ORIGINAL ARTICLE

Hippocampal Volume Reduction in Schizophrenia as Assessed by Magnetic Resonance Imaging

A Meta-analytic Study

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Background: Although many quantitative magnetic resonance imaging studies have found significant volume reductions in the hippocampi of patients with schizophrenia compared with those of normal control subjects, others have not. Therefore, the issue of hippocampal volume differences associated with schizophrenia remains in question.

Methods: Two meta-analyses were conducted to reduce the potential effects of sampling error and methodological differences in data acquisition and analysis. Eighteen studies with a total patient number of 522 and a total control number of 426 met the initial selection criteria.

Results: Meta-analysis 1 yielded mean effect sizes of 0.37 ($P<.001$) for the left hippocampus and 0.39 ($P<.001$) for the right, corresponding to a bilateral reduction of 4%. Meta-analysis 2 indicated that the inclusion of the amygdala in the region of interest significantly increased effect sizes across studies (effect size for the left hippocampus and amygdala, 0.67; for the right, 0.72), whereas variables such as illness duration, total slice width, magnet strength, the use of the intracranial volume as a covariate, measurement reliability, and study quality did not. No laterality differences were observed in these data.

Conclusions: Schizophrenia is associated with a bilateral volumetric reduction of the hippocampus and probably of the amygdala as well. These findings reinforce the importance of the medial temporal region in schizophrenia and are consistent with frequently reported memory deficits in these patients. Future quantitative magnetic resonance imaging studies evaluating the hippocampal volume should measure the hippocampus and amygdala separately and compare the volumetric reduction in these structures to that observed in other gray matter areas.

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THE HIPPOCAMPUS has long been considered an essential component of the medial temporal lobe memory system.[1,2] The literature on both humans and animals has established that hippocampal lesions result in memory deficits.[1,2] Patients with schizophrenia also have been shown to suffer from memory dysfunction, and several studies suggest that this selective impairment exceeds the global neuropsychological deficits reported.[3-5] Specific deficits have been found in verbal[3,5-9] and visual memory,[5] including semantic memory[10] and encoding,[8] digit span,[6,7] and design reproduction.[6,7,11] Although there is some evidence to suggest that patients with schizophrenia are less significantly impaired on recognition tasks,[3,6,11] this finding is somewhat equivocal.[8]

Recent studies have attempted to elucidate the anatomical correlates of memory impairment in schizophrenia as part of the general search for neuropathological correlates of the illness. Although some postmortem research has suggested that schizophrenia is associated with abnormal hippocampal pyramidal cell density[12] and orientation,[13,14] other studies[15,16] have failed to support these findings. In addition, schizophrenia has been correlated with smaller neuron size in the CA1 region, subiculum, and layer II of the entorhinal cortex.[17] Abnormalities also have been reported in the mossy fiber pathway,[18] which arises from the axons of hippocampal granule cells and travels to the pyramidal cells of the CA3 region.[19] Other postmortem evidence has suggested that schizophrenia is associated with reductions in overall volume of the hippocampus[12,20,21] and parahippocampal gyrus.[22]

Although postmortem techniques are useful in determining the neurohistological correlates of disease, their findings can be influenced by error variance associated with several variables, including the cause of death. Magnetic resonance imaging (MRI) allows for the in vivo volumetric measurement of various cerebral structures, and these techniques have been applied to the study of schizophrenia. Schizophrenia has been associated with an increased volume of the following brain components: total

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METHODS

STUDY SELECTION

Published reports that evaluated hippocampal volume differences between patients with schizophrenia and normal control subjects using MRI techniques were obtained through the use of computerized databases, including MEDLINE and PsychINFO, and by searching the bibliographies of relevant studies. This search identified 33 studies published between 1988 and 1997. To be included, published studies had to meet several initial criteria: means and SDs for hippocampal volumes had to be reported, a normal comparison group must have been evaluated, the region of interest (ROI) must have included the hippocampus alone or the hippocampal-amygdala complex, the mean patient age must have been between 25 and 40 years, and the study could not have used duplicate subjects from another included study. As many early studies were unable to distinguish between the hippocampus and the amygdala because of technical limitations, studies that measured the 2 structures together were not excluded. Four studies were excluded because of subject duplication,[35,45,59,60] 3 because means and SDs were not reported,[50,61,62] 6 because the hippocampal area was measured instead of the volume,[49,53,63-66] 1 because control subjects were not included,[67] 1 because the parahippocampal gyrus was included in the ROI,[68] and 1 because it evaluated elderly patients (mean age, 78.1 years).[69] Therefore, 18 studies were ultimately included in this meta-analytic study, including data from our laboratory.[70] Demographic information on patients and normal control subjects is provided in **Table 1**, and scan-related information and mean hippocampal volumes are reported in **Table 2**.

GENERAL META-ANALYTIC METHODS

All analyses were conducted according to the methods of Hedges and Olkin[71] as implemented by DStat,[72] a commercially available software program designed specifically for meta-analytic research. The DStat program computes both effect sizes and 95% confidence intervals. All analyses were conducted in several steps. First, Hedges *g* (an estimate of effect size) was computed for each study by subtracting the mean patient volume (m_p) from the mean control volume (m_c) and dividing by the pooled SD (*s*) according to the following formula[72]:

$$g = \frac{m_c - m_p}{s} \quad (1)$$

Although Hedges *g* does provide an estimate of effect size, it is susceptible to bias introduced by a low sample size.[72,73] Therefore, DStat was used to transform Hedges *g* into an unbiased measure of effect size, the Cohen *d*. Individual values of *d* were then combined across studies and weighted according to their variance (*v*) using the following formulas[71]:

$$v = \frac{n_1 + n_2}{n_1 n_2} + \frac{d^2}{2(n_1 + n_2)} \quad (2)$$

$$w_i = \frac{l}{v_i} \quad (3)$$

where w_i represents the individual weight for a given study. If more than 1 mean was reported (eg, separate volumes for men and women), a global mean for each hippocampus was computed using the weighted average of the individual means, a strategy that has been used previously in meta-analyses.[58]

Laterality differences were evaluated by converting the effect size for each subset (left vs right) into the Fisher Z_r and computing the difference between the 2 hippocampi (eg, subtracting the Z_r associated with the left hippocampus from the Z_r associated with the right hippocampus) according to the following formulas[74]:

$$r = SQRT[d^2/(d^2 + 4)] \quad (4)$$

Table 1. Demographic Information for 522 Patients With Schizophrenia and 426 Control Subjects*

Study	Diagnostic Criteria and Patient Type	No.	Age, y†	Illness Duration, y†	Age at Onset, y†	Male Sex, No. (%)
Torres et al, 1997[47]	*DSM-III-R*, inpatients	20	25.6 (6.6)	4.3 (4.8)	NA	14 (70)
Becker et al, 1996[44]	*DSM-III-R*, inpatients	20	27.0 (5.0)	4.25 (6.0)	22.0 (3.0)	20 (100)
Fukuzako et al, 1996[38]	*DSM-III-R*, chronic type	18	37.8 (5.3)	13.9 (7.7)	23.9 (6.2)	18 (100)
Flashman et al, 1995[70]	*DSM-IV*, inpatients	13	32.8 (9.2)	13.31 (8.04)	19.7 (3.7)	12 (92)
Flaum et al, 1995[39]	*DSM-III-R*, inpatients	102	31.8 (8.6)	9.7 (8.1)	22.6 (6.4)	70 (69)
Rossi et al, 1994[31]	*DSM-III*, inpatients	19	33.42 (7.32)	11.57 (6.33)	21.84 (4.08)	19 (100)
Zipursky et al, 1994[26]	*DSM-III-R*, chronic type inpatients	22	34.1 (5.5)	11.3 (6.1)	22.8 (4.3)	22 (100)
Bogerts et al, 1993[40]	*DSM-III-R*, chronic type inpatients	19	27.6 (5.6)	7.8 (5.8)	NA	19 (100)
Kawasaki et al, 1993[52]	*DSM-III-R*, inpatients, outpatients	20	28.5 (5.5)	6.72 (4.91)	21.8 (3.9)	20 (100)
McCarley et al, 1993[42]	*DSM-III-R*, chronic type inpatients	15	38.0 (9.0)	15.8 (8.8)	NA	15 (100)
Breier et al, 1992[32]	*DSM-III-R*, chronic type outpatients	44	35.8 (7.0)	14.0 (7.0)	NA	29 (66)
Hoff et al, 1992[54]	*DSM-III-R*, first-episode	43	26.69 (7.03)	NA	NA	27 (63)
Swayze et al, 1992[48]	*DSM-III*, inpatients	53	33.32 (NA)	NA	21.44 (4.44)	35 (66)
DeLisi et al, 1991[51]	*DSM-III-R*, chronic type inpatients	15	32.7 (7.2)	NA	24.53 (6.55)	9 (60)
Bogerts et al, 1990[28]	*DSM-III-R*, first-episode inpatients	35	25.0 (NA)	1.4 (6.0)	NA	22 (63)
Dauphinais et al, 1990[46]	*DSM-III-R*, outpatients	25	32.4 (6.0)	12.8 (5.8)	NA	13 (52)
Suddath et al, 1990[29]	*DSM-III-R*, chronic type	15	32.4 (5.3)	10.5 (5.5)	22.1 (4.9)	8 (53)
Kelsoe et al, 1988[55]	*DSM-III*, inpatients	24	29.0 (1.0)	8.4 (0.8)	21.0 (0.7)	19 (79)

*NA indicates not available; NIMH, National Institute of Mental Health.
†Data are given as mean (SD).

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$$Z_r = 0.5\{\log_e[(l + r)/(l - r)]\} \quad (5)$$

$$q = Z_{r1} - Z_{r2} \quad (6)$$

Significance (P) for Cohen q was computed in the following way[75]:

$$P = \frac{(Z_1 - Z_0)}{SQRT[1/(N - 3)]} \quad (7)$$

where $Z_1 = q = Z$ is associated with the experimental hypothesis (D ′ 0) and $Z_0 = Z$ is associated with the null hypothesis ($D = 0$). *SQRT* signifies square root; *D,* overall effect size.

Readers interested in further details of meta-analytic techniques are referred to the work of Hunter and Schmidt,[57] Hedges and Olkin,[71] Rosenthal,[73] and Cooper and Hedges.[76]

Meta-analysis 1

All 18 studies were included in the initial overall meta-analysis. During the initial analyses, however, it was determined that a significant outlier was present in the data set (**Figure 1**). Because the exclusion of outliers serves to increase the accuracy of the overall meta-analytic model through the reduction of extraneous variance,[71,72] all further analyses were conducted excluding the outlier. An overall effect size (D) for each hippocampus was then obtained by computing the weighted mean across the remaining 17 studies.

Meta-analysis 2

A second meta-analysis was conducted to evaluate possible moderator variables (factors that could affect results between studies). Each study was coded on several theoretically relevant variables (mean illness duration, total slice width, magnet strength, the adjustment of hippocampal volume for either hemispheric or intracranial volume, the inclusion of the amygdala in the ROI, and measurement reliability), and the studies were classified into subsets of each individual variable. As in previous meta-analyses,[37] studies were rated on several quality factors that were also treated as possible moderator variables. The first factor evaluated the completeness of the demographic information reported and the degree of patient-control matching. This dimension included patient-control matching by sex, age, handedness, height, weight, education level, and parental socioeconomic status. The reporting of demographic information, including illness duration, age at illness onset, diagnostic criteria, and the source of comparison subjects, was also considered. Studies were assigned 1 point for each item addressed, except in the case of patient-control matching by education level.

Because matching by education level may result in the selection of either high-functioning patients or low-functioning control subjects (or both),[77,78] studies were assigned no points if such matching was used and 1 point if it was not. The second factor was related to overall scan quality and included magnet strength, slice plus gap width, measurement reliability, the adjustment of hippocampal volume for hemispheric or total intracranial volume, and the inclusion of the amygdala in the ROI. Scores on each of these factors were then transformed into percentages. The third factor measured overall study quality, which was created by averaging the percentages from the first 2 factors.

Potential differences in effect size between variable subsets were analyzed using the method of Hedges and Olkin[71] as implemented by the categorical modeling feature in DStat. This procedure computes mean effect sizes and 95% confidence intervals for each variable subset and allows for the testing of the influence of each individual factor on the overall results. Because possible moderator variables were evaluated in a univariate manner, a Bonferroni correction was used, resulting in a critical P value of .005.

				Matched for				
Subject Source	No.	Age, y†	Male Sex, No. (%)	Hand	Height	Weight	Education Level	Parent Socioeconomic Status
Community	19	29.3 (8.9)	9 (47)	No	Yes	No	No	Yes
NA	20	26.0 (5.0)	20 (100)	Yes	No	No	No	No
Hospital staff and their relatives	18	38.1 (5.9)	18 (100)	Yes	Yes	Yes	No	No
Hospital staff, community	12	33.3 (9.1)	11 (92)	Yes	No	No	No	Yes
Community	87	30.4 (10.6)	45 (52)	Yes	No	No	No	Yes
Hospital staff, community	14	31.00 (3.92)	14 (100)	Yes	Yes	No	Yes	No
Community, military veterans	20	36.2 (7.0)	20 (100)	Yes	Yes	No	No	No
Hospital staff, community	18	28.1 (5.3)	18 (100)	No	No	No	No	No
Medical university graduates	10	30.0 (4.2)	10 (100)	Yes	Yes	Yes	No	No
NA	14	38.0 (9.0)	14 (100)	Yes	Yes	Yes	No	Yes
Community	29	34.4 (8.0)	20 (69)	Yes	Yes	Yes	No	No
Hospital lobby	24	28.0 (6.7)	14 (58)	Yes	No	No	No	No
Community	47	NA	28 (60)	Yes	Yes	Yes	Yes	No
Minor neurological patients	20	28.7 (7.4)	12 (60)	Yes	Yes	No	No	No
Community, hospital staff, other patients	25	28.2 (NA)	15 (60)	No	Yes	No	No	No
NIMH personnel, community	20	33.3 (6.6)	10 (50)	No	Yes	No	No	No
Monozygotic twins	15	32.4 (5.3)	8 (53)	Yes	Yes	Yes	No	Yes
Hospital staff	14	31.0 (1.0)	10 (71)	Yes	Yes	No	No	No

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Table 2. Scan Information for 522 Patients With Schizophrenia Compared With 426 Control Subjects*

Study	Slice Width, mm	Gap Width, mm	Magnet Strength, T	Volume Adjusted for Total Volume?	Hippocampal-Amygdala Boundary	Mean Hippocampal Volume, cm³†						Corrected Effect Size‡ (Cohen *d*)
						Reliability		Patients		Control Subjects		
						L	R	L	R	L	R	
Torres et al, 1997[47]	1.5	0.0	1.5	No	Separate	0.94	0.94	2.78 (0.48)	3.11 (0.44)	2.78 (0.39)	2.85 (0.40)	L hip 0.00 R hip −0.61
Becker et al, 1996[44]	4.0	0.0	1.5	Yes (by hemisphere)	Together	0.95	0.95	5.49 (0.52)	5.35 (0.51)	6.14 (0.34)	5.97 (0.44)	L hip 1.45 R hip 1.27
Fukuzako et al, 1996[38]	1.0	0.0	1.5	Yes (ICV)	Separate	0.92	0.94	2.72 (0.36)	2.80 (0.48)	2.93 (0.22)	3.08 (0.31)	L hip 0.69 R hip 0.68
Flashman et al, 1995[70]	1.5	0.0	1.5	Yes (by hemisphere)	Separate	0.94	0.94	3.40 (0.43)	3.30 (0.48)	3.70 (0.54)	3.76 (0.57)	L hip 0.60 R hip 0.85
Flaum et al, 1995[39]	3.0	1.5	1.5	Yes (ICV)	Separate	0.53	0.53	2.59 (0.40)	2.53 (0.34)	2.67 (0.35)	2.64 (0.40)	L hip 0.21 R hip 0.28
Rossi et al, 1994[31]	5.0	1.0	0.25	No	Together	0.88	0.88	2.03 (0.19)	2.03 (0.25)	2.29 (0.29)	2.21 (0.24)	L amg/hip 1.06 R amg/hip 0.71
Zipursky et al, 1994[26]	3.0	0.0	1.5	No (head size/ age corrected)	Separate	0.83	0.81	2.01 (0.06)	2.04 (0.09)	1.99 (0.08)	2.07 (0.08)	L hip −0.28 R hip 0.34
Bogerts et al, 1993[40]	3.1	0.0	1.0	No	Together	0.85	0.85	3.85 (0.60)	3.89 (0.47)	4.30 (0.47)	4.40 (0.41)	L hip 0.81 R hip 1.14
Kawasaki et al, 1993[52]	5.0	0.0	1.5	No	Separate	0.79	0.79	2.02 (0.30)	2.17 (0.44)	1.94 (0.27)	2.05 (0.45)	L hip −0.27 R hip −0.26
McCarley et al, 1993[42]	1.5	0.0	1.5	Yes (ICV)	Together	0.86	0.86	0.36§ (0.06)	0.38§ (0.05)	0.40§ (0.04)	0.41§ (0.04)	L amg/hip 0.80 R amg/hip 0.65
Breier et al, 1992[32]	3.0	0.0	1.5	No	Separate	0.90	0.90	3.50 (0.40)	3.50 (0.50)	3.80 (0.60)	3.70 (0.40)	L hip 0.61 R hip 0.43
Hoff et al, 1992[54]	5.0	2.0	1.5	Yes (total brain volume)	Separate	NA	NA	2.21 (0.51)	2.30 (0.54)	2.55 (0.47)	2.43 (0.54)	L hip 0.46 R hip 0.24
Swayze et al, 1992[48]	10.0	0.0	0.5	No	Separate	0.90	0.90	1.45 (0.44)	1.42 (0.55)	1.44 (0.41)	1.47 (0.36)	L hip −0.02 R hip 0.11
DeLisi et al, 1991[51]	5.0	2.0	1.5	Yes (total brain volume)	Together	0.90	0.90	4.24 (0.50)	4.41 (0.70)	4.44 (0.50)	4.49 (0.40)	L hip 0.35 R hip 0.36
Bogerts et al, 1990[28]	3.1	0.0	1.0	No	Together	0.85	0.85	4.49 (0.62)	4.54 (0.60)	4.70 (0.55)	4.81 (0.46)	L hip 0.36 R hip 0.49
Dauphinais et al, 1990[46]	10.0	0.0	0.5	No (adj for age, ht, gender)	Together	0.93	0.93	3.91 (0.85)	3.62 (0.67)	4.20 (1.00)	4.08 (0.82)	L hip 0.31 R hip 0.61
Suddath et al, 1990[29]	5.0	0.0	1.5	No	Separate	NA‖	NA‖	1.56 (0.30)	1.58 (0.26)	1.76 (0.24)	1.73 (0.36)	L hip 0.72 R hip 0.46
Kelsoe et al, 1988[55]	10.0	0.0	0.5	No	Together	0.97	0.97	7.10 (0.50)	7.00 (0.50)	6.20 (0.60)	6.10 (0.50)	L amg/hip −1.64 R amg/hip −1.76

*ICV indicates intracranial volume; amg, amygdala; adj, adjusted; ht, height; and NA, not available.
†Data are given as mean (SD).
‡Corrected for sample size.
§Relative volume (%).
‖Reliability information for the hippocampus was not reported. For other structures, reliability is 0.99.

cerebrospinal fluid,[23,24] overall ventricular cerebrospinal fluid,[24,25] lateral ventricles,[26-30] the third ventricle,[26,27,29,31] and the caudate.[32] Decreases in volume have been found in the following structures: whole brain,[24] global gray matter,[33] thalamus,[25,34] prefrontal cortex and white matter,[24,32] temporal lobe gray matter,[26,29] superior temporal gyrus,[35] amygdala,[31,32] parahippocampal gyrus,[35,36] and corpus callosum.[37] Magnetic resonance imaging volumetry has also been applied to the question of hippocampal volume differences in patients with schizophrenia, with inconclusive results. Many studies have reported substantial reductions of hippocampal volume in patients with schizophrenia when compared with normal control subjects,[28,29,31,32,35,38-46] but others have not.[26,47-55] In this context, the term "reduced" refers only to a smaller relative volume in patients compared with normal control subjects. Even less clear is the issue of laterality differences in hippocampal volume.[56] Considering that studies with negative findings are less likely to be published, definitive conclusions regarding hippocampal volume and laterality have remained elusive.

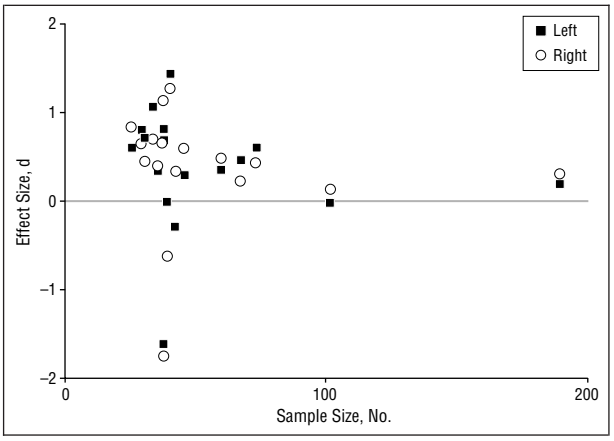

Figure 1. *Funnel plot (sample size vs effect size) for the 18 studies included in the initial meta-analysis. Note the presence of an outlier in the data set (lower left).*

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Table 3. Results of Meta-analyses*

Variable (Subject N/Study N)	Effect Size (Cohen *d*) Left	Effect Size (Cohen *d*) Right	95% Confidence Intervals Left	95% Confidence Intervals Right	Model *P*†‡ (Between Variable Subsets) Left	Model *P*†‡ (Between Variable Subsets) Right
Overall results (910/17)	0.37§	0.39§	0.25<δ<0.52	0.25<δ<0.52	. . .	. . .
Illness duration						
≤10 y (395/6)	0.34§	0.36§	0.13<δ<0.54	0.15<δ<0.56	.20	.13
>10 y (313/8)	0.52§	0.56§	0.29<δ<0.75	0.33<δ<0.79		
Missing data (202/3)	0.19	0.19	−0.09<δ<0.47	−0.09<δ<0.47		
Magnet strength, T						
1.5 (635/12)	0.38§	0.35§	0.22<δ<0.54	0.19<δ<0.51	.81	.45
<1.5 (275/5)	0.34	0.47§	0.10<δ<0.58	0.22<δ<0.71		
Total slice thickness, mm (slice + gap)						
≤3.1 (341/8)	0.42§	0.45§	0.20<δ<0.64	0.23<δ<0.67	.53	.46
>3.1 (569/9)	0.33§	0.35§	0.16<δ<0.50	0.18<δ<0.52		
Amygdala included in ROI?						
No (631/10)	0.24†	0.25†	0.08<δ<0.40	0.09<δ<0.41	.004	.002
Yes (279/7)	0.67§	0.72§	0.42<δ<0.91	0.47<δ<0.96		
Volume adjusted for ICV?						
Yes (494/8)	0.48§	0.46§	0.30<δ<0.67	0.28<δ<0.64	.07	.27
No (416/9)	0.23	0.30‖	0.03<δ<0.42	0.11<δ<0.50		
Reliability						
≥0.80 (594/13)	0.42§	0.46§	0.25<δ<0.59	0.30<δ<0.63	.18	.33
<0.80 (219/2)	0.15	0.23	−0.12<δ<0.42	−0.04<δ<0.50		
Missing data (97/2)	0.54§	0.31	0.12<δ<0.96	−0.10<δ<0.72		
Study quality						
Demographics/matching						
High (457/8)	0.41§	0.44§	0.22<δ<0.60	0.26<δ<0.63	.54	.42
Low (453/9)	0.32§	0.33§	0.13<δ<0.51	0.14<δ<0.52		
Scan quality						
High (433/7)	0.30†	0.33§	0.11<δ<0.50	0.14<δ<0.52	.39	.39
Low (477/10)	0.42§	0.44§	0.24<δ<0.61	0.26<δ<0.63		
Overall quality						
High (463/8)	0.33§	0.34§	0.15<δ<0.52	0.15<δ<0.52	.60	.44
Low (447/9)	0.40§	0.44§	0.21<δ<0.60	0.25<δ<0.64		

*ROI indicates region of interest; ICV, intracranial volume; and ellipses, data not applicable.
†Critical P = .005.
‡Model P refers to the probability that a given variable influenced results across studies for both left and right hippocampi.
§P<.001.
‖P<.005.

There are a number of reasons why results may have been equivocal. For example, the reported differences in hippocampal volume in patients with schizophrenia may be due in large part to sampling error and/or methodological variations such as magnet field strength, slice thickness, and the adjustment of hippocampal volume for either hemispheric or total intracranial volume. One of the best methods for controlling the effects of such mediating variables is the use of meta-analytic techniques.[57] Meta-analysis provides a quantitative method for integrating research findings within a given body of literature so that a more definitive overall conclusion can be reached. Meta-analytic reviews have recently been conducted on MRI studies of ventricular enlargement,[30] corpus callosum size in patients with schizophrenia,[37] and ventricular size in patients with bipolar disorder.[58] Because these studies helped to clarify many unresolved issues, a meta-analytic review of the literature evaluating hippocampal volumes is likely to be a useful tool in addressing the question of brain structural differences in schizophrenia.

This meta-analytic study was conducted to test 2 major hypotheses. First, patients with schizophrenia were predicted to have significantly smaller hippocampal volumes compared with normal control subjects. Second, we hypothesized that a moderator variable analysis would reveal important variables that could account for the divergence of results in the literature and thus inform future studies.

RESULTS

Results of both meta-analyses are provided in **Table 3**. The mean effect sizes and confidence intervals for left and right hippocampi are reported for each variable subset. Note that model *P* refers to the probability that a given variable affected results across studies for the left and right hippocampi. The results from the overall meta-analysis indicate that schizophrenia is significantly associated with bilaterally reduced hippocampal volume (D_L =0.37; D_R=0.39; P <.001 for both). As shown in **Figure 2**, these results correspond to a bilateral reduction of approximately 4%. The large number of significant mean effect sizes shown in Table 3 reflects the overall consistency of bilaterally reduced hippocampal volume. Similar effects were observed at most levels of the potential moderator variables. No laterality differences were seen in these data.

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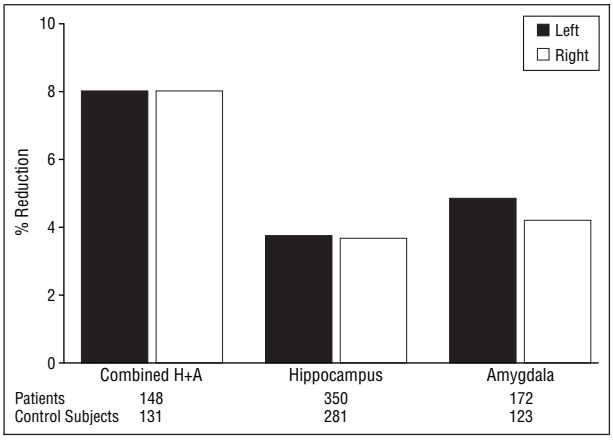

Figure 2. *Percentage reduction in the hippocampal-amygdala complex (H+A) in patients with schizophrenia. With 1 exception, the studies measuring the amygdala alone also provided hippocampal measurements. The combined H+A studies do not overlap with the other groups. See the "Comment" section for details.*

Only the inclusion of the amygdala in the ROI had a significant ($P<.005$) influence on effect sizes between studies, with those studies that measured both structures together having higher mean effect sizes (left, 0.67; right, 0.72), equaling a bilateral reduction of 8% (Figure 2). To further assess this potential relationship, studies[32,48,52,54,68] that measured the amygdala separately were evaluated, 4 of which were included in the hippocampal analyses.[33,48,52,54] Results of this analysis indicated a similar association between schizophrenia and volumetric reduction of the amygdala. The mean effect sizes were 0.29 for the left amygdala and 0.30 ($P<.05$ for both) for the right, equal to an approximately 4.5% reduction in volume (Figure 2). None of the other putative moderator variables had a significant effect on the results.

COMMENT

These meta-analyses produced several main results. First, there is a significant association between schizophrenia and bilateral volumetric reduction of the hippocampus. Second, the inclusion of the amygdala in the ROI significantly increased the magnitude of this relationship. No differences in volumetric reduction were observed between the left and right hippocampi. Finally, it appears that publication bias in favor of positive findings is unlikely to be a significant confounding variable in this literature because many of the studies evaluated in this meta-analysis reported results that were either nonsignificant or opposite the hypothesized direction (Figure 1 and Table 2).

These results have theoretical and methodological implications. Our finding of significant bilateral hippocampal volume reduction is consistent with the nature of the memory and cytoarchitectural abnormalities associated with schizophrenia. Patients with schizophrenia show specific memory deficits consistent with both left[3-7,9,11] and right[5-7,11] hippocampal disease. Schizophrenia also has been associated with reduced hippocampal pyramidal cell density, most notably in the left anterior CA3 and CA4 regions.[12]

The finding that the inclusion of the amygdala in the hippocampal ROI significantly increased the mean effect size suggests that volumetric reduction of the amygdala may also be associated with schizophrenia. Note that in Figure 2 the reduction observed in those studies that measured the hippocampus and the amygdala together ("Combined H+A") was approximately 8%. Because most of the studies in the group in which the hippocampus and the amygdala were measured together had large slice widths (Table 2), however, the greater hippocampus-amygdala reduction observed in these studies could be due to partial volume effects or other measurement factors. Therefore, we recommend measuring the hippocampus and amygdala separately and in their entirety so that the volume of each structure can be assessed independently. The ability of modern scanners to delineate the alveus allows for the accurate separation of the amygdala from the anterior hippocampus.[79]

Although neither the magnet strength nor the slice width had a significant effect on the quantitative volumetric measurement of the hippocampus in this sample, future MRI assessment of relatively small brain structures (ie, hippocampus) should be conducted using the best available scanning technology. For example, the total slice width has been shown to have a significant effect on the volumetric MRI measurement.[80] Using a calibrated phantom, Luft et al[80] demonstrated that slice widths greater than 3.0 mm lead to significantly increased error rates. Furthermore, it has been strongly recommended that MRI data be acquired or at least reformatted into a plane perpendicular to the long axis of the hippocampus, a process that helps correct for individual variations in head position.[79]

Although the adjustment of the volume of small cerebral structures for hemispheric or total intracranial volume has been thought to facilitate the accuracy of their measurement,[79] the results of the moderator variable analysis failed to confirm this hypothesis. Therefore, it is unlikely that the observed differences in the hippocampal volume in patients with schizophrenia are due to a reduction in overall brain volume. Because people with larger heads and brains tend to have larger hippocampi,[39,79] however, this correction appears warranted because it helps control for the confounding influence of overall brain volume.

Differences in interrater reliability, scan quality, demographic or subject matching quality, and overall quality did not influence the overall effect size in these meta-analyses. This may be due to a range restriction and the lack of variability in these dimensions, which were of consistently good quality across studies. These dimensions are clearly important. Large differences in interrater reliability can contribute to interstudy variation.[79] Also, the matching of patients and normal control subjects and the reporting of clinical and demographic information are necessary components of any quantitative MRI investigation involving clinical populations.

There are several limitations of this meta-analytic study. First, given the nature of the selection of studies that were included, there is no guarantee that many studies reporting either nonsignificant or countertheoretical results were not published. This problem is unlikely to have significantly influenced the overall conclusions of this study, however, because many of the analyzed studies did report negative results. Second, meta-analytic studies have been criticized for including studies of varying methods.[57] The inclusion of studies using different methodological techniques in this case revealed an important moderator variable that may account for some of the discrepancies in the published litera-

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ture. Third, it was not possible to adequately compare the level of hippocampal volume reduction with that of other gray matter structures (except the amygdala) in these patients. Therefore, it is unclear whether our results are indicative of specific hippocampal volume reduction or a more general reduction in gray matter in patients with schizophrenia.* Fourth, the influence of gender and handedness on hippocampal volume reduction could not be evaluated because of the inclusion of mostly right-handed men in the available studies. Finally, the total number of studies was sufficient for univariate analyses but not for multivariate meta-analytic techniques assessing conjoint and interactive effects of moderator variables.

Future research on the cerebral morphometric correlates of schizophrenia should focus on several issues. First, longitudinal studies should be undertaken to assess the independent effects of patient age and illness duration on the volume of the hippocampus and other structures. Such an approach is important because neuroanatomical abnormalities may be present early in the disease[25,50,51,67,82] and consequently interact with normal aging. Second, more female and left-handed subjects should be sampled to evaluate possible volumetric differences related to gender and handedness. Third, the relationship between the pattern of clinical symptoms and cognitive profile of patients with schizophrenia and the volume of implicated structures such as the parahippocampal gyrus, amygdala, prefrontal cortex, cingulate gyrus, and thalamus should be investigated. Fourth, concurrent volumetric and functional MRI studies should be undertaken to address the functional consequences and correlates of reduced hippocampal volume and differential role of the left and right hippocampus. Fifth, the volumetric reduction of the hippocampus vs that of other gray matter structures should be compared because, as noted earlier, such reductions have been associated with schizophrenia, including the first episode of the illness.[50,51,67,82] Sixth, the relative involvement of the anterior and posterior hippocampus in the disease process of schizophrenia should be compared. Because these 2 subdivisions of the hippocampus have different afferent and efferent connections,[67] it is possible that they may be differentially affected in schizophrenia. Seventh, studies should report the anatomical boundaries used to separate the hippocampus and amygdala in enough detail to allow others to replicate them because differences in these boundaries have the potential to affect volumetry results.[79] Finally, future studies need to elucidate the underlying mechanism of reduced hippocampal and amygdalar volume in advancing an etiologic understanding of this illness. Recent neurobiological studies in other mammalian species have indicated that environmental factors such as enrichment[83] and psychosocial stress[84] can alter neurogenesis in the hippocampus. The possible developmental interactions among genetic and other neurobehavioral risks and environmental advantages and stressors should be a fruitful area of investigation in schizophrenia.

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