Structural Neuroimaging Studies in Major Depressive Disorder

Meta-analysis and Comparison With Bipolar Disorder

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Context: Although differences in clinical characteristics exist between major depressive disorder (MDD) and bipolar disorder (BD), consistent structural brain abnormalities that distinguish the disorders have not been identified.

Objectives: To investigate structural brain changes in MDD using meta-analysis of primary studies; assess the effects of medication, demographic, and clinical variables; and compare the findings with those of a meta-analysis of studies on BD.

Data Sources: The MEDLINE, EMBASE, and PsycINFO databases were searched for studies from January 1, 1980, to February 2, 2010.

Study Selection: Two hundred twenty-five studies that used magnetic resonance imaging or x-ray computed tomography to compare brain structure in patients with MDD with that of controls were included in an online database, and 143 that measured common brain structures were selected for meta-analysis.

Data Extraction: Twenty-five variables, including demographic and clinical data, were extracted from each study, when available. For the meta-analysis, mean structure size and standard deviation were extracted for continuous variables, and the proportion of patients and controls with an abnormality in brain structure was extracted for categorical variables.

Data Synthesis: Compared with the structure of a healthy brain, MDD was associated with lateral ventricle enlargement; larger cerebrospinal fluid volume; and smaller volumes of the basal ganglia, thalamus, hippocampus, frontal lobe, orbitofrontal cortex, and gyrus rectus. Patients during depressive episodes had significantly smaller hippocampal volume than patients during remission. Compared with BD patients, those with MDD had reduced rates of deep white matter hyperintensities, increased corpus callosum cross-sectional area, and smaller hippocampus and basal ganglia. Both disorders were associated with increased lateral ventricle volume and increased rates of subcortical gray matter hyperintensities compared with healthy controls.

Conclusions: The meta-analyses revealed structural brain abnormalities in MDD that are distinct from those observed in BD. These findings may aid investigators attempting to discriminate mood disorders using structural magnetic resonance imaging data.

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EPIDEMIOLOGIC AND TREATMENT studies have confirmed differences in clinical characteristics between major depressive disorder (MDD) and bipolar disorder (BD). Major depressive disorder, compared to BD, has a higher lifetime prevalence (16% vs 2%),[1,2] has an older median age at onset (32 vs 25 years),[3] and is associated with a lower number of depressive episodes.[4] Antidepressants are the most commonly prescribed medication for MDD[5]; mood stabilizers, such as lithium, are the most frequently prescribed treatment for BD.[6] However, despite these differences, consistent biomarkers distinguishing the disorders have been elusive.

It is not clear whether changes in brain structure differentiate MDD from BD or whether common abnormalities are present in both disorders. Reviews[7,8] of imaging studies have attempted to identify structural differences specific to each disorder in a qualitative fashion. In addition, meta-analyses, which quantitatively summarize research findings, have revealed evidence of structural abnormalities in patients with BD[9-11] and MDD[12-16] compared with healthy individuals. However, to our knowledge, meta-analytical methods have not been used to establish whether the identified abnormalities distinguish the disorders.

In the present study, we conducted a comprehensive meta-analysis of studies on brain structural changes in patients with MDD compared with controls and examined the specificity of these abnormalities by comparing the findings with those

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found in patients with BD. In the meta-analysis of MDD imaging studies, we increased both the number of included publications and brain regions by a factor of 2 compared with the largest previous meta-analysis.[13] Using data from a meta-analysis of studies on BD,[9] we made direct statistical comparisons between structural measures from each disorder while attempting to control for differences in study characteristics such as scanning parameters and patient demographics. Previous meta-analyses[12,13] of studies on patients with MDD most consistently report hippocampal volumetric reduction; we applied meta-regression techniques to investigate the effect of clinical variables on hippocampal volume. Finally, we provide an online database of 225 MDD structural imaging studies, listing 25 variables from each study, when available (http://www.depressiondatabase.org). The database is presented as an open-access wiki,[17] enabling other researchers to add studies.

METHODS

The study was divided into 3 parts: (1) the construction of a database of 225 studies investigating structural abnormalities in MDD, (2) a meta-analysis comparing patients with MDD with controls from a subgroup of 143 studies, and (3) a statistical comparison of structural abnormalities between patients with MDD and those with BD.

DATABASE OF IMAGING STUDIES IN MDD

The inclusion criteria for the database required peer-reviewed studies that measured brain structure using x-ray computed tomography (CT) or magnetic resonance imaging (MRI) in patients with MDD and a control group. The MEDLINE, EMBASE, and PsycINFO databases were searched from January 1, 1980, to February 2, 2010, using a combination of relevant expanded subject headings and free-text searches; detailed search terms are given in our wiki database. A total of 3960 records of unique publications were initially examined; we excluded case studies, reviews, studies that had not used standard diagnostic criteria, studies that combined MDD with BD patients in a single group, duplicate publications, and investigations using voxel-based morphometry (VBM) because the results of these studies cannot be included in a traditional meta-analysis. We did not include epidemiologic studies that diagnosed depression based on cutoffs of rating scales or considered antidepressant use a proxy for MDD diagnosis because the agreement between these measures and standard diagnostic criteria is questionable.[18] Two hundred twenty-five publications fulfilled the inclusion criteria and were included in the database.

DATA RECORDED IN THE DATABASE

The following data were recorded from each study when available: number of MDD patients and controls, mean age, number of males and females in the patient and control groups, and the diagnostic classification system used. Mean age of the patient at onset of the disease and mean Hamilton Scale for Depression (HAM-D)[19] score were also recorded. The HAM-D scale was chosen over other depression rating scales because it is the most commonly reported. For current medication, we recorded the number of patients who were described as *drug free* (not necessarily medication naive), as well as the number using mood stabilizers, antipsychotics, and antidepressants, including the class of antidepressant (selective serotonin reuptake inhibitor, tricyclic, monoamine oxidase inhibitor, or other). Information on current medication use was extracted from the publications directly; because data regarding prior exposure to medication were rarely presented, this information was not systematically collected. For each study, we recorded all brain structures or abnormalities measured, whether the measurement was MRI or CT based, slice thickness, and field strength of the MRI scanner.

The majority of variables in the database were not normally distributed; therefore, correlations were assessed using Spearman rank correlation (SPSS 15.0; SPSS Inc, Chicago, Illinois).

MDD META-ANALYSIS

Identification of Brain Regions/Abnormalities to Be Included in the Meta-analysis

To ensure no bias in selecting brain regions/abnormalities for the meta-analysis, we recorded every structure or abnormality investigated in the 225 studies. As with previous meta-analyses, exact anatomic definitions of individual structures varied across studies. For a given structure, some studies reported left and right measurements separately, and other studies reported the combined measurement. For studies that reported measures for the left and right volumes but not the total, we determined the mean and standard deviation for the total volume, using a reported method[13] that requires an estimate of the correlation coefficient between the left and right volumes. This coefficient was set as 0.8, although it was varied in the sensitivity analysis (described in the "Sensitivity Analysis" subsection of the "Methods" section). To ensure that the meta-analysis was sufficiently powered, brain regions were included if there were 3 or more independent studies that reported a mean and SD in both the control and patient groups (continuous measures), and abnormalities were included if there were 3 or more independent studies that reported the number of patients and controls with the abnormality (categorical measure). From the 225 studies in the database, there were a total of 324 different brain regions examined; however, only 63 regions were examined by 3 or more studies, and these were entered in the meta-analysis. The total number of studies included in the meta-analysis was 143; many studies in the database did not examine 1 or more of the 63 identified regions. The studies in the meta-analysis included 9 publications that used CT measures of total lateral ventricle volume (analyzed as a subgroup), and all other brain structures were examined using MRI.

Combining Study Estimates

For continuous outcome measures, Hedges *g* was used, which is the Cohen effect size with a correction for bias from small sample sizes.[20] The percentage difference effect size is also provided to aid biological interpretation of the data.[21] The majority of studies report absolute volume measures; however, some report volumes as ratios of the entire brain or cross-sectional area measures. All such measurements have been included in the meta-analysis; however, because combining measures may increase heterogeneity, an additional analysis was carried out with volume measures only (see "Sensitivity Analysis" subsection of the "Methods" section). For categorical outcome measures, the odds ratio was used. Outcome measures were recorded from each study and were independently checked to ensure accuracy. For a given brain structure, if 2 or more studies by the same research group reported similar patient or control demographics, we contacted the authors of those studies to determine whether there was overlap in the sample and, if

this was the case, included only the largest relevant study. A total of 150 measures from 52 studies were excluded for this reason. A meta-analysis for each brain structure was performed (using the metan command in Stata 9.2, 2006; StataCorp LP, College Station, Texas). Outcome measures were combined using a random-effects inverse-weighted variance model.[22] Because the meta-analyses examined a large number of regions and are susceptible to type I errors, results that survive Bonferroni correction for multiple comparisons (corrected for 63 regions, $P < .0008$) are indicated.

Combining Patient Subgroups

A minority of imaging studies presented measures from subgroups of patients. For these studies, we entered the subgroups in the meta-analysis as if they were separate studies and, in each case, the number of individuals in the control group was considered the sample size of the control group divided by the number of patient subgroups. This method has been used in a previous meta-analysis.[9] If studies reported on males and females separately, we entered the results as if they were from 2 separate studies, a technique adopted by another previous meta-analysis.[23]

Assessing Between-Study Heterogeneity

To test for between-study heterogeneity, the Cochran *Q* test statistic was calculated.[24] The I^2 statistic, which is equal to the percentage of total variation across studies as the result of heterogeneity, was also calculated to aid interpretability of between-study heterogeneity.[25]

Small-Study Bias

The effect of small-study bias (which may include publication bias) was investigated for regions in which the pooled effect size revealed a significant group difference between MDD patients and controls and when at least 5 studies were included in the meta-analysis to ensure that the test was sufficiently powered. Small-study bias was assessed using the Egger regression test.[26]

Effect of Clinical Variables on Hippocampal Volume

The number of brain regions and clinical variables included in the database allows a potentially high number of correlations to be examined, which may lead to type I errors. Thus, the analysis was limited to the effect of clinical variables on total hippocampal volume. We selected this region because of the robust evidence of volumetric reduction in MDD[12,13] and because many studies have measured this structure, ensuring adequate statistical power. A random effects meta-regression was implemented (metareg command in Stata 9.2) to examine age at onset, HAM-D score, percentage of patients using antidepressants, number of depressive episodes, and patient age. In addition, we combined studies that directly compared the same MDD subgroups (eg, depressed vs remitted patients) in a supplementary meta-analysis. Finally, we determined whether the reduction in hippocampal volume remained when the meta-analysis was restricted to the following MDD patient groups: no comorbid anxiety disorders, no history of alcohol/substance abuse or dependence, first episode, adolescents, adults, and elderly patients.

Sensitivity Analysis

To test how robust the results were to variations in the meta-analysis method, the effect of the following was examined: (1) percentage difference in the patient and control mean volumes as an outcome measure for continuous data (calculation of this effect size and the effect size variance has been described in more detail in previous meta-analytical studies[21,23]); (2) excluding studies that reported continuous data as areas, lengths, or ratios rather than absolute volume; and (3) setting the correlation coefficient between the left and right regional volumes as 0.1, 0.5, and 1.

COMPARISON WITH BD

Stratified Meta-analysis

Two meta-analytical approaches may be taken to examine differences between MDD and BD: (1) meta-analysis of studies directly comparing the same brain structure in patients with MDD vs those with BD or (2) indirect analysis comparing the pooled effect size from studies comparing MDD patients vs controls with that from studies comparing BD patients vs controls. We adopted the second approach, which has the advantage of including more studies and brain structures because there are very few direct comparisons. Thus, to compare the results from the MDD meta-analysis with those of a previous meta-analysis of BD studies,[9] we combined the effect sizes from BD patients vs controls with MDD patients vs controls (effectively, a meta-analysis of studies on patients with affective disorder) and performed a stratified meta-analysis using a *z* test to compare across the 2 disorders. To match the method exactly, the BD meta-analysis was reanalyzed, using the technique of combining left and right brain structural measures adopted in the present MDD meta-analysis. To reduce the number of comparisons, we focused on brain regions that were significantly different from those of controls (before Bonferroni correction) in either the MDD or BD meta-analysis.

Verifying Diagnostic Differences

We adopted a 2-stage process to ensure that significant differences between the groups that were identified in the stratified meta-analysis were not the result of variations in patient demographics or scanning parameters rather than MDD or BD diagnosis. First, for each brain structure, we examined whether the following summary variables were significantly different between MDD and BD studies, using an independent-samples *t* test: percentage of patients who were female, medication free, using antidepressants, using neuroleptics, and using mood stabilizers; mean patient age; scanner magnetic field strength; and slice thickness. Second, when a significant difference was identified between BD and MDD studies for those variables, a meta-regression was performed separately in MDD and BD studies to examine the effect of the variable on the given brain structure.

RESULTS

Demographic and clinical data from the database are reported, followed by results from the MDD meta-analyses and comparison with the BD meta-analysis.

DATABASE OF IMAGING STUDIES IN MDD

Details from 225 studies that included a total of 9533 patients with MDD and 8846 controls were entered into the database. **Table 1** summarizes the variables recorded.

Table 1. Patient and Control Demographic and Clinical Data Recorded in the Database

Variable	No. of Studies Reporting Variable	Mean (SD) Between Studies	Pooled No. of Participants in Database
No. of patients	225	42.4 (39.1)	9533
No. of controls	225	39.3 (29.2)	8846
Age, y			
Patient, mean	182	52.2 (17.9)	
Patient, SD	176	9.1 (3.9)	
Control, mean	205	50.6 (18.3)	
Control, SD	196	8.7 (3.8)	
Age at onset	93	37.5 (15.2)	
HAM-D score[a]	90	20.3 (5.8)	
		Participants in Each Study, Mean (SD), %	
Female patients	207	65.4 (17.6)	6028
Female controls	207	61.2 (17.2)	4834
Current medication			
Medication free	69	68.5 (40.9)	1406
Antidepressant	87	32.9 (39.4)	930
SSRI	75	10.9 (15.8)	369
Tricyclic	74	6.9 (12.2)	215
MAOI	64	0.2 (0.9)	6
Other	69	8.8 (15.9)	289
Mood stabilizer	56	3.2 (8.7)	69
Antipsychotic	61	4.2 (12.3)	86

Abbreviations: HAM-D, Hamilton Scale for Depression; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Many studies did not report the HAM-D scale version used (eg, 17 or 21 questions); the value given is the mean of all HAM-D values and is thus an approximation of depression severity.

The classification systems used for defining MDD were *DSM-IV* (156 studies); *DSM-III-R* (46 studies); *DSM-III* (13 studies); *International Classification of Diseases, Ninth Revision* or *International Classification of Diseases, Tenth Revision* (5 studies); Research Diagnostic Criteria[27] (4 studies); and Chinese Classification of Mental Disorders[28] (1 study). Two hundred eight studies used MRI and 17 studies used CT imaging. Among MRI studies, 81% used a 1.5-T scanner; 11% used a lower field strength and 6% used a higher field strength. The mean (SD) slice thickness was 9.0 (1.0) mm in CT studies and 2.8 (2.1) mm in MRI studies. There was evidence that studies were recruiting larger numbers of patients over time ($R=0.21$; $P=.002$) and that the number of studies per year was increasing ($R=0.94$; $P<.001$).

MDD META-ANALYSIS

The 143 studies included in the meta-analysis[29-171] are listed in **Table 2**. Compared with controls, patients with MDD had larger lateral ventricular and cerebrospinal fluid (CSF) volumes and smaller volumes of the total caudate, putamen, globus pallidus, thalamus, hippocampus, frontal lobe, orbitofrontal gray matter, and gyrus rectus (**Figure 1** and **Table 3**). The pituitary gland was increased in volume, with borderline significance ($P=.054$). Patients with MDD had moderately increased rates of MRI signal hyperintensities, but this was dependent on the measurement technique used. When hyperintensity rating scales were used, periventricular hyperintensities were increased (Figure 1 and Table 3); when categorical classification was used (patient classified as having hyperintensities or no hyperintensities), subcortical gray matter hyperintensities were increased (**Figure 2** and **Table 4**). The differences that survived Bonferroni correction ($P<.0008$) were increased lateral ventricle and CSF volume and decreased hippocampal and gyrus rectus volume (Table 3). No small-study bias was detected in any of the brain regions identified in this paragraph (all $P>.11$).

Effect of Clinical Variables on Hippocampal Volume

Because outliers may have a disproportionate effect on meta-regression analysis, 2 outliers[113,167] were removed before investigating the effect of clinical variables on total hippocampal volume (effect sizes of outliers, –3.8 and –2.2; effect size range of the remaining 35 studies, –1.3 to +0.4; and pooled effect size after 2 studies were excluded, –0.40). There was no significant effect of age at onset (23 studies, $P=.75$), HAM-D score (18 studies, $P=.58$), percentage of patients using antidepressants (22 studies, $P=.61$), number of depressive episodes (20 studies, $P=.25$), or patient age (35 studies, $P=.54$) on the difference in hippocampal volume between patients and controls. For each meta-regression performed, the heterogeneity of the included studies remained significant ($I^2 > 28\%$). In terms of subgroups, patients with MDD in remission had a significantly larger hippocampal volume compared with patients who were currently depressed (4 studies, effect size, 0.34; 95% confidence interval, 0.02-0.67; $P=.04$); there was no significant difference in volume between patients with remitted MDD and controls (5 studies, $P=.25$). In addition, there was no significant difference in hippocampal volume between patients with first episode vs multiple episodes (4 studies, $P=.32$) or patients with early- vs late-onset depression (3 studies, $P=.24$). The significant reduction in hippocampal volume remained when the meta-analysis was limited to first-episode studies (6 studies; effect size, –0.22; $P=.04$); studies that excluded patients with a comorbid anxiety disorder (10 studies; effect size, –0.39; $P<.001$); and studies that excluded patients with a history of drug abuse/dependence or substance abuse/dependence (6 studies; effect size, –0.32; $P<.001$), adults (mean age, 20-60 years; 22 studies; effect size, –0.43; $P<.001$), and elderly patients (60-75 years; 8 studies; effect size, –0.34; $P<.001$). Although the effect size was similar to that of other subgroups, there was no significant reduction of hippocampal volume in adolescent patients (12-19 years; 5 studies; effect size, –0.35; $P=.11$).

Sensitivity Analysis

When percentage change was used as the effect size for continuous data, there was a reduction in the volume of the right orbitofrontal cortex and an increase in deep white matter hyperintensities as measured by rating scales in patients with MDD, and the decrease previously observed in the globus pallidus became a trend. If ratio,

Table 2. List of Studies Included in the MDD Meta-analysis

Study	No. of MDD Patients	No. of Controls	Diagnostic Criteria	Mean Patient Age, y	Imaging Modality
Scott et al,[29] 1983	10	10	*DSM-III*	39.2	CT
Iacono et al,[30] 1988	16	44	*DSM-III*	22.6	CT
Pearlson et al,[31] 1989	11	31	*DSM-III*	70.0	CT
Andreasen et al,[32] 1990	27	75	*DSM-III*	37.3	CT
Coffey et al,[33] 1990	35	22	*DSM-III*	71.7	MRI
Harvey et al,[34] 1990	5	50	RDC	NA	CT
Zubenko et al,[35] 1990	67	44	*DSM-III-R*	73.2	MRI
Husain et al,[36] 1991	41	44	*DSM-III-R*	55.3	MRI
Lammers et al,[37] 1991	20	20	*DSM-III-R*	53.8	MRI
Lewine et al,[38] 1991	12	68	*DSM-III*	NA	MRI
Brown et al,[39] 1992	28	154	*DSM-III-R*	40.3	MRI
Guze and Szuba,[40] 1992	119	60	*DSM-III-R*	54.1	MRI
Krishnan et al,[41] 1992	50	50	*DSM-III*	48.3	MRI
Lauer et al,[42] 1992	14	12	*DSM-III-R*	40.7	CT
Shah et al,[43] 1992	27	36	*DSM-III*	57.6	MRI
Axelson et al,[44] 1993	19	30	*DSM-III*	46.7	MRI
Krishnan et al,[45] 1993	25	20	*DSM-III*	74.1	MRI
Lisanby et al,[46] 1993	21	21	*DSM-III-R*	65.0	MRI
Wu et al,[47] 1993	20	16	*DSM-III-R*	32.9	MRI
Lesser et al,[48] 1994	39	20	*DSM-III-R*	60.9	MRI
Miller et al,[49] 1994	19	23	*DSM-III-R*	69.0	MRI
Dupont et al,[50] 1995	30	26	*DSM-III-R*	38.6	MRI
Dupont et al,[51] 1995	33	32	*DSM-III-R*	38.9	MRI
Lewine et al,[52] 1995	27	150	*DSM-III-R*	40.9	MRI
Wurthmann et al,[53] 1995	34	43	*DSM-III-R*	70.7	CT
Elkis et al,[54] 1996	24	40	*DSM-III-R*	38.7	CT
Greenwald et al,[55] 1996	48	39	*DSM-III-R*	74.6	MRI
Keshavan et al,[56] 1996	19	19	*DSM-III-R*	67.0	MRI
Lesser et al,[57] 1996	95	165	*DSM-III-R*	61.0	MRI
Marchesi et al,[58] 1996	11	11	*DSM-III-R*	64.8	CT
Drevets et al,[59] 1997	17	21	*DSM-III-R*	35.0	MRI
Kumar et al,[60] 1997	28	29	*DSM-III-R*	74.2	MRI
Pantel et al,[61] 1997	19	13	*DSM-III-R*	72.4	MRI
Pillay et al,[62] 1997	38	20	*DSM-III-R*	38.5	MRI
Kumar et al,[63] 1998	35	30	*DSM-IV*	74.6	MRI
Parashos et al,[64] 1998	72	38	*DSM-III-R*	55.4	MRI
Pillay et al,[65] 1998	38	20	*DSM-III-R*	38.5	MRI
Sheline et al,[66] 1998	20	20	*DSM-IV*	54.0	MRI
Ashtari et al,[67] 1999	40	46	*DSM-III-R*	74.3	MRI
Kramer-Ginsberg et al,[68] 1999	41	38	*DSM-III-R*	74.6	MRI
Lenze et al,[69] 1999	24	24	*DSM-IV*	52.7	MRI
Lenze and Sheline,[70] 1999	24	24	*DSM-IV*	53.0	MRI
Bremner et al,[71] 2000	16	16	*DSM-IV*	43.0	MRI
Kumar et al,[72] 2000	51	30	*DSM-IV*	74.3	MRI
Vakili et al,[73] 2000	38	20	*DSM-III-R*	38.5	MRI
Caetano et al,[74] 2001	17	39	*DSM-IV*	42.8	MRI
Greenwald et al,[75] 2001	81	70	*DSM-III-R*	74.7	MRI
McIntosh et al,[76] 2001	9	29	*DSM-III-R*	43.6	MRI
Novaretti et al,[77] 2001	30	20	*ICD-10*	71.0	MRI
Rusch et al,[78] 2001	25	15	*DSM-IV*	33.2	MRI
Sassi et al,[79] 2001	13	34	*DSM-IV*	41.2	MRI
Botteron et al,[80] 2002	48	48	*DSM-IV*	26.1	MRI
Brambilla et al,[81] 2002	18	38	*DSM-IV*	42.0	MRI
Bremner et al,[82] 2002	15	20	*DSM-IV*	43.0	MRI
Frodl et al,[83] 2002	30	30	*DSM-IV*	40.3	MRI
Nolan et al,[84] 2002	22	22	*DSM-IV*	13.7	MRI
Pujol et al,[85] 2002	57	37	*DSM-IV*	60.8	MRI
Salokangas et al,[86] 2002	37	19	*DSM-IV*	36.0	MRI
Steingard et al,[87] 2002	19	38	*DSM-III-R*	15.4	MRI
Tupler et al,[88] 2002	115	37	*DSM-III-R*	66.7	MRI
Agid et al,[89] 2003	37	27	*DSM-IV*	55.0	MRI
Almeida et al,[90] 2003	51	37	*DSM-IV*	74.2	MRI
Frodl et al,[91] 2003	57	57	*DSM-IV*	44.5	MRI
Lacerda et al,[92] 2003	25	48	*DSM-IV*	41.2	MRI

(continued)

Table 2. List of Studies Included in the MDD Meta-analysis (continued)

Study	No. of MDD Patients	No. of Controls	Diagnostic Criteria	Mean Patient Age, y	Imaging Modality
MacMillan et al,[93] 2003	23	23	*DSM-IV*	14.0	MRI
MacQueen et al,[94] 2003	37	37	*DSM-IV*	28.4	MRI
Posener et al,[95] 2003	27	42	*DSM-IV*	33.0	MRI
Sassi et al,[96] 2003	18	38	*DSM-IV*	42.8	MRI
Sheline et al,[97] 2003	38	38	*DSM-IV*	50.8	MRI
Silverstone et al,[98] 2003	11	19	*DSM-IV*	34.4	MRI
Baldwin et al,[99] 2004	50	35	*DSM-IV*	73.7	MRI
Ballmaier et al,[100] 2004	17	17	*DSM-IV*	75.2	MRI
Ballmaier et al,[101] 2004	24	19	*DSM-IV*	65.9	MRI
Caetano et al,[102] 2004	31	31	*DSM-IV*	39.2	MRI
Hastings et al,[103] 2004	18	18	*DSM-III-R*	38.9	MRI
Janssen et al,[104] 2004	28	41	*DSM-IV*	64.0	MRI
Lacerda et al,[105] 2004	31	34	*DSM-IV*	39.3	MRI
Lange and Irle,[106] 2004	17	17	*DSM-IV*	34.0	MRI
Lavretsky et al,[107] 2004	41	41	*DSM-IV*	70.5	MRI
Lloyd et al,[108] 2004	51	39	*DSM-IV*	74.0	MRI
MacMaster and Kusumakar,[109] 2004	17	17	*DSM-IV*	16.7	MRI
MacMaster and Kusumakar,[110] 2004	17	17	*DSM-IV*	16.7	MRI
Supprian et al,[111] 2004	10	10	*DSM-IV*	48.9	MRI
Vythilingam et al,[112] 2004	38	33	*DSM-IV*	41.0	MRI
Xia et al,[113] 2004	22	13	CCMD	39.5	MRI
Chen et al,[114] 2005	39	20	*DSM-IV*	69.9	MRI
Coryell et al,[115] 2005	10	10	*DSM-IV*	21.9	MRI
Hickie et al,[116] 2005	51	20	*DSM-IV*	53.5	MRI
Iosifescu et al,[117] 2005	50	35	*DSM-IV*	40.6	MRI
Lacerda et al,[118] 2005	22	39	*DSM-IV*	41.4	MRI
Lavretsky et al,[119] 2005	41	41	*DSM-IV*	70.5	MRI
Lin et al,[120] 2005	37	18	*DSM-IV*	72.2	MRI
Rosso et al,[121] 2005	20	24	*DSM-IV*	15.4	MRI
Taylor et al,[122] 2005	135	83	*DSM-IV*	70.0	MRI
Caetano et al,[123] 2006	31	31	*DSM-IV*	39.2	MRI
Frodl et al,[124] 2006	34	34	*DSM-IV*	45.5	MRI
Hannestad et al,[125] 2006	182	64	*DSM-IV*	70.2	MRI
Iosifescu et al,[126] 2006	84	35	*DSM-III-R*	40.5	MRI
MacMaster et al,[127] 2006	35	35	*DSM-IV*	14.5	MRI
Naish et al,[128] 2006	29	22	*DSM-IV*	71.0	MRI
Saylam et al,[129] 2006	24	24	*DSM-IV*	33.4	MRI
Velakoulis et al,[130] 2006	12	87	*DSM-III-R*	22.6	MRI
Weniger et al,[131] 2006	21	23	*DSM-IV*	34.0	MRI
Caetano et al,[132] 2007	19	24	*DSM-IV*	13.0	MRI
Colla et al,[133] 2007	24	14	*DSM-IV*	54.5	MRI
Hickie et al,[134] 2007	45	16	*DSM-IV*	52.0	MRI
Lavretsky et al,[135] 2007	43	41	*DSM-IV*	70.7	MRI
Maller et al,[136] 2007	45	30	*DSM-IV*	37.4	MRI
Munn et al,[137] 2007	26	18	*DSM-IV*	20.5	MRI
Taylor et al,[138] 2007	226	144	*DSM-IV*	70.0	MRI
Andreescu et al,[139] 2008	71	32	*DSM-IV*	72.2	MRI
Ballmaier et al,[140] 2008	46	34	*DSM-IV*	71.1	MRI
Ballmaier et al,[141] 2008	46	34	*DSM-IV*	71.1	MRI
Chen et al,[142] 2008	27	26	*DSM-IV*	14.4	MRI
Eker et al,[143] 2008	34	39	*DSM-IV*	31.7	MRI
Elderkin-Thompson et al,[144] 2008	43	41	*DSM-IV*	70.7	MRI
Frodl et al,[146] 2008	78	78	*DSM-IV*	44.7	MRI
Keller et al,[147] 2008	42	22	*DSM-IV*	36.5	MRI
Lenze et al,[148] 2008	31	24	*DSM-IV*	50.0	MRI
MacMaster et al,[149] 2008	32	35	*DSM-IV*	14.1	MRI
Matsuo et al,[150] 2008	27	26	*DSM-IV*	14.4	MRI
Tae et al,[151] 2008	21	20	*DSM-IV*	41.7	MRI
Zanetti et al,[152] 2008	28	102	*DSM-IV*	30.5	MRI
Bergouignan et al,[153] 2009	21	21	*DSM-IV*	33.2	MRI
Elderkin-Thompson et al,[145] 2009	26	23	*DSM-IV*	70.0	MRI
Exner et al,[154] 2009	35	26	*DSM-IV*	34.5	MRI
Jessen et al,[155] 2009	79	84	*DSM-IV*	48.2	MRI
Kronenberg et al,[156] 2009	24	14	*DSM-IV*	54.5	MRI

(continued)

Table 2. List of Studies Included in the MDD Meta-analysis (continued)

Study	No. of MDD Patients	No. of Controls	Diagnostic Criteria	Mean Patient Age, y	Imaging Modality
Kronmüller et al,[157] 2009	57	30	*DSM-IV*	43.5	MRI
Lorenzetti et al,[158] 2009	56	33	*DSM-IV*	33.7	MRI
Milne et al,[159] 2009	28	14	*DSM-IV*	39.7	MRI
Pan et al,[160] 2009	170	83	*DSM-IV*	69.4	MRI
Penttilä et al,[161] 2009	35	70	*DSM-IV*	47.2	MRI
Pizzagalli et al,[162]e 2009	30	31	*DSM-IV*	43.2	MRI
Sun et al,[163] 2009	45	30	*DSM-IV*	40.8	MRI
Tamburo et al,[164] 2009	14	11	*DSM-IV*	69.8	MRI
van Eijndhoven et al,[165] 2009	40	20	*DSM-IV*	35.7	MRI
Walterfang et al,[166] 2009	54	32	*DSM-IV*	34.3	MRI
Kaymak et al,[167] 2010	20	15	*DSM-IV*	32.0	MRI
Köhler et al,[168] 2010	35	29	*DSM-IV*	74.1	MRI
Lorenzetti et al,[169] 2010	56	31	*DSM-IV*	33.7	MRI
Meisenzahl et al,[170] 2010	92	138	*DSM-IV*	44.6	MRI
Weber et al,[171] 2010	38	62	*DSM-IV*	66.1	MRI

Abbreviations: CCMD, Chinese Classification of Mental Disorders; CT, computed tomography; MDD, major depressive disorder; MRI, magnetic resonance imaging; NA, not available; RDC, Research Diagnostic Criteria.

length, and area measurements were excluded, lateral, ventricle measures using CT imaging could not be included because all studies reported a ventricle to brain ratio measure; no other changes were noted. There was no change in the results when the correlation coefficient between left and right regions was set to 0, 0.5, or 1.

COMPARISON WITH BD

Stratified Meta-analysis

Nine regions included in both the MDD and BD meta-analyses showed significant differences from controls, allowing a comparison to be made (**Table 5**). Six of these regions differed between MDD and BD. Compared with BD patients or controls, patients with MDD had significantly reduced volumes of the caudate, putamen, globus pallidus, and hippocampus. Compared with MDD patients or controls, patients with BD had significantly reduced cross-sectional areas of the corpus callosum and increased rates of deep white matter hyperintensities. Compared with controls, both MDD and BD patients showed ventricular dilation and increased rates of subcortical gray matter hyperintensities, but there was no significant difference between the patient groups.

Verifying Diagnostic Differences

When we examined differences in study characteristics between BD and MDD investigations for each of the 6 brain regions identified in the previous paragraph, there were significant differences in terms of patient age (5 regions), sex (3 regions), and medication use (5 regions), but no significant differences in terms of scanner field strength or slice thickness. From the follow-up meta-regression analyses, there was no significant effect of patient age, sex, or medication use on any of the 6 regions in either BD or MDD studies. One exception was patient age in BD studies, in which increased age was associated with increased hippocampal volume compared with matched controls ($P=.001$).

COMMENT

In patients with MDD compared with controls, we identified increased lateral ventricle and CSF volume; reduced volume of the basal ganglia, thalamus, hippocampus, frontal lobe, orbitofrontal cortex, and gyrus rectus; and increased rates of periventricular and subcortical gray matter hyperintensities. Currently depressed MDD patients had smaller hippocampal volumes vs those with remitted MDD. Within mood disorders, basal ganglia and hippocampal volume reductions appear to be specific to MDD, and reduced corpus callosum cross-sectional area and increased rates of deep white matter hyperintensities appear to be specific to BD.

HIPPOCAMPUS AND HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

In MDD patients compared with controls, we found bilateral reductions in hippocampal volume (−5%) as reported by previous meta-analyses,[12,13,174] and also showed a strong significant trend for increased pituitary volume ($P=.054$, 5%). These findings may provide evidence for the involvement of the hypothalamic-pituitary-adrenal axis in MDD. The anterior pituitary produces adrenocorticotropic hormone, and it is conceivable that an increased volume of the pituitary may be associated with increased adrenocorticotropic hormone production. A primary role of adrenocorticotropic hormone is stimulation of the adrenal cortex, which responds by producing glucocorticoids. There is strong evidence that glucocorticoid levels are increased in MDD, and prolonged high levels may damage hippocampal neurons.[175] A small number of studies measured the adrenal gland in MDD; these were not included in our meta-analysis because only 2 (not meeting our criterion of 3) measured this structure in a group including only patients with MDD. However, because of the weight of evidence supporting the involvement of the hypothalamic-

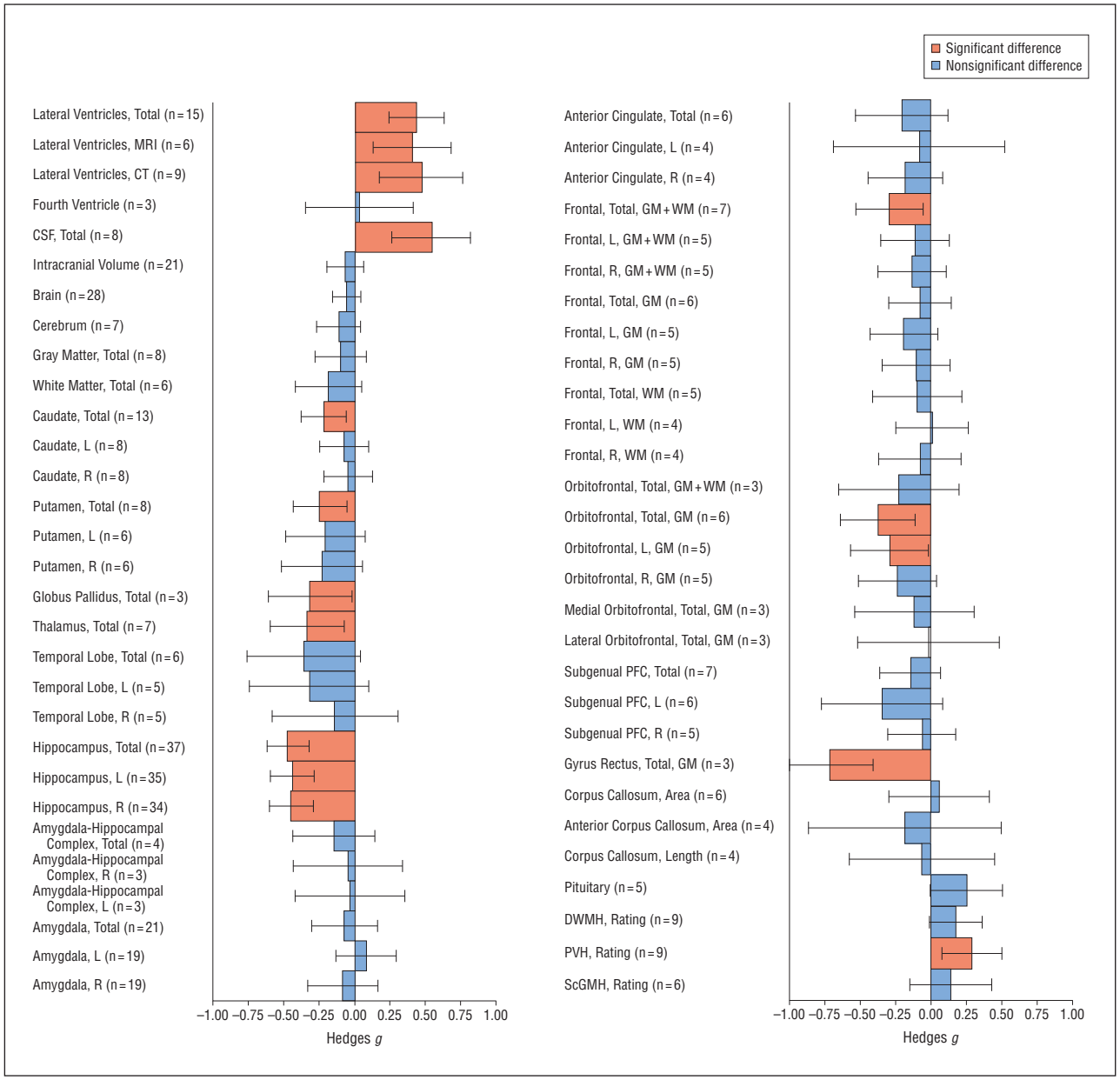

Figure 1. Continuous variables evaluated in major depressive disorder (MDD) meta-analysis. Hedges *g* (Cohen effect size with small sample correction) is shown for each structure, with 95% confidence intervals. The effect size is positive when the structure is larger in patients with MDD compared with controls and negative when the structure is smaller in MDD patients. The number of studies included in each meta-analysis is indicated with each structure. CSF indicates cerebrospinal fluid; CT, computed tomography; DWMH, deep white matter hyperintensities; GM, gray matter; L, left; MRI, magnetic resonance imaging; PFC, prefrontal cortex; PVH, periventricular hyperintensities; R, right; ScGMH, subcortical gray matter hyperintensities; and WM, white matter.

pituitary-adrenal axis, we entered these studies into an additional meta-analysis (not previously reported). The 3 case-control studies comprised 1 MRI study that evaluated 3 BD patients with 32 MDD patients as a single group[176] and 2 CT studies of MDD patients.[177,178] Adrenal volume was significantly increased compared with controls (effect size, 0.81; 95% confidence interval, 0.45-1.16; $P < .0001$), providing further evidence of an association between MDD and hypothalamic-pituitary-adrenal axis abnormalities. The finding that hippocampal volume was significantly smaller in patients with a depressed compared with remitted state raises the possibility that reductions in hippocampal volume may normalize during remission, and it is tempting to speculate that this may be the result of neurogenesis in the dentate gyrus.[179] A longitudinal study performing scans on the same patients during depression and after recovery would be an effective way of examining these putative changes in more detail. Although we did not detect an association between antidepressant use and hippocampal volume, there is growing evidence that antidepressants may upregulate neurogenesis. Malberg et al[180] reported that chronic antidepressant therapy increased neurogenesis in rats and an antipsychotic medication had no effect. More recently, a postmortem study[181] reported that depressed patients who had been treated with antidepressants had an increased number of neural progenitor cells in the dentate gyrus compared with un-

Table 3. Meta-analysis of Continuous Data Comparing Patients With MDD vs Controls[a]

Region	No. of Studies	No. of MDD/ Controls[a]	MDD Patients vs Controls			Heterogeneity			SS Bias, *P* Value[d]
			Effect Size (95% CI)	Effect Size *P* Value[b]	Size vs Controls, %	*Q*	I^{2c} (%)	*P* Value	
Lateral ventricles, total	**15**	**371/539**	**0.44 (0.24 to 0.63)**	**.00001[e]**	**122.4**	**25**	**39**	**.06**	**.15**
Lateral ventricles, MRI	**6**	**220/224**	**0.41 (0.13 to 0.68)**	**.004**	**124.0**	**8**	**40**	**.14**	**.59**
Lateral ventricles, CT	**9**	**151/315**	**0.47 (0.18 to 0.76)**	**.0016**	**121.4**	**16**	**45**	**.06**	**.20**
Fourth ventricle	3	46/75	0.03 (–0.35 to 0.41)	.86	103.6	2	1	.36	
CSF, total	**8**	**259/218**	**0.54 (0.26 to 0.82)**	**.00014[e]**	**113.9**	**19**	**52**	**.03**	**.60**
Intracranial volume	21	765/811	–0.07 (–0.20 to 0.06)	.30	99.4	37	36	.04	
Brain	28	1187/1014	–0.06 (–0.16 to 0.04)	.24	99.2	37	13	.26	
Cerebrum	7	392/283	–0.11 (–0.27 to 0.04)	.15	98.8	5	0	.56	
GM, total	8	261/253	–0.10 (–0.28 to 0.08)	.27	98.9	5	0	.87	
WM, total	6	196/157	–0.19 (–0.42 to 0.05)	.12	98.1	8	11	.35	
Caudate, total	**13**	**586/391**	**–0.22 (–0.38 to –0.06)**	**.0063**	**96.5**	**15**	**22**	**.22**	**.57**
Caudate, left	8	347/258	–0.07 (–0.25 to 0.10)	.40	98.6	4	0	.75	
Caudate, right	8	347/258	–0.05 (–0.22 to 0.12)	.59	99.1	6	0	.55	
Putamen, total	**8**	**460/298**	**–0.25 (–0.43 to –0.06)**	**.0087**	**95.9**	**10**	**28**	**.21**	**.69**
Putamen, left	6	313/256	–0.21 (–0.49 to 0.07)	.15	95.9	12	57	.04	
Putamen, right	6	313/256	–0.23 (–0.52 to 0.05)	.11	95.1	12	58	.03	
Globus pallidus, total	**3**	**122/111**	**–0.31 (–0.61 to –0.02)**	**.04**	**95.5**	**2**	**13**	**.32**	
Thalamus, total	**7**	**245/205**	**–0.34 (–0.60 to –0.07)**	**.012**	**93.3**	**10**	**40**	**.12**	**.78**
Temporal lobe, total	6	164/152	–0.36 (–0.76 to 0.04)	.08	95.5	14	65	.02	
Temporal lobe, left	5	113/122	–0.32 (–0.74 to 0.10)	.14	96.0	9	57	.05	
Temporal lobe, right	5	113/122	–0.14 (–0.59 to 0.30)	.53	98.3	10	62	.03	
Hippocampus, total	**37**	**1377/1281**	**–0.47 (–0.62 to –0.32)**	**<.00001[e]**	**94.5**	**131**	**67**	**<.01**	**.14**
Hippocampus, left	**35**	**1248/1214**	**–0.44 (–0.60 to –0.28)**	**<.00001[e]**	**94.7**	**130**	**68**	**<.01**	**.11**
Hippocampus, right	**34**	**1220/1200**	**–0.45 (–0.60 to –0.30)**	**<.0001[e]**	**94.5**	**119**	**66**	**<.01**	**.15**
Amygdala-hippocampal complex, total	4	87/118	–0.15 (–0.43 to 0.14)	.31	97.8	1	0	.78	
Amygdala-hippocampal complex, right	3	47/72	–0.05 (–0.43 to 0.33)	.80	99.1	0	0	.84	
Amygdala-hippocampal complex, left	3	47/72	–0.03 (–0.42 to 0.35)	.86	99.3	0	0	.80	
Amygdala, total	21	633/583	–0.07 (–0.31 to 0.16)	.54	98.8	87	73	<.01	
Amygdala, left	19	517/535	0.08 (–0.13 to 0.29)	.46	101.0	58	62	<.01	
Amygdala, right	19	517/535	–0.08 (–0.33 to 0.16)	.51	98.9	77	71	<.01	
Anterior cingulate, total	6	276/264	–0.21 (–0.53 to 0.12)	.22	96.0	17	70	<.01	
Anterior cingulate, left	4	190/212	–0.09 (–0.69 to 0.52)	.78	99.3	26	88	<.01	
Anterior cingulate, right	4	190/212	–0.18 (–0.44 to 0.08)	.17	95.3	5	40	.17	
Frontal, total, GM + WM	**7**	**262/213**	**–0.29 (–0.53 to –0.05)**	**.02**	**96.2**	**12**	**34**	**.14**	**.46**
Frontal, left, GM + WM	5	139/145	–0.11 (–0.36 to 0.13)	.35	98.6	4	0	.74	
Frontal, right, GM + WM	5	139/145	–0.13 (–0.37 to 0.11)	.28	98.9	4	0	.68	
Frontal, total, GM	6	171/166	–0.08 (–0.30 to 0.14)	.48	98.8	7	0	.44	
Frontal, left, GM	5	153/129	–0.19 (–0.43 to 0.05)	.12	98.4	4	0	.69	
Frontal, right, GM	5	153/129	–0.10 (–0.34 to 0.14)	.39	99.0	4	0	.67	
Frontal, total, WM	5	152/153	–0.10 (–0.41 to 0.22)	.54	99.1	10	42	.11	
Frontal, left, WM	4	134/116	0.01 (–0.25 to 0.26)	.95	99.7	4	0	.60	
Frontal, right, WM	4	134/116	–0.08 (–0.37 to 0.21)	.60	98.7	6	21	.28	
Orbitofrontal, total GM + WM	3	140/105	–0.23 (–0.66 to 0.20)	.30	95.4	7	59	.06	

(continued)

treated patients or controls. In previous meta-analyses, Videbech and Ravnkilde[12] reported that increased duration of illness was associated with smaller right hippocampal volume, and McKinnon et al[14] did not find hippocampal reduction in first episodes of MDD. Conversely, we did not find an association with duration of illness and determined that hippocampal volume reduction was present in patients at first episode. However, in our analysis, the effect size in first-episode studies (0.22) was numerically less than that in all studies combined (0.47), suggesting that the volumetric reduction may be less marked in the early stages of the illness.

VOLUME REDUCTIONS IN THE FRONTAL LOBE AND BASAL GANGLIA

Four frontal regions were smaller in MDD patients compared with controls. Although we could not confirm that the subgenual prefrontal cortex was reduced in volume in MDD, it is possible that functional,[59,182] rather than structural, abnormalities are of greater prominence in this region. The most significant effect sizes were observed in the orbitofrontal cortex and gyrus rectus. Deficits of prefrontal cortical activation in MDD are relatively consistent in functional neuroimaging studies,[183] and post-

Table 3. Meta-analysis of Continuous Data Comparing Patients With MDD vs Controls[a] (continued)

Region	No. of Studies	No. of MDD/ Controls[a]	MDD Patients vs Controls: Effect Size (95% CI)	Effect Size *P* Value[b]	Size vs Controls, %	Heterogeneity[c]: Q	I^2 (%)	*P* Value	SS Bias, *P* Value[d]
Orbitofrontal, total, GM	**6**	**424/318**	**–0.38 (–0.64 to –0.11)**	**.0054**	**92.5**	**14**	**57**	**.03**	**.41**
Orbitofrontal, left, GM	**5**	**355/286**	**–0.29 (–0.57 to –0.02)**	**.037**	**93.1**	**9**	**55**	**.06**	**.99**
Orbitofrontal, right, GM	5	355/286	–0.24 (–0.51 to 0.04)	.09	94.6	9	56	.06	
Medial orbitofrontal, total, GM	3	86/101	–0.12 (–0.54 to 0.30)	.58	97.2	4	52	.13	
Lateral orbitofrontal, total, GM	3	86/101	–0.02 (–0.52 to 0.48)	.95	99.7	6	66	.05	
Subgenual PFC, total	7	234/265	–0.14 (–0.36 to 0.07)	.20	94.4	8	17	.30	
Subgenual PFC, left	6	171/173	–0.35 (–0.78 to 0.08)	.11	88.5	17	65	<.01	
Subgenual PFC, right	5	154/152	–0.07 (–0.31 to 0.17)	.59	96.6	5	2	.40	
Gyrus rectus, total, GM	**3**	**112/75**	**–0.72 (–1.03 to –0.41)**	**<.00001[e]**	**84.5**	**1**	**0**	**.48**	
Corpus callosum, area	6	233/175	0.06 (–0.29 to 0.41)	.75	101.5	17	65	<.01	
Anterior corpus callosum, area	4	133/119	–0.18 (–0.86 to 0.50)	.60	97.6	20	85	<.01	
Corpus callosum, length	4	96/87	–0.06 (–0.58 to 0.45)	.81	99.6	9	65	.04	
Pituitary	5	161/158	0.25 (0.00 to 0.50)	.054	105.4	7	18	.30	
DWMH, rating[f]	9	357/318	0.17 (–0.01 to 0.36)	.07	116.4	15	27	.18	
PVH, rating[f]	**9**	**324/287**	**0.29 (0.08 to 0.50)**	**.006**	**122.4**	**17**	**35**	**.11**	**.21**
ScGMH, rating[f]	6	246/241	0.14 (–0.15 to 0.43)	.34	116.4	16	57	.02	

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; CT, computed tomography; DWMH, deep white matter hyperintensities; GM, gray matter; MDD, major depressive disorder; MRI, magnetic resonance imaging; PFC, prefrontal cortex; PVH, periventricular hyperintensities; ScGMH, subcortical gray matter hyperintensities; SS, small study; WM, white matter.

[a] Pooled numbers of patients and controls.

[b] Boldface indicates significant differences in effect sizes.

[c] Low, 25%; moderate, 50%; and high, 75%.

[d] Small-study bias was calculated only when there was a significant difference between patients and controls and when at least 5 studies were included in the meta-analysis to ensure that the test was sufficiently powered.

[e] Result remained significant after Bonferroni correction for multiple comparisons.

[f] The hyperintensity rating categories included the scales from Coffey et al,[33] Fazekas et al,[172] and Scheltens et al.[173]

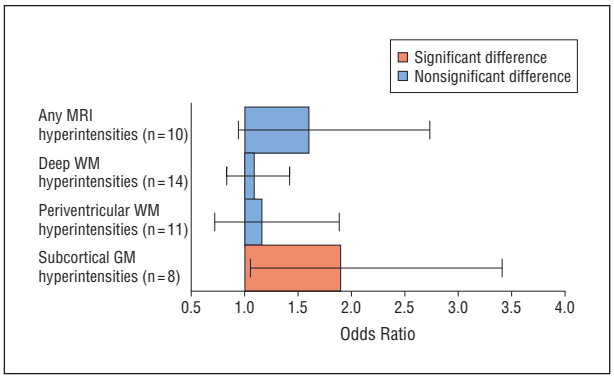

Figure 2. Categorical variables evaluated in major depressive disorder (MDD) meta-analysis. Odds ratio is shown for each type of hyperintensity, with 95% confidence intervals. Odds ratio larger than 1 indicates that the hyperintensity is more common in patients with MDD compared with control group members. The number of studies included in each meta-analysis is indicated with each type of hyperintensity. GM indicates gray matter; MRI, magnetic resonance imaging; and WM, white matter.

mortem studies[184] have reported reduced neuronal and glial density in the dorsal lateral and orbitofrontal cortex. We confirm the findings of a previous meta-analysis,[13] which reported reduced volume of the caudate and putamen in patients with MDD, but we also found significant volume reductions of the globus pallidus. Although the basal ganglia have primarily been linked to motor function, the ventral striatum, including the nucleus accumbens, has been strongly associated with limbic systems, particularly reward networks.[185]

MRI SIGNAL HYPERINTENSITIES

Although increased rates of hyperintensities are considered an established finding in MDD, particularly in older patients,[186] our meta-analysis showed only modest increases compared with healthy controls. The reported effect sizes in this meta-analysis were smaller than those in 2 earlier meta-analyses[16,187] of depression studies. Our meta-analysis included only studies on patients with MDD; however, both previous meta-analyses included studies that evaluated MDD and BD patients as a single group,[188-190] which may have inflated the effect size. Indeed, our study indicates that patients with BD have more than a 2-fold increase in rates of deep white matter hyperintensities compared with MDD patients (Table 5).

COMPARISON WITH VBM STUDIES

We excluded reports on VBM from the meta-analysis; however, a qualitative review of these studies partially supports our findings. In 12 VBM studies that examined gray matter volume, the most consistent findings were hippocampal volume reduction (7 studies)[191-197] and volumetric reductions within the frontal lobe (7 studies).[191,192,194-196,198,199] Changes shown with VBM that were not found in our meta-analysis included reductions within the amygdala (4 studies)[194-196,200] and cingulate cortex (6 studies),[193-195,199-201] although 1 study[198] found an increase in volume.

Table 4. Meta-analysis of Categorical Data Comparing Patients With MDD vs Controls

Abnormality	No. of Studies	No. of MDD/Controls[a]	MDD Patients vs Controls: OR (95% CI)	MDD Patients vs Controls: OR *P* Value[b]	Heterogeneity: *Q*	Heterogeneity: I^{2c} (%)	Heterogeneity: *P* Value	SS Bias, *P* Value[d]
Any MRI hyperintensities	10	491/532	1.60 (0.94 to 2.73)	.08	24	63	<.01	
Deep WM hyperintensities	14	765/957	1.09 (0.84 to 1.42)	.51	9	0	.77	
Periventricular WM hyperintensities	11	419/498	1.17 (0.73 to 1.89)	.52	11	8	.37	
Subcortical GM hyperintensities	**8**	**503/343**	**1.90 (1.05 to 3.41)**	**.03**	**12**	**40**	**.12**	**.99**

Abbreviations: CI, confidence interval; GM, gray matter; MDD, major depressive disorder; MRI, magnetic resonance imaging; OR, odds ratio; SS, small-study; WM, white matter.

[a] Pooled numbers of patients and controls.

[b] Boldface indicates a significant difference.

[c] Low, 25%; moderate, 50%; and high, 75%.

[d] Small-study bias was calculated only when there was a significant difference between patients and controls and when at least 5 studies were included in the meta-analysis to ensure that the test was sufficiently powered.

Table 5. Statistical Comparison of the Present MDD Meta-analysis With a Previous Meta-analysis of BD[9]

Region	MDD vs Control Meta-analysis: No. of Studies	MDD vs Control Meta-analysis: Effect Size	MDD vs Control Meta-analysis: *P* Value	BD vs Control Meta-Analysis: No. of Studies	BD vs Control Meta-Analysis: Effect Size	BD vs Control Meta-Analysis: *P* Value	MDD vs BD[a]: Effect Size	MDD vs BD[a]: *P* Value
Lateral ventricles, total	15	0.44	<.001	17	0.39	<.001	0.04	.73
Caudate, total	**13**	**–0.22**	**.006**	**17**	**0.03**	**.69**	**–0.25**	**.03**
Putamen, total	**8**	**–0.25**	**.009**	**10**	**0.05**	**.56**	**–0.30**	**.02**
Globus pallidus, total	**3**	**–0.31**	**.04**	**6**	**0.39**	**.10**	**–0.70**	**.01**
Thalamus, total	7	–0.34	.01	13	–0.05	.73	–0.29	.13
Hippocampus, total	**37**	**–0.47**	**<.001**	**18**	**–0.06**	**.48**	**–0.41**	**<.001**
Corpus callosum, cross-sectional area	**6**	**0.06**	**.75**	**4**	**–0.43**	**.006**	**0.49**	**.04**
DWMH	**14**	**OR, 1.09**	**.51**	**13**	**OR, 2.49**	**<.001**	**OR, 0.44**	**.001**
ScGMH	8	OR, 1.90	.03	6	OR, 2.84	.01	OR, 0.67	.42

Abbreviations: BD, bipolar disorder; DWMH, deep white matter hyperintensities; MDD, major depressive disorder; OR, odds ratio; ScGMH, subcortical gray matter hyperintensities.

[a] For the MDD vs BD comparison, negative effect sizes indicate that the region is smaller in MDD patients; positive effect sizes indicate that the region is smaller in BD patients. An OR less than 1 indicates that hyperintensities are less common in MDD patients compared with BD patients. Effect sizes for BD have been recalculated by combining left and right measures (see the "Methods" section) and, as such, may vary from those reported in the previous BD meta-analysis.[9] Boldface indicates significant differences between BD and MDD patients.

MDD STRUCTURAL CHANGES COMPARED WITH BD

Based on findings from a large number of independent studies in the meta-analysis comparison, MDD is associated with reductions in basal ganglia and hippocampal volume, and BD is more strongly associated with white matter abnormalities, specifically deep white matter hyperintensities and reduced corpus callosum area. In terms of similarities, both disorders showed ventricular enlargement and increased rates of subcortical gray matter hyperintensities. The positive association between patient age and hippocampal volume in the BD sample reinforces the identified difference in hippocampal volume between patients with MDD and those with BD; if studies on BD had recruited older patients in the same way as MDD studies did, the difference would have been greater. The larger extent of gray matter volume reductions in MDD was surprising, given that BD is considered a more chronic illness and is associated with an earlier age at onset[2] and more episodes of major depression compared with MDD.[4] The finding that white matter abnormalities were more strongly associated with BD than MDD was also unexpected; however, this is supported in a review by Mahon et al,[202] who reported evidence of abnormal white matter in BD from studies using a variety of neuroimaging techniques in addition to neuropathologic and genetic studies. Because studies of twins have shown that there are both overlapping and distinct genetic risk factors for BD and MDD,[203] it is possible that the unique genetic factors for each disorder are associated with the distinct structural abnormalities identified in this meta-analysis. Twin studies have also shown that environmental factors have a stronger influence in MDD than in BD.[204] It is possible that the reduction in hippocampal volume observed in MDD but not BD is linked to stressful life events playing a more prominent role in the development of MDD.

LIMITATIONS

Although the case-control meta-analysis is statistically highly powered, the meta-regression analysis of clinical variables lacks power and may be prone to type I and type II errors. In the comparison between MDD and BD, we limited the analysis to regions that were significantly different from controls in either the MDD or BD meta-analysis. This strategy reduces the number of comparisons and associated type I

errors; however, it is possible that brain regions that distinguish the disorders were overlooked. Although we attempted to take into account differences in medications between the groups, it was not possible to account for this entirely because of the limited information reported in studies. A previous meta-analysis of BD studies[9] and other studies[205,206] have shown that use of lithium may increase gray matter volume, and it is possible that lithium may be masking abnormalities that would have been observed if patients with BD were not using this medication. The results from a long-term prospective study[207] suggest an approximate 1% conversion rate from MDD to BD every year, which complicates the comparison of MDD and BD studies. Therefore, it is possible that the differences in brain structure between MDD patients who do not convert and BD patients are more pronounced than the differences reported in this study.

In conclusion, in this meta-analysis, we have shown robust structural brain abnormalities in MDD and particular changes in brain volume that may distinguish MDD from BD. These results may aid imaging studies aiming to use structural MRI data to distinguish patients with MDD from those with BD. Further studies may reveal whether these abnormalities are a risk factor for developing MDD, when they first occur, and whether they are predictive of treatment response.

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