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A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder

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Background: Some, although not all, studies report small hippocampal volume in patients with major depressive disorder (MDD) relative to healthy controls. Here, we explore the contribution of key demographic and clinical variables to this difference. **Methods:** We used meta-analytic techniques to provide an updated analysis of data from 32 magnetic resonance imaging studies of hippocampal volume in patients with MDD. **Results:** Our analysis confirmed the difference in hippocampal volume, but only among patients with MDD whose duration of illness was longer than 2 years or who had more than 1 disease episode. We found no such effect in studies that included patients who did not fit these criteria. The effect was limited to children and middle-aged or older adults. Analyzed collectively, studies including young adult patients showed equivalent hippocampal volumes across MDD patients and controls, a result that may be attributable to a reduced burden of illness in this population. Age at onset of disease, severity of depression at the time of scanning, sex and slice thickness did not contribute to differences in hippocampal volume between patients with MDD and controls. **Limitations:** The small size of many of the clinical and demographic subgroups may have limited statistical power to detect between-group differences. **Conclusion:** Although all studies were cross-sectional, our results suggest that hippocampal volume reductions generally occur after disease onset in patients with MDD. These findings have implications for the timing of clinical interventions aimed at reducing the impact of MDD on neuronal structure and function.

Contexte : Certaines études, mais pas toutes, signalent que le volume de l'hippocampe est plus petit chez les patients atteints de syndrome dépressif majeur (SDM) que chez les témoins en bonne santé. Nous explorons ici la contribution à cette différence de variables démographiques et cliniques clés. **Méthodes :** Nous avons utilisé des techniques méta-analytiques pour effectuer une synthèse à jour des données de 32 études ayant mesuré le volume de l'hippocampe chez des patients atteints de SDM au moyen de l'imagerie par résonance magnétique. **Résultats :** Notre analyse a confirmé la différence de volume de l'hippocampe, mais uniquement chez les patients qui souffraient de SDM depuis plus de 2 ans, ou qui avaient présenté plus d'un épisode de la maladie. Nous n'avons pas observé d'effets semblables dans les études qui incluaient des patients ne répondant pas à ces critères. L'effet a semblé se limiter aux enfants et aux adultes d'âge moyen ou plus avancé. Regroupées aux fins de l'analyse, les études incluant des patients adultes moins âgés ont fait état de volumes hippocampiques équivalents chez les patients souffrant de SDM et les témoins, un résultat potentiellement attribuable au fardeau moins lourd de la maladie chez cette population. Le sexe du patient, son âge lors du déclenchement de la maladie, la gravité de la dépression au moment de l'épreuve d'imagerie et l'épaisseur des coupes n'ont pas influé sur les différences de volume hippocampique entre les patients atteints de SDM et les témoins. **Limites :** Le petit échantillon de plusieurs des sous-groupes cliniques et démographiques peut avoir réduit la puissance statistique et empêché la détection des différences entre les groupes. **Conclusion :** Même s'il s'agissait dans tous les cas d'études transversales, nos résultats indiquent qu'une diminution du volume de l'hippocampe survient généralement après le déclenchement de la maladie chez les patients atteints de SDM. De telles observations ont une incidence sur le moment choisi pour intervenir cliniquement dans le but d'atténuer l'impact du SDM sur la structure et la fonction neuronales.

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Introduction

A number of factors implicate the hippocampus in the pathogenesis of major depressive disorder (MDD), including the fact that the hippocampus is a highly stress-sensitive brain region[1] and that MDD is a highly stress-sensitive illness.[2] Preclinical studies suggest that stress can result in structural changes to the hippocampus[3–5] and that effective antidepressant therapy may mitigate stress-associated changes in the hippocampus.[6–12] A previous analysis examining performance on an array of cognitive domains found that, compared with controls, patients with MDD were most impaired on measures of memory dependent on the hippocampus.[13] Two previous meta-analyses examining magnetic resonance imaging (MRI) volumetric studies in patients with MDD concluded that the hippocampus is smaller bilaterally in people with MDD than in age- and sex-matched controls.[14,15] Although these meta-analyses were consistent in their conclusions, neither group was able to identify demographic and clinical variables that predict small hippocampus volumes, although Videbech and Ravnkilde[15] did report an association between the total number of depressive episodes and right, but not left, hippocampus volume. These meta-analyses were restricted to the 12 studies published before 2004. Since then, more than 20 studies have been published, bringing the total number of patients with MDD and controls scanned to more than 2000 people, with many studies now reporting on clinically relevant variables that may impact hippocampus volume.

Important inconsistencies exist with respect to the relation between clinical variables (e.g., age at illness onset, duration of illness) and reductions in hippocampus volume. For example, some studies report no relations between hippocampus volumes and age at onset of illness.[16–21] A similar absence of association between illness burden and hippocampus volume characterizes other investigations.[16,18–20,22–29] These findings do not support the idea that small hippocampus volume in patients with MDD results from a long duration of depression.[9,30] Other studies, however, report that smaller hippocampus volumes have been linked to severity of depression,[31,32] age at onset of illness,[22,23,33–35] nonresponsiveness to treatment,[16,32,36] untreated days of illness,[17] illness burden,[9,30,37,38] history of childhood abuse[39] and level of anxiety.[40,41] There is also evidence of an association between small hippocampus volume and polymorphisms in the serotonin (5-HT) transporter gene 5-HTTLPR[34] and in the brain-derived neurotrophic factor gene at position 66 (Val66Met[25]).

In addition to the 12 studies included in previous meta-analyses, we reviewed 20 studies published after 2004 to determine whether key clinical variables such as illness burden and treatment responsiveness are associated with hippocampus volumes in patients with MDD. Meta-analyses published before 2004 showed that factors related to MRI acquisition (e.g., slice thickness) influence the pattern of results. We focussed on examining clinical and demographic factors that may be associated with hippocampus volume in patients with MDD, although we briefly examined factors related to MRI acquisition.

Methods

We searched MEDLINE for listings published between August 1960 and June 2007 using the medical subject headings "depression," "major depressive disorder," "unipolar depression," "MRI," "magnetic resonance imaging" and "hippocampus." We also performed a free text search on the keywords "depression," "MRI" and "hippocampus" and reviewed cited references in articles or review papers concerning hippocampus volume in patients with MDD.

We included studies if the patient population had a primary diagnosis of MDD according to recognized criteria, if hippocampus volume was a dependent variable, if MRI analysis was used to assess hippocampus volume, if volume measurements were not combined with structures and if healthy controls were included in the study. In studies where authors divided their patient populations into groups, we retained those divisions in our analysis. In studies where data were reported in combination, authors provided data for each group on request.

Data abstraction

A review of the literature identified several demographic and clinical variables that may impact hippocampus volumes and for which sufficient data were available to conduct analyses. To examine the impact of patient age on hippocampus volume both at the time of scanning and at onset of illness, we divided data into the following 4 age categories. We classified patients as children if they were aged 18 years or younger at the time of scanning (3 studies) or at onset of illness (4 studies). Young adults referred to patients aged 18–33 years at the time of scanning (6 studies) or at onset of illness (10 studies). Middle-aged adults were patients aged 34–64 years at the time of scanning (23 studies) or at onset of illness (10 studies). We classified patients as older adults if they were aged 65 years or older at the time of scanning (6 studies) or at onset of illness (insufficient data, 2 studies). To examine the effect of illness duration, we divided data into the following durations: brief (≤ 2 yr, 4 studies), moderate (2–9 yr, 13 studies) and chronic (≥ 10 yr, 10 studies). To examine the effects of number of illness episodes, we divided data as follows: first episode (1 episode, 4 studies), moderate number of episodes (2–4 episodes, 10 studies) and high number of episodes (≥ 5 episodes, 6 studies). To examine the effect of illness severity at the time of scanning, we divided data into 2 categories: euthymic or mild illness (6 studies) and moderate to severe illness (21 studies). Finally, there were 9 study groups in which the MDD and control groups comprised only women, allowing us to form a partial examination of whether sex impacts hippocampus volume in MDD.

Our demographic and clinical variables, therefore, included patient age at the time of scanning, patient age at onset of illness, duration of illness, number of episodes, severity of illness and sex. In cases where data related to these parameters were not provided, we either contacted study authors and asked them to provide additional information or calculated values from information already presented (e.g., in some

cases, we calculated mean duration of illness by subtracting mean age at onset of illness from mean patient age at time of scanning). When neither approach proved fruitful, we excluded data from the relevant subanalysis categories.

To examine the impact of slice thickness of MRI acquisitions, we divided data into thin slices (≤ 1.5 mm, 25 studies) and thick slices (> 1.5 mm, 5 studies).

Statistical analysis

We performed χ^2 analyses to determine whether these studies were equally distributed across each of the subgroups forming the clinical analysis variables. Although the inter-rater reliability coefficients for volumetric measurement ranged from 0.69 to 0.99, there was insufficient variability between studies to perform a principled analysis of the effects of this variable.

We performed the Egger regression test ($\alpha = 0.05$, 2-tailed) to measure funnel plot asymmetry and the risk of a publication bias in the aggregate data.[42] We analyzed left and right hippocampus volume measurements independently. We pooled standard deviations (SDs) within studies and calculated *z* scores for all studies in an aggregate analysis that weighted each study by sample size. We summed the *z* scores for each analysis and tested them for significance using a confidence level of 95%.

We repeated this procedure for each of the demographic and clinical variables. To determine whether significant between-group differences emerged between the subgroups of these variables, we examined confidence intervals (CIs) following the assumption that samples with nonoverlapping 95% CIs differ significantly at $p < 0.05$.[43]

We performed the omnibus analysis after removing studies that reported data for patients with bipolar disorder[22,44,45] or patients with a psychiatric diagnosis comorbid to MDD, including generalized anxiety disorder,[26,39] posttraumatic stress disorder,[39] social phobia,[26,39] specific phobia,[39,40] panic disorder,[39,46] obsessive–compulsive disorder,[39] somatoform disorder,[39] substance abuse or dependency,[38,46,47] oppositional defiant disorder[38] or concurrent axis II disorder.[48] We included the study by MacMillan and colleagues[24] in this group because mean anxiety levels in MDD participants in this study fell just below the clinical threshold. We also excluded studies with patients who had previously received electroconvulsive shock therapy, as noted by the study authors.[9,23,28,37,44,48] Excluding these patients from the aggregate findings did not alter our overall pattern of results, so the subanalyses included patients from these studies.

Results

Literature search and study selection

Our search returned 47 scientific papers; 36 met our inclusion criteria. Five papers combined volume measurements with structures and were thus excluded. In 4 of these studies, hippocampus measurements were reported in combination with amygdala measurements,[49–52] and in 1,[53] the hippocampus was measured in combination with the parahippocampal gyrus. One additional study[54] combined volume measurements with structures and did not include controls. Two papers relied on voxel-based morphometry analysis;[55,56] because this method has not been shown to identify hippocampus boundaries reliably, we excluded these papers. Finally, we excluded 3 additional papers[36,57,58] because they did not include healthy controls.

Of the 36 papers selected, 1 did not provide measurement data for hippocampus volumes and was thus excluded.[21] Sheline and colleagues[30] included the patient group from a previous study performed in 1996 in their 1999 study;[9] we excluded the 1996 study from our analysis. In studies where left and right hippocampus volumes were combined and reported as total hippocampus volume,[25,33,48,59] we contacted study authors and requested measurement data for the left and right hippocampus. In 1 case, these data were unavailable for our analysis, so we excluded that study.[33] We retained 32 papers for use in our meta-analysis.

Study characteristics

The authors of 6 papers divided their patient populations into 2 groups, and we retained that division for our analysis. Vythilingam and colleagues[39] compared depressed patients with and without a history of abuse to healthy controls. MacQueen and colleagues[37] compared patients experiencing a first episode of depression with patients experiencing a recurrent episode, and Monkul and colleagues[20] compared suicidal and nonsuicidal female patients. Two studies compared patients with early- and late-onset depression to healthy controls.[23,34] Frodl and colleagues[25] reported data for patients experiencing a first episode and patients experiencing recurrent episodes in combination. On request, they provided data for each group.

Our aggregate analysis included a total of 1167 patients and 1088 controls. Clinical and demographic characteristics of participants are summarized in Table 1. The mean age of patient groups scanned in each study varied widely, ranging from a group mean of 13.7 (SD 2.7) years in a pediatric population[24] to 75.1 (SD 5.8) years in patients with late-onset MDD.[23] Only 6 studies included patients who were medication-free for periods of 2–6 weeks before scanning.[20–22,31,37,40] One study included a group of never-treated first-episode patients who began treatment no more than 4 weeks before scanning.[37] A summary of the medication status of all patient groups can be found in Table 1. There was no evidence of publication bias; results of the Egger regression test for publication bias were not significant for the left ($p = 0.84$) or right hippocampus ($p = 0.63$).

Two papers included a small subset of patients for whom data were reported previously as part of a larger cohort.[17,48] Given that removal of these studies did not alter the overall pattern of our results and that each contributed important information on the clinical and demographic characteristics of the subsamples, we retained these data for analysis. MRI parameters are shown in Table 2. Slice thickness varied between 1.0 and 5.0 mm.

Table 1: Demographic and clinical characteristics of study participants (part 1 of 2)

Study	Population sample	No. of patients (sex, M/F)	Characteristic; mean (SD)*						Medication status
			Age, yr	Age at onset, yr	Illness duration	No. of previous episodes	Depression		
							Test	Score	
Sheline et al.[9]	Women w/history of recurrent MDD	24 pts 24 controls	52.8 (18.4) 52.8 (17.8)	—	Mean no. lifetime d depressed: 1058 (1032)	4.8	HAM-D	5.9 (4.8)	• 16 taking antidepressants
Bremner et al.[46]	Pts w/MDD in remission	16 pts (10/6) 16 controls (10/6)	43.0 (8.0) 45.0 (10.0)	—	—	2.0 (3.0)	—		• All taking medications
Mervaala et al.[44]	Drug-resistant inpatients w/MDD	34 pts (16/18) 17 controls (6/11)	42.2 (12.2) 42.1 (14.6)	39.6	31.0 mo	—	HAM-D	30.6	• All taking medications
Steffens et al.[35]	Elderly pts w/MDD	66 pts (15/51) 18 controls (9/9)	71.7 (8.4) 67.1 (5.0)	EOD pts: 25.6 LOD pts: 65.2	—	—	HAM-D	24.9 (5.8)	—
Vakili et al.[32]	Adult pts w/MDD	38 pts (17/21) 20 controls (9/11)	38.5 (10.0) 40.3 (10.4)	—	—	—	HAM-D17	Baseline ≥ 16.0	• All taking fluoxetine treatment for 8 wk
Von Gunten et al.[45]	Nondemented depressed pts w/memory complaints	14 pts (6/8) 14 controls (6/8)	57.6 (9.4) 58.1	51.0 (9.3)	6.4 (3.7) yr	—	—		• 11 taking medications
Rusch et al.[40]	Adult pts w/MDD	25 pts (10/15) 15 controls (6/9)	33.2 (9.5) 37.4 (14.4)	—	—	—	HAM-D17	19.4 (4.4)	• All were medication-free for at least 4 wk immediately preceding the study
Frodl et al.[19]	Adult pts w/FE	30 pts (13/17) 30 controls (13/17)	40.3 (12.6) 40.6 (12.5)	40.0 (12.5)	0.7 (0.9) yr	CE	HAM-D21	24.8 (5.2)	—
Vythilingam et al.[39]	Women w/current MDD with or without a history of childhood sexual/physical abuse	32 pts 21 w/history of childhood abuse 11 w/no such history 14 controls	33.0 (6.0) 34.0 (8.0) 27.0 (5.0)	—	—	—	HAM-D17	 18.0 (6.0) 19.0 (2.0)	• All were free of psychotropic medication at the time of the study
MacMillan et al.[24]	Psychotropic drug-naïve pediatric pts w/MDD	23 pts (10/13) 23 controls (10/13)	M 13.8 (2.7) F 14.2 (1.8)	11.8 (3.1)	2.2 yr	—	CDRS-R	57.0 (8.3)	—
MacQueen et al.[37]	Adult pts w/MDD	20 FE pts (7/13) 20 controls (7/13) 17 ME pts (6/11) 17 controls (6/11)	28.4 (11.8) 28.4 (11.5) 35.9 (11.1) 36.2 (11.9)	26.3 (12.0) 24.9 (11.6)	2.1 yr 10.0 yr	CE 6.0 (6.0)	HAM-D21	19.1 (4.5) 17.5 (6.0)	• FE: All were medication-naive (antidepressant medication was initiated at a maximum of 4 wk prescanning) • ME: All received at least a trial of an SSRI with an average of 3 trials of medication per patient
Posener et al.[29]	Adult pts w/MDD	27 pts (12/15) 42 controls (19/23)	33.0 (10.7) 33.2 (10.8)	—	Mean no. lifetime mo depressed: 98.8 (143.4) mo	0.8 (1.2)	HAM-D21	27.3 (5.2)	• 14 taking psychiatric medications; 13 medication-free
Sheline et al.[17]	Remitted adult outpatients w/MDD; all women	38 pts 38 controls	50.8 (17.1) Matched	—	Mean no. lifetime d depressed: 1341 (1096)	5.4	HAM-D17	6.7 (4.7)	• Mean of no. of days untreated was 824 (834) d and treated with antidepressants was 517 (606) d
Caetano et al.[47]	Adult pts w/remitted and current MDD§	31 pts (7/24) 31 controls (7/24)	39.2 (11.9) 36.7 (10.7)	27.9 (11.8)	11.4 (10.8) yr	5.1 (6.1)	HAM-D	11.8 (5.6)	• All were medication-free for at least 2 wk immediately preceding the study; 5 had taken antipsychotics in the past
Frodl et al.[16]	Adult pts w/MDD	30 pts (12/18) 18 remitted (7/11) 12 nonremitted (5/7) 30 controls (12/18)	48.4 (13.4) 46.4 (15.4) 51.3 (9.6) 45.7 (12.9)	39.3 (13.4) 36.5 (15.5) 43.5 (8.3)	9.1 (10.2) yr 9.9 (11.5) yr 7.8 (8.2) yr	—	HAM-D17	23.7 (6.9) 24.7 (7.0) 22.2 (6.7)	• 8 taking tricylic antidepressants; 9 on SSRIs; 11 on new antidepressants; 7 on lithium; 2 medication-free at baseline
Janssen et al.[27]	Middle aged and older women w/EOD	28 pts 41 controls	64.0 (10.9) 62.4 (11.4)	33.0 (9.5)	93.5 (17.5) mo	—	MADRS	18.3 (13.0)	• 22 taking psychotropic medication
Lange et al[61]	Inpatients w/MDD; all women	17 pts 17 controls	34.0 (10.0) 32.0 (6.0)	29.0 (10.0)	5.0 (5.0) yr	2.0 (1.0)	HAM-D	22.0 (4.0)	• All taking antidepressant medication

Table 1: Demographic and clinical characteristics of study participants (part 2 of 2)

Study	Population sample	No. of patients (sex, M/F)	Characteristic; mean (SD)*						Medication status
			Age, yr	Age at onset, yr	Illness duration	No. of previous episodes	Depression		
							Test	Score	
Lloyd et al.[23]	Older pts w/MDD	51 pts (10/41)	74.0 (6.3)				MADRS	30.5 (7.2)	• Majority taking medication
		23 EOD pts (1/22)	72.7 (6.7)	38.7	34.0 yr	5.1 (95% CI 3.7–6.6)			
		28 LOD pts (9/19)	75.1 (5.8)	72.0	3.1 yr	2.0 (95% CI 1.4–2.5)			
		39 controls (10/29)	73.1 (6.7)						
MacMaster et al[38]	Adolescent pts w/MDD	17 pts (8/9)	16.7 (1.8)	14.1 (2.0)	2.9 (1.7) yr	—	CDRS	65.4 (13.9)	• 3 recently started medication; 14 treatment-naïve
		17 controls (8/9)	16.2 (1.6)						
OBrien et al.[28]	Pts w/MDD over 60 yr	61 pts (13/48)	73.9 (6.7)	56.8 (19.2)	17.2 yr	2.2 (2.7)	MADRS	30.7 (7.1)	• 51 taking medications; 7 on lithium
		40 controls (10/30)	73.3 (6.7)						
Vythilingam et al.[26]	Medication-free nonelderly depressed outpatients	38 pts (15/23)	41.0 (11.0)	25.0 (12.0)	16.0 yr	2.0 (2.0)	Yale Depression Inventory	34.0 (7.0)	• 15 medication-free; 23 free of antidepressant medications for at least 6 wk • Mean duration of antidepressant treatment was 7 (3) mo
		33 controls (12/21)	34.0 (10.0)						
Xia et al.[62]	Adult pts w/MDD	22 pts (12/10)	39.5 (12.4)	36.0	1293 (1067) d	—	HAM-D17	21.4 (7.2)	—
		13 controls (5/8)	35.4 (8.9)						
Hickie et al.[22]	Adult pts w/MDD	66 pts (22/44)	53.5 (13.5)	38.4 (16.3)	15.0 (15.8) yr	—	HAM-D21	24.9 (9.2)	—
		20 controls (9/11)	55.8 (10.0)						
Neumeister et al.[59]	Adult pts w/recurrent MDD in full remission and unmedicated	31 pts (8/23)	40.1 (13.1)	24.6 (10.3)	15.5 yr	3.2 (2.1)	HAM-D	1.3 (1.4)	• 8 medication-free; 23 had a treatment history with psychotropic medications
		57 controls (21/36)	38.0 (10.9)						
Taylor et al.[34]	Elderly pts ≥ 60 yr w/MDD	135 pts (45/90)	70.1 (7.3)	46.9 (21.0)		—	MADRS	26.5 (7.4)	—
		72 w/EOD (21/51)	68.7 (6.4)	30.2 (12.8)	38.2 yr			25.4 (7.4)	
		63 w/LOD (24/39)	71.5 (7.9)	70.0 (8.7)	1.5 yr			26.7 (6.8)	
		83 controls (19/64)	69.4 (6.3)						
Frodl et al.[18]	Inpatients w/a previous or current episode of MDD	34 pts (19/15)	45.5 (11.9)	38.8 (12.4)	6.8 (8.8) yr	—	HAM-D21	24.8 (5.2)	• 31 taking antidepressants; 4 taking neuroleptics; 3 medication-free
		34 controls (19/15)	43.6 (13.2)						
Saylam et al.[31]	Drug-free pts w/MDD	24 pts (6/18)	33.4 (9.3)	—	54.4 (56.7) wk	1.7 (0.6)	HAM-D17	24.4 (5)	• All were medication-free for at least 4 wk immediately preceding the study • 11 had their first episode and were drug-free. Other patients were free of psychotropic drugs (including anxiolytics) for a mean of 33.6 d
		24 controls (6/18)	30.2 (6.1)						
Weniger et al.[41]	Adult pts w/recent-onset MDD; all women	21 pts (0/21)	34.0 (9.0)	28.0 (10.0)	5.0 (6.0) yr	1.4 (0.6)	HAM-D	23.0 (5.0)	• All were taking antidepressants • Lifetime antidepressant medication 124 (125) (no. of defined daily dose)
		23 controls (0/23)	32.0 (7.0)						
Frodl et al.[25]†	Inpatients w/MDD	30 FE pts (14/16)	41.0 (12.8)	37.7 (11.7)‡	6.7 (8.7) yr‡	CE	HAM-D21	23.0 (6.3)‡	• 17 taking SSRIs; 11 taking tricyclic antidepressants; 23 taking other antidepressants; 9 medication-free
		30 controls (14/16)	39.1 (12.7)						
		30 ME pts (17/13)	47.5 (10.0)			—			• Patients taking antidepressants had a mean duration of treatment of 15.2 (12.9) d
		30 controls (17/13)	44.0 (11.6)						
Hickie et al.[48]	Older pts w/MDD	45 pts (15/30)	52.0 (12.8)	36.1 (17.2)	15.6 (16.1) yr	6.9 (9.8)	HAM-D21	26.8 (6.2)	• 29 taking antidepressants
		16 controls (7/9)	55.8 (10.0)						
Monkul et al.[20]	Suicidal and nonsuicidal female pts w/MDD	7 suicidal pts (0/7)	31.4 (13.9)	16.0 (4.5)	15.6 (15.0) yr	18.6 (35.6)	HAM-D	13.7 (10.9)	• All were medication-free for at least 2 wk immediately preceding the study
		10 nonsuicidal pts (0/10)	36.5 (7.5)	26.9 (10.5)	9.7 (11.6) yr	3.9 (3.4)		10.9 (8.0)	
		17 controls (0/17)	31.3 (8.3)						
MacMaster et al.[60]	Psychotropic-naive pts w/ familial MDD, aged 8–21 yr	32 pts (12/20)	14.1 (2.9)	11.8 (2.9)	27.7 (27.7) mo	—	CDRS-R	55.3 (8.8)	• All were medication-free
		35 controls (13/22), matched	14.5 (2.7)						

BDI = Beck Depression Inventory; CDRS = Childhood Depression Rating Scale; CDRS-R = Childhood Depression Rating Scale Revised; CE = current episode; CI = confidence interval; EOD = early-onset depression; FE: first episode; HAM-D = Hamilton Rating Scale for Depression, 17-item (HAM-D17) and 21-item (HAM-D21); LOD = late-onset depression; MADRS = Montgomery-Åsberg Depression Rating Scale; ME = multiple episode; MDD = major depressive disorder; pts = patients; w/ = with.
*Unless indicated otherwise.
†FE and ME data combined in original report; subgroup data provided by senior author.
‡Combined data; not included in key variable analysis.
§Pooled data for remitted and currently depressed groups presented.

Table 2: Magnetic resonance imaging acquisition parameters and anatomic definitions of hippocampus in studies analyzed

Study	Sequence	TE, ms	TR, ms	Orientation	Slice, mm	Inter-rater reliability, ICC	Anatomic definition
Sheline et al.[9]	MPRAGE	10	4	Sagittal	1.2	L = 0.90; R = 0.95	Alveus and fimbria excluded. From the slice in which the HC was visualized to the slice in which HC first appeared adjacent to the trigone of the LV.
Bremner et al.[46]	GRASS	25	5	Coronal plus axial	3.0	L = 0.93; R = 0.94	Mid-hippocampal segment only.
Mervaala et al.[44]	3D, gradient echo	10	4	Tilted coronal	3.0	Total = 0.95	Alveus and fimbria included. From the slice in which uncal recess of the temporal horn of the LV was seen to the slice in which the crus of the fornix was seen at its full length.
Steffens et al.[35]	Dual echo fast spin echo	4000	30/135	Coronal oblique	3.0	L = 0.79; R = 0.69	From the slice in which CILV appeared horizontally without any body of grey matter visible below them to the slice in which pulvinar nucleus of the thalamus obscured the crura fornicis.
Vakili et al.[32]	3D, SPGR	35	5	Coronal	3.0	Intra, total = 0.90	Alveus and fimbria excluded. From the slice in which the HC was visualized to the slice in which HC first appeared adjacent to the trigone of the LV.
Von Gunten et al.[45]	SPGR echo	35	5	Coronal	1.5	—	Alveus included. The posterior limit was arbitrarily defined as the coronal slice where the fornix was seen in its longest unbroken extent.
Rusch et al.[40]	3D, SPGR	30	14	Axial	1.2	L = 0.97; R = 0.80	Alveus and fimbria excluded.
Frodl et al.[19]	3D, MPRAGE	12	5	Coronal	1.5	Total = 0.97 (grey matter)	From the slice in which CILV becomes vertically oriented to the slice in which HC was clearly detectable.
Vythilingam et al.[39]	SPGR	25	5	Coronal	1.5	L = 0.90; R = 0.80	Alveus and fimbria included. The posterior limit was as the slice 3 mm anterior to where the crura of the fornix separate from the HC.
MacMillan et al.[24]	3D, spoiled gradient echo pulse	25	5	Coronal	1.5	—	Alveus included. From the slice where the cistern pontis was visible to the slice in which an ovoid mass of grey matter appeared inferiomedially to the trigone of the LV.
MacQueen et al.[37]	3D, Fast SPGR	21	4	Sagittal	1.2	L = 0.87; R = 0.83	Alveus and fimbria excluded.
Posener et al.[29]	3D, turbo FLASH	20	5	—	1.0	—	A magnetic resonance scan collected from an additional healthy comparison subject was used to construct the neuroanatomical template; traced by guidelines.
Sheline et al.[17]	MPRAGE	10	4	Sagittal	1.2	Total = 0.90	(see Sheline et al.[9])
Caetano et al.[47]	—	25	5	—	1.5	Intra, total > 0.93	From the coronal slice where the thalamus was connected with the superior colliculus to one slice before the mammillary bodies appeared.
Frodl et al.[16]	3D, MPRAGE	12	5	Coronal	1.5	Total = 0.97 (grey matter)	Alveus included. From the slice in which CILV becomes vertically oriented to the slice in which HC was clearly detectable.
Janssen et al.[27]	3D, FFE	30	5	Coronal	1.2	Intra, L = 0.95 Intra, R = 0.91	From the coronal slice in which the mamillary bodies were visible to the slice where fornix was visible as a continuous tract.
Lange et al.[61]	3D	24	6	Sagittal	1.3	Intra, total = 0.94	Alveus and fimbria included. From the slice which was identified by the emergence of the uncal recess in the superomedial region of the HC to the slice where an ovoid mass of grey matter started to appear inferomedially to the trigone of the LV.
Lloyd et al.[23]	3D, MPRAGE	11	4	Sagittal	1.0	Intra, L = 0.97 Intra, R = 0.99	From the slice in which the head of the HC was visible according to a priori defined boundaries and/or by visualization of a small, but distinct, bulge of the hippocampal head into the medial aspect of the temporal horn to the slice in which the fornix was visible in its longest length.
MacMaster et al.[38]	3D, FLASH	25	5	Coronal	1.5	Total = 0.98	Alveus included. From the slice where the cistern pontis was visible to the slice in which an ovoid mass of grey matter appeared inferiomedially to the trigone of the LV.
O'Brien et al.[28]	3D, MPRAGE	11	4	Sagittal	1.0	Intra, L = 0.97 Intra, R = 0.99	Alveus excluded. From the slice in which the head of the HC was visible to the slice on which the fornix was visible in its longest length.
Vythilingam et al.[26]	3D, SPGR	25	5	Coronal	1.5	L = 0.92; R = 0.89	Body: Between superior colliculus and bifurcation of basillary artery. Head of HC before that slice, and tail after that slice.
Xia et al.[62]	3D, SPGR	11	5	Coronal	1.2	—	Alveus and fimbria included. The most posterior section measured was the section with the crus of the fornix clearly separating from the HC and its fimbria.
Hickie et al.[22]	High resolution	24	5	Coronal	1.5	—	Alveus and fimbria included. From the coronal slice in which uncal recess of the temporal horn of the LV was seen until the slice at which the crus of the fornix was seen at its full length.
Neumeister et al.[59]	MPRAGE	8	2	Axial	0.6	Intra, L = 0.98 Intra, R = 0.98	Alveus excluded. The anterior pole of the HC was defined as the subiculum grey matter lying within white matter between amygdala and parahippocampal gyrus.
Taylor et al.[34]	Fast spin-echo acquisition	4000	30/135	Coronal oblique	3.0	L = 0.80; R = 0.70	From the coronal slice on which the inferior LV appeared horizontally without any body of grey matter visible below it to the slice when the pulvinar nucleus of the thalamus obscured the crura fornicis.
Frodl et al.[18]	3D, MPRAGE	12	5	Coronal	1.5	Total = 0.95	Alveus included. From the slice where the CILV becomes vertically oriented until the most posterior slice where HC was clearly detectable.
Saylam et al.[31]	3D, MPRAGE	1600	4	Coronal	2.0	—	Alveus and fimbria included. The posterior limit was the slice in which the crus of the fornix was visible.
Weniger et al.[41]	T_1-weighted 3D sequence	24	6	Sagittal	1.0	Total = 0.96	(see Lange et al.[61])
Frodl et al.[25]	3D, MPRAGE	12	5	Coronal	1.5	Total = 0.90	Alveus and fimbria excluded. From the coronal slice where the CILV looses its slit-like appearance to the slice rostral to the trigonum where the cella media, the CILV and occipital horn fuse.
Hickie et al.[48]	—	24	5	Coronal	1.5	Total = 0.97	No data given.
Monkul et al.[20]	3D, SPGR	25	5	Coronal	1.5	Total > 0.90	(see Caetano et al.[47])
MacMaster et al.[60]	3D, SPGR	25	5	Coronal*	1.5	Total = 0.98	Alveus included. From cistern pontis to the slice where ovoid mass of grey matter appeared inferiomedially to the trigone of the LV.

CILV = cornu inferius of lateral ventricle; DTSE = dual turbo spin echo; FFE = fast field echo; FLASH = fast low angle shot; GRASS = gradient recall acquisition in steady state; HC = hippocampus; ICC = intraclass correlation; L = left; LV = lateral ventricle MPRAGE = magnetization-prepared rapid gradient echo; PSIF = reversed fast imaging with steady state precession; R = right; SPGR = spoiled gradient recall acquisition; TE = echo time; TR = repetition time.
*Perpendicular to anteroposterior line.

Aggregate analysis

Our aggregate analysis confirmed that the samples of patients with MDD had smaller left and right hippocampus volumes than controls (95% CI of *z* scores –0.299 to –0.473 in the left and –0.316 to –0.489 in the right hippocampus). There was no evidence of a differential effect of the left compared with the right hippocampus. A summary of the hippocampus volume measurements is presented in Table 3. On average, patients had hippocampal volumes that were about 4% (standardized weighted average) smaller than matched controls in the left and right hippocampus. These effects are illustrated in Figure 1 and Figure 2. There were no differences in hippocampal volume loss across the left and right hippocampus (i.e., CIs overlapped; $p > 0.05$).

The difference in hippocampal volume between patients and controls exceeded 1.5 times the intraquartile range above the third quartile for 2 studies.[38,62] Removal of these outlying values from the analysis did not alter the overall pattern of our findings, and we retained the studies for further subgroup analyses.

Studies including patients with bipolar disorder, comorbid psychiatric disorders or treatment with electroconvulsive therapy

Removal from the aggregrate analysis of studies that included patients with bipolar disorder (95% CI of *z* scores –0.270 to –0.450 in the left and –0.302 to –0.482 in the right hippocampus), comorbid psychiatric disorders (95% CI of *z* scores –0.284 to –0.475 in the left and –0.315 to –0.506 in the right hippocampus) or previous treatment with electroconvulsive therapy (95% CI of z scores –0.288 to –0.485 in the left and –0.295 to –0.491 in the right hippocampus) did not affect the pattern of findings. Moreover, distribution of these studies was similar across the subgroups forming each of the clinical analysis variables ($p > 0.05$).

Patient age at scanning

Comparison of data for each of the age groups indicated that, whereas the aggregate effect was maintained in children (95% CI of *z* scores –0.307 to –1.025 in the left and –0.273 to –0.965 in the right hippocampus) and middle-aged participants (95% CI of *z* scores –0.413 to –0.647 in the left and –0.395 to –0.631 in the right hippocampus) and for the right hippocampus in older adults (95% CI of *z* scores –0.083 to –0.412), it was no longer significant for young adults (95% CI of *z* scores 0.104 to –0.404 in the left and 0.110 to –0.395 in the right hippocampus; Fig. 1) or for the left hippocampus in older adults (95% CI of *z* scores 0.019 to –0.310). The pattern of hippocampal volume loss differed in participants in all age groups: 6.7% in the left and 6.2% in the right hippocampus among children, 1.5% in the left and 1.4% in the right hippocampus among young adults, 5.3% in the left and 5.1% in the right hippocampus among middle-aged adults, and 1.5% in the left and 2.5% in the right hippocampus among older adults. Both younger (left and right hippocampus, $p < 0.05$) and older adults (left hippocampus only, $p < 0.05$) experienced less volume loss than did middle-aged adults.

Patient age at onset of illness

We observed differences in hippocampal volume among patients who experienced onset of illness in childhood (95% CI of *z* scores –0.201 to –0.866 in the left and –0.194 to –0.838 in the right hippocampus), in young adulthood (95% CI of *z* scores –0.111 to –0.432 in the left and –0.246 to –0.570 in the right hippocampus) and in middle adulthood (95% CI of *z* scores –0.370 to –0.714 in the left and –0.271 to –0.614 in the right hippocampus) compared with controls. The average reductions in volume were 5.3% for the left and 5.2% for the right hippocampus in childhood. Young adults with MDD had left hippocampus volumes that were 2.7% smaller and right hippocampus volumes that were 4.1% smaller than those of controls. Middle-aged adults experienced the largest volume loss; left hippocampus volumes were 6.1% smaller and right hippocampus volumes were 4.6% smaller than those of controls. These between-group differences in mean volume loss did not achieve statistical significance.

Duration of illness

Patients with a moderate (95% CI of *z* scores –0.432 to –0.786 in the left and –0.505 to –0.859 in the right hippocampus) or an extensive (95% CI of *z* scores –0.152 to –0.456 in the left and –0.188 to –0.491 in the right hippocampus) length of illness had small hippocampus volumes compared with controls. However, patients with a brief duration of illness (≤ 2.1 yr) did not show the effect (95% CI of *z* scores 0.034 to –0.495 in the left and 0.137 to –0.389 in the right hippocampus; Fig. 3). The pattern of volume loss across the left and right hippocampus differed in patients with a brief (1.5% in the left and 0.5% in the right hippocampus), moderate (6.1% in the left and 6.8% in the right hippocampus) and extensive (3.4% in the left and 3.0% in the right hippocampus) illness duration. Volume loss was more severe in the right hippocampus of patients with a moderate illness duration than in patients with a brief or an extensive duration of illness ($p < 0.05$).

Number of illness episodes

Patients with a moderate (95% CI of *z* scores –0.287 to –0.629 in the left and –0.364 to –0.708 in the right hippocampus) or high (95% CI of *z* scores –0.175 to –0.641 in the left and –0.185 to –0.649 in the right hippocampus) number of illness episodes had smaller hippocampus volumes than controls. By contrast, patients experiencing a first episode did not differ from controls (95% CI of *z* scores 0.034 to –0.495 in the left and 0.137 to –0.389 in the right hippocampus; Fig. 3). The average reduction in hippocampus volume in patients experiencing a first episode was 2.3% for the left and 1.3% for the right hippocampus. Those with a moderate number of episodes averaged a 4.6% reduction for the left and 5.4% for the right hippocampus. Patients with a high number of

episodes on average had a reduction of 4.1% in the left and 4.2% in the right hippocampus compared with controls. Differences in hippocampus volume loss between these subgroups did not achieve significance.

Severity of illness

There was no effect of illness severity at the time of scanning. We observed differences between controls and patients in both the euthymic/mild (95% CI of *z* scores –0.247 to –0.702 in the left and –0.212 to –0.665 in the right hippocampus) and moderate/severe (95% CI of *z* scores –0.254 to –0.485 in the left and –0.248 to –0.479 in the right hippocampus) illness groups. The average reduction in volume across the left and right hippocampus was similar in the euthymic/mild (4.8% in the left and 4.4% in the right hippocampus), and moderate/severe groups (3.7% in the left and 3.6% in the right hippocampus). Differences in hippocampus volume loss between these subgroups did not achieve significance.

Sex

Small hippocampus volumes in patients compared with controls remained apparent when study groups comprised women only (95% CI of *z* scores –0.241 to –0.657 in the left and –0.363 to –0.783 in the right hippocampus). The groups comprising only women had hippocampus volumes that were 4.5% smaller in the left and 5.7% smaller in the right hippocampus than in controls.

Slice thickness

Slice thickness had no effect on hippocampal volume. Both thick (95% CI of *z* scores –0.343 to –0.545 in the left and –0.358 to –0.560 in the right hippocampus) and thin (95% CI of *z* scores –0.337 to –0.485 in the left and –0.322 to –0.470 in the right hippocampus) slices revealed smaller hippocampus volume in patients compared with controls. The average reduction in volume across the left and right hippocampus

Table 3: Summary of hippocampal and total brain volumes of patients with major depressive disorder and comparison subjects and results of studies included in the meta-analysis (part 1 of 2)

		Patients; parameter, mean (SD)			Controls; parameter, mean (SD)			
		Hippocampal volume, mm^3			Hippocampal volume, mm^3			
Study	Subgroup	Left	Right	TCV, cm^3	Left	Right	TCV, cm^3	Results
Sheline et al.[9]		2230 (323)	2264 (320)	1075 (170)	2482 (305)	2468 (309)	1078 (168)	Smaller HC volume in MDD pts compared with controls
Bremner et al.[46]		940 (208)	982 (269)	1405 (180)	1166 (248)	1113 (194)	1391 (154)	Smaller left HC volume in pts compared with controls
Mervaala et al.[44]		3104 (391)	3462 (405)	—	3441 (436)	3700 (467)	—	Smaller left HC volume in pts than controls, and a trend for right HC volume
Steffens et al.[35]		2920 (360)	2980 (390)	—	3170 (440)	3300 (440)	—	Smaller HC volume in MDD pts compared with controls
Vakili et al.[32]		2640 (550)	2610 (580)	—	2460 (380)	2600 (510)	—	No change in HC volume
Von Gunten et al.[45]		2499 (294)	2598 (244)	1325 (114)	2644 (410)	2700 (322)	1415 (176)	No change in HC volume
Rusch et al.[40]		2170 (260)	2290 (300)	—	2130 (270)	2200 (240)	—	No change in HC volume
Frodl et al.[19]	Total Grey matter White matter	3681 (393) 3564 (386) 118 (38)	3847 (400) 3745 (397) 102 (41)	—	3772 (397) 3616 (381) 156 (55)	3763 (411) 3641 (394) 122 (49)	—	Males w/FE had smaller left HC volume than male controls. Females w/FE had a tendency toward a larger right HC volume than female controls. Pts w/FE had smaller white matter HC volume than controls
Vythilingam et al.[39]	Abuse (+) Abuse (–)	2705 (486) 3292 (385)	2690 (527) 3078 (418)	1122 (237) 1103 (226)	3179 (460)	3037 (501)	1115 (324)	Abuse (+) patients had left HC volume reduction compared with Abuse (–) patients and controls
MacMillan et al.[24]		3150 (390)	3170 (520)	—	3240 (440)	3260 (400)	—	No change in HC volume after co-varying for age and brain size
MacQueen et al.[37]	First-episode Multiple episode	2738 (301) 2381 (274)	2793 (304) 2392 (257)	—	2761 (368) 2703 (249)	2784 (342) 2692 (190)	—	Multiple-episode pts had smaller HC volume than first-episode pts and controls
Posener et al.[29]		2546 (393)	2948 (447)	1003 (130)	2475 (359)	2994 (414)	993 (106)	No change in HC volume
Sheline et al.[17]	Grey matter	2171 (316)	2203 (315)	1057 (152)	2421 (318)	2429 (326)	1054 (154)	Smaller HC volume in pts compared with controls
Caetano et al.[47]		3320 (480)	3220 (390)	1413 (109)	3370 (420)	3320 (430)	1418 (126)	No change in HC volume. Currently depressed pts had smaller bilateral HC volume compared with remitted depressed pts
Frodl et al.[16]	Baseline total Follow-up total	3700 (330) 3720 (280)	3800 (310) 3770 (310)	—	3820 (340) 3820 (400)	3930 (350) 3930 (390)	—	No change in HC volumes in 1 year follow-up in pts and controls. Nonremitted pts had smaller bilateral HC volume compared w/remitted pts at baseline and follow-up, and smaller right HC volume compared w/controls at baseline and follow-up
Janssen et al.[27]		3100 (370)	2840 (390)	Total brain vol: 981 (88) TCV: 1373 (90)	3200 (520)	3120 (450)	Total brain vol: 965 (107) TCV: 1331 (105)	Right HC was smaller in pts than controls
Lange et al.[61]		2790 (410)	2670 (500)	1136 (97)	2990 (460)	3190 (370)	3190 (370)	Smaller right HC volume in pts compared with controls

was similar in the groups scanned at thick (4.4% in the left and 4.6% in the right hippocampus) and at thin (4.1% in the left and 4.0% in the right hippocampus) slice resolution; this difference did not achieve statistical significance. Furthermore, distribution of the studies including thick and thin slices was similar across the subgroups forming each of the clinical analysis variables ($p > 0.05$).

Discussion

Our analyses, which in some cases included more than 2000 scanned participants, confirm the findings of meta-analyses of hippocampus volume in patients with MDD published before 2004.[14,15] The 20 new studies published between 2004 and 2007 included in our analysis allowed for a systematic examination of demographic and clinical factors that may mediate hippocampal volume in patients with MDD. We found differences in hippocampus volume only for those patients with MDD whose illnesses persisted longer than 2 years or who experienced more than 1 disease episode. Interestingly, this effect was limited to samples comprising children and middle-aged and older adults, whereas the hippocampus volumes of young adults were equivalent among MDD patients and controls. The results cannot be explained by the inclusion of patients with bipolar disorder, comorbid psychiatric diagnoses or previous electroconvulsive therapy, because removal of these patients from the sample did not alter our findings. Moreover, there was no evidence that a publication bias toward positive findings contributed to these results.

Equivalent hippocampus volume in patients with less than 2.1 years of illness or only 1 disease episode is consistent with the notion that small hippocampus volumes are associated with protracted illness. Five studies demonstrated this relation. Two studies[38,47] reported a significant inverse correlation between left hippocampus volume and illness duration, a finding in accordance with an earlier report of a logarithmic relation between hippocampus volume and duration of illness in adult patients with MDD.[37] Another study reported

Table 3: Summary of hippocampal and total brain volumes of patients with major depressive disorder and comparison subjects and results of studies included in the meta-analysis (part 2 of 2)

		Patients; parameter, mean (SD)			Controls; parameter, mean (SD)			
		Hippocampal volume, mm^3			Hippocampal volume, mm^3			
Study	Subgroup	Left	Right	TCV, cm^3	Left	Right	TCV, cm^3	Results
Lloyd et al.[23]	All depressed	2700 (400)	2800 (500)	963 (97)	2800 (400)	3000 (400)	969 (83)	Smaller HC volume in pts w/ LOD than those of the controls
	EOD	2900 (400)	3000 (400)	974 (92)				
	LOD	2600 (400)	2700 (500)	953 (101)				
MacMaster et al.[38]		2530 (90)	2540 (120)	—	3050 (110)	2880 (110)	—	Smaller HC in young pts w/MDD, more strongly in left (more prominent in males)
O'Brien et al.[28]		2720 (420)	2830 (480)	963 (97)	2820 (420)	3000 (410)	968 (83)	Smaller right HC volume in pts compared with controls
Vythilingam et al.[26]		3305 (380)	3132 (417)	1194 (132)	3334 (390)	3235 (407)	1240 (121)	No change in HC volume
Xia et al.[62]		3110 (84)	3487 (63)	—	3352 (46)	3710 (37)	—	Smaller HC volume in pts compared with controls
Hickie et al.[22]		2900 (400)	3000 (400)	1256 (119)	3300 (500)	3300 (600)	1354 (172)	Smaller HC volume in MDD pts compared with controls
Neumeister et al.[59]		3325 (366)	3433 (370)	1158 (133)	3576 (342)	3679 (351)	1173 (121)	Pts had smaller total and posterior HC volume than the controls
Taylor et al.[34]	All depressed	2950 (430)	3090 (420)	—	2960 (450)	3120 (440)	—	Pts w/LOD and L/L serotonin genotype had smaller right HC volume compared with pts EOD pts and controls
	EOD	2940 (380)	3080 (400)					
	LOD	2960 (490)	3100 (450)					
Frodl et al.[18]	Grey matter	2790 (310)	2920 (290)	1247 (86)	3060 (300)	3140 (300)	1247 (86)	Smaller grey and white matter volumes of HC in pts w/MDD compared with controls
	White matter	80 (35)	70 (29)		140 (47)	100 (32)		
Saylam et al.[31]		2639 (249)	2696 (194)	1525 (178)	2787 (249)	2806 (257)	1526 (115)	Smaller left HC volume in pts w/MDD compared with controls
Weniger et al.[47]		2700 (400)	2700 (500)	1461 (110)	3000 (500)	3200 (400)	1406 (119)	Smaller HC volume in pts w/MDD compared with controls
Frodl et al.[25]	First episode	3560 (340)	3716 (403)	1218 (98)	3886 (412)	3970 (434)	1252 (125)	Smaller HC grey and white matter HC volumes in pts compared with controls. First-episode pts had smaller HC white matter volume in pts carrying the Met-BDNF allele
	Recurrent episode	3642 (454)	3765 (400)	1251 (118)	3790 (379)	3890 (417)	1256 (126)	
Hickie et al.[48]		2890 (360)	3040 (370)	1272 (112)	3190 (280)	3220 (470)	1325 (118)	Smaller HC volume in MDD pts compared with controls
Monkul et al.[20]	Suicidal	3440 (700)	3350 (490)	—	3320 (270)	3290 (340)	—	Suicidal pts and nonsuicidal pts did not differ from controls in HC volume
	Nonsuicidal	3380 (430)	3470 (420)					
MacMaster et al.[60]		2950 (440)	3000 (500)	1190 (139)	3150 (460)	3160 (420)	1137 (108)	Smaller left and right HC in pts w/familial MDD

Abuse (+) = history of childhood abuse; Abuse (–) = no history of childhood abuse; EOD = early-onset depression; FE = first episode of depression; HC = hippocampus; LOD = late-onset depression; MDD = major depressive disorder; Pts = patients; SD = standard deviation; TCV = total cranial volume; w/ = with.
— Data not stated.
*Baseline data only included in meta-analysis.
†Measured only midhippocampal segment.

that volume in the left hippocampus showed a marginally significant relation with duration of illness in a group of drug-free patients with MDD.[31] Finally, Sheline and colleagues[9] reported that a greater total number of days ill predicted left hippocampus volume size in female patients with a recurrent history of MDD.

Other studies, however, have not found evidence of an effect of illness duration on hippocampus volume.[16,18,19,22,23,25,27–29,47,60,62] These negative findings may reflect small sample sizes,[20,62] the inclusion of patients with bipolar disorder,[22] and samples comprised of primarily young adult patients[20,29,61] and of patients with a low number of illness episodes.[29] In particular, younger patients with limited disease exposure may have yet to experience the pattern of hippocampal volume loss reported in patients with protracted illness. This suggestion is in line with Videbech and Ravnkilde's[15] earlier meta-analysis showing an association between total number of depressive episodes and hippocampus volume, a finding replicated here. In contrast to the earlier report, however, with the inclusion of additional studies, we found this relation to hold bilaterally, as opposed to being significant for the right hippocampus only.

Medication status may play an important role in modulating hippocampus volume in MDD and, consequently, some studies did not find a relation between extended illness course and small hippocampus volume. A systematic examination of differences in hippocampus volume among patients who did and did not receive pharmacotherapy was not possible; however, preclinical literature suggests that antidepressant medication may have neurotroprotective

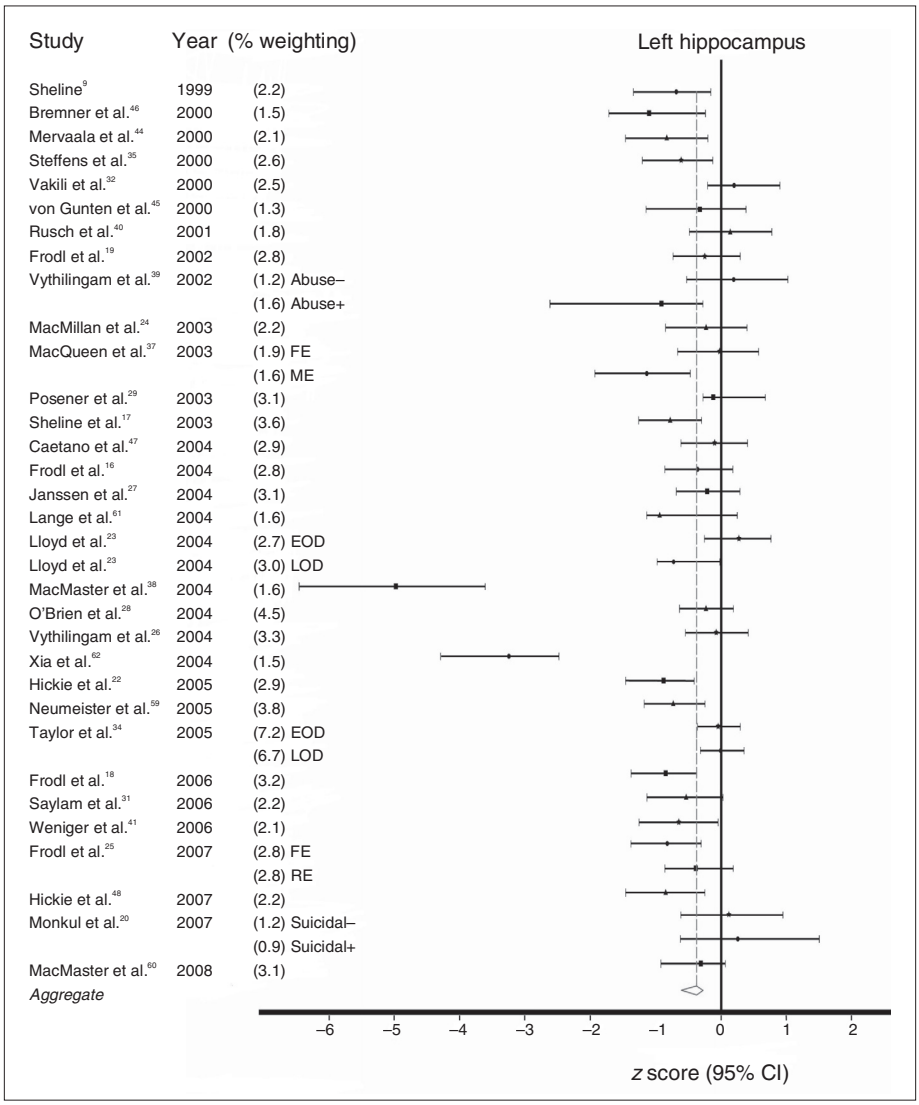

Fig. 1. Standardized mean difference of left hippocampal volumes in patients with major depressive disorder and matched controls. Positive values indicate a nonsignificant difference between groups. CI = confidence interval; EOD = early-onset depression; FE = first episode; LOD = late-onset depression; ME = multiple episode; RE = repeat episode.

effects,[63] a finding mirrored in preliminary work in patient populations. Notably, in the studies included here, the differences in hippocampus volume between patients and controls were greatest for patients with a moderate compared with an extensive duration of illness (6.5% v. 3%). It is possible that presumed long-term treatment with antidepressant medication in these patients may have resulted in hippocampus volume increase and a partial reversal of tissue loss. One study reported that time spent untreated predicted small hippocampus volume, whereas time treated with antidepressants did not correlate significantly with hippocampus volume.[17] Patients with posttraumatic stress disorder had increased hippocampus volume following a year of treatment with paroxetine.[5] Lithium augmentation is sometimes used concurrently with antidepressant treatment in patients with MDD. Bipolar patients receiving short-term treatment with lithium had larger hippocampus volumes than did matched controls when assessed cross-sectionally,[11] and in a related study, bipolar patients had increases in hippocampus volume over 2–4 years of lithium therapy.[12] An alternative explanation, however, is that MDD represents a process equivalent to accelerated aging, where the differences between patients and controls are greatest in middle adulthood but then plateau as both patients and controls age. Longitudinal studies are required to examine the effect of medication and other treatment methods on hippocampus volume over time.

Of interest is the finding that hippocampus volumes did not differ between young adults with MDD and matched controls. Moreover, these participants experienced substantially less hippocampal volume loss than did middle-aged

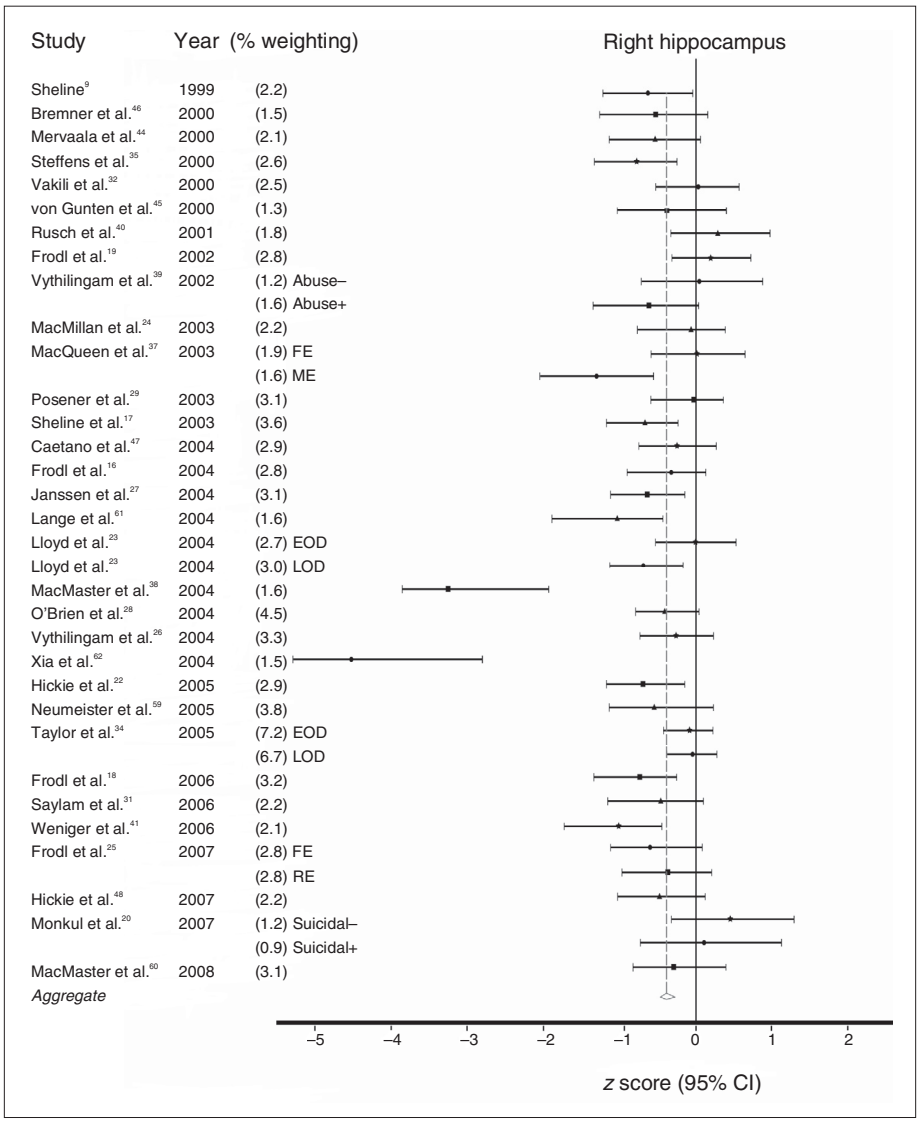

Fig. 2. Standardized mean difference of right hippocampal volumes in patients with major depressive disorder and matched controls. Positive values indicate a nonsignificant difference between groups. CI = confidence interval; EOD = early-onset depression; FE = first episode; LOD = late-onset depression; ME = multiple episode; RE = repeat episode.

adults. One explanation is that young adults have a reduced burden of illness compared with older participants, and the limited data available on the duration of illness and number of illness episodes in the young adult population support this hypothesis.[20] These data, however, are incomplete. Studies reporting hippocampal volume loss in this population may reflect a confounding of illness duration and age, where young adults with an extended course of illness are more likely to show atrophy. An alternate explanation is that the young adult period confers a period of reduced vulnerability to the effects of MDD on hippocampus volume. Specifically, hypercortisolemia, linked to hippocampus volume loss in prolonged MDD,[64] is more common with advancing age,[65] rendering the aged hippocampus particularly vulnerable to the effects of protracted stress.[66] Hippocampal volume loss has also been reported in other neuropsychiatric illnesses (e.g., schizophrenia, posttraumatic stress disorder, bipolar disorder); it will be interesting to determine whether similar findings emerge for young adults when compared developmentally (for a review see Sala et al.[67]).

Children with MDD had small hippocampus volumes relative to matched controls. This period of rapid brain development[68] may represent a special period of neural vulnerability to the stress associated with MDD, or there may be unique pathophysiological processes associated with pediatric onset MDD. There was no evidence, however, that this population had small hippocampus volumes before or proximate to onset of illness; the mean duration of illness was 2.45 (SD 0.39) years, comparable to the aggregate onset data (information on number of episodes unavailable). The studies of children with MDD, therefore, do not discriminate between the possibility that small hippocampus volume antedates or follows clinical symptoms in this population.

Although we found no evidence that the presence of comorbidity contributed to differences in hippocampus volume, studies involving patients with comorbid disorders were few in number and heterogeneous in comorbid diagnoses. A stringent test of publication bias found no evidence that differences in hippocampus volume are attributable to the biased reporting of positive findings. Indeed, it is noteworthy that the literature concerning hippocampus volume reductions contains a substantial number of negative findings,[24,62] possibly mediated by the clinical and demographic factors identified here. Finally, it will be important to explore further the effects of comorbidity in MDD by conducting replicable, systematic studies examining participants with MDD and comorbid conditions (e.g., substance abuse, posttraumatic stress disorder, social anxiety disorder).

Our findings extend the results of previous meta-analyses[14,15] that revealed little evidence of an effect of slice thickness on differences in hippocampus volume between patients with MDD and controls. We confirmed this finding; both levels of MRI resolution continued to reveal hippocampus volume reductions in our updated analysis.

Limitations

One limitation to our meta-analysis is the small size of many of the clinical and demographic subgroups, which may have limited statistical power to detect between-group differences. This is reflected in the fact that only a small number of comparisons between average hippocampal volume loss in each of the subgroups forming the clinical variables achieved significance. In our study, differences in rates of volume loss did not differ significantly across the subgroups formed by examining the age of onset, illness episodes and illness duration analyses.

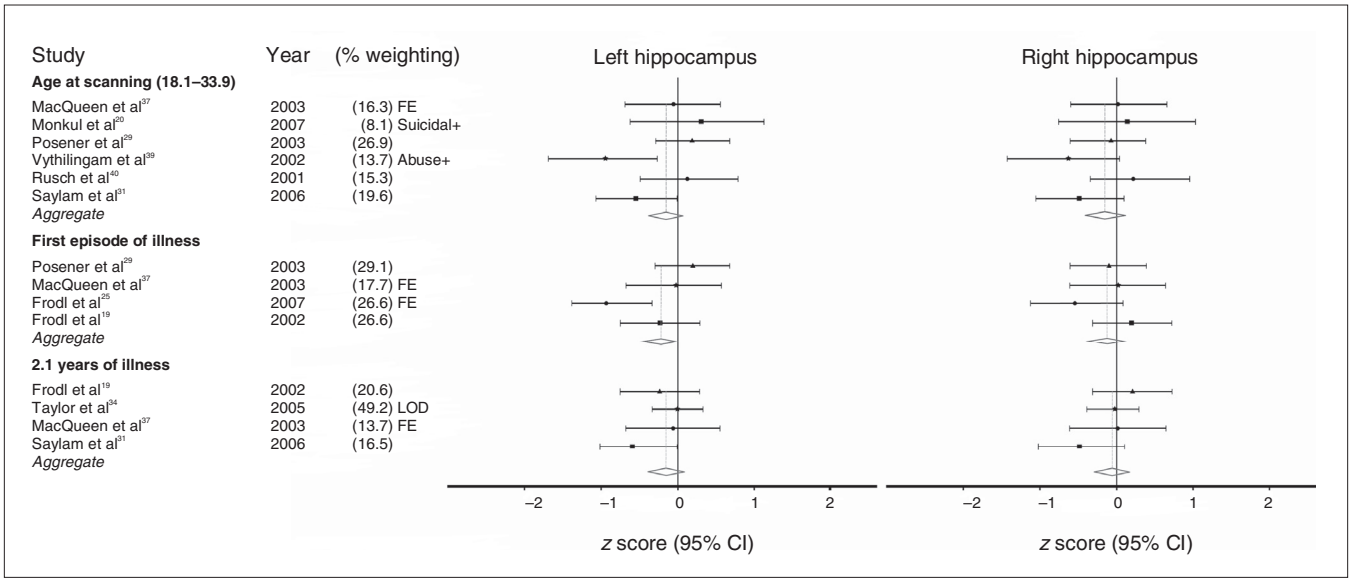

Fig. 3. Standardized mean difference of left and right hippocampal volumes in i) patients with major depressive disorder (MDD) younger than 18 years of age and matched controls; ii) patients with a first episode of MDD and matched controls and iii) patients with a duration of MDD ≤ 2.5 years and matched controls. Positive values indicate a nonsignificant difference between groups. CI = confidence interval; FE = first episode; LOD = late-onset depression.

Conclusion

In summary, this analysis of more than 2000 scanned participants found that hippocampus volumes are smaller in patients with MDD than in controls, but duration of illness plays an important role, as this difference is detectable only in patients who have an illness of greater than about 2 years duration or more than 1 episode of illness. Difference in hippocampus volumes is detectable in children, middle-aged and older adults, but not in young adults, where reduced burden of illness may play an important role. To date, studies examining the hippocampus in MDD have been mostly conducted cross-sectionally. Longitudinal studies that track patients over disease onset and through follow-up, particularly those involving systematic reporting of medication status and comorbidity, are urgently needed. Careful collection and reporting of data concerning burden of illness will also be essential if future studies are to advance our understanding of the factors that mediate small hippocampus volume in patients with recurrent MDD.

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Contributors: Drs. McKinnon, Yucel and MacQueen designed the study, acquired and analyzed data and wrote and reviewed the article. Mr. Nazarov also acquired data and reviewed the article. All authors gave final approval for publication.

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