1 *Review*

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

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

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

33

34 1. Introduction

35   As mood disorders, we have according with the Diagnostic and Statistical Manual of Mental
36 Disorders (DSM) IV classification, the spectrum between Depression and Mania or its compounds,
37 specially these two and the bipolar disorders. Is also important to delight that the new version of this
38 Manual, the DSM V, published in 2013, changed some of the criterias to include patients into these
39 groups according with their symptoms, but the classification of the mood disorders did not suffer
40 structural changes [1].
41   In general, the diagnostic in mood spectrum runs through three dimensions: severity, qualitative
42 syndromic spectrum and temperament traits considering associated disorders. It helps us to define
43 and connect the mood disorders with their personality characteristics between a depressive
44 (depression), a cyclothymic (bipolar disorders) and a hyperthymic (mania) temperament [1].

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

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.

137   *2.3.1. Search Strategy*

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

141   *2.3.2. Assessment of Methodological Quality*

142   The methodological quality assessment was performed by two authors and any discrepancies
143   were resolved by consensus.
144   The quality of each individual article included in this word was assessed by modified Cochrane
145   review criteria [8] for clinical trials and the Agency for Healthcare Research and Quality (AHRQ)
146   criteria for observational studies [9]. Only studies scoring at least 50 points in one of both scales were
147   included on the analysis. Methodological assessment criteria are described in Table 1 and Table 2.

148   **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

149

150   **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

151

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153   *2.3. Search Methods for study identification*

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

156   **3. Results**

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

PRISMA Flow Diagram
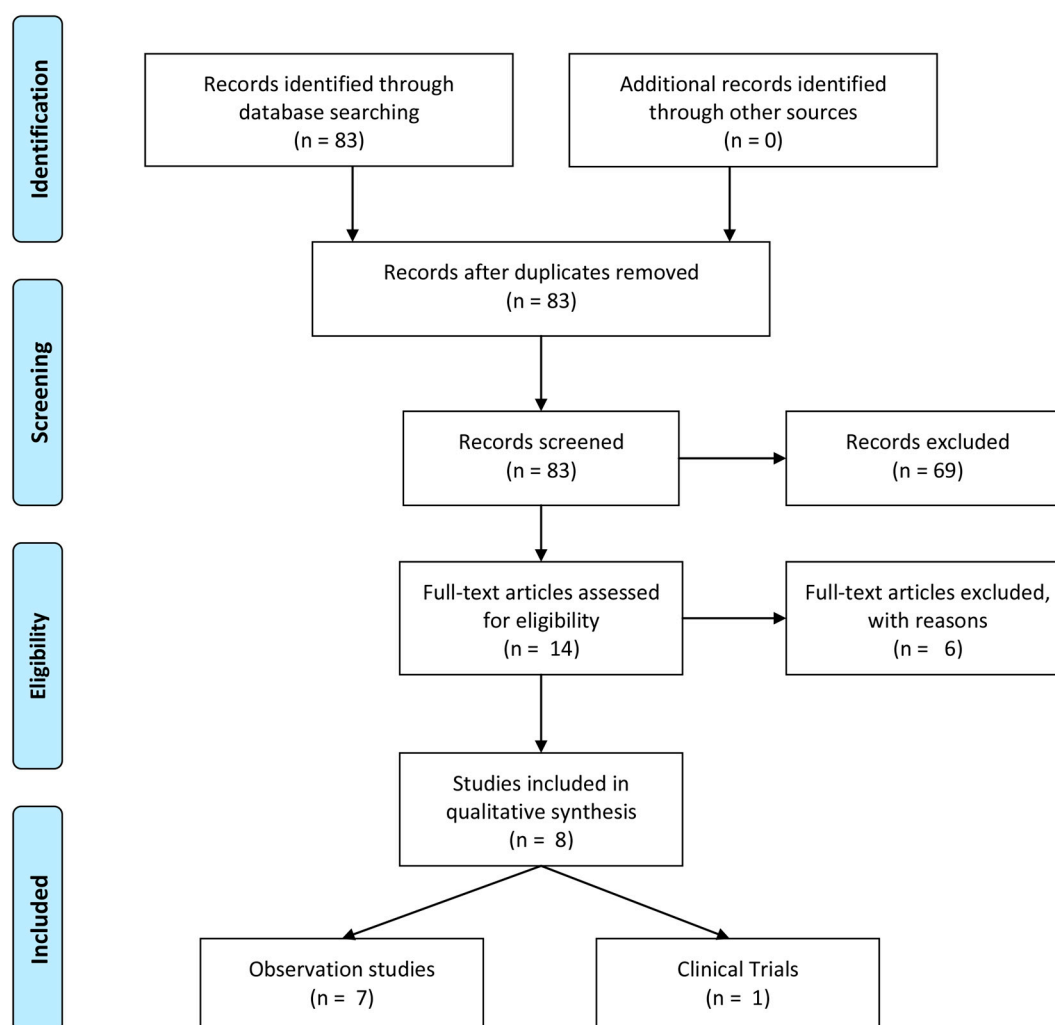
159
160   **Figure 1**. PRISMA flow diagram of studies.
161

162   From clinical trials, 2 met the established inclusion criteria [10,11]. The study of Miskowiak et al.
163   [10] was excluded because intervention involved erythropoietin administration in patients. The result
164   of the methodological quality assessment of clinical trials is illustrated in Table 2. The quality
165   assessment criteria ranged was 52 points for evidence synthesis.
166   From observational studies, 12 met the established inclusion criteria [12-23]. Five of them were
167   excluded from qualitative synthesis: Philips et al [12] analyzed gene polymorphism related to
168   hippocampal changes; Stratmann et al [13] did not excluded patients with anxiety from studied
169   sample; Taylor et al [14] used National Institute of Mental Health (NIHM) Diagnostic Interview
170   Schedule as diagnostic criteria in place of DSM-IV; Han et al [15] collected the MRI images with
171   experimental group being drug-naive, not receiving any treatment at that point; Elvsåshagen et al
172   [16] studied patients affect by various associated comorbidities like alcohol abuse. The results of the

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,

	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.

177

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

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

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

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

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

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

216 Redlich et al [21] studied 58 patients with Bipolar Depression, 58 with Unipolar Depression and
217 58 healthy controls. HRSD were used to assess gravity of depressive symptoms, Young Mania Rating
218 Scale (YMRS) for determining mania and trait anxiety determined by State-Trait Anxiety Inventory
219 (STAI). MRI scans analyzed white and grey matter volumes and amygdala. Individuals with BD
220 showed strong gray matter volume reductions in the bilateral hippocampus extending to other
221 cortical areas related to limbic system.

222 Sämann et al [22] compared 167 patients with depressive episodes, hospitalized over 3 years to
223 92 healthy controls. Symptoms were evaluated using a 21 item HRSD at baseline and within 5 weeks.
224 Significant reduction was detected in left hippocampus, especially in recurrent unipolar patients.
225 Besides, differences in response to treatment was significantly associated with left hippocampus.

226 Zannas et al [23] followed a cohort of 89 individuals with MDD and a 70-healthy group during
227 2 years.   At baselines MADRS assessed depressive symptoms. Besides MRI scan, 5-HTTLPR
228 genotyping was proceeded. Statistically significant relationship between stressful life events and
229 right hippocampal volume reduction and effect of 5-HTTLPR genotype and two-year change in
230 perceived stress severity predicting two-year change in left hippocampal volume was found (N = 121,
231 $F_{1,111}$ = 10.20, p = 0.0018).

4. Discussion

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

237 Hippocampal formation is conventionally defined by entorhinal cortex, dentate gyrus (DG) and
238 cornu ammonis (CA) and subiculum, which also receives projections from the entorhinal, perirhinal,
239 and prefrontal cortex. CA can be anatomically divided into the CA1, CA2, CA3 and CA4 sub-areas
240 [24,25].

241 Subjects with first episode MDD have presented reduced cortical volume of the caudal anterior
242 cingulate cortex (ACC), structure that plays an important role in emotional regulation, and also
243 changes at the with matter integrity of the corpus callosum, responsible for alterations in the inter-
244 hemispheric integration related to cognition, learning, emotional regulation and volitional processes
245 [15]. On the other hand, individuals with BD-II had a left and total fimbria and DG-CA4 reduction
246 [16].

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

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

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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