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Review

Hippocampal volume changes in patients with mood disorders: a systematic review of MRI studies

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Abstract: *Background and objectives:* due to the neurotoxic effect caused by high levels of cortisol, studies suggest that stress and certain psychiatric disorders, such as mood disorders, have influences under the hippocampus, causing a decrease in volume and consequent memory changes. This study aims to evaluate the relationship between hippocampal volume in patients with mood disorders under therapy. *Materials and Methods:* the PRISMA protocol for systematic reviews was followed. Pubmed, Cochraine and Scielo databases were searched by terms "Hippocampus", "Mood Disorders" and "MRI", and variants in other languages, in human, from January 2011 to September 2016. The individual quality of the articles was analyzed using the Cochraine modified scale for clinical trials and the Agency for Healthcare Research and Quality scale for observational studies. *Results:* all studies showed reduction of hippocampal volume in depressive patients. Change in hippocampal volume is not related to the use of antidepressant. Particularly the sub-region of the subculum is more reduced, without lateralizations. Significant relationship between stress and right hippocampal reduction. The findings seem to point out: a common pathway of hippocampus reduction, mediated by stress, explaining memory deficits due to depression, where the cortisol pathway seems to act; alteration in the prefrontal cortex; reduction in the subiculum related to inhibition of the hypothalamic-pituitary-adrenal axis, corroborating the hypothesis of cortisol. *Conclusions:* the papers suggest: association between global hippocampal atrophy with mood disorders; reduction of hippocampal subiculum; refractoriness to clinical treatment among patients with lower hippocampal volume.

Keywords: Hippocampus volume; Mood Disorders; MRI; Depression; Subiculum; CA1

1. Introduction

As mood disorders, we have according with the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV classification, the spectrum between Depression and Mania or its compounds, specially these two and the bipolar disorders. Is also important to delight that the new version of this Manual, the DSM V, published in 2013, changed some of the criterias to include patients into these groups according with their symptoms, but the classification of the mood disorders did not suffer structural changes [1].

In general, the diagnostic in mood spectrum runs through three dimensions: severity, qualitative syndromic spectrum and temperament traits considering associated disorders. It helps us to define and connect the mood disorders with their personality characteristics between a depressive (depression), a cyclothymic (bipolar disorders) and a hyperthymic (mania) temperament [1].

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Major Depressive Disorder (MDD) is the most prevalent mood disorder and is the first leading cause of living with disability for years [1,2]. Pathologically, MDD is responsible for cognitive and emotional changes, including the neurovegetative system and also in the regulation of mood, anxiety and memory. The most recent studies have presented some histopathological alterations in the neural substrates including hippocampus, amygdala and related medial prefrontal cortical areas [2,3], or even a reduction in the number and density of the glial cells [3].

As a complex disease, that combines biological, psychological and social factors, the treatments for MDD consider different possibilities that usually have better results when applied together. The drugs most commonly prescribed are the antidepressants, especially selective serotonin re-uptake inhibitors (SSRIs), which are considered first-line option as pharmacological treatment [4]. Some examples of SSRIs are escitalopram, fluoxetine and sertraline. The non-pharmacological treatment figures with Psychotherapy and practice of regular physical activity, that brings direct benefits to mental health, besides a better social interaction and improving muscle strength and cardiorespiratory fitness, the last two being side effects of the SSRIs.

Bipolar disorder (BD), as the MDD, is a chronic mood disorder that can cause cognitive and emotional disturbances [5]. There is an alternance between depressive and manic or hypomanic episodes [2], and even BD-I being more severe than BD-II both present an important group of symptoms and do not differ when it comes to clinical severity [4]. Symptoms include behavior and cognitive disturbances, and new studies have shown in the presence of depressive episodes the apparition of deficits in verbal and visual memory and in executive functioning [5].

One of the main cerebral areas affected in individuals with mood disorders is the hippocampus, highly responsible for memory (short to long-term), cognition, spatial orientation and mood. Those who suffer with different pathologies that elevate cortisol levels, including metabolic diseases as Cushing syndrome, seems to present alterations on the hippocampus volume, even if not globally but in specific segments. Between the diseases involved with this system are epilepsy and Posttraumatic Stress Disorder (PTSD). Stress can cause important changes in the hypothalamic-pituitary-adrenal (HPA) axis functioning that includes the hypothalamic paraventricular nucleus (PVN), the cortex of adrenal glands and the pituitary gland, on glucocorticoid hormones and the locus coeruleus/norepinephrine-autonomic systems, and subsequently their end-products, norepinephrine and epinephrine [6].

Some neural stem cells (NSCs), also known as neural progenitor cells, show a self-renewal ability to differentiate into several distinct neural cells, including neurons, astrocytes and oligodendrocytes, being the last two the most consistently implicated glial cells in histological alterations in MDD and BD cases [2,3,6]. Hippocampus NSCs are related with cognitive and memory processes and also at the patients' response to anti-depressive treatment or consequent recovery from mood disorders. The regulation of mood and behavior is another hippocampus role, but the involvement of progenitor cells on it is more complex than we observe in memory and learning, once anti-depressants intake suggests stimulation at neurogenesis [6]. By the other side when we have a disruption in any glial cell function there is a deregulation in brain energy supplies and more chances for developing neuropsychiatric disorders [3].

Evidences have supported the idea that acute exposure to stress decreases proliferation of NSCs in the dentate gyrus (DG), and when the exposure is chronic there is also suppress at neuronal differentiation and/or cell survival. Another suggestion points that the stress effects would not only affect adults' hippocampal neurogenesis, but could also impacts the fetus during prenatal when the mother is exposed to stress, damaging the brain development and bringing long-life consequences [6].

Neuromorphometric abnormalities are observed in individuals with early-onset mood disorders that appear anatomically related structures within the temporal lobe, thalamus, striatum and posterior cingulate [2]. In depressed subjects the time spent without pharmacological treatment seems to decrease the hippocampus volume, the same way that evidences show a decrease in the amygdala volume in patients with BD. Both represent the way that the limbic system can be related

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with neurotrophic effects in subjects with mood disorders [2,5] and the fruits of these alterations on patients' life.

The main objective of this study was study the relation between hippocampal volume changes and mood disorders.

Secondary objectives were: analyze the response of hippocampus volume to use of medication; verify if hippocampal changes are related to the disease, to the medication use or both of them together; verify if there is any predictive relation between hippocampus volume and patients' response to treatment.

2. Materials and Methods

The methodology used in this work follow the systematic review process derived from the PRISMA statement [7].

Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at:

www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016046404.

2.1. Inclusion Criteria

2.1.1. Type of studies

Two authors reviewed the abstract of studies in all languages against the defined inclusion criteria for the study. All possibly relevant full text articles were so retrieved for assessment of quality and satisfaction of inclusion criteria.

The review covered all types of study except case reports. All studies providing MRI studies with patients under some kind of treatment, pharmacological or non-pharmacological, were reviewed. Studies which sample groups were below 20 patients or in which patients presented any other neuropsychiatric or metabolic condition associated were excluded.

2.1.2. Type of participants

Participants were adults aged at least 18 years with diagnosis of mood disorder according criteria of Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), under pharmacological or psychotherapy treatment.

2.1.3. Type of Intervention/Exposition

The expositions considered were acute and chronic episodes in mood disorders

2.1.3. Type of Outcome

The outcome was the measurement of hippocampal volume in patients' brains using Magnetic Resonance Imaging (MRI).

2.2. Review Criteria

The search in the databases was performed independently by two authors who selected articles for analysis. Any disagreement was solved by consensus.

2.3. Search Methods for study identification

Searches were performed from the following sources: Pubmed, The Cochraine Library and Scielo. Search period included from January 2011 through September 2016.

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2.3.1. Search Strategy

The search terminology included the terms "Hippocampus", "Mood Disorders" and "MRI". At least two of the reviewer authors, performed each search. Any disagreements were solved by consensus

2.3.2. Assessment of Methodological Quality

The methodological quality assessment was performed by two authors and any discrepancies were resolved by consensus.

The quality of each individual article included in this word was assessed by modified Cochrane review criteria [8] for clinical trials and the Agency for Healthcare Research and Quality (AHRQ) criteria for observational studies [9]. Only studies scoring at least 50 points in one of both scales were included on the analysis. Methodological assessment criteria are described in Table 1 and Table 2.

Table 1. Methodical assessment for observational study.

Criteria	Weighted Score Points	Elbjeijjani et al [17].	Phillips et al [18].	Wise et al [19].	Sivakumar et al [20].	Redlich et al.[21]	Sämann et al [22].	Zannas et al.[23]
Study Question	(0-2)	2	2	2	2	2	2	2
Study Population	(0-8)	8	8	8	5	8	8	5
Comparability of subjects	(0-22)	21	14	17	16	16	16	14
Exposure or Intervention	(0-11)	6	11	11	6	11	8	11
Outcome measure	(0-20)	15	15	15	20	15	15	15
Statistical analysis	(0-19)	12	12	12	12	12	12	12
Results	(0-8)	8	8	8	5	8	8	8
Discussion	(0-5)	5	5	5	5	5	5	5
Funding	(0-5)	5	5	5	5	5	5	5
TOTAL	(0-100)	78	77	88	71	77	74	77

Table 2. Methodical assessment for clinical studies.

Criteria	Weighted Score Points	Sheline et al [11].
Study Population	(0-25)	12
Intervention	(0-25)	15
Effect	(0-30)	15
Data presentation and analysis	(0-10)	12
TOTAL	(0-90)	52

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2.3. Search Methods for study identification

The data was extracted by two independent authors using a standard form. Disagreements were solved by consensus.

3. Results

From the initial search (n=83), 14 studies were reviewed: 2 clinical trials and 12 observational studies as demonstrated in Figure 1.

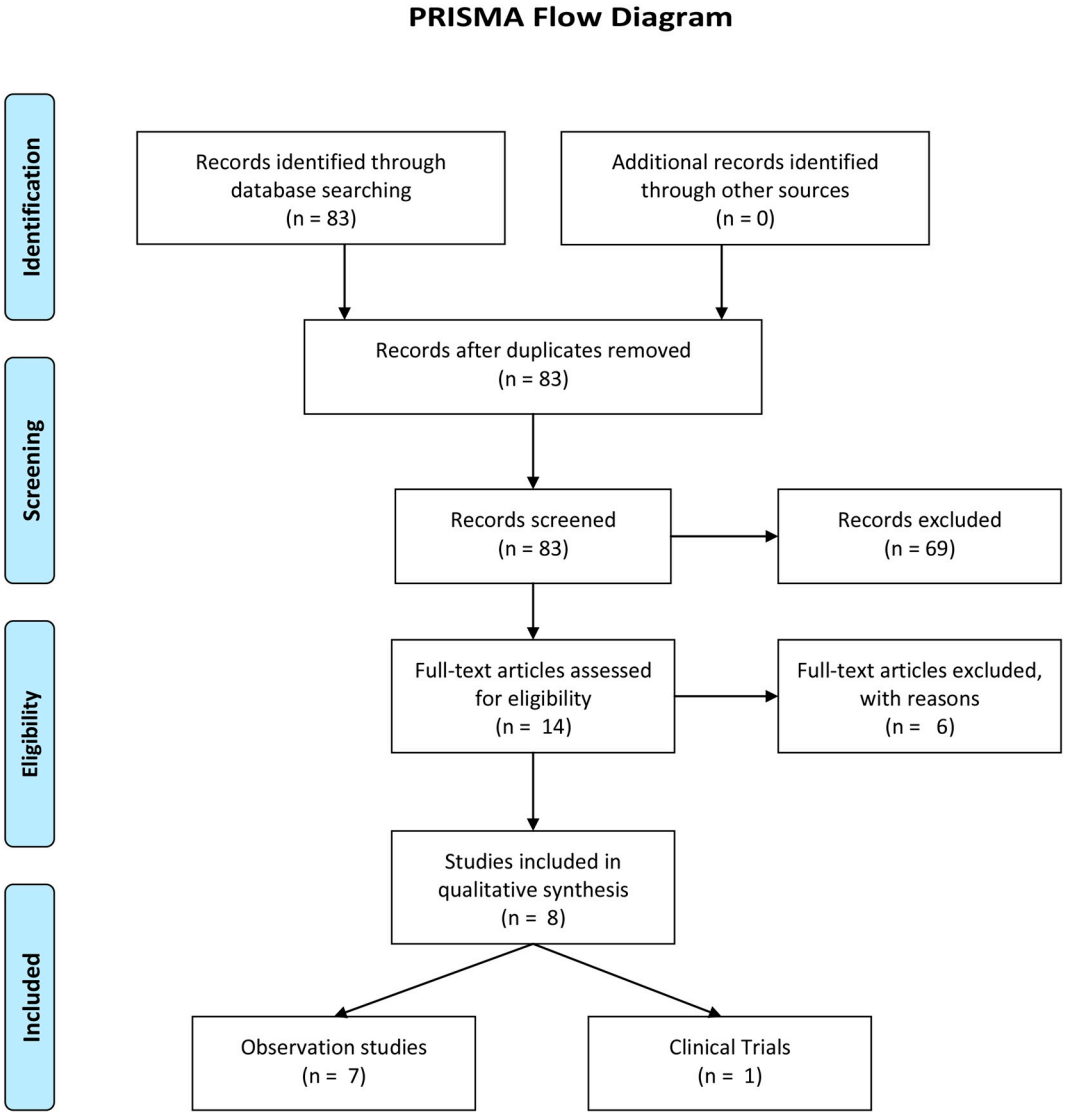

Figure 1. PRISMA flow diagram of studies.

From clinical trials, 2 met the established inclusion criteria [10,11]. The study of Miskowiak et al. [10] was excluded because intervention involved erythropoietin administration in patients. The result of the methodological quality assessment of clinical trials is illustrated in Table 2. The quality assessment criteria ranged was 52 points for evidence synthesis.

From observational studies, 12 met the established inclusion criteria [12-23]. Five of them were excluded from qualitative synthesis: Philips et al [12] analyzed gene polymorphism related to hippocampal changes; Stratmann et al [13] did not excluded patients with anxiety from studied sample; Taylor et al [14] used National Institute of Mental Health (NIHM) Diagnostic Interview Schedule as diagnostic criteria in place of DSM-IV; Han et al [15] collected the MRI images with experimental group being drug-naive, not receiving any treatment at that point; Elvsåshagen et al [16] studied patients affect by various associated comorbidities like alcohol abuse. The results of the

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173 methodological quality assessment of observational are illustrated in Table 3. The quality assessment
174 criteria ranged from 71 to 88 points for evidence synthesis.
175
176 **Table 3.** Methodical assessment for clinical studies

Author/Country/ Year/Disorder	Participants	Design of study	Outcome(s)	Result (s)
Elbeijani et al, FR, 2015, MDD	Follow up for 4 years of 1328 patients. Excluded: people with dementia,> 80 years, without second MRI or of low quality.	Prospective cohort. At baseline and every two years, depressive symptoms were assessed by the CES-D scale and hippocampal measurement by the end of the 4 years.	Initial HcV and subsequent changes were compared and expressed as percent annual change.	Association between more depressive symptoms and lower HcV at baseline; antidepressants is non-HcV-related; recurrence of disease and age not associated with hippocampal hypotrophy; antidepressant use significantly associated with slower hippocampal atrophy in men
Phillips et al, CA, 2015, Refractory depression	26 patients with refractory depression, 18-65 years and 28 healthy controls with 1-year follow-up. Excluded: organic diseases, alcoholism, chemical dependence, exposed to steroids.	Prospective cohort. MRI performed at baseline and after 6 months of disease remission or 12 months with therapeutic failure. Symptoms assessed with depression scales: HRSD and MADRS	Volume of the rostral portion of the frontal-middle gyrus, orbitofrontal cortex, rostral anterior cingulate gyrus, caudate gyrus and inferior temporal gyrus.	Significant remission state versus interaction effect for VHc, rostral frontal-middle gyrus, orbitofrontal cortex and inferior temporal gyrus; Significant negative correlation between mean volume of anterior caudal cingulate cortex and change in MADRS score.
Wise et al, NE, 2015, MDD	47 patients with major depression, 60 years (± 10), follow-up of 84 months. Compared to 78 patients in the control group. Patients with dementia and organic diseases were excluded.	Prospective study. Patients assessed at baseline and after 6, 12, 39 and 84 months. They were categorized as "non MDE" and "ever MDE" based on the 7-year follow-up period. The intesity of symptoms was assessed by the PHQ-9 questionnaire.	Volumetry performed in the subiculum region, comu ammonis (CA) 1 to 3, gyrus and CA4 and entorhinal cortex.	With the exception of CA3, the volume of all hippocampal segments was smaller than in the group "ever MDE" (no statistical significance); Increase in the number of depressive episodes significantly associated with subiculum reduction.
Sivakumar et al, IN, 2015, Late Onset Depression	25 patients with LOD, compared to 20 controls. Inclusion:> 60 years, first depressive episode> 50 years. Excluded: other mental disorders, chemical dependence, organic diseases or under electroconvulsive therapy.	Cross-sectional study. Patients assessed with the MADRS scale and Hindi Mental State Examination.	Evaluation of bilateral hippocampal volume and its antero-posterior segments.	HcV posterior right and lower global left HcV in the group with late onset depression; Significant negative correlation between bilateral HRV with MADRS scores.
Redlich et al, DD, 2014, Uni and Bipolar depression	58 patients with unipolar depression, 58 patients with bipolar depression and 58 controls.	Transverse cohort study. Analysis of depressive symptoms by the HDRS scale. Mania evaluated by the Young Mania Rating Scale. Anxiety determined by State-Trait Anxiety Inventory.	Evaluation of the white and gray mass of the brain, hippocampus and amygdala.	Bipolar depression showed a large reduction in the volume of the gray substance bilaterally in the hippocampus, fusiform, lingual, amygdala, caudate nucleus, putamen, thalamus, insula and dorsal prefrontal cortex; negative association between duration of disease and volume of anterior cingulate gyrus.
Sämann et al, DD, 2013, MDD	167 patients with depression and hospitalized in the	Cross-sectional study. Analysis of the symptoms was done by	Analysis of HcV. The volumes of the right hippocampus	Abnormal volume reduction in the left hippocampus, especially in unipolar depression; Left HcV,

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	last 3 years and 92 control patients. Patients with depressive symptoms due to other medical causes were excluded.	the slave HDRS-21 at the beginning of the follow-up and 5 weeks after.	and lateral temporal cortex were adjusted by multiple linear regression.	left temporal gyrus lateral area, subcalosa region are highly related to differences in response to treatment.
Zanna et al, USA, 2013, MDD	89 patients with MDD and 70 controls. Inclusion: ≥ 60 years, followed by 2 years with MRI. Excluded: other psychiatric and neurological diseases, MMSE score <25.	Prospective cohort. At follow-up baseline, patients had the symptoms evaluated by MADRS. Genotyping was performed for 5-HTTLPR polymorphism.	Changes in HcV, considering stress and presence of the 5-HTTLPR genotype as independent variables	Statistical significance between stressful events and right hippocampal reduction; There was no effect of the 5-HTTLPR genotype on stress and HcV, except in relation to the prediction of left HcV alteration related to greater perception of stress.
Sheline et al, USA, 2012, MDD	168 patients with MDD. Control 50 patients. Included:> 60 years. Exclusion: cognitive deficits, other medical conditions.	Non-randomized clinical trial. Initial dose of sertraline 25mg on day 1, then 50mg / day increasing 50mg / day every 2 weeks to a total of 200mg / day in the 6th week. Patients assessed on MADRS scale at baseline and then weekly.	Remission, which was determined as MADRS <7 at the end of the 12th week under sertraline use.	Lower HcV predicts lower rate of response to drug treatment; Patients who did not achieve remission had significantly lower HcV.

Most works found were prospective studies. The main mood disorder in which hippocampal volume was most studied was Major Depressive Disorder (MDD) (n=5). The following conditions were also found: refractory depression (n=1), Late onset depression (n=1), bipolar and unipolar depression (n=1).

Elbeijani et al [17] studied 1328 patients during a 4-years follow-up. They took 1.5 Teslas (T) MRI scans at baseline and a second one to measure HcV. At baseline and each biennial wave Center for Epidemiologic Studies-Depression (CES-D) scale scores were collected to measure depressive symptoms. It was found a cross-sectional association between more baseline depressive symptoms and smaller HcV [0.05 cm3, 95% confidence interval (CI) −0.09 to −0.01 cm3 reduction per 10-unit increase in CES-D scores]. Antidepressant use was not associated with HcV. Recurrence and age at first and last depression episodes were not associated with hippocampal atrophy. Antidepressant use at baseline was significantly associated with slower hippocampal atrophy in men ($\beta = -0.71$, $p = 0.04$).

Philips et al [18] submitted both 26 patients with treatment-resistant depression and 28 healthy controls to 1.5T MRI scans at baseline. During 1-year follow-up, a second MRI was made after 6-month period of sustained remission or after 12-month period of failure to remit. Depressive symptoms were analyzed using Hamilton Rate Scale for Depression (HRSD) and Montgomery-Âsberg Depression Rate Scale (MADRS). It was found a significant remission status × time interaction effects for HcV and rostral middle frontal gyrus, orbitofrontal cortex, and inferior temporal gyrus cortical thickness. There was a significant negative correlation between patients mean right caudal anterior cingulate cortical thickness and change in MADRS score over follow-up ($r = -0.50$, $P = .009$).

Wise et al [19] studied 47 patients aged 60 years (±10) with Major Depressive Episodes (MDE) in an 84-months follow-up and compared them to a healthy group of 78 individuals. Patients were categorized into “no MDE” and “ever MDE” group, according if they had MDE during the observation time. The severity of symptoms was assessed using the Patient Health Questionnaire-9 (PHQ-9). MRI scans were taken at baseline and after 6, 12, 39 and 84 months and evaluated the subiculum, cornus ammonis (CA) to 3, dentate gyrus and entorhinal cortex. 13% patients were under antidepressants use at time of MRI. They found reduction of all hippocampal subfields, except CA3, in the MDE group, but there was not statistical significance. Increasing number of MDEs was

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significantly associated with smaller subiculum volume (B=−0.03 mL/MDE; 95% CI −0.06; −0.003), but not with any of the other volumes. No lateralization was observed.

Sivakumar et al [20] compared 25 patients with MDD older than 60 years and that presented the first depressive episode after 50 years to 20 healthy control. MADRS and Hindi Mental State Examination (HMSE) were used to evaluate depressive symptoms. Patients with Later Onset Depression (LOD) had lower HMSE compared to control group. Left posterior hippocampal volume was significantly smaller in LOD group than the control group ($p = 0.009$). Right posterior HcV and left HcV were smaller in LOD group ($p = -0.08$ and 0.06, respectively). Right posterior and left posterior hippocampal volume had significant negative correlation with depression severity assessed by MADRS score ($r = -0.37$, $p = 0.012$ and $r = -0.46$, $p = 0.001$, respectively).

Redlich et al [21] studied 58 patients with Bipolar Depression, 58 with Unipolar Depression and 58 healthy controls. HRSD were used to assess gravity of depressive symptoms, Young Mania Rating Scale (YMRS) for determining mania and trait anxiety determined by State-Trait Anxiety Inventory (STAI). MRI scans analyzed white and grey matter volumes and amygdala. Individuals with BD showed strong gray matter volume reductions in the bilateral hippocampus extending to other cortical areas related to limbic system.

Sämann et al [22] compared 167 patients with depressive episodes, hospitalized over 3 years to 92 healthy controls. Symptoms were evaluated using a 21 item HRSD at baseline and within 5 weeks. Significant reduction was detected in left hippocampus, especially in recurrent unipolar patients. Besides, differences in response to treatment was significantly associated with left hippocampus.

Zannas et al [23] followed a cohort of 89 individuals with MDD and a 70-healthy group during 2 years. At baselines MADRS assessed depressive symptoms. Besides MRI scan, 5-HTTLPR genotyping was proceeded. Statistically significant relationship between stressful life events and right hippocampal volume reduction and effect of 5-HTTLPR genotype and two-year change in perceived stress severity predicting two-year change in left hippocampal volume was found ($N = 121$, $F_{1,111} = 10.20$, $p = 0.0018$).

4. Discussion

To our knowledge, this is the first review study to examine the relation between HcV and mood disorders. Most of studies found analyzes basically MDD and its relation to hippocampus and limbic system related areas. Results of all studies analyzed reinforce the literature findings which shows presence of hippocampus atrophy in patients affected by depression [11-23].

Hippocampal formation is conventionally defined by entorhinal cortex, dentate gyrus (DG) and cornu ammonis (CA) and subiculum, which also receives projections from the entorhinal, perirhinal, and prefrontal cortex. CA can be anatomically divided into the CA1, CA2, CA3 and CA4 sub-areas [24,25].

Subjects with first episode MDD have presented reduced cortical volume of the caudal anterior cingulate cortex (ACC), structure that plays an important role in emotional regulation, and also changes at the with matter integrity of the corpus callosum, responsible for alterations in the inter-hemispheric integration related to cognition, learning, emotional regulation and volitional processes [15]. On the other hand, individuals with BD-II had a left and total fimbria and DG-CA4 reduction [16].

Patients with aging and late-life depression have a poorer antidepressant response showing that persistent depression severity is associated with reduced HcV. In these models, cognitive processing speed seems to have a special improvement, but also others neuropsychological factors as executive function, episodic memory and language [11,14]. As an alternative for traditional antidepressant therapy in cases of treatment-resistant depression (TRD) and BD, the treatment with Erythropoietin evidences a prevention of brain matter loss in a region of the left hippocampus involving the CA1-3 and subiculum [10].

The HcV alterations are structurally different according with the type and severity of the mood disorder. Patients with a more severe affection as Bipolar Depression seems to have more chances of

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developing alterations in both hippocampus compared with Unipolar Depression. The main areas related with these abnormalities are reduced amygdala and gray matter volumes in the hippocampal constitution. The anterior cingulate gyrus establishes an exception, being smaller in individuals with Unipolar Depression compared with the bipolar cases [21].

As Wise et al [19] found, subiculum volume was significantly smaller as more depressive episodes the patients had. The subiculum is the area from which most of the efferent projections depart from hippocampus to other brain regions. In addition, the ventral portion of the subiculum sends a projection pathway to the limbic system that is directly related to inhibition of the Hypothalamic-Hypophysis-Adrenal (HHA) axis, resulting in the limitation of the response of this axis to stress. The release of cortisol during stress also modulates the CA1-subiculum pathway (CASP) by reducing long-term potentiation (LTP) [25]. In this case CA3 volume remained untouched [19], although this finding was not statistically significant, probably because its physiological functions are more related to episodic memory processing, as well as the susceptibility to seizures and neurodegenerative diseases [24]. Even so, the results of Zannas et al [23] show the perception of stress severity predicts left HcV change and help to support the cortisol theory.

Besides the LTP paper explaining the mechanisms involving the CASP and cortisol regulation by HHA, another important supporting actor is the Glutamate NMDA-channel present in inhibitory neurons that compose this pathway. Subicular neurons make a synapse with a hypothalamic neuron, inhibiting it through NMDA receptors. The hypothalamic neuron modulates the corticotrophs cell stimulating it through gamma aminobutyric acid (GABA) liberation which culminates on production and releasing of the adrenocorticotropic hormone (ACTH) and cortisol seric concentration increasing by its release by adrenal gland [26-28]. The most active the CASP is, there is less activation HHA axis and cortisol seric concentration decreases as illustrated in Figure 2.

Studies in rats with depression induced by ocular bulb ablation show hippocampal structural modification: decreased proliferation of neuronal circuits in DG; hypotrophy with decreased density and rearrange of neuronal circuits in CA1; decrease in long-term plasticity in DG and CA1, partially explained by the reduction of membrane expression of NMDA receptors. Use of citalopram has the ability to modify the neurogenesis in DG of these rats, rivastinamine may plasticity and global hippocampal neurogenesis [29]. As well, another study in animal models for depression found that the use of ketamine, a non-NMDA glutamatergic antidepressant drug, improves vascularization and neuroplasticity in hippocampus [28]. All evidences that help to support the CASP-HHA-Cortisol hypothesis.

5. Conclusions

Data about this subject available in the literature is very scarce. The main relation studied was HcV versus depressive disorder. Our findings corroborate for findings in others studies that show high level of relation between HcV reduction and depressive symptoms. These findings also suggest: reduction on subiculum, which we thought be related to cortisol or CASP-HHA-Cortisol theory and that refractivity to treatment is often associated to reduction of HcV and can maybe be a positive predictive variable to response to drug treatment.

Unfortunately, there is a few number of studies about these subject. Most of the presents biases and conclusion are hard to be interpreted. Bigger studies with best design like bigger population samples, big double-blinded clinical trials, should be performed for accurate conclusions with better grade of evidence than what literature has available until today.

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References

1. Angst J, Ajdacic-Gross V, Rössler W. Classification of mood disorders. Psychiatr. Pol. 2015; 49(4): 663–671.
2. Price JL, Drevets WC. Neural circuits underlying the pathophysiology of mood disorders. Trends in Cognitive Sciences. 2012; 16(1): 61-71.doi: 10.1016/j.tics.2011.12.011
3. Sanacora G, Banasr M. From Pathophysiology to Novel Antidepressant Drugs: Glial Contributions to the Pathology and Treatment of Mood Disorders. Biol psychiatry 2013;73:1172–1179.
4. Schuch FB, Vancampfort D, Rosenbaum S, Richards J, Ward PB, Veronese N, et al. Exercise for depression in older adults: a meta-analysis of randomized controlled trials adjusting for publication bias. Rev Bras Psiquiatr. 2016;38(3):247-254.
5. Kapczinski NS, Narvaez JC, Magalhães PV, Bücker J, Peuker AC, Loredo AC, et al. Cognition and functioning in bipolar depression. Rev Bras Psiquiatr. 2016;38(3):201-206X Li, D Li, Q Li, Y Li, K Li, S Li, Y Han. Hippocampal subfield volumetry in patients with subcortical vascular mild cognitive impairment. Scientific Reports 6; 2016.
6. Kino T. Stress, glucocorticoid hormones, and hippocampal neural progenitor cells: implications to mood disorders. Frontiers in Physiology. 2015;6:230. doi:10.3389/fphys.2015.00230.
7. Moher D, Liberati A, Telzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151(4):264-269. doi: 10.7326/0003-4819-151-4-200908180-00135.
8. Koes BW, Sholten RJPM, Mens JMA, Bouter LM. Efficacy of epidural steroid injections for low-back pain and sciatica: A systematic review of randomized clinical trials. Pain. 1995; 63:279-288
9. West et al. Rating system to measure the strength of evidence, evidence report, technology assessment No. 47 AHQR Publication No. 02-016 (11).
10. Miskowiak KW et al. Effects of Erythropoietin on Hippocampal Volume and Memory in Mood Disorders. Biol Psychiatry. 2015;78(4):270-7. doi: 10.1016/j.biopsych.2014.12.013.
11. Sheline YL et al. Treatment course with antidepressant therapy in late-life depression. Am J Psychiatry. 2012;169(11):1185-93. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3752387/
12. Phillips JL, Batten LA, Tremblay P, Aldosary F, Du L, Blier P. Impact of monoamine-related gene polymorphisms on hippocampal volume in treatment-resistant depression. Acta Neuropsychiatr. 2015;27(6):353-61. doi: 10.1017/neu.2015.25
13. Stratmann M et al. Insular and hippocampal gray matter volume reductions in patients with major depressive disorder. PLoS One. 2014;9(7):e102692. doi: 10.1371/journal.pone.0102692.
14. Taylor WD, McQuoid DR, Payne ME, Zannas AS, MacFall JR, Steffens DC. Hippocampus atrophy and the longitudinal course of late-life depression. Am J Geriatr Psychiatry. 2014;22(12):1504-12. doi: 10.1016/j.jagp.2013.11.004.
15. Han KM et al. Cortical thickness, cortical and subcortical volume, and white matter integrity in patients with their first episode of major depression. J Affect Disord. 2014;155:42-8. doi: 10.1016/j.jad.2013.10.021.
16. Elvsåshagen T et al. Evidence for reduced dentate gyrus and fimbria volume in bipolar II disorder. Bipolar Disord. 2013;15(2):167-76. doi: 10.1111/bdi.12046.
17. Elbejjani M. Depression, depressive symptoms, and rate of hippocampal atrophy in a longitudinal cohort of older men and women. Psychol Med. 2015;45(9):1931-44. doi: 10.1017/S0033291714003055.
18. Phillips JL, Batten LA, Tremblay P, Aldosary F, Blier P. A Prospective, Longitudinal Study of the Effect of Remission on Cortical Thickness and Hippocampal Volume in Patients with Treatment-Resistant Depression. Int J Neuropsychopharmacol. 2015;18(8). pii: pyv037. doi: 10.1093/ijnp/pyv037
19. Wisse LE, Biessels GJ, Stegenga BT, Kooistra M, van der Veen PH et al. Major depressive episodes over the course of 7 years and hippocampal subfield volumes at 7 tesla MRI: the PREDICT-MR study. J Affect Disord. 2015;175:1-7. doi: 10.1016/j.jad.2014.12.052.
20. Sivakumar PT, Kalmady SV, Venkatasubramanian G, Bharath S, Reddy NN et al. Volumetric analysis of hippocampal sub-regions in late onset depression: a 3 tesla magnetic resonance imaging study. Asian J Psychiatr. 2015;13:38-43. doi: 10.1016/j.ajp.2014.11.005.
21. Redlich R, Almeida JJ, Grotegerd D, Opel N, Kugel H et al. Brain morphometric biomarkers distinguishing unipolar and bipolar depression. A voxel-based morphometry-pattern classification approach. JAMA Psychiatry. 2014;71(11):1222-30. doi: 10.1001/jamapsychiatry.2014.1100.

22. Sämann PG, Höhn D, Chechko N, Kloiber S, Lucae S et al. Prediction of antidepressant treatment response from gray matter volume across diagnostic categories. Eur Neuropsychopharmacol. 2013 Nov;23(11):1503-15. doi: 10.1016/j.euroneuro.2013.07.004.
23. Zannas AS, McQuoid DR, Payne ME, Steffens DC, MacFall JR et al. Negative life stress and longitudinal hippocampal volume changes in older adults with and without depression. J Psychiatr Res. 2013;47(6):829-34. doi: 10.1016/j.jpsychires.2013.02.008.
24. Cherubini E, Miles R. The CA3 region of the hippocampus: how is it? What is it for? How does it do it? Frontiers in Cellular Neuroscience. 2015;9:19. doi:10.3389/fncel.2015.00019.
25. O'Mara S. The subiculum: what it does, what it might do, and what neuroanatomy has yet to tell us. Journal of Anatomy. 2005;207(3):271-282. doi:10.1111/j.1469-7580.2005.00446.
26. Radley JJ. Toward a limbic cortical inhibitory network: implictions for hypothalamic-pituitary-adrenal response following chronic stress. Front. Neurosci. 2012; 6:7.
27. Kang SJ, Kaang BK. Metabotropic glutamate receptor dependent long-term depression in the cortex. Korean J Physiol Pharmacol 2016;20(6):557-564. doi: 10.4196/kjpp.2016.20.6.557
28. 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; pii: pyw098. doi: 10.1093/ijnp/pyw098
29. Morales-Medina JC, Iannitti T, Freeman A, Caldwell HK. The olfactory bulbectomized rat as a model of depression: the hippocampal pathway. Behav Brain Res. 2016 Sep 12. pii: S0166-4328(16)30612-X. doi: 10.1016/j.bbr.2016.09.02.