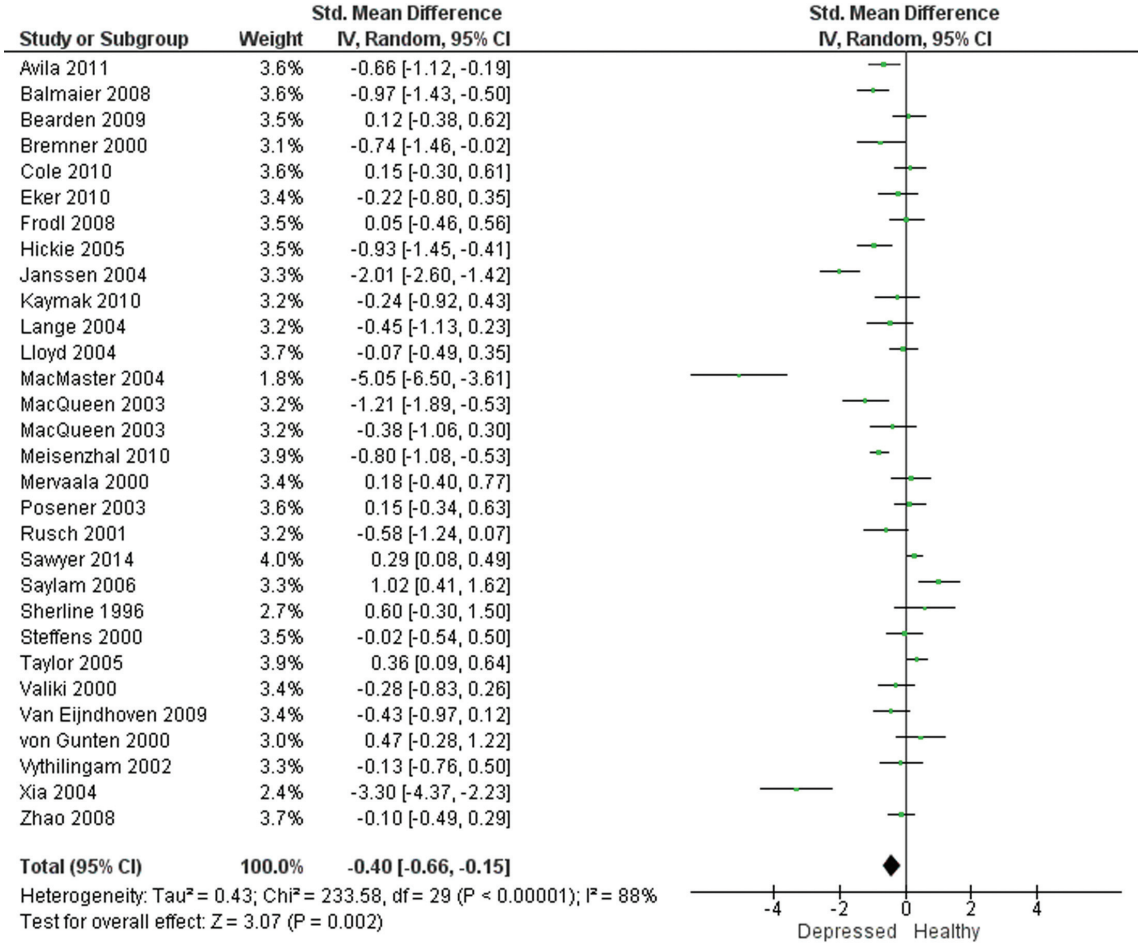

Figure 3 - Standardized mean difference of left hippocampal volume in patients with depression relative to comparison subjects from a meta-analysis of 29 magnetic resonance imaging studies. 95%CI = 95% confidence interval; Std = standard.

Study limitations

In principle, cross-sectional studies such as those included in the present analysis do not allow conclusions about causality to be drawn.

Further, socioeconomic and lifestyle characteristics from specific population groups can act as confounders. For example, the habit of regular exercise training is a protective factor against hippocampal atrophy and may be responsible for hippocampus hypertrophy in healthy participants.[48]

Other factors can also act as confounders, such as the comorbidity of MDD and anxiety disorders,[49] which was not assessed in any of the studies.

Longitudinal follow-up studies with large samples are the best design to allow the drawing of conclusions about the association between hippocampal atrophy and MDD.

Conclusions

Although the studies available in the literature are quite heterogeneous, MDD seems to be associated with global HcV atrophy. Many confounding factors may have influenced the divergence between studies, in particular sociocultural variables, which are responsible for the construction of social identity and affect the way in which stressful and depressive situations may contribute to changes in hippocampal neuronal circuits. Nevertheless, idiosyncratic biological factors may influence neuronal circuitry development and plasticity and play a role in the fine adjustment of hippocampal dynamics.

Larger longitudinal follow-up studies that consider these aspects are needed to yield better evidence about this topic.

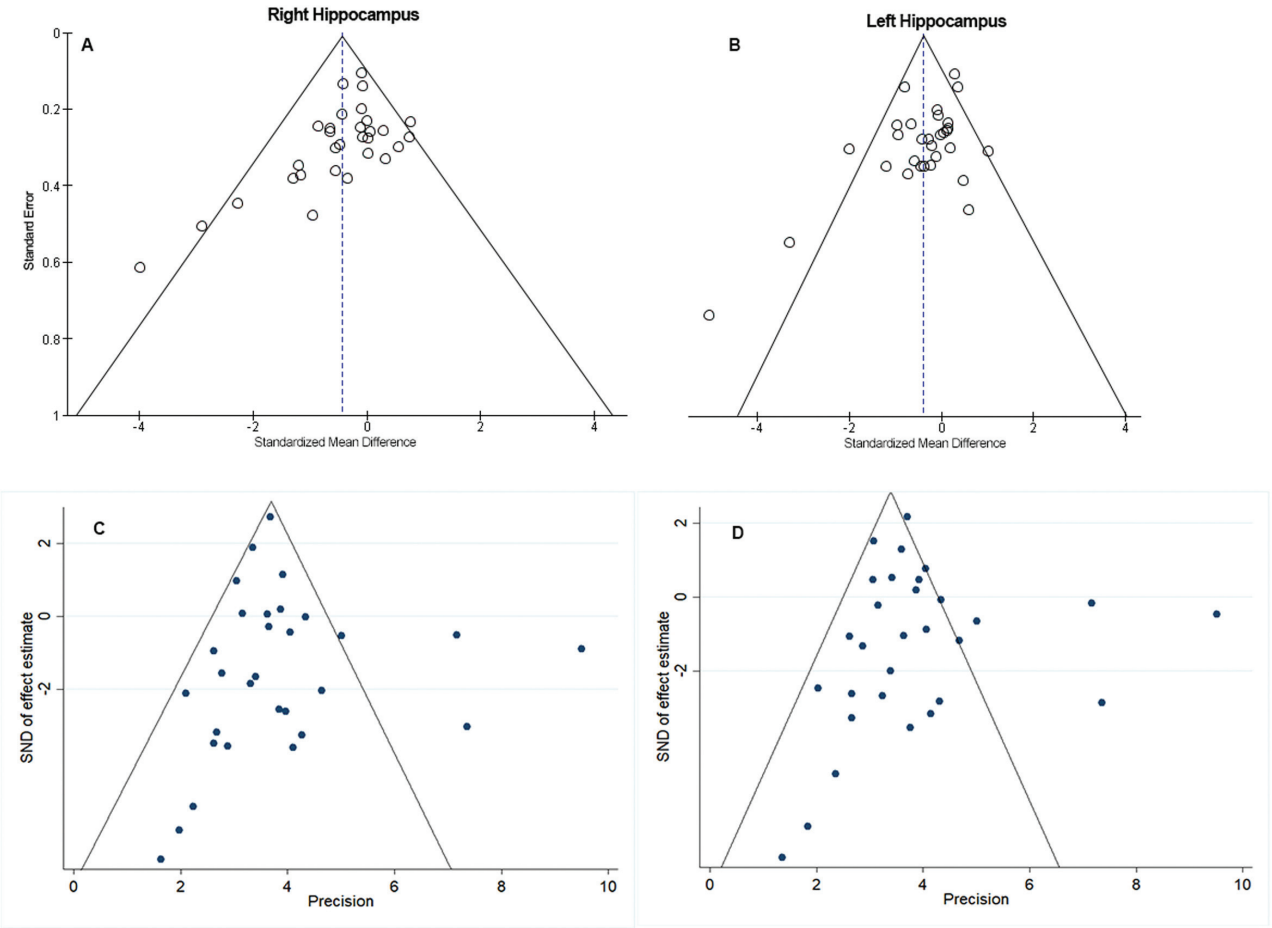

Figure 4 - A, B) Begg's funnel plots, and C, D) Egger's funnel plots showing no obvious signs of publication bias for the meta-analysis results.

Disclosure

No conflicts of interest declared concerning the publication of this article.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorder. 5th ed. Washington: American Psychiatric Publishing; 2013.
2. Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, et al. Cross-national epidemiology of DSM-IV major depressive episode. BMC Med. 2011;9:90.
3. Pizzagalli DA. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology. 2011;36:183-206.
4. Schwert C, Aschenbrenner S, Weisbrod M, Schröder A. Cognitive impairments in unipolar depression: the impact of rumination. Psychopathology. 2017;50:347-54.
5. Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. Biol Psychiatry. 2000;48:766-77.
6. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci U S A. 1996;93:3908-13.
7. Steffens DC, Byrum CE, McQuoid DR, Greenberg DL, Payne ME, Blitchington TF, et al. Hippocampal volume in geriatric depression. Biol Psychiatry. 2017;48:301-9.
8. Mervaala E, Föhr J, Könönen M, Valkonen-Korhonen M, Vainio P, Partanen K, et al. Quantitative MRI of the hippocampus and amygdala in severe depression. Psychol Med. 2000;30:117-25.
9. Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. Am J Psychiatry. 2000;157:115-8.
10. Vakili K, Pillay SS, Lafer B, Fava M, Renshaw PF, Bonello-Cintron CM, et al. Hippocampal volume in primary unipolar major depression: a magnetic resonance imaging study. Biol Psychiatry. 2017;47:1087-90.
11. von Gunten A, Fox NC, Cipolotti L, Ron MA. A volumetric study of hippocampus and amygdala in depressed patients with subjective memory problems. J Neuropsychiatry Clin Neurosci. 2000;12:493-8.
12. Saylam C, Üçerler H, Kitiş Ö, Ozand E, Gönül AS. Reduced hippocampal volume in drug-free depressed patients. Surg Radiol Anat. 2006;28:82-7.
13. Zhao Z, Taylor WD, Styner M, Steffens DC, Krishnan KRR, MacFall JR. Hippocampus shape analysis and late-life depression. PLoS One. 2008;3:e1837.
14. Ballmaier M, Narr KL, Toga AW, Elderkin-Thompson V, Thompson PM, Hamilton L, et al. Hippocampal morphology and sistinguishing late-onset from early-onset elderly depression. Am J Psychiatry. 2008;165:229-37.
15. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009;6:e1000097.
16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344-9.
17. Cole J, Toga AW, Hojatkashani C, Thompson P, Costafreda SG, Cleare AJ, et al. Subregional hippocampal deformations in major depressive disorder. J Affect Disord. 2010;126:272-7.
18. Eker C, Kitis O, Taneli F, Eker OD, Ozan E, Yucel K, et al. Correlation of serum BDNF levels with hippocampal volumes in first episode, medication-free depressed patients. Eur Arch Psychiatry Clin Neurosci. 2010;260:527-33.
19. Frodl T, Jäger M, Smajstrlova I, Born C, Bottlender R, Palladino T, et al. Effect of hippocampal and amygdala volumes on clinical outcomes in major depression: a 3-year prospective magnetic resonance imaging study. J Psychiatry Neurosci. 2008;33:423-30.
20. Hickie I, Naismith S, Ward PB, Turner K, Scott E, Mitchell P, et al. Reduced hippocampal volumes and memory loss in patients with early- and late-onset depression. Br J Psychiatry. 2005;186:197-202.
21. Janssen J, Pol HEH, de Leeuw F, Schnack HG, Lampe IK, Kok RM, et al. Hippocampal volume and subcortical white matter lesions in late life depression: comparison of early and late onset depression. J Neurol Neurosurg Psychiatry. 2007;78:638-40.
22. Kaymak SU, Demir B, Şentürk S, Tatar I, Aldur MM, Uluğ B. Hippocampus, glucocorticoids and neurocognitive functions in patients with first-episode major depressive disorders. Eur Arch Psychiatry Clin Neurosci. 2010;260:217-23.
23. Lange C, Irle E. Enlarged amygdala volume and reduced hippocampal volume in young women with major depression. Psychol Med. 2004;34:1059-64.
24. Lloyd AJ, Ferrier IN, Barber R, Gholkar A, Young AH, O'Brien JT. Hippocampal volume change in depression: late- and early-onset illness compared. Br J Psychiatry. 2004;184:488-95.
25. MacMaster FP, Kusumakar V. Hippocampal volume in early onset depression. BMC Med. 2004;2:2.
26. MacQueen GM, Campbell S, McEwen BS, Macdonald K, Amano S, Joffe RT, et al. Course of illness, hippocampal function, and hippocampal volume in major depression. Proc Natl Acad Sci U S A. 2003;100:1387-92.
27. Meisenzahl EM, Seifert D, Bottlender R, Teipel S, Zetzsche T, Jäger M, et al. Differences in hippocampal volume between major depression and schizophrenia: a comparative neuroimaging study. Eur Arch Psychiatry Clin Neurosci. 2010;260:127-37.
28. Posener JA, Wang L, Price JL, Gado MH, Province MA, Miller MI, et al. High-dimensional mapping of the hippocampus in depression. Am J Psychiatry. 2003;160:83-9.
29. Rusch BD, Abercrombie HC, Oakes TR, Schaefer SM, Davidson RJ. Hippocampal morphometry in depressed patients and control subjects: relations to anxiety symptoms. Biol Psychiatry. 2001;50:960-4.
30. Sawyer K, Corsentino E, Sachs-Ericsson N, Steffens DC. Depression, Hippocampal volume changes, and cognitive decline in a clinical sample of older depressed outpatients and non-depressed controls. Aging Ment Health. 2012;16:753-62.
31. Taylor WD, Steffens DC, Payne ME, MacFall JR, Marchuk DA, Svenson IK, et al. Influence of serotonin transporter promoter region polymorphisms on hippocampal volumes in late-life depression. Arch Gen Psychiatry. 2005;62:537.
32. Vakili K, Pillay SS, Lafer B, Fava M, Renshaw PF, Bonello-Cintron CM, et al. Hippocampal volume in primary unipolar major depression: a magnetic resonance imaging study. Biol Psychiatry. 2000;47:1087-90.
33. van Eijndhoven P, van Wingen G, van Oijen K, Rijpkema M, Goraj B, Jan Verkes R, et al. Amygdala volume marks the acute state in the early course of depression. Biol Psychiatry. 2009;65:812-8.
34. Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, et al. Childhood trauma associated with smaller hippocampal volume in women with major depression. Am J Psychiatry. 2002;159:2072-80.
35. Xia J, Chen J, Zhou Y, Zhang J, Yang B, Xia L, et al. Volumetric MRI analysis of the amygdala and hippocampus in subjects with major depression. J Huazhong Univ Sci Technolog Med Sci. 2004;24:500-2, 506.
36. Avila R, Ribeiz S, Duran FLS, Arrais JPJ, Moscoso MAA, Bezerra DM, et al. Effect of temporal lobe structure volume on memory in elderly depressed patients. Neurobiol Aging. 2011;32:1857-67.
37. Bearden CE, Thompson PM, Avedissian C, Klunder AD, Nicoletti M, Dierschke N, et al. Altered hippocampal morphology in unmedicated patients with major depressive illness. ASN Neuro. 2009;1:AN20090026.
38. Shah PJ, Ebmeier KP, Glabus MF, Goodwin GM. Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. Controlled magnetic resonance imaging study. Br J Psychiatry. 1998;172:527-32.
39. Andreescu C, Butters MA, Begley A, Rajji T, Wu M, Meltzer CC, et al. Gray matter changes in late life depression -- a structural MRI analysis. Neuropsychopharmacology. 2008;33:2566-72.
40. Pantel J, Schröder J, Essig M, Schad LR, Popp D, Eysenbach K, et al. [Volumetric brain findings in late depression. A study with quantified magnetic resonance tomography]. Nervenarzt. 1998;69:968-74.
41. Driscoll I, Hamilton DA, Petropoulos H, Yeo RA, Brooks WM, Baumgartner RN, et al. The aging hippocampus: cognitive, biochemical and structural findings. Cereb Cortex. 2003;13:1344-51.

42. Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci. 1999;19:5034-43.
43. Sapolsky RM. Depression, antidepressants, and the shrinking hippocampus. Proc Natl Acad Sci U S A. 2001;98:12320-2.
44. Radley JJ. Toward a limbic cortical inhibitory network: implications for hypothalamic-pituitary-adrenal responses following chronic stress. Front Behav Neurosci. 2012;6:7.
45. Kang SJ, Kaang B-K. Metabotropic glutamate receptor dependent long-term depression in the cortex. Korean J Physiol Pharmacol. 2016;20:557-64.
46. Ardalan M, Wegener G, Rafati AH, Nyengaard JR. S-ketamine rapidly reverses synaptic and vascular deficits of hippocampus in genetic animal model of depression. Int J Neuropsychopharmacol. 2016;20:247-56.
47. Liechti FD, Grandgirard D, Leib SL. The antidepressant fluoxetine protects the hippocampus from brain damage in experimental pneumococcal meningitis. Neuroscience. 2015;297:89-94.
48. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A. 2011;108:3017-22.
49. Hirschfeld RMA. The comorbidity of major depression and anxiety disorders: recognition and management in primary care. Prim Care Companion J Clin Psychiatry. 2001;3:244-54.

Correspondence:
Marcelo Antônio Oliveira Santos
Rua Jonathas de Vasconcelos, 316, Boa Viagem
51021-140 - Recife, PE - Brazil
E-mail: marcelosantos.med@gmail.com