Hippocampal and Amygdalar Volume Changes in Major Depressive Disorder: A Targeted Review and Focus on Stress

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Abstract

Medial temporal lobe structures have long been implicated in the pathogenesis of major depressive disorder. Although findings of smaller hippocampal and amygdalar volumes are common, inconsistencies remain in the literature. In this targeted review, we examine recent and significant neuroimaging papers examining the volumes of these structures in major depressive disorder. A targeted PubMed/Google Scholar search was undertaken focusing on volumetric neuroimaging studies of the hippocampus and amygdala in major depressive disorder. Where possible, mean volumes and accompanying standard deviations were extracted allowing computation of Cohen's d_s effect sizes. Although not a meta-analysis, this allows a broad comparison of volume changes across studies. Thirty-nine studies in total were assessed. Hippocampal substructures and amygdale substructures were investigated in 11 and 2 studies, respectively. The hippocampus was more consistently smaller than the amygdala across studies, which is reflected in the larger cumulative difference in volume found with the Cohen's d_s calculations. The left and right hippocampi were, respectively, 92% and 91.3% of the volume found in controls, and the left and right amygdalae were, respectively, 94.8% and 92.6% of the volume of controls across all included studies. The role of stress in temporal lobe structure volume reduction in major depressive disorder is discussed.

Introduction

Major depressive disorder (MDD) is an increasingly prevalent condition resulting in significant morbidity and mortality.[1] Consistent with the variation in illness presentation, diagnostic criteria for MDD encapsulate a wide range of signs and symptoms.[2] Core symptoms of MDD comprise pervasively low mood, increased fatiguability and anhedonia.[3] However, deficits in neurocognitive function frequently accompany these affective phenomena and include impairment of memory, visuospatial processing and attention.[4,5] This heterogeneity of illness presentation is unsurprising given the multifactorial aetiology of the condition.[6] Such heterogeneity implicates several brain regions in the neuropathology of MDD.[7]

Characterisation of the links between the neuropathology of depression and a patient's symptoms is of fundamental importance to academic psychiatrists worldwide. This is evident in the proliferation of neuroimaging studies over the last few years. Significant advances have been made towards understanding the neurobiology of MDD, with imaging studies identifying multiple loci exhibiting volumetric differences in depressed patients versus healthy controls. In particular, medial temporal lobe (MTL) structures such as the

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amygdala and hippocampus, along with frontal regions, have been implicated as potential biomarkers for depression, with most studies demonstrating volume reduction.[8,9] Many studies have emerged within the literature focusing on hippocampal and amygdalar volumes, but these have yielded some contradictory findings. Understanding these findings may aid our understanding of MDD neurobiology and focus targeted research into these structures.

Background

Ambiguity surrounds the anatomical terminology of these temporal lobe structures, and the definitions of these terms vary in the literature. The hippocampus proper consists of the allocortical cornu ammonis subfields 1-4 (CA1-4), and the hippocampal formation consists of the dentate gyrus (DG) medially along its transverse axis, and the subiculum inferiorly.[9] Recent research has also illustrated long-axis specialisation of the hippocampus, with both anatomical and functional segregation noted along the anterior and posterior segments.[10] The CA1-4 subfields are components of the canonical trisynaptic circuit (Figure 1). This comprises the perforant path from the entorhinal cortex to granule cells of the DG, which in turn project mossy fibres to pyramidal cells in CA3 from which Schaffer collaterals project to CA1.[7] The hippocampus is the cardinal neural structure in memory, emotional and cognitive processing, transmitting information across the cortex and to the hypothalamus via the classic Papez circuit.[11] The amygdala is arguably even more critical to emotional processing, with reciprocal connections to almost every part of the cortex (Figure 2). There are numerous anatomical and functional regions of the amygdala, which can be further divided into nuclei and nuclear groups.
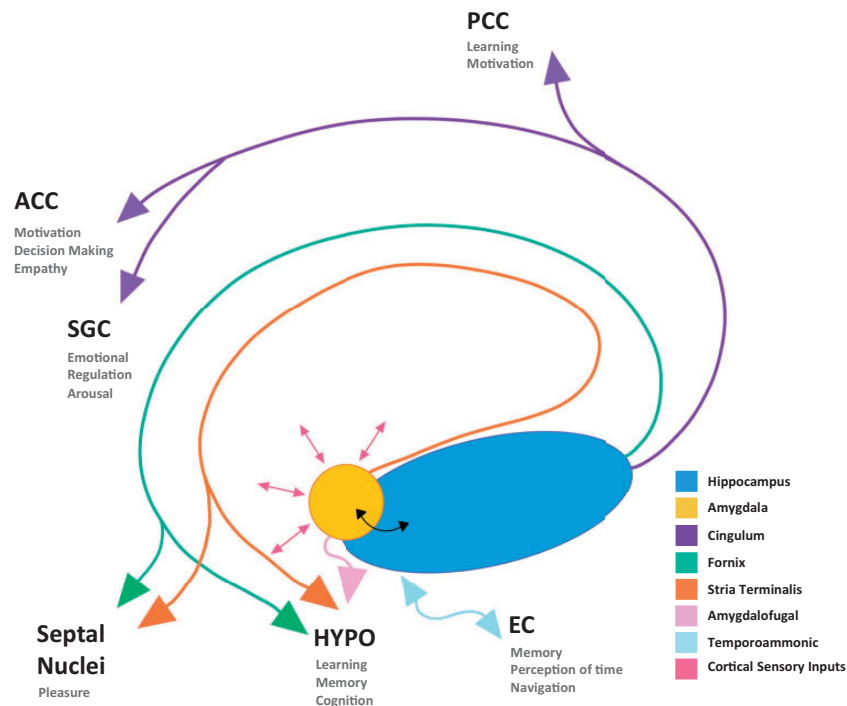
Although multiple classification systems exist, amygdala nuclei are commonly categorised into three groups: the deep laterobasal amygdala containing the lateral (LA) and basal nuclei; the superficial cortical-like nuclei; and centromedial amygdala containing the central (CE) and medial nuclei.[12] Morphometric deviations in both hippocampal and amygdalar substructures have been also studied in MDD more recently with the advent of higher resolution magnetic resonance imaging (MRI) and advanced cortical segmentation.

The role of stressful life events in triggering and perpetuating major depressive episodes (MDEs) has received considerable attention in the literature.[13–15] The hippocampus and the amygdala are key players in mediating behavioural and neuroendocrine responses to stress[16] as well as being vulnerable to the neurotoxic effects of stress themselves.[17] Indeed, the role of stress in the development of MDEs has been increasingly investigated in recent years, and a number of mechanisms have been proposed to explain this link including hypothalamic–pituitary–adrenal (HPA) axis dysfunction, neuroinflammation and neurotransmitter perturbations.[18–20]

Significant heterogeneity exists in studies of these two key MTL substructures, most notably in those of the amygdala.[21–24] Difficulties in the analysis of multiple papers on this topic arise for several reasons. Firstly, there is a significant disparity in anatomical and imaging definitions of the hippocampus and the amygdale used in research. Automated tissue-segmentation protocols using atlas probabilistic based segmentation, such as the Desikan–Killiany atlas, are an emerging method of examination of neural substructures and allow for greater standardisation and reduced inter-study variability in the future. Secondly, findings must be interpreted with caution due to inter-study variability in terms of study
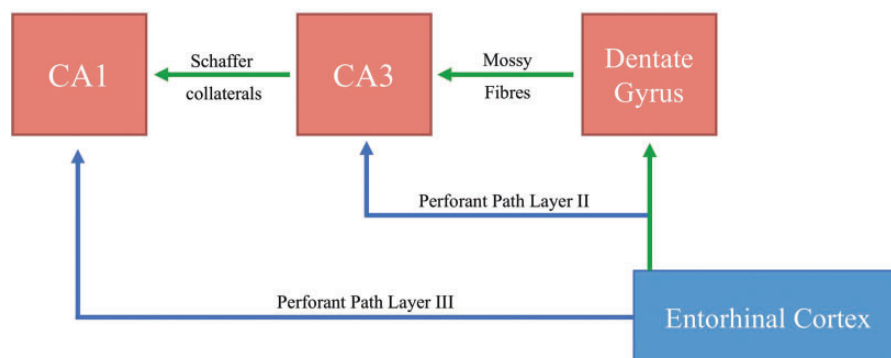
Figure 1. Classic trisynaptic circuit. The classic trisynaptic circuit is demonstrated with the green arrows. Information flows into the hippocampus from the adjacent entorhinal cortex through the perforant pathway. It is then processed through the dentate, CA3 and CA1 substructures via the mossy fibre and Schaffer collateral pathways. Information from the entorhinal cortex also bypasses the trisynpatic circuit and enters the CA regions directly by collateral perforant pathways (blue arrows). This facilitates parallel processing of information through the hippocampus. CA: cornu ammonis.

PCC
Learning
Motivation

ACC
Motivation
Decision Making
Empathy

SGC
Emotional
Regulation
Arousal

Septal
Nuclei
Pleasure

HYPO
Learning
Memory
Cognition

EC
Memory
Perception of time
Navigation

■ Hippocampus
■ Amygdala
■ Cingulum
■ Fornix
■ Stria Terminalis
■ Amygdalofugal
■ Temporoammonic
■ Cortical Sensory Inputs

Figure 2. Hippocampal and amygdalar functional connectivity. The major efferent and afferent connections of the hippocampus and amygdala are shown. Internal and environmental information enters the hippocampus via the entorhinal cortex and outflows via the fornix, cingulum and entorhinal cortex. The amygdala has reciprocal connections with almost every cortical area, including the hippocampus. Amygdalar information also outflows via the stria terminalis and amygdalofugal pathways. ACC: anterior cingulate cortex; EC: entorhinal cortex; Hypo: hypothalamus; PCC: posterior cingulate cortex; SGC: subgenual cortex.

design, including variation in clinical phenotype (including first-episode, remitted, recurrent and treatment-resistant depression), depression severity, patient age, the role of stressful life events and the effects of medication. For example, it has been suggested that multiple MDEs and stress may result in neurotoxic effects, exacerbating global neuronal loss across multiple neural substructures including the hippocampus.[15,25,26] Furthermore, antidepressant medication has been shown to ameliorate such changes in these neural structures, and therefore, patient medication status is an important factor in the interpretation of study findings.[27] These factors likely contribute to the heterogeneity of study findings. It is, therefore, difficult to extrapolate these findings to all patients who fall under the broad singular clinical definition of MDD.

The aims of our study were threefold: (1) to review studies examining global and substructural volumes in the hippocampus and amygdala in depressed patients compared to non-depressed individuals, (2) to generate an approximate volume difference for each structure (limitation of the methods not withstanding) and (3) explore the role of stress and neurotoxic processes in these studies. It is hoped that this review will contribute to a deeper understanding of the role of these MTL structures in MDD.

Methods

A targeted search of the literature was undertaken to review recent papers on this subject. We searched MEDLINE, Embase and Cochrane Library databases, using the keywords 'depression', 'amygdala', 'hippocampus', 'MRI' and 'volume', along with the correct medical subject heading codes and abbreviations. These were paired with the appropriate Boolean operators, and the search was conducted for papers published from 1 January 2009 to present 25 June 2019.

Inclusion criteria were (1) adult patients with a primary diagnosis of MDD by DSM-IV/DSM-V or ICD-10 by a psychiatrist; (2) comparison to healthy controls who were screened for neurological, psychiatric and other medical disorders that may affect brain structure; (3) assessment of volumetric differences using MRI; (4) patients reporting depressive symptoms without a formal diagnosis of MDD; and (5) systematic reviews and meta-analyses of studies fitting the above specifications. Studies were commonly excluded for examining a paediatric cohort. Studies which solely analysed volume following treatment, and articles which assessed volumetric differences post-mortem were also excluded. The references of the included papers were inspected for relevant articles, and other key

articles known to the reviewers were also included in our review.

A Cohen's d_s effect size was calculated by extraction of means and standard deviations of hippocampal and amygdala volumes reported in each study. Only studies that reported means and standard deviation were included in this calculation. Cohen's d_s is a modified calculation of the Cohen's d score allowing pooling of means from samples that are not equal in size to be compared. This metric provides a standardised difference between means, i.e. allowing a comparison of the effect sizes between different studies. The calculation was made using the following equation:

$$Cohen's\ d_s = \frac{M_2 - M_1}{Pooled\ SD}$$

$$Pooled\ SD = \sqrt{\frac{(n_1 - 1) \times SD_1^2 + (n_2 - 1) \times SD_2^2}{n_1 + n_2}}$$

$M_1 = The\ mean\ of\ group\ 1$
$M_2 = The\ mean\ of\ group\ 2$
$SD_1 = The\ standard\ deviation\ of\ group\ 1$
$SD_2 = The\ standard\ deviation\ of\ group\ 2$
$n_1 = The\ size\ of\ group\ 1$
$n_2 = The\ size\ of\ group\ 2$

A negative Cohen's d_s value from our data denotes that the structure volume is smaller in MDD, while a positive value means it is larger in depression. The further away the value is from 0, the larger the difference between controls and depressed in each study. The use of this metric allows for a standardised comparison of the effect size between the means of the groups being discussed across different studies. A percentage decrease in the size of volumes was determined by calculation of the mean value of the average volume sizes in different studies and dividing the mean from depressed participants by the mean from non-depressed participants.

Results

Thirty-nine studies were identified with 21 measuring hippocampus volumes, 9 measuring amygdalar volumes and 9 measuring both hippocampal and amygdalar volumes. A total of 7270 MDD patients and 12,996 controls were investigated across all studies. In addition, six meta-analyses of hippocampal volumes in MDD and four meta-analyses of amygdalar volumes in MDD were also returned. Moreover, 24 studies found smaller hippocampal volumes in MDD (80% of hippocampal studies) and 12 studies found smaller amygdala volumes in MDD (67%); 13 hippocampal studies used automated segmentation, 9 used manual segmentation and 6 used a combination of both. Eight amygdalar studies used

automated segmentation, 6 used manual segmentation and 4 used a combination of both; 11 hippocampal studies examined the structure at a substructural level compared to only 2 amygdalar studies. Sixteen hippocampal studies investigated MDD patients with medication compared to 8 without medication, with 4 not reporting medication status. Moreover, 12 amygdalar studies investigated MDD patients with medication compared to 4 without medication, with 1 not reporting medication status. Only two studies overall appeared to control for medication effects.[26,28]

Using the Cohen's d_s calculation as the standardized difference between the means, smaller bilateral hippocampi across all studies in MDD was revealed (mean effect size −0.341, range −1.211 to 0.673). The left and right hippocampi were respectively 92% and 91.3% the volume found in controls. Similarly, Cohen's d_s calculation revealed smaller bilateral amygdalae (mean effect size −0.701, range: −2.927, −0.0293) with the left and right amygdalae showing 94.8% and 92.6% of the volume of controls across all studies.

Discussion

This targeted review explored neuroimaging studies measuring hippocampal (Table 1) and amygdala (Table 2) volumes in MDD. Of the 39 studies returned, the majority showed smaller hippocampi and amygdalae in the disorder. Although not a meta-analysis, by pooling the means and standard deviations from studies that supplied the data we were able to calculate an estimate of the overall differences in hippocampal and amygdala volumes in MDD (Table 3). Across the studies, both structures were smaller in MDD, with the hippocampus showing an approximate 8% volume difference bilaterally and the amygdala showing an approximate 7% difference on the right and 5% difference on the left.

Global Hippocampal Changes in MDD

Within the neuroimaging literature, smaller hippocampal volumes are amongst the most widely replicated findings in MDD. We identified 24 studies showing smaller hippocampi compared to controls. Our Cohen's d_s calculation strongly supports this wider consensus with an 8% hippocampal volume reduction bilaterally. This is consistent with meta-analyses investigating the hippocampus as a single structure[29–31] or as part of a greater limbic system analysis[21,32,33] reporting volume reductions of 4%–10%. Meta-analyses of voxel-based morphometry data also provides evidence of hippocampal grey matter loss in MDD.[34–36] Most available evidence indicates that volume reduction is associated with longer durations of depressive illness (i.e. MDD chronicity), a

greater number of depressive episodes and earlier age of onset of MDD.[9,37] From these findings emerged the concept of the so-called cumulative depressive load, a combination of duration of episodes and number of episodes over a person's lifetime.[38] A cumulative depressive load of longer than 2 years is associated with smaller hippocampi in MDD.[31,38] This suggests that a 'depressive dose' effect depending on the length of time the individual suffers from active depression may influence hippocampal size. However, hippocampal changes have also been found in first episode patients,[9,39] suggesting that changes in the structure either occur early in the illness or smaller hippocampal size may represent a vulnerability for the development of MDD.

Some studies show that hippocampal volumes are smaller during depressive episodes and resolve upon illness resolution.[40] Hippocampal size may represent a state marker of the illness, i.e. present during episodes and absent in recovery. The neuroplastic capacity of the hippocampus is illustrated by normalization/recovery of volumes following pharmacological treatment for MDD,[28,40–43] further giving weight to the notion that hippocampal volume may serve as a biomarker of disease state. One study found that hippocampal volumes increase greater than controls following long-term (three years) antidepressant treatment.[44] Neurogenesis in the DG of the hippocampus has been proposed as a potential mechanism for the action of antidepressants.[45]

A minority of studies found hippocampal volumes were not smaller in MDD. In particular, two large studies with a combined sample size of 1767 patients failed to demonstrate volumetric differences in the hippocampus between depressed and non-depressed individuals.[1,46] There are some difficulties in interpreting these results. Shen et al. used a composite of self-reported symptoms and hospital admission data to estimate probable MDD, rather than an operational MDD diagnosis based on strict structured clinical interviews.[46] Ancelin et al. investigated a community-based sample and most of the MDD patient group only had one episode at some point in their lifetime, potentially accounting for the lack of hippocampal findings.[1]

Although care is needed when interpreting these findings in their totality, the majority of available evidence points towards a disease process at work in the hippocampus in MDD. Hippocampal atrophy may already be present at first episode, with greater volume reduction occurring with further depressive episodes as the disease progresses.[9,25,29] However, the hippocampus is not a unitary structure and has many individual yet interdependent parts. Changes may occur discretely in subfields rather than across the whole structure. Recently, increased efforts have been made to localise differences found in MDD to individual substructures.

Dentate Gyrus

Various structural neuroimaging studies have found dentate volume reductions along with other substructure changes in depression.[9,42,47,48] A study comparing 52 medication-free patients to 51 healthy controls found that the number of prior depressive episodes was correlated with reduced dentate volumes using FreeSurfer 5.3 automated segmentation.[48] Using the same methods, 20 medication naïve females with MDD were found to have smaller dentate regions compared to 21 controls.[47] A high-field (4.7 T) manual segmentation study showed smaller dentate volume in nine unmedicated patients compared to eleven medicated patients and twenty seven controls as well as smaller CA (1–3) in the depressed patients.[42] The dentate was also found to be smaller in a study of 83 depressed individuals compared to 80 controls, using FreeSurfer 6.0 with the difference more pronounced on the left and in those with recurrent depression.[9]

The dentate represents the input circuitry of the hippocampus (Figure 1), funnelling information from the entorhinal cortex into the hippocampus.[11] It is one of only two locations where adult neurogenesis occurs.[49] Decreased dentate neurogenesis may play a role in MDD,[7] and increased dentate neurogenesis may be a mechanism for the action of antidepressants.[45] The granule cells of the dentate express high concentrations of glucocorticoid and mineralocorticoid receptors[50] and appear to be exceptionally vulnerable to circulating cortisol levels compared to other brain regions.[7] This may be particularly important in MDD which is associated with HPA axis and cortisol perturbations.

Subiculum

The subiculum has been shown to be smaller in some MRI studies in depression (see Table 1).[9,47,51] A high-field (7 T) manual tracing study of 13 patients with one episode of MDD and 5 patients with multiple episodes, showed smaller subicular volumes with multiple episodes, but these findings are limited in power by small sample size.[51] Moreover, 20 medication naïve females with MDD were found to have smaller subiculum regions compared to 21 controls in a FreeSurfer 5.3 study.[47] Using the same automated technique, the subiculum was found to be smaller in a study of thirty older patients with MDD.[52] A FreeSurfer 6.0 study found the subiculum to be smaller in 83 depressed individuals compared to 80 controls, with the difference more pronounced on the left and in those recurrent depression.[9] The left subiculum was also smaller in a similar study of 102 patients with MDD and 135 controls.[53] Hippocampal atrophy has also been found in individuals

Table 1. Hippocampal studies in MDD.

Study	Segmentation	MDD/HC	Drug Status	Illness Duration	Male/Female	Key finding
Studies showing smaller hippocampus in MDD						
Han et al.[54]	Automated (FreeSurfer 6.0)	102/135	80 medicated	44.76 months	99/138	Bilateral atrophy in CA1, CA4, granule layer, molecular layer, whole hippocampus in cMDD [Cohen's d = −0.4976 (left), −0.4802(right)]. Left CA2/3 and right presubiculum and subiculum atrophy in cMDD. Degree of atrophy not correlated with illness duration.
Roddy et al.[9]	Automated (FreeSurfer 6.0)	80/83	64 medicated	29 months	57/106	Bilateral atrophy in CA1-4, DG, subiculum in cMDD, more pronounced on left and in rMDD. Left CA1 atrophy most marked change overall. CA2-4 only structures showing atrophy in first MDE.
Yao et al.[70]	Automated (FIRST)	25/28	19 medicated	-	30/23	Bilateral CA1, subiculum and hippocampal atrophy in cMDD. [Cohen's d = −0.2917 (left), −0.5819 (right)]
Zaremba et al.,[90]	Automated(SPM8)	213/213	202 medicated	30.58 months (Cumulative lifetime duration)	198/228	Atrophy correlated to number of inpatient hospitalisations.
Han et al.[47]	Automated (FreeSurfer 5.3)	20/21	Medication free	114.22 months	0/41	Left subiculum, CA2–4, DG and whole hippocampus atrophy in cMDD [Cohen's d = −0.5819]. Right subiculum atrophy in cMDD.
Treadway et al.[48]	Automated (MAGeT Brain)	51/52	Medication free	–	56/47	DG atrophy correlated to number of MDEs.
Brown et al.[54]	Automated (FIRST)	1946 persons	480 medicated	-	804/1132	Severity of depressive symptoms correlated to global hippocampal atrophy, but not left/right individually, Correlation strongest in older persons.
Stratmann et al.[26]	Automated (SPM8)	132/132	126 medicated	14.66 months	114/150	Bilateral hippocampus and parahippocampus atrophy in cMDD. Right hippocampus atrophy correlated to number of MDEs.

Table 1. Continued

Study	Segmentation	MDD/HC	Drug Status	Illness Duration	Male/Female	Key finding
Arnone et al.[40]	Automated (SPM8)	64/66	Medication free	—	37/93	Bilateral hippocampus atrophy in cMDD and remitted untreated MDD. State marker of illness. Hippocampus enlargement in medicated MDD. Included in Zhao[35] meta-analysis
Huang et al.[42]	Manual	20/27	11 medicated	—	18/29	CA1-3 and DG atrophy in unmedicated cMDD.
Buddeke et al.[55]	Manual	636 persons	~50 medicated	—	515/121	Atrophy correlated with severity of depressive symptoms.
Maller et al.,[94]	Manual	182/76	Unclear	—	135/123	Global hippocampal atrophy most marked in tails in TRD. [Cohen's d = −0.8302 (left), −0.6805(right)]
Schuhmacher et al.[27]	Manual	86/87	86 medicated	1-year fMDD, 15.51 years rMDD	77/96	Bilateral hippocampus atrophy in rMDD. [Cohen's d = −0.7373(left), −0.7777 (right)]
Cole et al.[92]	Manual	37/37	Medication free	—	18/56	Right hippocampus atrophy in first MDE. Bilateral hippocampus atrophy in rMDD. Subiculum and CA1 atrophy most marked, predominantly in tail. CA2-3 also displayed atrophy. Included in Santos 2018, Cole 2011 meta-analysis
Malykhin et al.[28]	Manual	39/34	16 medicated	-	17/56	Right hippocampus head, and right total hippocampus atrophy in cMDD. [Cohen's d = −0.5417] Bilateral hippocampus tail atrophy in cMDD. Hippocampus body enlargement in medicated MDD patients vs. HCs and unmedicated cMDD.
Bearden et al.[41]	Manual	31/31	Medication free	11.42 years	14/48	Left hippocampus atrophy, particularly CA1 and subiculum, in severe MDD. Left hippocampal enlargement with previous medication. Included in Santos 2018 meta-analysis
Kronmuller et al.,[95]	Manual	57/30	57 medicated	5 years 34.90 weeks current episode	35/52	Left hippocampus atrophy in male patients with first MDE. [Cohen's d = −1.2106] No hippocampus atrophy in female patients with first MDE. No difference between hippocampus volume in rMDD vs. HCs. Included in Cole 2011 meta-analysis.

(continued)

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Table I. Continued

Study	Segmentation	MDD/HC	Drug Status	Illness Duration	Male/Female	Key finding
Santos et al.,[96] Schmaal et al.[25]	Mixed Mixed	1327/1004 1728/7199	Medication free 623 Medicated	Range: 7–57 months	965/1366	Bilateral hippocampus atrophy in MDD. Bilateral hippocampus atrophy in rMDD, but not in first MDE. Earlier age of MDD onset correlated with hippocampus atrophy. Proportion of medication in studies did not moderate alterations in hippocampus volumes.
Zhao et al.[35]	Mixed	400/424	Medication free	Range: 0.22–7.5 years first onset	142/258	Bilateral hippocampus and parahippocampus atrophy in MDD. Bilateral hippocampus atrophy correlated to illness duration. Right hippocampus atrophy correlated to percentage of female patients in each study.
Cole et al.[29]	Mixed	191/282	93 medicated	months average = 14.4 (range is from 4.7–25.2)	169/304	Bilateral hippocampus atrophy in first MDE.
Videbech and Ravnkilde[30]	Mixed	351/279	N/A	–	–	Bilateral hippocampus atrophy in MDD. Right hippocampus atrophy correlated to number of MDEs.
Belleau et al.[15]	N/A	N/A	N/A	–	–	HPA-axis dysfunction, inflammation, oxidative stress, neurotransmitter abnormalities are neurotoxic and facilitate atrophy in MDD. Stress-sensitisation: with each successive MDE, it takes less stress to trigger these neurotoxic pathways.
Malykhin and Coupland[91]	N/A	N/A	N/A	–	–	Hippocampus atrophy in MDD specific to the DG and CA subfields. Antidepressant treatment causes DG enlargement by stimulating neurogenesis, and reverses hippocampus atrophy in MDD.
Studies not showing smaller hippocampus in MDD						
Ancelin et al.[1]	Automated (FreeSurfer 5.3)	162/448	31 medicated	–	290/230	No hippocampus atrophy in lifetime MDD vs. HCs. [Cohen's d = 0.6739]

(continued)

Table 1. Continued

Study	Segmentation	MDD/HC	Drug Status	Illness Duration	Male/Female	Key finding
Brown et al.[72]	Automated (FreeSurfer 6.0)	24/20	Medication free	80.7 months	44/14	No hippocampal subfield atrophy in depressed patients and no correlation to illness duration or severity
Shen et al.[46]	Automated (FAST)	354/803	N/A	–	529/628	No hippocampus atrophy in MDD vs. HCs.
Schermuly et al.[43]	Automated (SPM2)	15/13	15 medicated	Duration illness: 35.7 m Duration episode: 7.0 m	9/19	No hippocampus atrophy in MDD vs. healthy controls. [Cohen's d = 0.3461] Posterior hippocampus enlargement during treatment with medication.
Wisse et al.[51]	Manual	13/34	4 medicated	–	18/29	No hippocampus subfield atrophy in patients who had MDE in previous 7 years vs. HCs. [Cohen's d = 0] Subiculum atrophy correlated to number of MDEs.
Bora et al.[69]	Mixed	986/937	Mixed	–	878/1045	No hippocampus atrophy in MDD vs. HCs.

The table is divided into studies showing smaller hippocampus in MDD and those showing no smaller hippocampus in MDD. Each section is stratified into automated, manual and mixed segmentation techniques. CA, cornu ammonis; cMDD, current major depressive disorder; DG, dentate gyrus; FAST, FMRIBs automated segmentation tool; FIRST, FMRIBs integrated and registration segmentation tool; HC, healthy controls; N/A, not available; MAGet, multiple automatically generated templates; MDD, major depressive disorder; MDE, major depressive episode; rMDD, recurrent major depression; SPM, statistical parametric mapping.

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Table 2. Amygdalar studies in MDD.

Study	Segmentation	MDD/HC	Drug Status	Illness Duration	Male/Female	Key finding
Studies showing smaller amygdala in MDD						
Ancelin et al.[1]	Automated (FreeSurfer 5.3)	162/448	31 medicated	–	290/230	Lower global amygdala volume in men associated with lifetime diagnosis of MDD. [Cohen's d = −2.9271]
Brown et al.[72]	Automated (FreeSurfer 6.0)	24/20	Medication free	80.7 months	44/14	Left cortical nucleus, left accessory basal nucleus, bilateral corticoamygdaloid transition area – significant negative associations with MDD severity. No relationship to duration.
Daftary et al.[75]	Automated (FreeSurfer 4.4)	1797 persons	320 medicated	–	726/1071	Right amygdala volume negatively correlated to depressive symptom severity in 18–39 years age group.
Yao et al.[70]	Automated (FSL)	25/28	19 medicated	–	30/23	Atrophy of bilateral LA, BLVM; and right LA, BLVM, CE, ASTR, ACO and AAA. Right amygdala atrophy [Cohen's d = −0.5581]
Stratmann et al.[26]	Automated (SPM8)	132/132	126 medicated	14.66 months	114/150	Right amygdala volume negatively correlated to number of MDEs.
Zavorotnyy et al.,[97]	Manual	23/30	18 medicated	4.4	12/41	Larger left amygdala in late-onset MDD [Cohen's d = −0.02933] Amygdala volume negatively correlated to illness duration.
Schuhmacher et al.[27]	Manual	86/87	86 medicated	1-year fMDD, 15.51 years rMDD	77/96	Bilateral amygdala atrophy in first MDE. [Cohen's d = −0.5452(left), −0.7988 (right)] Bilateral volume normalisation with medication in recurrent MDD.
Kronenberg et al.[74]	Manual	24/14	Medication free	–	15/23	Bilateral amygdala atrophy in cMDD. [Cohen's d = −0.8294 (left), −0.8519 (right)] Amygdala volume negatively correlated to number of MDEs. Volume not related to severity of MDE.
Sheline et al.[71]	Manual	20/20	14 medicated	–	0/40	Bilateral laterobasal nuclei atrophy, no global atrophy. [Cohen's d = −0.94984 (left core nuclei), −0.96168 (right core nuclei)]
Zhao et al.[35]	Mixed	400/424	Medication free	Range: 0.22–7.5 years first onset	142/258	Right amygdala atrophy in first-episode medication-naïve MDD.
Bora et al.[69]	Mixed	986/937	Mixed	–	878/1045	Amygdala atrophy in medication-free first MDE vs. HCs and rMDD.

Table 2. Continued

Study	Segmentation	MDD/HC	Drug Status	Illness Duration	Male/Female	Key finding
Hamilton et al.[68]	Mixed	299/268	183 medicated	–	136/431	Amygdala atrophy in unmedicated MDD vs. HCs. Amygdala volume increased in medicated MDD vs. HCs.
Studies not showing smaller amygdala in MDD						
Yuksel et al.,[98]	Automated (SPM8)	37/54	Medicated	–	50/41	No differences in amygdala volume in MDD vs. HCs initially. Significant grey matter volume increase in bilateral amygdala in MDD during follow up compared to HCs. Milder courses of MDD exhibited increased grey matter volume increases in left amygdala compared to severe course of MDD on follow up. Volumetric changes in left amygdala may be reversible and dependent on clinical phenotype.
Sandu et al.[77]	Automated (SPM8)	81/44	74 medicated	Non TRD: 18.01 Y TRD: 18.9 Y	60/65	No difference in amygdala volume between HCs and group consisting of TRD and remitted MDD. Amygdala enlargement in TRD vs. remitted MDD. Larger amygdala may indicate vulnerability to develop medication resistance.
Shen et al.[46]	Automated (FAST)	354/803	N/A	–	529/628	No difference in amygdala volumes in MDD vs. HCs.
van Eijndhoven et al.[76]	Manual	40/20	Medication free	current first episode: 7.1 months recovered first episode: 21.6 months	20/40	Amygdala enlargement in cMDD vs. HCs (Cohen's d = 0.4974 (left), 0.5786 (right)) No difference in amygdala volume between remitted MDD and HCs. Included in Cole 2011 meta-analysis
Lorenzetti et al.[73]	Manual	56/21	33 medicated in previous 6 months	cMDD: 11.45 rMDD: 9.04	26/61	No amygdala volume difference in cMDD vs. HCs. Left amygdala enlargement in remitted MDD vs. HCs.
Schmaal et al.[25]	Mixed	1728/7199	623 Medicated	–	–	Smaller amygdala with earlier age of onset; however, this did not survive correction for multiple comparisons.

Note: The table is divided into studies showing smaller amygdala in MDD and those showing no smaller amygdala in MDD. Each section is stratified into automated, manual and mixed segmentation techniques. AAA: anterior amygdaloid area; ACO: anterior cortical; ASTR: amygdalostriatal transition area; BLVM: basolateral ventrolateral; CA: cornu ammonis; CE: Central; cMDD: current major depressive disorder; DG: dentate gyrus; FAST: FMRIBs automated segmentation tool; HC: healthy controls; HPA: hypothalamic-pituitary-adrenal; LA: lateral; MDD: major depressive disorder; MDE: major depressive episode; N/A: not available; rMDD: recurrent major depression; SPM: statistical parametric mapping.

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Table 3. Cohen's ds for hippocampal and volumetric studies in MDD.

Study	Area	No depression			Depression			Cohen's d_s
		Mean	SD	N	Mean	SD	N	
Amygdala studies								
Ancelin et al.[1]	Global amygdala	2634.1	14.88	448	2580.7	25.34	162	-2.9271056
Yao et al.[70]	Left amygdala	1405.3	349.9	28	1247.7	540.7	25	-0.3503127
	Right amygdala	1510.7	511.3	28	1205.6	583.9	25	-0.5581094
Zavorotnyy et al.,[97]	Left amygdala	2.101	0.292	30	2.093	0.245	23	-0.029334
	Right amygdala	1.977	0.242	30	1.915	0.176	23	-0.2870146
Schuhmacher et al.[27]	Left amygdala	0.136	0.021	87	0.124	0.0246	32	-0.5451756
	Right amygdala	0.136	0.0188	87	0.12	0.0231	32	-0.7988252
Kronenberg et al.[74]	Left amygdala	1.97	0.26	14	1.71	0.34	24	-0.8294118
	Right amygdala	1.97	0.27	14	1.74	0.27	24	-0.8518519
Sheline et al.[71]	Left amygdala	1782	296	20	1650	310	20	-0.43553
	Right amygdala	1752	295	20	1724	304	20	-0.09348
Hippocampus studies								
Han et al.[53]	Left hippocampus	3471.5	376.32	135	3290.4	346.66	102	-0.4976274
	Right hippocampus	3589.7	386.91	135	3414.5	333.22	102	-0.4802339
	Left CA1	669.69	88.449	135	631.78	83.848	102	-0.4382812
	Right CA1	704.07	85.319	135	660.78	76.182	102	-0.5309772
	Left CA4	269.87	33.777	135	253.74	32.272	102	-0.4869254
	Right CA4	276.57	33.936	135	263.89	29.735	102	-0.3938791
	Left CA2-3	216.62	33.64	135	202.5	35.014	102	-0.4123575
	Right subiculum	429.86	51.484	135	411.72	41.205	102	-0.3832026
Yao et al.[70]	Left hippocampus	4701.4	991.6	28	4303.5	1687.2	25	-0.2917425
	Right hippocampus	5161.7	926.6	28	4494.7	1351.2	25	-0.5819352
Han et al.[47]	Left subiculum	640.79	46.89	21	586.9	77.4	20	-0.8472077
	Left CA2-3	927.31	104.38	21	862.45	108.92	20	-0.6083518
	Left CA4-DG	490.94	62.51	21	527.62	59.99	20	0.598415
	Left hippocampus	2940.7	256.66	21	2737.2	341.09	20	-0.6767011
	Right hippocampus	3040.1	310.46	21	2849	391.43	20	-0.5423863
	Right subiculum	655.14	52.48	21	603.3	76.97	20	-0.7906793
Huang et al.[42]	CA1-3	1618	282	27	1646	277	20	0.1000358
	DG	1281	179	27	1261	244	20	-0.0957278
Maller et al.,[94]	Left hippocampus	2773.4	409.85	76	2446.5	386.93	182	-0.830178
	Right hippocampus	2629.3	403.73	76	2344.4	424.76	182	-0.6805215
Schuhmacher et al.[27]	Left hippocampus	0.23	0.0285	87	0.207	0.0337	86	-0.737337
	Right hippocampus	0.233	0.0299	87	0.209	0.0318	86	-0.7777292
Malykhin et al.[28]	Left hippocampus	2798	257	34	2747	297	39	-0.1827156
	Right hippocampus	2982	244	34	2829	312	39	-0.5417117
Kronmuller et al.,[95]	Left hippocampus	3.19	0.25	30	2.81	0.36	26	-1.2105645
	Right hippocampus	3.3	0.29	30	3	0.57	26	-0.6783556

(continued)

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Table 3. Continued

Study	Area	No depression			Depression			Cohen's d_s
		Mean	SD	N	Mean	SD	N	
van Eijndhoven et al.[76]	Left amygdala	2222	412	20	2389	236	20	0.4974117
	Right amygdala	2153	396	20	2358	307	20	0.5785965
Ancelin et al.[1]	Global hippocampus	7033	33.88	448	7061	57.73	162	0.6738832
Ota et al.,[99]	Global hippocampus	5583.7	489.9	35	5578.4	521.8	19	−0.0105752
Wisse et al.[51]	Global hippocampus	3.1	0.5	34	3.1	0.4	13	0
Schermuly et al.[43]	Global hippocampus	2.67	0.29	13	2.83	0.57	15	0.346063

Note: A Cohen's d_s metric is provided for a standardized comparison of the effect size between the depressed and non-depressed group means. Meta-analyses and studies providing insufficient information (e.g. no mean volumes or SDs) for calculation of Cohen's d_s have been excluded from the table. Cohen's d_s for specific subfields have also been excluded in instances where the study does not report the metrics needed for Cohen's d_s calculation. CA: cornu ammonis; DG: dentate gyrus; N: number; SD: standard deviation.

who reported depressive symptoms,[54] and this atrophy is correlated to an increasing course of these symptoms.[55]

The subiculum is part of the exit circuitry of the hippocampus (Figure 1) and, along with CA1, outputs information back to the adjacent entorhinal cortex and to the wider cortex and hypothalamus via the fornix.[11] Subicular output inhibits HPA activity resulting in reduced circulating cortisol. Smaller subiculums found in MDD may disrupt the negative feedback mechanisms of the HPA axis causing escalating cortisol levels, known to be detrimental to mood and cognition[56,57] as well as directly damaging brain areas including the DG.[50,58]

Ca1

The CA1 has been found to be bilaterally smaller in a study of 102 patients with chronic MDD and 135 controls.[53] The left CA1 region was also smaller in 83 depressed individuals compared to 80 controls and was reported as a predictor of depressive illness duration.[9] Previous studies that have identified changes in various other hippocampal substructures, however, have failed to demonstrate CA1 changes.[59] Failure to do so may be accounted by the well-documented methodological issues with previous versions of automated segmentation that have underestimated the size of CA1.[51]

The CA1 region has a particularly high expression of multiple 5-HT receptor subtypes[60] and is the most vulnerable hippocampal substructure to excitotoxicity.[61] Long-term corticosteroid exposure, a model of MDD and chronic stress in rats, has been shown to lead to attenuated serotonin responses in the CA1 region.[62] Evidence showing extensive post-mortem CA1 neural apoptosis[63] and reduced CA1 thickness[64] in MDD also strongly suggests CA1 involvement in the disorder.

Ca2/3

Hippocampal segmentation often combines these two subfields into a single CA2/3 region due to the inability to distinguish the CA2 from the adjacent CA3 region using MR imaging, the diminutive size of CA2 and the similarity between the pyramidal layers of both subfields. Left CA2/3 volume in MDD was reduced in a study of 83 depressed patients compared to 80 controls, particularly in patients with recurrent depression,[9] and also of 102 patients with MDD and 135 controls.[53] CA3 was also found to be reduced in Parkinson's patients with comorbid depression. These volumes normalized following L-DOPA treatment.[59] Similar reductions were found in CA2/3 subfields in an unmedicated MDD female only cohort.[47] Smaller CA2/3 subfields have been found in later life patients[52] and associated with cerebrovascular events.[65]

Although small, the CA2 subfield receives prominent hypothalamic input, including directly from the paraventricular nucleus, suggesting a role in HPA feedback.[66] The CA3 displays rich connectivity within the hippocampus and has roles as a hippocampal 'pacemaker' critical for encoding and decoding of information.[59,67] Smaller CA2 and CA3 in MDD could result in the aberrant stress/HPA responses found in the disorder as well as the neurocognitive difficulties found in some individuals with MDD.

Global Amygdala Changes in MDD

While a relative abundance of literature exists detailing structural alterations of the hippocampus in MDD, there is a relative dearth of research detailing amygdala volumes in the illness. We identified 12 studies showing smaller amygdala compared to controls. Our Cohen's d_s calculation showed a 5.2% reduction in amygdala volume on the left and a 7.4% reduction on the right in MDD patients. This largely corresponds with previous meta-analyses focusing on the amygdala as a single structure[68] or part of a broader brain analyses.[25,35,69] Structural neuroimaging studies of the amygdala in the literature are hindered by the same inter-study variability as those of hippocampal studies. Due to the particular difficulties in categorization and identification of amygdalar nuclei, there has been less focus in measuring amygdalar subregions. However, effort has focused on identifying global changes and also the lateralisation of differences. Debate has also centred around whether amygdala volume alterations represent a state marker for depression.

Amygdala Substructures

Unfortunately, due to difficulties in substructure definitions and visualization on MRI, only a handful of studies have investigated the amygdala at a deeper level in MDD. A recent automated segmentation study of 25 patients and 28 controls reported specific subregional volumetric loss not apparent when examining global amygdala volume.[70] Specifically, the lateral and basolateral ventromedial nuclei were bilaterally smaller in MDD, along with right central and anterior cortical nucleus volume reductions. Smaller laterobasal nuclei were found bilaterally in a manual tracing study of twenty MDD patients.[71] A recent 7 T automated segmentation of study of 24 patients and 20 controls found no reduction in whole volumes or nuclei volumes in MDD, but did find the right lateral and left cortical and accessory basal nuclei correlated negatively with depressive symptoms.[72]

Amygdala as a State Marker of Illness

It is clear that there is significantly greater heterogeneity in the findings from studies of the amygdala, particularly when comparing studies with differing disease stages. Many have established the case that volumetric alterations may represent a trait of neurobiological vulnerability for depression.[73] A trend towards increasing atrophy with increasing number of depressive episodes has also been detected.[74] A previous meta-analysis has found evidence of reduction of volume in the right amygdala in first episode depression.[69] Younger patients aged 18–39 years reporting depressive symptoms but not formally diagnosed with MDD have also been shown to display atrophy in the right amygdala.[75] No relationship between depression severity and smaller amygdala volume has been found.[74] This is in contrast to conflicting studies showing enlarged amygdalae in first-episode depression is correlated to episode severity.[76]

These volume changes have been shown to resolve in patients treated with antidepressant medication. A meta-analysis shows that smaller amygdala volumes found in MDD increase in size with medications, even beyond that seen in controls.[68] Conversely, normalisation of volumes of initial enlarged amygdala after treatment has also been described.[76] This may be underpinned by protection from excess glucocorticoid stimulation. In one study there appeared to be a correlation between bilateral normalization of amygdalar volumes following medication administration (in the context of pre-treatment bilateral atrophy) with reductions in HPA-axis activity.[27] Suggesting that the effects of antidepressants on circulating cortisol may reverse amygdala volume loss from MDD. Additionally, others have concluded that amygdala volume may be a predictor of treatment response, finding higher amygdala volumes in treatment-resistant patients versus non-treatment resistant patients.[77] However, it must be noted that comorbid anxiety may be present in these cohorts, and this could have an effect on amygdala volumes.[78]

Although amygdalar volume has been suggested to be a marker of treatment response, one study did not demonstrate volumetric differences between currently depressed individuals and controls; however, there was volumetric enlargement in patients in remission not related to the use of medication.[73] This was suggested to represent a vulnerability factor for depression relapse and may constitute a reaction to the stress induced by previous depressive episodes enhancing synaptogenesis in the amygdala. This is in contradiction to other findings whereby stress in the previous six months has been associated with atrophy of the left amygdala.[79]

Stress, Neurotoxicity and Temporal Lobe Structures in MDD

HPA axis dysfunction, neuroinflammation and neurotransmitter perturbations are implicated in the link between MDD and stress. Belleau et al. proposed a unifying model of these mechanisms.[15] In this model, chronic life stress is proposed to trigger dysregulation of the HPA axis, ultimately resulting in altered levels of basal cortisol in those with MDD.[19] This finding has been widely replicated with a majority of studies indicating HPA-axis overactivity, perhaps underpinning the association between MDD and chronic metabolic and neurodegenerative diseases.[18,80,81] HPA activity depends on balanced integration of amygdalar activation and hippocampal inhibition of the periventricular nucleus of the hypothalamus.[82,83] MDD may cause a shift from hippocampal inhibition to amygdala-mediated release of corticotrophin releasing hormone from the hypothalamus.[27] These increased cortisol levels have been associated with damage to both amygdala and hippocampal neurons.

This hyperactive endocrine state cultures a neuroinflammatory milieu, coupled with direct immune activation by stress itself.[15] Chronic stress, therefore, promotes the expression of pro-inflammatory cytokines such as interleukins 6 and 1β and tumour necrosis factor alpha. This is supported by reports of elevations in inflammatory marker levels in the hippocampus in animal models of chronic unpredictable stress.[84] The effects of peripheral pro-inflammatory cytokines on central nervous system microglia may result in reduced hippocampal neurogenesis.[20] Additionally, pro-inflammatory cytokines have been shown to activate indoleamine 2, 3-dioxygenase, an enzyme that shunts tryptophan into the kynurenine pathway, yielding neurotoxic end-products such as 3-hydroxykynurenine and quinolinic acid. Kynurenine pathway activation and associated elevated immune response has been shown to be associated with smaller hippocampi in MDD.[85] Abnormal membrane turnover in the hippocampus in MDD is greater in patients with highly recurrent illness and is further evidenced by magnetic resonance spectroscopy (MRS) studies.[86]

Following from the shift to a pro-inflammatory state and the production of neurotoxic end-products, as well as a direct effect from chronic stress, perturbations in neurotransmission also occur in the pathogenesis of MDD. In particular, there are changes in glutamatergic signalling, as seen in MRS studies.[87,88] Glutamate, the primary excitatory neurotransmitter in the central nervous system exerts an excitotoxic effect on neurons. Disruptions in glutamatergic signalling may result from excessive release and reduced clearance from the synaptic cleft, thereby facilitating direct neurotoxic effects.

Stress Sensitisation and Recurrent Depressive Episodes

The 'stress sensitisation' or 'kindling' model of affective illness[13] proposes that while an initial MDE often follows a period of intense life stress, the strength of the relationship between life stressors and subsequent MDEs declines as a function of the number of MDEs. This leads to the unfortunate situation where progressively lower levels of stress have the ability to trigger recurrent MDEs as the disease progresses. An extension of the kindling model is the 'stress autonomy' model, which proposes that recurrent MDEs can generate independent of life stressors.[15] Assuming that the above formulation of pathogenesis correctly encapsulates the neurobiological underpinnings of MDD, it could be postulated that lesser levels of stress may trigger these increasing neuroendocrine and inflammatory disturbances with each successive MDE. One strong line of evidence for the kindling model is the clear association between early life stressors and MDD.[14] Opel et al. have recently reported a significant association between childhood maltreatment and hippocampal volume in both healthy controls and individuals with MDD, and to the development of MDD.[14,17] Childhood maltreatment has also been linked to an earlier onset of MDD, perhaps explained by the induction of HPA-axis and immune dysregulation.[89] In contrast to this, Lenze et al. did not find an association between childhood maltreatment and hippocampal volume.

Ultimately, a cumulative effect of chronic stress, and of the neurotoxic implications of such stress in MDEs, may be reflected in morphometric disturbances. Naturally, numerous investigators have proposed the hippocampus as a marker of illness progression, with increasing atrophy with each successive depressive episode.[15,25,26] Zaremba et al. proposed that atrophy is not related to total illness duration, but to the number of hospitalisations, suggesting that increasing atrophy may be linked to the severity of the depressive episodes. Attempts have also been made to localise these volume reductions. CA1-4 and DG have consistently been shown to display the most marked changes.[9,41,42,70,90,91,92]

Limitations

The main limitation of any review of hippocampal and amygdalar volumes is the difficulty in comparing results across the variety of different techniques used. Of the 39 studies examined, 30 utilised automated tissue segmentation protocols in some fashion and the remainder relied solely on manual tracing. Although automated tissue segmentation and increasingly capable analysis software allow for more reliable and replicable

identification of hippocampal and amygdalar subfields, there is some debate over the validity of these techniques compared to the 'gold standard' manual tracing. Automated techniques allow much faster assessment of greater numbers of subjects and will probably become more common in the future as dataset numbers increase. Voxel-based methods have been shown to exhibit relative insensitivity in segmenting tissue into grey and white matter in regions such as the hippocampus wherein grey and white matter sheets are convoluted into each other, perhaps resulting in non-significant findings in some cases.[69] Similarly, studies use different definitions of amygdalar and hippocampal volumes. A review of MRI volumetrics has suggested that approximately 60 different anatomical guidelines exist for hippocampal volumes.[93] To view 'volume reduction' in the hippocampus and amygdala as the sole characteristic of MDD-related changes in brain structure may also be overly simplistic. Rather, both differences in structure and connectivity/function may serve as more accurate illness biomarkers. Clearly, these subtle changes in MDD have yet to be fully elucidated. The Cohen's d_s metric used in this study facilitates a standardised comparison of the effect sizes across different studies, yielding an easily interpretable if somewhat blunt measure of overall effect size for each structure. Unfortunately, a full meta-analysis identifying a common effect size, controlling for the multiple confounders and causes of heterogeneity across all these studies is outside the scope of this review. This is currently in progress.

Future Directions

Considerable work is needed to further elucidate the precise link between neuropathology of MTL structures and the clinical presentation of depression. Larger studies are needed with standardised patient groups (age, sex, demographics, etc.), disease characteristics (numbers of episodes, medication status, etc.), MRI protocols and anatomical definitions. As MRI technology and computer processing advances, greater focus on individual substructures, particularly with respect to the under-studied substructures of the amygdala, may provide further insight. As noted above, homogenisation of the definitions of these MTL structures and their substructures will permit greater standardisation across studies and inter-study comparison. No study to date has focused on automated segmentation of the hippocampal subfields into their anterior and posterior components. It is known that the hippocampus has anatomical and functional differences along its anterior–posterior axis[10] (e.g. a lower proportion of dentate is found in the anterior division of the hippocampus than in the posterior hippocampus).[28] Newer automated techniques are now able to divide the hippocampus and

substructures longitudinally along this axis. Not only will future use of these fine grain techniques improve standardisation, but the greater anatomical specificity may form the basis for future hypotheses based on precise substructure localisation. This may yield a more specific and sensitive biomarker – a holy grail of academic psychiatry.

Conclusion

On balance, the overwhelming consensus across all the studies is that both the hippocampus and amygdala are smaller in MDD. The hippocampus most commonly exhibits atrophy proportional to disease chronicity and the amygdala potentially representing a state marker of illness. Several factors contribute to the heterogeneity of study findings, including the impact of stress, number of depressive episodes, impact of medication and the age of depression onset. It is therefore necessary to be cognisant of the impact of these factors in the interpretation and extrapolation of study findings. Recent developments in automated tissue segmentation software have allowed a more nuanced examination of the volumetric changes in the hippocampal and amygdalar substructures. This presents an exciting prospect for future research in this field. Future understanding of the relationship between stress, cognitive and affective processing in depression, and these key temporal lobe structures may help elucidate the pathophysiology of MDD.

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