Research Paper

Structural changes in the hippocampus in major depressive disorder: contributions of disease and treatment

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Background: Previous magnetic resonance imaging (MRI) studies of patients with major depressive disorder (MDD) have consistently shown bilateral and unilateral reductions in hippocampal volume relative to healthy controls. Recent structural MRI studies have addressed the question of whether changes in the volume of hippocampal subregions may be associated with MDD. **Methods:** We used a comprehensive and reliable 3-dimensional tracing protocol that enables delineation of hippocampal subregions (head, body, tail) to study changes in the hippocampus of patients with MDD. We recruited 39 MDD patients (16 medicated, 23 unmedicated) and 34 healthy age- and sex-matched controls. We acquired images using a magnetization-prepared rapid acquisition gradient echo sequence on a 1.5-T scanner with a spatial resolution of 1.5 mm x 0.5 mm x 0.5 mm. We performed volumetric analyses, blinded to diagnosis, using the interactive software package Display. All volumes were adjusted for intracranial volume. **Results:** We found a significant reduction in the volume of the hippocampal tail bilaterally, right hippocampal head and right total hippocampus in MDD patients. Medicated MDD patients showed increased hippocampal body volume compared with both healthy controls and unmedicated patients. **Limitations:** This study was cross-sectional. Further prospective studies are needed to determine the direct effect of antidepressant treatment. **Conclusion:** Our results suggest that decreased hippocampal tail and hippocampal head volumes could be trait changes, whereas hippocampal body changes may be dependent on treatment. We showed that long-term antidepressant treatment may affect hippocampal volume in patients with MDD.

Introduction

Because of its roles in cognition and regulation of the hypothalamic–pituitary–adrenal (HPA) axis, the hippocampus is one of several limbic structures that has been extensively studied in individuals with major depressive disorder (MDD). Based on preclinical studies, several mechanisms, including dendritic retraction, neuronal death and suppressed adult neurogenesis, all apparently due to elevated levels of glucocorticoids, have been suggested as major causative factors in hippocampal shrinkage.[1,2] Magnetic resonance imaging (MRI) studies involving patients with MDD have consistently shown bilateral and unilateral reductions in hippocampal volume relative to healthy controls,[3,4] and such reductions have been associated with episode recurrence,[5] history of childhood maltreatment[6] and deficits in visual and verbal memory performance in depressed people.[7] Only a few MRI studies have analyzed the hippocampus in medication-free MDD patients,[5,8–10] whereas most studies have included patients receiving antidepressant treatment.[3,4]

The hippocampus contains anatomically and functionally different subregions[11] that are not uniformly affected by disease processes.[12–14] In recent years, MRI volumetric protocols have been introduced to segment the hippocampus into its anatomic parts (head, body and tail) and to include the tail in the calculation of total hippocampal volume.[15,16] Recent structural MRI studies have addressed the question of whether changes in the volume of specific hippocampal subregions may be associated with MDD. Maller and colleagues[12] reported reduced hippocampal tail volume in medicated MDD patients

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compared with healthy controls. Neumeister and colleagues[17] found reduced posterior and total hippocampal volume in remitted unmedicated MDD patients relative to controls. MacQueen and colleagues[18] reported that MDD patients who met the criteria for clinical remission at 8 weeks of treatment had larger pretreatment hippocampal body and tail volumes bilaterally compared with those not in remission. However, these studies did not analyze the 3 parts of the hippocampus separately and subdivided it into sections comprised of the tail and the rest of the hippocampus (body and head) or the head and the rest of the hippocampus (body and tail). Therefore, it remains unclear whether there are any differences in the relative vulnerabilities of the various hippocampal parts in MDD.

Our main goal was, therefore, to analyze changes in the hippocampus in MDD patients using a comprehensive and reliable 3-dimensional (3-D) tracing protocol that enables separate analysis of all hippocampal subregions[16] and to determine whether antidepressant treatment is associated with changes in hippocampal volume. Based on previous volumetric studies of the hippocampus in MDD, we hypothesized that depressed patients would show a reduction of hippocampal tail volume bilaterally compared with healthy controls. In addition, we hypothesized that medicated depressed patients would show changes in hippocampal volumes compared with unmedicated MDD patients and controls, although we had no a priori hypothesis about the localization of the findings. Finally, we examined potential clinical correlates of hippocampal parts volumes in MDD patients.

Methods

Participants

We recruited 39 patients with MDD (10 men, 29 women) with moderate or severe episodes of MDD according to DSM-IV criteria, and 34 healthy controls (7 men, 27 women). Participants were recruited via local notices and assessed by a clinical psychiatrist (N.C.) in the outpatient psychiatry department. We included patients with MDD who met the DSM-IV criteria for moderate or severe MDD on the basis of a full clinical assessment and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).[19] Sixteen of the MDD patients had received continuous antidepressant treatment for 6 months or more. The remaining 23 MDD patients had been medication free for 12 months or more. We used the Childhood Trauma Questionnaire[20] to assess sexual and physical abuse. We assessed depression symptom severity using the Hamilton Rating Scale for Depression (HAM-D)[21] and the Mood and Anxiety Symptom Questionnaire.[22]

We excluded MDD participants with mild depressive episodes, psychotic or atypical features, seasonal affective disorder, lifetime schizophrenia, bipolar disorder, alcohol or substance dependence, anorexia nervosa, antisocial or borderline personality disorder, predominately anxiety disorder, systemic corticosteroid use, significant medical or neurologic disease, pregnancy or lactation, obesity and the use of lithium or anticonvulsant mood stabilizers. We matched controls for age sex, education and smoking, and we included those who had no lifetime history of psychiatric disorders or reported psychosis or mood disorders in first-degree relatives.

We obtained written informed consent, and this study was approved by the University of Alberta Health Research Ethics Board.

MRI acquisition and data analysis

We acquired T_1-weighted 3-D magnetization-prepared rapid acquisition gradient echo (MPRAGE) images oriented perpendicular to the anterior–posterior commissure line at 1.5-T (Siemens Sonata) with the following parameters: repetition time 1800 ms, echo time 3.82 ms, TI 1100 ms, 1 average, flip angle 15º, field of view 256 mm, image matrix 256 × 256, 1.5-mm slice thickness, no gap, 128 coronal slices, scan time 9 minutes. Native spatial resolution was 1.5 mm × 1.0 mm × 1.0 mm, which was subsequently zero-filled to 1.5 mm × 0.5 mm × 0.5 mm. An experienced tracer (N.M.) outlined the regions of interest manually with a mouse-driven cursor using the interactive public domain software program Display (Montreal Neurological Institute), which displays all 3 planes simultaneously.

We also used the Display program for volumetric measurements of intracranial volume (ICV) following the protocol of Eritaia and colleagues.[23] The hippocampus was traced following a protocol for which a comprehensive description and illustrations have been previously reported.[16] Interrater (intrarater) intraclass correlations were 0.95 (0.88) for the hippocampal tail, 0.83 (0.93) for the hippocampal body, 0.95 (0.92) for the hippocampal head, 0.96 (0.86) for the total hippocampus and 0.98 (0.99) for ICV. The volumes of all hippocampal parts were normalized to individual ICVs using the following formula[24] for volume correction:

$$\text{Normalized hippocampus volume} = \frac{\text{raw hippocampus volume}}{\text{ICV}} \times 1000\,\text{mm}^3$$

Statistical analyses

We compared group characteristics and ICVs by analysis of variance (ANOVA) with the between-subject factors of age, group and sex. We analyzed volumetric data using ANOVA. Significant interactions were resolved by post-hoc analysis (Fisher least significant difference and Bonferroni correction). The significance level for ANOVA and post-hoc analysis was set at $p < 0.05$, 2-sided. We used the Spearman correlation coefficient to examine the relation between hippocampal volume and clinical variables; the p values for these correlations were not corrected for multiple comparisons.

Results

Characteristics of patients with MDD and healthy controls are shown in Table 1. Patients with MDD did not differ significantly from healthy controls with respect to demographic characteristics or ICV. There were also no significant differences in demographic characteristics or ICV between medicated MDD, unmedicated MDD and healthy controls (Table 1). Medicated and unmedicated MDD patients did not

differ in clinical variables ($p > 0.05$), except for their respective HAM-D scores, which were significantly higher for unmedicated MDD patients.

Patients with MDD (medicated and unmedicated patients together) showed significant reductions in the volume of the right hippocampus, hippocampal tail bilaterally and right hippocampal head compared with controls (Table 2, Table 3). There was no significant difference in the volume of the hippocampal body between these 2 groups.

A significant reduction in the volume of the hippocampal tail compared with controls was present bilaterally in unmedicated but not medicated MDD patients (Table 2, Table 3). However, medicated and unmedicated MDD patients did not differ in hippocampal tail volume. In contrast, medicated MDD patients had a significantly larger hippocampal body volume bilaterally compared with both healthy controls and unmedicated MDD patients (Table 2, Table 3). Compared with healthy controls, the volumes of the total right hippocampus and right hippocampal head were significantly smaller in unmedicated MDD patients but not in medicated patients, whereas there was no difference between both MDD groups.

Family history of MDD and HAM-D score did not influence hippocampal volume (all $p > 0.05$). Physical abuse was negatively correlated (all $p < 0.05$) with the volumes of the left and right hippocampal tail (Spearman correlation coefficient –0.3 for left hippocampal tail and –0.3 for the right hippocampal tail) and right hippocampal head (Spearman correlation coefficient –0.32).

Discussion

To our knowledge, this is the first volumetric MRI study to examine regional differences in all hippocampal parts in patients with MDD. In a sample of 39 MDD patients compared with 34 matched healthy controls, we found significant reductions in the volume of the right hippocampus, hippocampal tail bilaterally and right hippocampal head. Our results suggest that decreased volume of the hippocampal tail and head can be trait changes, whereas changes in the hippocampal body may be dependent on treatment. We found that long-term antidepressant treatment may affect hippocampal volume in patients with MDD and, therefore, can be neuroprotective.

The majority of volumetric MRI studies of the hippocampus in MDD patients have reported smaller hippocampal volume in MDD patients compared with healthy controls.[5,6,25–30] However, several studies did not report a significant difference between depressed patients and controls.[8,31–33] It also remains unclear if changes in the hippocampus are present since adolescence[29,34] or if they develop after multiple episodes of depression.[5]

Most of the MRI studies of the hippocampus in MDD have reported changes in global hippocampal volume.[3,4] More recent MRI studies emphasized the importance of hippocampal subdivisions and included the hippocampal tail in the total hippocampal volume. Neumeister and colleagues[17] found that the posterior part of the hippocampus (posterior to the hippocampus head [i.e., the hippocampal body and tail]) and total hip-

Table 1: Characteristics of controls and medicated and unmedicated patients with major depressive disorder

Characteristic	Controls, $n = 34$	MDD unmedicated, $n = 23$	MDD medicated, $n = 16$	p value*		
				Controls v. MDD unmedicated	Controls v. MDD medicated	MDD unmedicated v. MDD medicated
Age, yr, mean (SD)	33.5 (8.1)	35.7 (8.5)	32.2 (7.8)	0.33	0.59	0.20
Education, yr, mean (SD)	14.6 (1.4)	14.4 (1.9)	14.9 (1.5)	0.73	0.52	0.43
Female, no. (%) of participants	27 (79)	15 (65)	14 (88)	0.23	0.70	0.15
Caucasian, no. (%) of participants	29 (85)	18 (78)	15 (94)	0.50	0.65	0.37
Smoker, no. (%) of participants	4 (12)	5 (22)	2 (13)	0.46	0.99	0.68
Childhood Trauma Questionnaire,[20] median (quartile) score						
Total	30 (25–34)	47 (39–59)	57 (39–69)	< 0.001	< 0.001	0.24
Physical abuse	5 (5–7)	6 (5–9)	6 (5–7)	0.09	0.04	0.72
Sexual abuse	5 (5–5)	7 (5–11)	6 (5–15)	0.001	0.001	0.92
Emotional abuse	5 (5–8)	10 (7–16)	16 (7–21)	0.001	< 0.001	0.12
Emotional neglect	7 (5–9)	14 (9–17)	14 (9–21)	< 0.001	0.001	0.62
Physical neglect	5 (5–7)	8 (6–9)	8 (6–11)	< 0.001	0.002	0.86
Hamilton Rating Scale for Depression,[21] mean (SD) score	—	22.0 (3.6)	18.3 (6.8)			0.03
Mood and Anxiety Symptoms Questionnaire, short form,[22] mean (SD) score						
Anhedonic depression	54 (11)	87 (8)	84 (12)	< 0.001	< 0.001	0.35
General distress	26 (7)	62 (13)	62 (18)	< 0.001	< 0.001	0.97
Somatic anxiety	25 (4)	39 (12)	45 (14)	< 0.001	< 0.001	0.19
Age at onset, mean (SD) yr	—	25.9 (9.7)	22.3 (8.8)			0.25
≥ 3 episodes, no. (%) of participants	—	14 (61)	8 (50)			0.73
Family history of pure MDD, no. (%) of participants	—	8 (36)	10 (63)			0.20

MDD = major depressive disorder; SD = standard deviation.
*Calculated by t test, χ^2 or Fisher exact tests, or the Mann–Whitney U test.

pocampal volume were smaller bilaterally in both drug-naive (n = 8) and previously medicated (n = 23) patients with recurrent MDD. Maller and colleagues,[12] with a sample of 45 treatment-resistant MDD patients, found that hippocampal atrophy was limited primarily to the tail. Furthermore, these authors suggested that the hippocampal tail was the only section affected in women. In contrast, in men, they found that the part of the hippocampus anterior to the tail (hippocampal body and head) was also affected along with the tail. However, their sample did not include unmedicated patients, and the authors did not analyze the hippocampal body and head separately.

In a study using voxel-based morphometry, de Geus and colleagues[34] reported volume reduction in the left posterior hippocampal region in participants at high risk of anxiety and depression. In addition, Szeszko and colleagues[35] found that in healthy participants, stress correlated significantly more strongly with the volume of the anterior hippocampus than with that of the posterior hippocampus. Posener and colleagues,[8] using high-dimensional brain mapping, found that MDD patients and healthy controls did not differ in total hippocampal volume. However, the authors reported specific patterns of hippocampal surface deformation in MDD patients, which is in agreement with the results of our study. They showed that the most prominent inward deformation of hippocampal shape was located in the hippocampal head (asymmetrically more profound on the right side) and tail. This corresponds well with our findings of volume reduction in those subregions. Furthermore, the most prominent outward deformation of hippocampal shape was in the hippocampal body (both sides). These findings are also in agreement with our results showing increased hippocampal body volume in medicated MDD patients. Vythilingam and colleagues[9] did not find significant differences in the volume of hippocampal parts between patients with untreated MDD and healthy controls. However, the authors reported reliability results only for total hippocampal volume but not for the hippocampal parts.

Table 2: Hippocampal volumes in patients with major depressive disorder and controls

Hippocampal region	Group; mean (SD) normalized volume, mm^3			
	MDD, n = 39	MDD unmedicated, n = 23	MDD medicated, n = 16	Controls, n = 34
Tail				
Left	520 (107)	507 (116)	538 (95)	578 (91)
Right	532 (119)	524 (130)	543 (103)	601 (78)
Body				
Left	765 (126)	724 (117)	823 (119)	739 (126)
Right	795 (140)	750 (135)	859 (125)	756 (129)
Head				
Left	1463 (228)	1476 (267)	1443 (161)	1481 (191)
Right	1503 (206)	1498 (242)	1510 (146)	1625 (207)
Total				
Left	2747 (297)	2707 (344)	2805 (211)	2798 (257)
Right	2829 (312)	2772 (349)	2912 (236)	2982 (244)
Intracranial volume, cm^3	1402 (127)	1419 (137)	1378 (233)	1382 (123)

MDD = major depressive disorder; SD = standard deviation.

Because stressful life events are associated with an increased risk of depression, preclinical studies in which animals are exposed to chronic stress have been used to understand hippocampal changes in depressed patients. In both rats and primates, the cornu ammonis (CA) subfields of the hippocampus, particularly CA3 pyramidal cells, have been found to be the cells most vulnerable to neuronal damage and cell loss associated with prolonged social stress and glucocorticoid overexposure.[1,36] However, glucocorticoid-induced neuronal damage of the hippocampus has not yet been confirmed in human postmortem brain tissue from severely depressed patients. Lucassen and colleagues[37] suggested that, in human postmortem tissue, hippocampal apoptosis in major depression was a minor event and was absent from the CA3 region of the hippocampal pyramidal cell layer. The authors also found that cells undergoing apoptotic death were localized in the hippocampal areas CA1, CA4 and the entorhinal cortex but were absent in the CA3 area.

The largest postmortem study to date[38] reported reduced thickness of the CA and dentate gyrus subfield layers, together with increased densities of the cell bodies of granule cells and glia in the dentate gyrus and of pyramidal neurons and glia in all CA regions, and decreased average cell body size of the pyramidal neurons. Because structural changes in hippocampal subfields have not been examined in volumetric MRI studies of MDD patients owing to the limited spatial resolution of conventional MRI, it is difficult to predict which hippocampal subfield is responsible for hippocampal volume reduction in MDD patients. Our recent study of hippocampal subfields in healthy participants found that the differences in vulnerability of hippocampal parts might be explained by their different structural organization.[39] We reported that the hippocampal head and tail have the largest proportion of the

Table 3: Comparison of hippocampal volume in medicated and unmedicated patients with major depressive disorder and controls

Hippocampal region	MDD v. controls		MDD unmedicated v. controls		MDD medicated v. controls		MDD unmedicated v. MDD medicated	
	$F_{1,71}$	p*	p†	p‡	p†	p‡	p†	p‡
Tail								
Left	6.27	0.015	0.010	0.02	0.19	0.57	0.33	0.99
Right	8.49	0.005	0.007	0.02	0.06	0.19	0.56	1.0
Body								
Left	0.74	0.39	0.64	1.0	0.02	0.07	0.01	0.04
Right	1.48	0.22	0.86	1.0	0.01	0.03	0.01	0.03
Head								
Left	0.13	0.71	0.93	1.0	0.56	1.0	0.63	1.0
Right	6.31	0.01	0.02	0.08	0.07	0.22	0.85	1.0
Total								
Left	0.61	0.43	0.22	0.68	0.93	1.0	0.28	0.85
Right	5.30	0.02	0.007	0.02	0.40	1.0	0.13	0.39
Intracranial volume, cm^3	0.43	0.51	0.28	0.86	0.89	0.86	0.31	0.86

MDD = major depressive disorder.
*Analysis of variance.
†Fisher least significant difference test.
‡Bonferroni correction.

CA, and, therefore, processes that preferentially affect the CA may have a greater impact on the hippocampal head and tail. In addition, since the hippocampal body has the largest part of the dentate gyrus and the highest ratio of dentate gyrus to CA, we speculated that it also plays a major role in hippocampal neurogenesis. However, the most convincing evidence for glucocorticoid-induced atrophy of CA subfields or alterations in the dentate gyrus would come from visualization of these structures directly in MDD patients.

A growing number of preclinical studies have shown that, in both acute and chronic stress paradigms and various animal models of depression, adult hippocampal neurogenesis was suppressed.[40–42] Chronic, but not acute, treatment with several types of antidepressants reverses stress-induced suppression, increases hippocampal neurogenesis and blocks the effects of stress.[40,43–45] Although the neurogenic effects of antidepressant treatment have been well established in rodents, there are very few studies to date showing the same effects in humans.[46] A recent postmortem study[47] reported that MDD patients who took selective serotonin reuptake inhibitors (SSRIs) had more neural progenitor cells in the dentate gyrus than untreated MDD patients and controls. Furthermore, the number of dividing cells was greater in MDD patients treated with tricyclic antidepressants than in untreated MDD, SSRI-treated MDD and controls. In addition, treated MDD patients had a larger dentate gyrus volume compared with untreated MDD or controls. Only a few MRI studies have analyzed the hippocampus in medication-free patients with MDD, whereas most studies have included patients taking antidepressants.[3,4] Increased global hippocampal volume during antidepressant treatment has only emerged following 3 years[10] and not at 1-year follow-up.[5,9] Furthermore, lower hippocampal volumes have predicted a lower response rate to antidepressant treatment. MacQueen and colleagues[18] found that MDD patients who met the criteria for clinical remission at 8 weeks of treatment had larger pretreatment hippocampal body or tail volumes bilaterally compared with those who were not in remission. This difference was not apparent in either the right or left hippocampal head.

Although functional and receptor measures show relatively short-term changes with antidepressant treatment, positron emission tomography studies in MDD have revealed increased blood flow to the hippocampus in unmedicated MDD patients and that hippocampal metabolism was normalized after successful antidepressant treatment.[48,49] Other studies[50,51] found significant reductions in serotonin receptor binding potential in the hippocampus that was more prominent in unmedicated MDD patients. Frodl and colleagues[52] reported that MDD patients with the L/L homozygous phenotype of the serotonin transporter gene had significantly smaller hippocampal grey matter. Vakili and colleagues[31] found that women with MDD who responded to SSRIs therapy had statistically significant larger right hippocampal volumes than nonresponders. In their prospective study, Vythilingam and colleagues[9] reported no significant differences between untreated patients with MDD and healthy controls and that successful antidepressant treatment (7 mo) did not change hippocampal volume or memory deficits related to depression.

Few studies have included unmedicated MDD patients in their sample, which might explain why many studies involving medicated MDD patients did not report any changes in hippocampal volume associated with depression. For example, only 6 published MRI studies out of 36 included MDD patients who were medication-free for periods of 2–6 weeks before scanning.[4] Because a systematic examination of differences in hippocampal volume among MDD patients who did and did not receive pharmacotherapy was not possible in this meta-analysis,[4] it is currently unknown whether medication status can affect differences in hippocampal volume. Our results suggest that future MRI studies of the hippocampus in MDD should control for treatment effects on hippocampal subdivisions.

We did not find any correlation between hippocampal volume reduction and severity of depression, which is in agreement with previous studies.[28,30,53] In contrast, Caetano and colleagues[33] did not find differences in hippocampal volume between MDD patients and controls, but they reported that currently depressed patients had smaller hippocampal volumes as remitted MDD patients. In our sample, family history of MDD did not influence hippocampal volumes. However, physical abuse was negatively correlated with the volume of the hippocampal tail bilaterally and the right hippocampal head. Increasing evidence suggests that adult stressors and adverse childhood experiences including maltreatment, abuse, neglect and social isolation increase the risk of adult major depressive disorder.[54–56] Furthermore, early maltreatment also predicts low hippocampal volume:[6,57] this might result from stress during development, altered HPA axis reactivity or more frequent adult trauma and episode recurrence in this population.[58]

The findings of our study are in agreement with those of Vythilingam and colleagues,[6] who reported that depressed patients with childhood abuse had smaller left hippocampal volumes than nonabused depressed patients and healthy controls. However, it remains unclear whether stress exposure during early development or during recurrent depressive episodes in adulthood leads to low hippocampal volume in MDD. An absence of hippocampal volume reduction in pediatric MDD was confirmed in 2 previous studies[59,60] but not in another study that reported significantly smaller hippocampal volume in this population.[61] In adults with MDD, episode recurrence predicted low hippocampal volume,[4] which declined over 3 years in the absence of sustained remission.[10]

Previous studies[4] found no evidence that the presence of comorbidity contributed to differences in hippocampal volume. Because we excluded MDD patients with comorbid disorders, we cannot predict how the presence or absence of comorbidity affects hippocampal volume in MDD patients.

Limitations

A limitation of our study was the small number of male participants. Excluding MDD patients with psychiatric comorbidities may result in bias and problems in generalizing the results. Therefore, additional adequately powered studies are required to determine the effects of sex and comorbidity on hippocampal structures. It was not determined whether the reported

volume differences were associated with differences in cognitive or affective functions. This study was cross-sectional and therefore further longitudinal studies are needed to determine the direct effect of antidepressant treatment on hippocampal volume. Although our study did not examine the relation between cortisol level and hippocampal volume, it still remains one of the major theories that may explain shrinkage of the hippocampus in MDD.

Conclusion

Our study showed that decreased hippocampal tail and hippocampal head volumes could be trait changes, whereas hippocampal body changes may be dependent on treatment. We found that long-term antidepressant use may affect hippocampal volume in patients with MDD.

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