Brief Report

Decreased Regional Brain Metabolism After ECT

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Objective: The antidepressant action of ECT may be related to its anticonvulsant properties. Positron emission tomography (PET) studies of regional cerebral metabolic rate for glucose were used to test this hypothesis.

Method: Ten patients with major depression were studied with PET before and approximately 5 days after a course of bilateral ECT. Statistical parametric mapping was used to identify regions of decreased cerebral glucose metabolism.

Results: Widespread regions of decreased regional cerebral glucose metabolism were identified after ECT, especially in the frontal and parietal cortex, anterior and posterior cingulate gyrus, and left temporal cortex. A region-of-interest analysis similarly indicated post-ECT reductions in regional cerebral glucose metabolism.

Conclusions: ECT reduces neuronal activity in selected cortical regions, a potential anticonvulsant and antidepressant effect.

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The precise mechanism of action of ECT remains unknown. One line of research has focused on the anticonvulsant properties of ECT, postulating that endogenous processes involved in the termination of seizures are critical to therapeutic mechanisms (1). This research has included examination of change in seizure threshold during a course of ECT and in concentrations of inhibitory neurotransmitters (2) and endogenous opioids (3). Both bioelectric suppression immediately after seizure termination (4) and the magnitude of delta activity in prefrontal regions in the interictal EEG (5) have been associated with superior ECT outcome, suggesting that reductions in neural activity may be critical to efficacy. Finally, imaging studies consistently have found reductions of regional cerebral blood flow (rCBF) or regional cerebral metabolic rate after ECT, again pointing to suppression of functional brain activity (6).

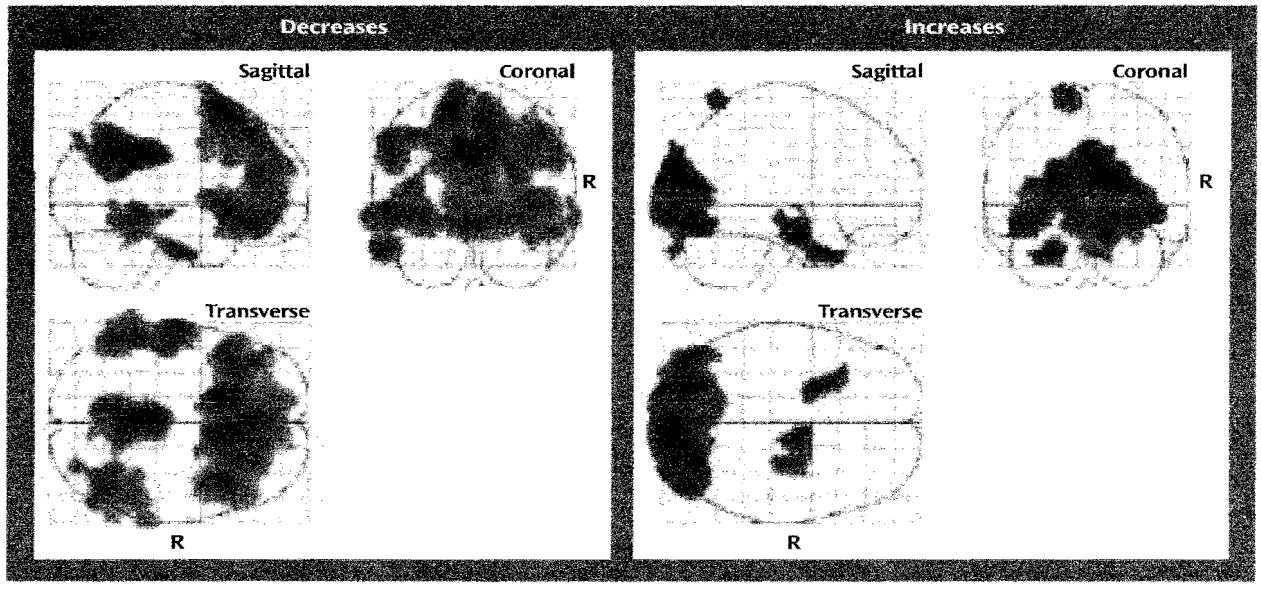
In a study that used the xenon inhalation technique, we previously found that post-ECT reductions in rCBF in prefrontal regions were associated with better clinical outcome (7). Positron emission tomography (PET) offers the advantages of measurement of regional metabolism, superior spatial resolution, and the ability to image subcortical brain regions. We report on 10 patients with major depression who underwent [^{18}F]fluorodeoxyglucose (FDG) PET before and after a course of bilateral ECT.

Method

Ten inpatients (mean age=45.5 years, SD=12.3; seven female; six with unipolar depression; nine right-handed) who met DSM-III-R criteria for a major depressive episode on the basis of interviews with the Structured Clinical Interview for DSM-III-R–Patient Edition, and who had a score of at least 16 on the 17-item Hamilton Depression Rating Scale, were referred for ECT on clinical grounds. Patients were medication free for at least 2 weeks (6 weeks for fluoxetine and 4 weeks for oral neuroleptics) before baseline imaging and until completion of post-ECT assessments. After complete description of the study, written informed consent was obtained.

ECT was administered with a constant current, brief-pulse device. Medications at ECT were atropine (0.4 mg), methohexital (0.75 mg/kg), and succinylcholine (0.75 mg/kg), with dose adjustment after the first treatment. Motor and EEG seizure manifestations were monitored to ensure adequate duration. Patients were treated with the standard bifrontotemporal electrode placement, with stimulus intensity 2–2.5 times the initial seizure threshold, as determined at the first treatment (8). ECT treatments were continued until the patients were asymptomatic or had not shown further improvement over at least two consecutive treatments (mean=13.7 treatments, SD=6.4; range=6–25). Patients were considered responders if they achieved ≥50% reduction in the Hamil-

FIGURE 1. Statistical Maps of Decreases and Increases in Normalized Regional Glucose Metabolism in 10 Patients With Major Depression After a Course of Bilateral ECT[a]



[a] Pixel-by-pixel analyses of changes in regional cerebral metabolic rate for glucose, after control for global glucose metabolic levels. "R" indicates right side. For regions of interest in which decreases were found, peak statistical parametric mapping voxel-level z scores were 5.81 at stereotactic coordinates –14, 16, 68 in the superior frontal lobe ($p<0.001$, df=8, one-tailed), 4.95 at coordinates 0, –42, 32 in the parietal lobe ($p=0.005$, df=8, one-tailed), and 4.65 at coordinates –52, –42, 0 in the left middle temporal lobe ($p<0.02$, df=8, one-tailed).

ton depression scale score from baseline, and remitters if they had ≥60% reduction in the Hamilton depression scale scores and a final Hamilton depression scale score ≤10.

Patients were scanned 1–3 days before their first ECT and a mean of 4.8 days (SD=2.6) after the end of the treatment course. PET scans began 40 minutes after intravenous bolus injection of 5 mCi FDG. During the FDG distribution phase, subjects were provided with a uniform visual stimulus in a partly dimmed and quiet examination room. A thermoplastic mask was used to minimize head movement and facilitate reproducibility of positioning for the second PET study. A Siemens (Knoxville, Tenn.) ECAT EXACT 47 scanner (spatial resolution 5.8 mm full width at half maximum at center) was used in two-dimensional mode to acquire a series of 12 5-minute frames. Images were reconstructed by using attenuation correction measured by a 15-minute transmission scan.

Regions with significant differences in regional cerebral metabolic rate for glucose from pre- to post-ECT were evaluated by using Statistical Parametric Mapping, Version 1996, as previously described (9). Analysis of covariance (ANCOVA) was applied within each condition to control for differences across studies in global regional cerebral metabolic rate for glucose. Then, within each condition (pre- or post-ECT), the adjusted mean metabolic rate and variance were computed at each pixel. These were used to compute t tests of the differences of the means between conditions at each pixel, and converted to z scores for graphical display as parametric maps. Regions with increases or decreases in regional cerebral metabolic rate for glucose were considered significant on the basis of pixel intensity and spatial extent estimated by using distributional approximations from Gaussian field theory (10). The foci of change were characterized in terms of the probability that the number of pixels of significant change ($p<0.01$) in a contiguous group exceeded that which could have occurred by chance. We further required that there be pixels with a z score >3 overlying the region and that the region extend over more than one transverse plane. By using this approach, significance values were corrected for multiple comparisons. As we examined separately peak changes in areas of decreased and increased regional cerebral metabolic rate for glucose, all tests were one-tailed. Analyses were done blind to clinical response status and time of the scan (pre- versus post-ECT).

Results

There were widespread, highly significant decreases in regional cerebral metabolic rate for glucose after the course of ECT (Figure 1). The largest area encompassed reductions in bilateral superior frontal lobe and the dorsolateral and medial prefrontal cortices bilaterally. The second largest area involved reductions in bilateral parietal regions and the posterior cingulate gyrus. A third area primarily involved reductions in the left medial temporal lobe, and a fourth region, encompassing the left inferior temporal lobe, had reductions that approached statistical significance. Significant increases in regional cerebral metabolic rate for glucose were limited to occipital regions (Figure 1). The large relative decreases in frontal regions and the relative increase in occipital regions indicated a shift in the anteroposterior gradient, consistent with previous rCBF research (7). The relative increase in occipital regions likely reflected the lack of absolute quantification (and the large relative decreases in other regions).

Four regions of interest were drawn on the areas corresponding to the pixels of most significant change within the areas of statistically significant change (epicenter pixels), on the basis of a statistical parametric mapping analysis set at an elevated z-score threshold {u}=3.090, (p=

0.001, uncorrected). The stereotactic coordinates (and locations) of the regions of interest were –14, 16, 68 (left superior frontal gyrus), –2, 40, –14 (subgenual region of left medial frontal gyrus), 0, –42, 32 (precuneus region of the left parietal lobe), and –52, –42, 0 (left middle temporal gyrus). Proportionately normalized counts were determined in each of these four regions of interest, and the difference in counts (pre- versus post-ECT) was evaluated with a two-tailed, paired t test. The differences all indicated significant decreases post-ECT, with p values ranging from $p=0.0005$ to $p<0.0001$ ($t=5.23$ to $t=8.58$, $df=9$). There was a significant Pearson's correlation between the number of ECT treatments and the percentage change in regional cerebral metabolic rate for glucose in the left middle temporal gyrus ($r=-0.73$, $df=8$, $p=0.01$) and a similar, but nonsignificant, effect in the left medial frontal gyrus ($r=-0.56$, $df=8$, $p=0.09$). In both areas, a larger number of treatments was associated with greater decreases in regional cerebral metabolic rate for glucose. All patients showed clinically significant improvement (eight achieved remission, and 10 met the response criterion), which prevented examination of correlations between clinical improvement and changes in regional cerebral metabolic rate for glucose.

Discussion

The major finding of this study was that a course of bilateral ECT reduced regional cerebral metabolic rate for glucose in medication-free patients with major depression. These decreases were widespread and most significant in the frontal, prefrontal, and parietal cortexes. Further, both statistical parametric mapping and region-of-interest analyses were consistent in identifying metabolic reductions. This finding extends our earlier report of reduced cortical rCBF after ECT and is in agreement with the majority of studies in this area (6, 11–14). Limitations of this study include the modest sample size, the absence of matched comparison subjects to determine baseline abnormalities of regional cerebral metabolic rate for glucose in the patients, and the use of nonquantitative PET, given that ECT is known to cause changes in global cerebral perfusion (7) and metabolic rate (14).

The main implication of these findings is that the mechanism of therapeutic action of ECT may be related to the suppression of functional brain activity, especially in the prefrontal cortex. Since the majority of imaging studies have demonstrated baseline (pretreatment) deficits in similar regions among depressed patients (15), such a finding may appear counterintuitive. However, our results are consistent with other data indicating ECT-related decreases in neuronal activity, as elaborated in the anticonvulsant theory of ECT (1). Moreover, there is a growing body of literature that similarly indicates reduced functional brain activity after treatment with antidepressant medications (15). Larger controlled studies are needed to examine state versus trait functional brain abnormalities in major depression.

Also noteworthy were the findings of reduced regional cerebral metabolic rate for glucose in left temporal regions after ECT, as well as a significant correlation between an increased number of ECT treatments and the percentage reduction of the regional cerebral metabolic rate for glucose in the left middle temporal gyrus. Since dysfunction in medial temporal lobe structures is hypothesized to mediate the amnestic side effects of ECT (16), such findings may represent evidence of ECT-related physiologic disturbance in temporal lobe function. It would be expected that reduced functional brain activity may result in cognitive deficits (17). Too few patients in this study received cognitive evaluation to permit meaningful analysis. Determining functional pathways associated with the therapeutic and adverse effects of ECT is an important issue for future research.

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Hippocampal Volume and Depression: A Meta-Analysis of MRI Studies

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Objective: Several studies have found reduced hippocampal volume in patients with unipolar depression, but discrepancies exist. The authors performed a systematic review and meta-analysis of volumetric studies of the hippocampus in patients with mood disorders.

Method: Studies of hippocampal volume in unipolar and bipolar patients were identified. A meta-analysis of the 12 studies of unipolar depression fulfilling specific criteria was performed. The sample comprised 351 patients and 279 healthy subjects.

Results: The studies were highly heterogeneous regarding age and gender distribution, age at onset of the disorder, average number of episodes, and responsiveness to treatment, but the pooled effect size of depression was significant in both hemispheres for the unipolar patients. The weighted average showed a reduction of hippocampal volume of 8% on the left side and 10% on the right side. The causes of the heterogeneity were analyzed, and a meta-regression showed that the total number of depressive episodes was significantly correlated to right but not left hippocampal volume reduction.

Conclusions: Hippocampal volume is reduced in patients with unipolar depression, maybe as a consequence of repeated periods of major depressive disorder. Bipolar patients did not seem to show a reduction in hippocampal volume, but this has been much less investigated.

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Increasing evidence has shown structural cerebral abnormalities in patients with unipolar and bipolar depression. Several studies have thus indicated an increased ventricle/brain ratio and other signs of both generalized and localized cerebral atrophy of the prefrontal cortex, cingulate gyrus, caudate nucleus, cerebellum, and hippocampus (for reviews see references 1–4). Often this atrophy is found to correlate with poor treatment response and shorter time to recurrence of the disease. Functional neuroimaging has also pointed to widespread abnormalities in the brain during depression (5).

The hippocampus is one of the areas in the brain that has been extensively studied in patients with mood disorders. This interest rests on a large body of neuropsychological and neuroimaging studies. The hippocampus is involved in episodic, declarative, contextual, and spatial learning and memory (6, 7), deficits which often accompany depression (8, 9). Furthermore, extensive rodent and human research has shown that its mnemonic functions and its neuroplasticity are highly sensitive to stress, i.e., increased cortisol levels (see reference 10 for an excellent review), which is found in a large proportion of patients with major depression (11).

In a Danish positron emission tomography (PET) study that included 42 acutely depressed patients and 47 matched healthy volunteers, one of the main findings was increased blood flow to the right hippocampus (12, 13). Accordingly, several other PET studies have found abnormalities in this structure in depression under various scanning conditions (14–19).

The hippocampus of patients with unipolar depression has been studied since 1993 using magnetic resonance imaging (MRI) techniques to reveal changes in volume, density, and water contents. Some volumetric studies have found significant bilateral volume deficits in depression (20–22). Others have found significantly lower volume in the right hemisphere (23, 24) or in the left hemisphere (25–27), but several studies have failed to find any differences (28–34).

Likewise, the picture is inconsistent regarding the correlation between measurements of hippocampal volume and clinical characteristics of the patient groups. One study found a correlation between age at onset of depression and hippocampal volume, namely that patients with late onset tended to have smaller hippocampi, especially in the right hemisphere (24). Other studies found the opposite to be the case (23) or could not confirm any relationship at all (33). Several authors have also tried to correlate the accumulated duration of episodes of depression to the volume of hippocampus and found that longer total duration of the disease or more episodes was correlated to smaller volumes (20–22). Important discrepancies do, however, still exist (26, 28, 33, 34). Finally, responsiveness to treatment has been correlated to volume reduction, which is often most pronounced in the right hippocampus (27, 32, 35).

TABLE 1. Studies of Hippocampal Volume in Patients With Unipolar Depression

Study and Year	Magnet Strength (T)	Slice Thickness (mm)	Patients								
				Age (years)		Male	Left Volume (mm^3)		Right Volume (mm^3)		
			N	Mean	SD	(%)	Mean	SD	Mean	SD	RECUR[a]
Posener et al. (28), 2003	1.5	1.0	27	33.0	10.7	44	2546.0	392.7	2948.4	446.7	3
MacQueen et al. (20)[b], 2003	1.5	1.2	20	28.4	11.8	35	2738.0	301.1	2793.0	303.8	1
MacQueen et al. (20)[b], 2003	1.5	1.2	17	35.9	11.1	35	2381.0	273.5	2392.0	256.7	3
Frodl et al. (29), 2002	1.5	1.0	30	40.3	12.6	43	3681.0	393.0	3847.0	400.0	1
Rusch et al. (30), 2001	1.5	1.2	25	33.2	9.5	44	1770.0	230.0	1870.0	240.0	2
Mervaala et al. (25), 2000	1.5	3.0	34	42.2	12.2	47	3104.0	391.0	3462.0	405.0	3
Vakili et al. (32), 2000	1.5	3.0	38	38.5	10.0	45	2640.0	550.0	2610.0	580.0	2
von Gunten et al. (31), 2000	1.5	1.5	14	57.6		42	2498.6	294.8	2597.9	244.0	1
Steffens et al. (24), 2000	1.5	3.0	66	71.7	8.4	23	2920.0	360.0	2980.0	390.0	3
Bremner et al. (26), 2000	1.5	—[c]	16	43.0	8.0	63	940.0	208.0	982.0	269.0	3
Ashtari et al. (33), 1999	1.0	3.1	40	74.3	6.0	29	1745.0	380.0	1742.0	345.0	3
Sheline et al. (50), 2003	1.5	1.3	24	50.8	17.1	0	2171.0	316.0	2203.0	315.0	3

[a] 1=first-episode patients, 2=mixed group, 3=patients with recurrent depression.
[b] Data on first time depression and recurrent depression presented separately in this table.
[c] Data not given.

Because of these discrepancies, which make it very difficult to reach a conclusion by simple summation of previous results, we decided to perform a meta-analysis of the effect of depression on hippocampal volume, hypothesizing that at least some of the discrepancies can be explained by between-group differences in number of recurrences.

Method

The MEDLINE and EMBASE electronic databases were searched using the following medical subject heading (MeSH): "Mood disorders" and "Magnetic Resonance Imaging" and "Hippocampus." To make sure no study was missed, a free-text search was performed on the words "depression" and "MRI" and "hippocampus." The search covered the years from 1966 through 2003. Furthermore, all reference lists of the obtained papers were scrutinized for studies not indexed in the electronic databases.

If not otherwise stated, all the studies reviewed herein fulfill the following criteria: 1) thorough clinical characterization of the patients with DSM-IV, ICD-10, or an equivalent system used as a diagnostic tool; 2) a comparison group of nearly the same size or larger than that of the probands, with approximately the same average age; 3) exclusion of patients and comparison subjects with neurological disorders or medical diseases that could affect brain function; 4) exclusion of subjects with alcohol or drug dependency/abuse; and 5) comparison groups screened for psychiatric disorders. Since the first studies used scanners with low resolution unable to distinguish between the hippocampus and the adjacent amygdala, these studies were not considered.

In the present report all relevant studies were scrutinized, but only studies stating the mean and standard deviation of the hippocampal volume in each hemisphere separately were included in the meta-analysis. We converted all volumes to mm^3 before entering them into the meta-analysis. Furthermore, this analysis was only carried out for studies of patients with unipolar depression and not for bipolar disorder patients, since these studies were few and very heterogeneous regarding the scanning techniques and actual measurements of hippocampal volume compared with the studies of unipolar depression patients.

The calculations were performed by using STATA, version 8 (Stata Corp., College Station, Tex.) by means of the Metan, Metareg, Metainf, and Metabias programs. The meta-analyses were performed by using a random effects model weighting the studies by the inverse variance and calculating the Dersimonian-Laird effect size. The random effects model was chosen because it is considered more conservative than a fixed effects model, since it takes into account the variability between studies leading to wider confidence intervals (CIs). Furthermore, the analyses were repeated excluding one study at a time to ensure that the results were not skewed by a single outlier. Heterogeneity, i.e., whether the differences between studies were greater than would be expected by chance alone, was assessed by the Q test and further analyzed by so-called meta-regression, a linear regression of the effect sizes against selected covariates. Meta-regression using the Metareg program was conducted to evaluate factors that could affect results between studies, such as differences in gender distribution or average age. A variable called RECUR was defined for each study and assigned a value of 1 if the study comprised patients with first-episode depression only and a value of 3 if all the patients participating in the study had recurrent depression. In three studies a value of 2 was assigned because the patient group was considered to consist of both

Comparison Subjects								
	Age (years)		Male	Left Volume (mm^3)		Right Volume (mm^3)		Hippocampal Volume: Between-Group Differences and Clinical Correlations
N	Mean	SD	(%)	Mean	SD	Mean	SD	
42	33.2	10.8	45	2475.0	359.4	2993.9	414.2	No significant between-group difference. No correlation with number of episodes or accumulated duration of disease.
20	28.4	11.5	35	2761.0	368.4	2784.0	342.2	No significant between-group difference.
17	36.2	11.9	35	2703.0	249.0	2692.0	190.1	Bilateral hippocampal volume deficits in patients relative to comparison subjects. Correlation between bilateral hippocampal volume deficits and length of illness.
30	40.6	12.5	43	3772.0	397.0	3763.0	411.0	No significant between-group difference.
15	37.4	14.4	40	1760.0	250.0	1810.0	210.0	No significant between-group difference.
17	42.1	14.6	35	3441.0	436.0	3700.0	467.0	Significantly lower left hippocampal volume in patients relative to comparison subjects.
20	40.3	10.4	45	2460.0	380.0	2600.0	510.0	No significant between-group difference. Correlation between smaller right hippocampal volume and poor antidepressant response in women.
14	58.1		42	2644.4	409.4	2699.5	321.7	No significant between-group difference.
18	67.1	5.0	50	3170.0	440.0	3300.0	440.0	Significantly lower right hippocampal volume in patients relative to comparison subjects. Negative correlation between hippocampal volume and age at onset (older onset age associated with smaller hippocampus).
16	45.0	10.0	63	1166.0	248.0	1113.0	194.0	Significantly lower left hippocampal volume in patients relative to comparison subjects. No correlation with number of episodes.
46	71.4	0.3	40	1853.0	348.0	1843.0	337.0	No significant between-group difference. No correlation with number of episodes or age at onset.
24	52.8	17.8	0	2421.0	318.0	2429.0	326.0	Bilateral hippocampal volume deficits in patients relative to comparison subjects. Correlation between total hippocampus volume and days of untreated depression.

types of patients (Table 1). This variable was also used in a meta-regression.

Begg's and Egger's tests were used to test for publication bias, i.e., the phenomenon in which for instance studies with negative results are not published.

Results

Unipolar Depression

Twelve studies comprising 351 patients and 279 healthy subjects fulfilled the aforementioned criteria and were entered into the meta-analysis (Table 1). The studies deviate markedly on several demographic characteristics of the study groups: the mean age varies from 28 to 74 years and the percentage of male subjects in each group varies from 0 to 63. Clinically, some of the studies comprise patients with first-episode depression (20, 29, 31) or treatment-resistant depression (25). Furthermore, the average volumes measured varied somewhat, with one study deviating especially noticeably (26).

The Q test of heterogeneity (df=11) was highly significant as expected (left side: $p<0.003$; right side: $p<0.01$). For this reason the effect size was calculated under the assumption of a random effects model. The Derimonian-Laird pooled effect size revealed bilateral statistical significance: –0.38 (95% CI=–0.65 to –0.11) for the left hippocampus (Figure 1) and –0.32 (95% CI=–0.56 to –0.08) for the right hippocampus (Figure 2). The average volume reduction weighted by sample size was 8% in the left hemisphere and 10% in the right.

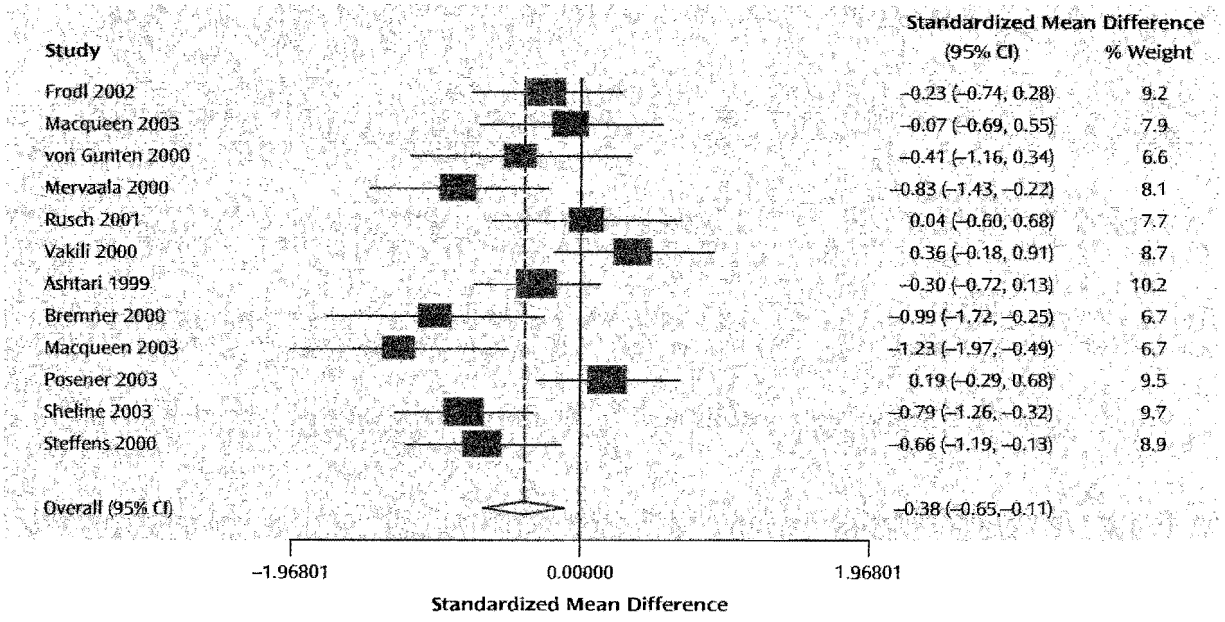
Begg's and Egger's tests for publication bias were both far from significant (smallest $p=0.135$), confirmed graphically by a funnel plot (Figure 3). The meta-analysis was repeated omitting one study at a time to ensure that the result was not skewed by a single study. This procedure did not change the random-effect estimate notably, as it in all cases continued to be statistically significant.

The significant heterogeneity was then analyzed using meta-regression. A priori we assumed that interstudy differences in age and gender distribution could explain some of the variation. Analyzed separately and together these variables were, however, not significantly correlated with the random effect estimate in either hemisphere (data available upon request). Meta-regression using the variable RECUR (Table 1) as covariate showed a significant negative correlation with the random-effect estimate in the right hemisphere ($r=-0.30$; $z=-2.36$, $p<0.02$) and nonsignificant correlation in the left ($r=-0.20$; $z=-1.18$, $p<0.24$). This means that the higher the proportion of patients with recurrent depression, the smaller the volume of the right hippocampus.

Bipolar Patients

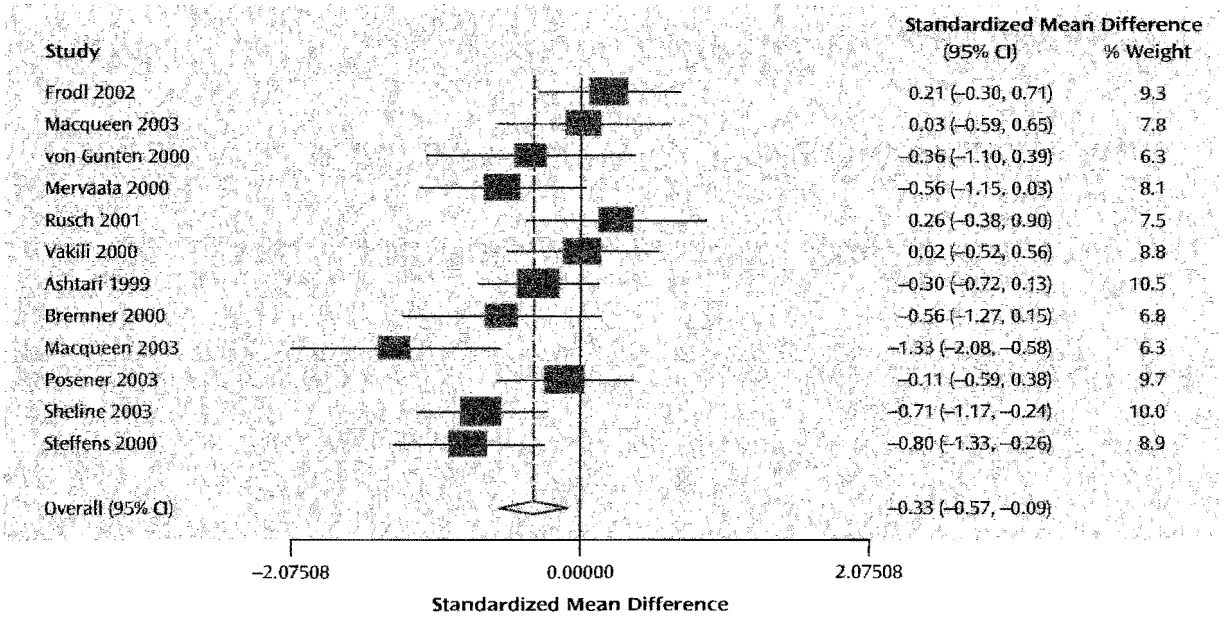
Studies of the hippocampus in bipolar disorder patients are shown in Table 2. Most of the studies except one (36) showed no significant differences between patients and

FIGURE 1. Standardized Mean Difference of Left Hippocampal Volume in Patients With Depression Relative to Comparison Subjects From a Meta-Analysis of 12 MRI Studies[a]



[a] Overall difference represents the Derimonian-Laird pooled effect size, calculated under the assumption of a random effects model. Studies are grouped by their RECUR variable, a value assigned on the basis of patient group type (1=first-episode patients, 2=mixed group, 3=patients with recurrent depression).

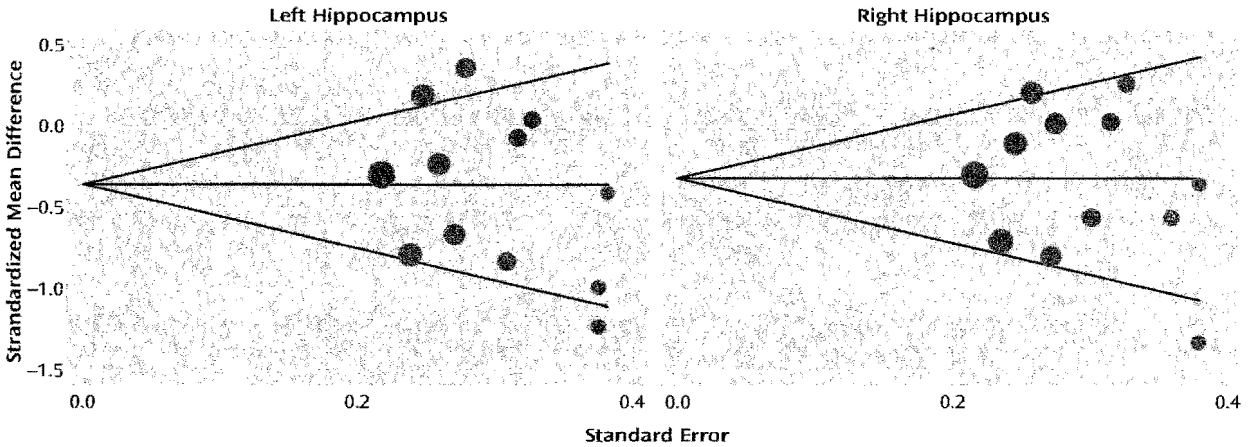
FIGURE 2. Standardized Mean Difference of Right Hippocampal Volume in Patients With Depression Relative to Comparison Subjects From a Meta-Analysis of 12 MRI Studies[a]



[a] Overall difference represents the Derimonian-Laird pooled effect size, calculated under the assumption of a random effects model. Studies are grouped by their RECUR variable, a value assigned on the basis of patient group type (1=first-episode patients, 2=mixed group, 3=patients with recurrent depression).

comparison subjects (37–42). Several of the studies did, however, use a very crude slice thickness to calculate the volumes, which increased the variation. Furthermore, one of the studies reports very deviating volumes of the hippocampus. Despite such methodological shortcomings the results are rather uniform, indicating that the volume of hippocampus is not changed in bipolar disorder. However, in an uncontrolled study Ali et al. (43, 44) found that

FIGURE 3. Publication Bias Test of Meta-Analysis Results[a]



[a] For the 12 studies that showed an overall statistically significant difference in hippocampal volume between depressed patients and healthy subjects, the Begg's funnel plot confirms no obvious signs of publication bias.

larger right hippocampal volume was associated with longer duration of the illness and poorer neuropsychological functioning.

Discussion

The question whether depression is associated with shrinkage of the hippocampus is indeed important for our understanding of the disease. From Table 1 it is seen that two studies found significant bilateral volume deficits, one found significantly reduced volume in the right hemisphere, and two found reduction in the left, whereas seven studies failed to find any differences. In contrast, the meta-analysis of the 12 studies included showed a significant effect size of depression on the volume of hippocampus in both hemispheres, most pronounced in the right. Furthermore, the volume reduction in the right hippocampus was significantly correlated to the number of episodes. Tests for publication bias both fell out negatively.

Heterogeneity of Studies

The marked differences among patient groups regarding age and gender distribution, age at first depression, average number of episodes, and responsiveness to treatment were a priori expected to increase the variation of hippocampal volume. Further increase in variation was expected considering differences in scanning protocols and delineation of the structures in question. Meta-analysis plays an important role precisely because of these possible serious confounders, since it is most likely that some of the confounding effects are diluted or even cancel each other out in the large number of patients analyzed. This increases the extendibility of the results to the general population of depressed patients (45). The risk, of course, is that the results of the studies point in so many directions that they too cancel each other out and obscure important links between volume and depression in certain subpopulations of patients.

It is therefore important to analyze the causes of the significant heterogeneity found among the studies included. The studies of unipolar depression patients are comparable regarding the MRI scanner used and spatial resolution applied in contrast to the studies of bipolar disorder patients. None of the studies showed any statistical differences in total intracranial volume between patients and healthy subjects, but all authors corrected for this, either by using relative measurements or by using total intracranial volume as a covariate in the statistical analysis.

Differences in scanning protocols and the delineation of the hippocampal boundaries on the MRI scans are thus important sources of variation between the measurements (46, 47). The meta-analysis is, however, relatively robust against this, since the effect of such moderators in the individual studies were the same in both patients and comparison subjects, and studies using protocols that cause large variance have less influence on the summarized effect size in the meta-analysis because of the weighting of studies. One study especially stood out with very deviating measurements (26) but did not skew the analysis, since stepwise exclusion of one study at a time did not change the effect sizes significantly. The results of the meta-analysis thus cannot be attributed to any single study with extreme results. Clinical and demographical variables can, however, play an important role and were therefore controlled.

Age and Gender

The hippocampus is generally larger in men than in women, a fact accounted for in the selection of comparison subjects or, in a few of the included studies, by statistical means. Furthermore, decreased hippocampal volume has been reported with increasing age in male but not female healthy volunteers (48). Moreover, significant interaction between hippocampal size, depression, and gender

TABLE 2. Studies of Hippocampal Volume in Patients With Bipolar Depression

Study and Year	Magnet Strength (T)	Slice Thickness (mm)	Patients							
			N	Age (years)		Male (%)	Left Volume (mm^3)		Right Volume (mm^3)	
				Mean	SD		Mean	SD	Mean	SD
Brambilla et al. (40), 2003	1.5	1.5	24	35.0	10.0	63	3930.0	680.0	3910.0	710.0
Hauser et al. (41), 2000	0.5	5.0	25	41.8	10.5	48	6.8[a]	1.1[a]	6.4[a]	0.8[a]
Strakowski et al. (42), 1999	1.5	1.0	24	27.0	6.0	71	4300.0	600.0	4300.0	600
Altshuler et al. (38), 1998	1.5	1.4	12	50.8	13.3	100	2306.0	406.0	2462.0	412.0
Pearlson et al. (37)[b], 1997	1.5	5.0	11	34.9	8.6	0	399.0	145.0	384.0	45.0
Pearlson et al. (37)[b], 1997	1.5	5.0	16	34.9	8.6	100	408.0	76.0	414.0	77.0
Swayze et al. (36), 1992	0.5	10.0	48	33.9	—[b]	60	1340.0	380.0	1310.0	380.0

[a] Unit of measurement not stated in paper.
[b] Data on male and female subjects given separately.
[c] Data not given

was observed in at least one study of patients with first-episode depression (29). In this study, the volume of the left hippocampus was smaller in male patients, whereas the right was larger in female patients. If correct, this could confound the results of the studies mentioned in Table 1 as the female-to-male ratio varies considerably (from 0% to 63% male). Generally it is also problematic to draw any conclusions from a study of predominantly male participants to the predominantly female population of depressed patients. Using linear meta-regression we were, however, unable to demonstrate any significant confounding of age and gender on the summarized effect size.

Treatment Response

The ratio between treatment response and treatment resistance in the study populations may also influence the results. In three studies smaller volume in right hippocampus (32, 35) or reduced density in the left (27) was linked to poor response to antidepressant medication. It is difficult to account for the importance of this fact, since the frequency of refractory depression is practically never stated in the studies. If this result is confirmed, it is clinically very interesting as a potential predictor of treatment response.

Cumulative Time Being Depressed

Several studies (20, 23) have found a negative correlation between total lifetime duration of depression and volume of the hippocampus since Sheline et al. (21, 22) reported this in women. However, others did not find any relationship between duration of depression or number of episodes and hippocampal volume (26, 28, 33). One study in fact even found nearly the opposite to be the case: smaller hippocampal volumes in late-onset depression (24), supporting the notion that late-onset depression has a different etiology and pathophysiology compared with early-onset depression (1, 49). Omitting this study from the present analysis does not, however, change the results significantly.

Two studies of first-episode patients found no differences in hippocampal volume (20, 29). Accordingly, a meta-regression with the variable RECUR designating the proportion of first-episode patients versus patients with recurrent depression showed a highly significant correlation with the estimate of effect size in the right hemisphere. This means that the number of depressed episodes was correlated with lower volume of right but not left hippocampus, and that some of the heterogeneity can be explained by this variable. The RECUR variable is indeed a very crude measurement of recurrences and probably only loosely correlated to the accumulated time of depression. This crudeness will increase the risk of type II error, thus making our conclusion even stronger. Sheline et al. extended their original data using a much more precise estimate, namely the number of days of untreated depression, and correlated it with hippocampal volume. Their results (R^2=0.28, p=0.0006) revealed that 28% of the variation in volume can be explained by this variable (50).

Other studies have used statistical parametric mapping to estimate hippocampal size and found significantly smaller right hippocampi in depressed patients, particularly in patients with a longer course of illness (23). Others found that subjects with chronic depression showed reduced gray matter density in the left temporal cortex, including the hippocampus, and a tendency toward reduction in the right hippocampus (27).

Limitations of the Study

In principle, cross-sectional studies such as those included in the present analyses cannot conclude about causality. Does the depression cause shrinkage of the hippocampus or are subjects with small hippocampi susceptible to depression? It is tempting to conclude the former on the basis of our meta-regression and the data of Sheline et al. (50), but longitudinal follow-up studies are necessary. We have therefore initiated a study along these lines at our department.

A confounding effect of posttraumatic stress disorder and early lifetime stress, which both are often followed by

Comparison Subjects								
	Age (years)		Male	Left Volume (mm^3)		Right Volume (mm^3)		Hippocampal Volume: Between-Group Differences and Clinical Correlations
N	Mean	SD	(%)	Mean	SD	Mean	SD	
36	37.0	10.0	63	4040.0	600.0	3850.0	540.0	No significant between-group difference. No correlation between hippocampal volume and age at onset, accumulated duration of disease, number of episodes, or lithium treatment.
19	33.2	7.1	53	6.6[a]	0.6[a]	6.4[a]	0.7[a]	No significant between-group difference.
22	28.0	6.0	59	4200.0	400.0	4200.0	400.0	No significant between-group difference. No correlation between hippocampal volume and accumulated duration of disease, number of episodes, or treatment.
18	53.4	11.1	100	2098.0	324.0	2222.0	388.0	No significant between-group difference.
17	31.6	8.0	0	376.0	100.0	420.0	131.0	No significant between-group difference.
43	31.6	8.0	100	385.0	87.0	416.0	105.0	No significant between-group difference.
47	—[c]	—[c]	60	1440.0	410.0	1470.0	360.0	Significant lower right hippocampal volume in patients relative to comparison subjects.

depression, cannot be completely excluded. In some studies, but not all, these conditions have been associated with reduced hippocampal size (51, 52). Hence, it is important in future studies to account for such factors.

Other factors can also act as confounders, such as adolescent-onset alcohol abuse, which has been connected to smaller hippocampi (53), but this has been accounted for in the studies.

We abstained from performing a meta-analysis of the data on bipolar disorder patients because of the small number of studies and because some of the studies used scanning techniques that today must be considered suboptimal. The conclusions on this topic are therefore tentative.

Depression, Hippocampal Shrinkage, Cognitive Deficits, Dementia?

Volume reduction of the hippocampus offers an explanation of recent epidemiological and clinical findings of depression being a risk factor for dementia. A large register study showing that affective patients had an increased risk of developing dementia compared with the general Danish population (54) has recently been confirmed by meta-analyses (55, 56). Moreover, cognitive impairment has been demonstrated even in the euthymic phase in patients with unipolar depression and bipolar disorder (57, 58), and severity of the deficits has been shown to correlate with the number of affective episodes (59).

A few MRI studies have supported a connection between hippocampal abnormalities in depressed patients and cognitive deficits. In a study of patients with chronic depression, reduced gray matter density was found in the left temporal cortex, including the hippocampus, as well as a tendency toward reduction in the right hippocampus. Left hippocampal gray matter density was correlated with verbal recognition memory: the higher the density, the better the performance (27). Relative to matched comparison subjects, euthymic women with recurrent depression showed smaller bilateral hippocampal volumes and a lower score in verbal memory, which is a neuropsychological measure of hippocampal function. In contrast, no difference in overall brain size or general intellectual performance was found (22). Concurrently, another study found impairments on hippocampus-dependent verbal memory tests in both patients with first-episode depression and those with multiple episodes. However, only the latter group had hippocampal volume reductions, which suggests that dysfunctions of the hippocampus predate detectable structural changes (20).

Two studies of geriatric depression found correlations between the brief assessment of memory and attention from the Mini-Mental State Examination and volume deficits in the left (24) and bilateral (33) hippocampus, although one study did not find any associations (23). It is of interest that having a small left hippocampus has been found to predict dementia at 5-year follow-up in a group of 115 older nondemented depressed individuals (60).

What Is the Mechanism Behind the Decreased Hippocampal Volume?

The nature of the volume reduction of hippocampus is not known. The elevated glucocorticoid levels often seen in severely depressed patients (11) along with the decreased hippocampal volume suggest a mechanism for putative neuronal loss seen within depressive patients either by apoptosis (programmed cell death) or inhibition of neurogenesis (61–63). Other mechanisms are, however, also possible, such as reduction of the volume of individual neurons or reduction of glia tissue (64, 65). Numerous animal studies have shown that glucocorticoids are toxic to the hippocampus, analogous to what is seen in Cushing's syndrome, in which the patients exhibit cognitive dysfunction, depression, and reduced hippocampal volume in addition to the other symptoms characteristic for this disease (66). It is thus well established that approximately half of depressed patients have hypothalamic-pituitary-adrenal (HPA) axis hyperactivity (11, 67, 68). This

abnormality could implicate hippocampal dysfunction because of its inhibitory influence on the HPA axis (69–71). In a PET study of relatively acutely depressed patients, we found markedly increased blood flow to the hippocampus (12), whereas others have found decreased activity in the parahippocampal area in a study of patients with treatment-resistant depression with a very long depression history (72). It is therefore tempting to hypothesize that in some types of depression, stressful life events may initiate a vicious circle in which increased cortisol levels gradually overstimulate the hippocampal cells, leading to their death and further decreasing the inhibitory regulation of the HPA axis (73–76). However, only one volumetric study of depression has been performed where the authors also measured cortisol after a dexamethasone suppression test, but unfortunately their MRI technique did not allow separation of amygdala from the hippocampus (77). In future research the combination of measuring HPA activity together with hippocampal volume in longitudinal studies is important.

It is not known whether the reduction in volume is reversible. Several studies have, however, suggested that treatment of depression can stop hippocampal atrophy or even reduce it (78–80), and a recent study has suggested that the behavioral effects of chronic antidepressant treatment may be mediated by the stimulation of neurogenesis in the hippocampus (81). Furthermore, neuropathological evidence from postmortem studies of patients with major depressive disorder or bipolar disorder suggests that depression is a disorder of neuroplasticity and cellular resilience and not a neurodegenerative disease (65, 82). The aforementioned connection between depression, stress, cortisol, and reduced hippocampal volume is intriguing. It is tempting to speculate that the hippocampus in patients with bipolar disorder being of normal size points to differences in pathogenesis between unipolar depression and bipolar disorder, but this requires further research because of the small number of volumetric studies of bipolar disorder patients.

Conclusion

In the present meta-analysis we found an average reduction of hippocampal volume of 8% in the left hemisphere and 10% in the right hemisphere in depressed patients relative to comparison subjects. It is interesting that a recent PET study of acutely depressed patients also found abnormalities in the right hippocampus (12). Reduced hippocampal volume is, however, not specific for depression, since it is also seen to a much larger degree in Alzheimer's disease (83).

The present findings of reduced hippocampal volume in unipolar depression and a correlation with the number of episodes are clinically interesting and in accordance with the predictions of the so-called glucocorticoid cascade hypothesis, although other explanations are also possible. If hippocampal volume reduction is a consequence of untreated depression, secondary prophylaxis to prevent the damage to the hippocampus becomes extremely important, especially since several studies suggest that treatment can stop the shrinkage or even reduce it. To test these hypotheses, longitudinal studies are necessary.

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