Meta-analysis, Database, and Meta-regression of 98 Structural Imaging Studies in Bipolar Disorder

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Context: Despite 25 years of structural imaging in bipolar disorder, brain regions affected in the disorder are ill defined.

Objectives: To use meta-analytical techniques to investigate structural brain changes in bipolar disorder and to assess the effect of medication use and demographic and clinical variables.

Data Sources: The MEDLINE, EMBASE, and PsycINFO databases were searched from 1980-2007 for studies using magnetic resonance imaging or x-ray computed tomography to compare brain structure in patients with bipolar disorder and controls.

Study Selection: We identified 1471 unique publications from which 141 studies were included in a database and 98 were selected for meta-analysis.

Data Extraction: Twenty-six demographic and clinical variables were extracted from each study where available. For the meta-analysis, mean structure size and standard deviation were extracted for continuous variables, and numbers of patients and controls with an abnormality were extracted for binary variables.

Data Synthesis: Bipolar disorder was associated with lateral ventricle enlargement (effect size = 0.39; 95% confidence interval, 0.24-0.55; $P = 8\times10^{-7}$) and increased rates of deep white matter hyperintensities (odds ratio = 2.49; 95% confidence interval, 1.64-3.79; $P = 2\times10^{-5}$) but not periventricular hyperintensities. Gray matter volume increased among patients when the proportion of patients using lithium increased ($P = .004$). Calculations from this meta-analysis show current imaging studies (which typically examine 8 regions) have a 34% chance of making a type I error. Type II errors are also appreciable (for example, 70% when measuring the lateral ventricular volume in a typical study involving 25 patients and 33 controls).

Conclusions: The meta-analyses revealed robust but regionally nonspecific changes of brain structure in bipolar disorder. Individual studies will remain underpowered unless sample size is increased or improvements in phenotypic selection and imaging methods are made to reduce within-study heterogeneity. The provision of online databases, as illustrated herein, may facilitate a more refined design and analysis of structural imaging data sets in bipolar disorder.

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DESPITE 25 YEARS OF STRUCTURAL neuroimaging of patients with bipolar disorder, including more than 7000 magnetic resonance imaging (MRI) scans, there remains considerable debate over the sensitivity and specificity of structural brain changes in bipolar disorder. Studies continue to report conflicting findings, such as both significantly larger or smaller volumes of the amygdala,[1,2] hippocampus,[3,4] and thalamus[3,5] among patients with bipolar disorder. Meta-analyses are beginning to reveal consistent abnormalities in bipolar disorder, such as increased rates of hyperintensities[6,7] and perhaps lateral ventricular enlargement.[8,9] Studies may be contradictory because of between-study heterogeneity in the patient and control groups in terms of medication use[10,11] and demographic[12,13] and clinical variables[14,15] and because individual studies may suffer from high rates of type I and type II errors. There is good evidence to suggest medication may affect brain structure; cross-sectional studies[16-18] and a longitudinal study[19] have suggested lithium increases gray matter volume, possibly through its neurotrophic effects,[20] and typical neuroleptic medication may be associated with striatal enlargement.[21,22] In addition, type I and II errors are prevalent because of the large number of measures made in individual studies and small sample sizes, respectively. Finally, although effect

sizes may be calculated from individual studies, there is little published information from meta-analyses on the pooled Cohen effect sizes of structural differences between patients with bipolar disorder and controls, making it difficult to accurately calculate a priori the number of participants necessary to show a significant group difference.

In the present meta-analysis, we directly address these problems while extending the scope and methods of previous meta-analyses. The number of studies included is approximately 4 times the largest previous meta-analysis[9] in bipolar disorder. We have maximized the number of brain regions analyzed by comprehensively listing all brain structures reported in 3 or more studies. In addition, we used meta-regression techniques to investigate the effect of medication use and clinical and demographic variables, which had not been attempted previously. We present the results as Cohen effect sizes (with a correction for small sample sizes), enabling researchers to calculate subject numbers required for future studies to be sufficiently powered. In addition, we present a small supplementary meta-analysis comparing patients with bipolar disorder to patients with schizophrenia (when included as a subgroup in a bipolar study) to evaluate the diagnostic specificity of our findings. Finally, we provide an online database of structural imaging results in bipolar disorder, listing 26 clinical and demographic variables, where available, from 141 studies.

METHODS

The study was divided into 2 parts, the construction of a database of 141 studies investigating structural abnormalities in bipolar disorder and a meta-analysis comparing patients with bipolar disorder to controls from a subgroup of 98 studies in the database. A smaller, supplementary meta-analysis compared brain structure between patients with bipolar disorder and schizophrenia from a subgroup of 23 studies.

DATABASE STUDY SELECTION

The inclusion criteria for the database required peer-reviewed studies that made a structural brain measure using x-ray computed tomography (CT) or MRI in patients with bipolar disorder and a control group. We excluded case studies, reviews, publications without standard diagnostic criteria, studies combining patients with bipolar disorder and major depressive disorder, duplicate publications, and investigations using voxel-based morphometry, which cannot be included in a traditional meta-analysis. The MEDLINE, EMBASE, and PsycINFO databases were searched up to October 2007 using relevant expanded subject headings and free text searches; detailed search terms are available from the authors on request. A total of 1471 unique publications were examined. One hundred forty-one publications fulfilled the inclusion criteria and were included in the database.

DATA RECORDED IN THE DATABASE

The following were recorded from each study where available: number of patients with bipolar disorder and controls, mean (SD) age, number of females in the patient and control groups, diagnostic classification system (eg, *DSM-IV*), and number of patients with bipolar I and bipolar II disorder. Patients with bipolar disorder were assumed to have bipolar I disorder if described as having mania or psychosis. For current medication use within the bipolar group, we recorded the number of patients who were described as being drug free, using mood stabilizers, or taking lithium, anticonvulsants, sodium valproate, carbamazepine, antipsychotics, antidepressants, or benzodiazepines. In addition, the number of patients previously treated with electroconvulsive therapy was recorded if available. For each study, we recorded all structures or abnormalities measured, the number of separate measurements made, if the measurement was MRI or CT based, the field strength of the MRI scanner, and slice thickness.

DATABASE STATISTICAL ANALYSIS

Because the majority of variables in the database were not normally distributed, correlations were assessed in SPSS 15.0 (SPSS Inc, Chicago, Illinois) using the Spearman ρ. Power calculations were carried out using GPOWER 2.0.[23]

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 141 studies. As with previous meta-analyses, exact anatomical definitions of individual structures varied across studies. For a given structure, some studies reported left and right measurements separately, while others reported the total combined measure. In this meta-analysis, the left, right, and total measurements were treated as separate measures. To ensure the meta-analysis was sufficiently powered, brain region measures were included if there were 3 or more studies reporting a mean and standard deviation in both the control and patient groups (continuous measures), and abnormalities were included if there were 3 or more studies reporting the number of patients and controls with the abnormality (binary measure). After this process, 47 regions or abnormalities from a total of 98 studies were selected for the bipolar vs control meta-analysis and 12 regions/ abnormalities from 23 studies were selected for the bipolar vs schizophrenia meta-analysis. Eight studies using CT measures of total lateral ventricle volume were included in the meta-analyses; all other brain structures were imaged using MRI.

META-ANALYSIS

The meta-analyses were performed in STATA 9.2 (StataCorp, College Station, Texas) using the METAN command. For continuous outcome measures (eg, volume of a brain region), Hedges g was used, which is Cohen effect size with a correction for bias from small sample sizes.[24] This metric is commonly used in meta-analyses and is representative of the difference in structural measurement between the control and patient distribution. However, we also show percentage difference effect size to aid biological interpretation of the data.[9] While the majority of studies report absolute volume measures, some studies report volumes as ratios of the entire brain or cross-sectional area measures. All such measurements have been included in the meta-analysis. However, as combining measures may increase heterogeneity, an additional analysis was carried out with volume measures only (see "Sensitivity Analysis" subsection).

For binary outcome measures (eg, number of patients and controls with deep white matter hyperintensities), the odds ratio was used. Outcome measures from each study were rechecked on a separate occasion by the same investigator (M.J.K.) to ensure accuracy. In addition, no inconsistencies were found when a second investigator (U.E.) verified a random sample of 50 sets of outcome measures.

COMBINING STUDY ESTIMATES

A separate meta-analysis was performed for each brain region/abnormality. Where 2 or more studies reported similar patient or control demographics, we contacted the authors directly to verify there was not a significant overlap in the sample. Outcome measures were combined using a random-effects, inverse-weighted variance model (DerSimonian and Laird method).[25] Because the bipolar vs control meta-analysis examined a large number of regions, type I errors should be considered, and thus, results that pass Bonferroni correction for multiple comparisons are indicated.

PATIENT SUBGROUPS

A minority of imaging studies presented measures from patient subgroups rather than a combined patient group. In such cases, we entered the subgroups into the meta-analysis as if they were separate studies, with the number of subjects in the control group being divided by the number of patient subgroups. Where studies reported males and females separately, we entered the results as if they were from 2 separate studies, a technique adopted by a previous meta-analysis.[26]

ASSESSING BETWEEN-STUDY HETEROGENEITY

To test for between-study heterogeneity, the Cochran Q test statistic was used, and where $P<.10$, the studies were concluded to be heterogeneous.[27] The I^2 statistic (equal to the percentage of total variation across studies due to heterogeneity) was used to aid interpretability of between-study heterogeneity.[28]

PUBLICATION BIAS

Publication bias was investigated for regions where the pooled effect size revealed a significant group difference and where at least 5 studies were included in the meta-analysis. Although publication bias may be assessed by visually inspecting a funnel plot, we used the Egger regression test, which is a more quantitative method of assessing publication bias.[29] Evidence of bias is indicated if the intercept of a regression line of effect size/standard error against 1/standard error significantly deviates from zero.

META-REGRESSION OF CLINICAL VARIABLES AND STUDY QUALITY

The effects of clinical variables and study quality were assessed using a random-effects meta-regression implemented using the METAREG command in STATA 9.2. The default option using residual maximum likelihood was selected. To avoid type I errors, demographic and clinical variables were chosen based on key clinical questions and the availability of the variables reported in studies.[30] For structures where there was a significant difference between patients with bipolar disorder and controls, we investigated whether effect size was modulated by study quality. Study quality was scored in 6 key areas by 2 independent investigators (M.J.K. and U.E.), with disputes resolved by consensus. One point was given for each of the following categories: age matching (not stated/significant difference = 0, matched = 1), sex matching (not stated/significant difference = 0, matched = 1), control subjects had no psychiatric illness (not stated = 0, no psychiatric illness = 1), same CT/MRI scanner and sequence used for each subject (different scanner or sequence = 0, same scanner and sequence = 1), good reliability of measures (intraclass correlation coefficient/κ <0.8/not stated = 0, intraclass correlation coefficient/κ $\geq 0.8 = 1$), and small slice thickness ($\geq$4 mm = 0, $>$1.5 mm and $<$4 mm = 0.5 , and $\leq$1.5 mm = 1).

SENSITIVITY ANALYSIS

To test how robust the results were to variations in meta-analysis inputs, we examined the effect of the following: (1) percentage difference in the patient mean volume compared with the control mean volume as an outcome measure for continuous data (the calculation of this effect size and the effect size variance has been described in more detail in previous meta-analytical studies)[9,26]; (2) excluding studies with patients with bipolar II disorder; and (3) excluding studies reporting continuous data as area, length, or ratios rather than absolute volume.

RESULTS

Demographic and clinical data from the database are reported, followed by results from the meta-analyses.

DATABASE

One hundred forty-one studies, including 3509 patients with bipolar disorder and 4687 controls, were entered into the database (**Table 1**). **Table 2** summarizes the variables recorded. Bipolar disorder was defined using *DSM-IV* (69 studies), *DSM-III-R* (38 studies), *DSM-III* (22 studies), Research Diagnostic Criteria (11 studies), and *International Statistical Classification of Diseases, 10th Revision* (1 study). For image acquisition, 125 studies used MRI and 16 studies used CT imaging. Among MRI studies, 78% used a field strength of 1.5 T, 18% used lower field strength, and 3% used higher field strength. The mean (SD) slice thickness was 9.3 (1.0) mm in CT studies and 3.5 (2.5) mm in MRI studies. The Bipolar Disorder Neuroimaging Database (BiND) is freely available at http://www.bipolardatabase.org.

TRENDS IN STUDY VARIABLES OVER TIME

Studies did not recruit a larger number of subjects over time ($R=-0.10$; $P=.22$) (**Figure 1**), although the number of studies per year increased ($R=0.79$; $P<.001$) (**Figure 2**). The mean age of participants decreased during the review period (patients, $R=-0.34$; $P<.001$; controls, $R=-0.34$; $P<.001$), with recent studies recruiting adolescent patients. In addition, studies recorded increasing numbers of demographic variables over time ($R=0.50$; $P<.001$).

IMPLICATIONS FOR TYPE I ERRORS IN INDIVIDUAL STUDIES

The mean number of regions or abnormalities measured per study was 8, and there was a negative correlation between the number of measures made and the total number of subjects included in each study ($R=-0.23$; $P=.007$).

DIFFERENT REGIONS/ ABNORMALITIES MEASURED

From the 141 studies, 377 different regions or abnormalities were measured. Only 47 were analyzed by 3 or more studies and hence were included in the bipolar vs control meta-analysis. Twelve structures were also measured in patients with schizophrenia in 3 or more studies, and these were included in the bipolar vs schizophrenia meta-analysis.

Table 1. List of Studies Included in the Database[a]

Source (Year)	No. of Patients With Bipolar Disorder	No. of Controls	Diagnostic Criteria	Mean Patient Age, y	Imaging Modality
Nasrallah et al[31] (1981)	15	36	*DSM-III*	NS	CT
Lippmann et al[32] (1982)	18	79	*DSM-III*	NS	CT
Nasrallah et al[33] (1982)	24	27	*DSM-III*	31.8	CT
Nasrallah et al[34] (1982)	**24**	**27**	***DSM-III***	**31.8**	**CT**
Rangel-Guerra et al[35] (1983)	20	18	*DSM-III*	38.6	MRI
Pearlson et al[36] (1984)	**27**	**27**	***DSM-III***	**30.8**	**CT**
Lippmann et al[37] (1985)	18	79	*DSM-III*	NS	CT
Pearlson et al[38] (1985)	27	27	*DSM-III*	30.8	CT
Dewan et al[39] (1987)	25	25	*DSM-III*	32.6	CT
Dupont et al[40] (1987)	**14**	**8**	**RDC**	**38**	**MRI**
Yates et al[41] (1987)	24	74	*DSM-III*	35.5	CT
Dewan et al[42] (1988)	23	22	*DSM-III*	32.9	CT
Dewan et al[43] (1988)	**26**	**22**	***DSM-III***	**32.7**	**CT**
Iacono et al[44] (1988)	**18**	**44**	***DSM-III***	**26.1**	**CT**
Hauser et al[45] (1989)	**22**	**25**	***DSM-III***	**40.4**	**MRI**
Johnstone et al[46] (1989)	**20**	**21**	***DSM-III***	**38.1**	**MRI**
Andreasen et al[47] (1990)	**24**	**75**	***DSM-III***	**36.5**	**CT**
Coffman et al[48] (1990)	**25**	**29**	***DSM-III-R***	NS	**MRI**
Dolan et al[49] (1990)	14	13	RDC	39	MRI
Dupont et al[50] (1990)	**19**	**10**	**RDC**	NS	**MRI**
Harvey et al[51] (1990)	**11**	**50**	**RDC**	NS	**CT**
Swayze et al[52] (1990)	**48**	**47**	***DSM-III***	**33.9**	**MRI**
Altshuler et al[53] (1991)	10	10	RDC	39.8	MRI
Figiel et al[54] (1991)	**18**	**18**	***DSM-III***	**37.5**	**MRI**
Lewine et al[55] (1991)	**7**	**68**	***DSM-III***	NS	**MRI**
McDonald et al[56] (1991)	**12**	**12**	***DSM-III-R***	**68.3**	**MRI**
Brown et al[57] (1992)	**22**	**154**	***DSM-III-R***	**37.7**	**MRI**
Risch et al[58] (1992)	6	68	RDC	NS	MRI
Swayze et al[59] (1992)	**48**	**47**	***DSM-III***	**33.9**	**MRI**
Strakowski et al[60] (1993)	**18**	**15**	***DSM-III-R***	**31.3**	**MRI**
Strakowski et al[61] (1993)	**17**	**16**	***DSM-III-R***	**28.4**	**MRI**
Aylward et al[62] (1994)	**33**	**32**	***DSM-III-R***	**39.3**	**MRI**
Bullmore et al[63] (1994)	26	36	*DSM-III-R*	NS	MRI
Harvey et al[64] (1994)	26	34	*DSM-III-R*	35.6	MRI
Kato et al[65] (1994)	39	60	*DSM-III-R*	42	MRI
Schlaepfer et al[66] (1994)	**27**	**60**	***DSM-III-R***	**34.9**	**MRI**
Altshuler et al[6] (1995)	**55**	**20**	**RDC**	**40.8**	**MRI**
Botteron et al[67] (1995)	**8**	**5**	***DSM-III-R***	**11.3**	**MRI**
Dupont et al[5] (1995)	**36**	**26**	***DSM-III-R***	**36.6**	**MRI**
Dupont et al[68] (1995)	**44**	**32**	***DSM-III-R***	**36.6**	**MRI**
Lewine et al[69] (1995)	**20**	**150**	***DSM-III-R***	**37.9**	**MRI**
Ohaeri et al[70] (1995)	**14**	**41**	**RDC**	**34.4**	**CT**
Woods et al[71] (1995)	52	38	*DSM-III-R*	36.3	MRI
Shioiri et al[72] (1996)	69	92	*DSM-III-R*	45	MRI
Drevets et al[73] (1997)	**21**	**21**	***DSM-III-R***	**35**	**MRI**
Pearlson et al[74] (1997)	**27**	**60**	***DSM-III-R***	**34.9**	**MRI**
Persaud et al[75] (1997)	**26**	**34**	**RDC**	**35.6**	**MRI**
Zipursky et al[76] (1997)	**14**	**17**	***DSM-III-R***	**35.9**	**MRI**
Altshuler et al[77] (1998)	**12**	**18**	***DSM-III***	**50.8**	**MRI**
Roy et al[78] (1998)	**14**	**15**	***DSM-III-R***	**35.9**	**MRI**
Bilder et al[79] (1999)	20	67	*DSM-III-R*	NS	MRI
Dasari et al[80] (1999)	**15**	**16**	***DSM-III-R***	**15.3**	**MRI**
DelBello et al[81] (1999)	**30**	**15**	***DSM-III-R***	**26.3**	**MRI**
Friedman et al[82] (1999)	15	16	*DSM-III-R*	15.3	MRI
Lim et al[83] (1999)	**9**	**16**	***DSM-III-R***	**44.4**	**MRI**
McDonald et al[84] (1999)	**70**	**70**	***DSM-III-R***	**50.7**	**MRI**
Sax et al[85] (1999)	**17**	**12**	***DSM-III-R***	**27**	**MRI**
Strakowski et al[86] (1999)	**24**	**22**	***DSM-III-R***	**27**	**MRI**
Young et al[87] (1999)	**30**	**18**	**RDC**	**71.4**	**CT**
Altshuler et al[2] (2000)	**24**	**18**	***DSM-III-R***	**50.2**	**MRI**
Hauser et al[88] (2000)	**47**	**19**	**RDC**	**40.7**	**MRI**
Hirayasu et al[89] (2000)	24	22	*DSM-III-R*	23.6	MRI
Krabbendam et al[90] (2000)	**22**	**22**	***DSM-IV***	**47.7**	**MRI**
Rabins et al[91] (2000)	14	21	*DSM-III-R*	73	MRI
Brambilla et al[92] (2001)	**22**	**22**	***DSM-IV***	**36**	**MRI**
Brambilla et al[93] (2001)	**22**	**22**	***DSM-IV***	**36**	**MRI**
Brambilla et al[94] (2001)	**22**	**22**	***DSM-IV***	**36**	**MRI**
Caetano et al[95] (2001)	**25**	**39**	***DSM-IV***	**34.4**	**MRI**
McIntosh et al[96] (2001)	**14**	**29**	***DSM-III-R***	**40.2**	**MRI**
Moore et al[97] (2001)	29	15	*DSM-IV*	44.7	MRI
Moore et al[98] (2001)	**79**	**33**	***DSM-IV***	**35.4**	**MRI**

(continued)

Table 1. List of Studies Included in the Database[a] (cont)

Source (Year)	No. of Patients With Bipolar Disorder	No. of Controls	Diagnostic Criteria	Mean Patient Age, y	Imaging Modality
Noga et al[99] (2001)	**6**	**22**	***DSM-III-R***	**34.5**	**MRI**
Sassi et al[100] (2001)	**23**	**34**	***DSM-IV***	**34.3**	**MRI**
Brambilla et al[101] (2002)	**27**	**38**	***DSM-IV***	**35**	**MRI**
Getz et al[102] (2002)	**12**	**12**	***DSM-IV***	**29.2**	**MRI**
López-Larson et al[11] (2002)	**17**	**12**	***DSM-IV***	**29**	**MRI**
Lyoo et al[103] (2002)	**56**	**83**	***DSM-III***	**13.6**	**MRI**
Pillai et al[104] (2002)	**15**	**16**	***DSM-III-R***	**15**	**MRI**
Sassi et al[16] (2002)	**29**	**46**	***DSM-IV***	**33.8**	**MRI**
Strakowski et al[105] (2002)	**35**	**32**	***DSM-IV***	**23.5**	**MRI**
Bertolino et al[106] (2003)	17	17	*DSM-IV*	40.1	MRI
Blumberg et al[107] (2003)	**36**	**56**	***DSM-IV***	**31**	**MRI**
Brambilla et al[108] (2003)	**24**	**36**	***DSM-IV***	**35**	**MRI**
Brambilla et al[109] (2003)	**16**	**27**	***DSM-IV***	**34**	**MRI**
Kieseppä et al[17] (2003)	24	27	*DSM-IV*	44.4	MRI
Sassi et al[110] (2003)	**24**	**38**	***DSM-IV***	**34.2**	**MRI**
Sharma et al[111] (2003)	**12**	**8**	***DSM-III-R***	**38.3**	**MRI**
Silverstone et al[112] (2003)	**13**	**19**	***DSM-IV***	**40.2**	**MRI**
Ahn et al[113] (2004)	**43**	**39**	***DSM-IV***	**36.9**	**MRI**
Beyer et al[114] (2004)	**36**	**35**	***DSM-IV***	**58.8**	**MRI**
Beyer et al[4] (2004)	**36**	**29**	***DSM-IV***	**58.2**	**MRI**
Brambilla et al[115] (2004)	29	36	*DSM-IV*	35	MRI
Chen et al[116] (2004)	**16**	**21**	***DSM-IV***	**16**	**MRI**
Chen et al[117] (2004)	**16**	**21**	***DSM-IV***	**15.5**	**MRI**
Chen et al[118] (2004)	16	21	*DSM-IV*	15.5	MRI
Connor et al[119] (2004)	39	219	*DSM-III-R*	41	MRI
Davis et al[120] (2004)	**22**	**32**	***DSM-IV***	**43.1**	**MRI**
DelBello et al[121] (2004)	**23**	**20**	***DSM-IV***	**16.3**	**MRI**
Hirashima et al[122] (2004)	21	12	*DSM-IV*	34	MRI
Sassi et al[123] (2004)	**27**	**39**	***DSM-IV***	**35.1**	**MRI**
Supprian et al[124] (2004)	**10**	**10**	***DSM-IV***	**48.6**	**MRI**
Blumberg et al[125] (2005)	**10**	**8**	***DSM-IV***	**15**	**MRI**
Chang et al[1] (2005)	**20**	**20**	***DSM-IV***	**14.6**	**MRI**
Chang et al[126] (2005)	**20**	**20**	***DSM-IV***	**14.6**	**MRI**
Frazier et al[3] (2005)	**43**	**20**	***DSM-IV***	**11.3**	**MRI**
Frazier et al[127] (2005)	**32**	**15**	***DSM-IV***	**11.2**	**MRI**
Haznedar et al[14] (2005)	**40**	**36**	***DSM-IV***	**42.2**	**MRI**
Kaur et al[13] (2005)	**16**	**21**	***DSM-IV***	**15.5**	**MRI**
Mills et al[128] (2005)	**39**	**32**	***DSM-IV***	**23.6**	**MRI**
Pariante et al[129] (2005)	16	78	*ICD-10*	NS	MRI
Sanches et al[130] (2005)	**15**	**21**	***DSM-IV***	**15.5**	**MRI**
Sanches et al[131] (2005)	**15**	**21**	***DSM-IV***	**15.9**	**MRI**
Strasser et al[132] (2005)	**38**	**44**	***DSM-IV***	**38.1**	**MRI**
Atmaca et al[133] (2006)	**12**	**12**	***DSM-IV***	**28.2**	**MRI**
Blumberg et al[134] (2006)	37	56	*DSM-IV*	31.5	MRI
Coyle et al[135] (2006)	19	35	*DSM-IV*	38	MRI
de Asis et al[12] (2006)	40	15	*DSM-IV*	69.8	MRI
El-Badri et al[136] (2006)	**50**	**26**	***DSM-IV***	**30.2**	**MRI**
Gulseren et al[10] (2006)	**12**	**12**	***DSM-IV***	**30.9**	**MRI**
Hwang et al[137] (2006)	**49**	**37**	***DSM-IV***	**32.4**	**MRI**
McDonald et al[138] (2006)	**38**	**54**	***DSM-IV***	**41**	**MRI**
Monkul et al[139] (2006)	**16**	**21**	***DSM-IV***	**15.5**	**MRI**
Pardo et al[140] (2006)	10	8	*DSM-III-R*	15.4	MRI
Velakoulis et al[141] (2006)	**22**	**87**	***DSM-III-R***	**21.7**	**MRI**
Voelbel et al[142] (2006)	12	13	***DSM-IV***	10.1	MRI
Yasar et al[143] (2006)	16	21	*DSM-IV*	15.5	MRI
Zimmerman et al[15] (2006)	27	22	*DSM-IV*	24	MRI
Ahn et al[144] (2007)	**46**	**22**	***DSM-IV***	**11.3**	**MRI**
Atmaca et al[145] (2007)	30	10	*DSM-IV*	29.8	MRI
Atmaca et al[146] (2007)	**12**	**12**	***DSM-IV***	**28.2**	**MRI**
Atmaca et al[147] (2007)	**30**	**10**	***DSM-IV***	**24.7**	**MRI**
Bearden et al[18] (2007)	28	28	*DSM-IV*	36.1	MRI
Bearden et al[148] (2007)	33	62	*DSM-IV*	34.2	MRI
Chiu et al[149] (2007)	**16**	**15**	***DSM-IV***	**10.6**	**MRI**
Kim et al[150] (2007)	41	41	*DSM-IV*	35.4	MRI
Molina et al[151] (2007)	**13**	**10**	***DSM-IV***	**37.8**	**MRI**
Najt et al[152] (2007)	14	20	*DSM-IV*	15.5	MRI
Rosso et al[153] (2007)	**20**	**23**	***DSM-IV***	**23**	**MRI**
Salisbury et al[154] (2007)	21	32	*DSM-IV*	21.8	MRI
Yucel et al[155] (2007)	**28**	**30**	***DSM-IV***	**25.3**	**MRI**
Yucel et al[156] (2007)	12	40	*DSM-IV*	28.4	MRI

Abbreviations: CT, x-ray computed tomography; *ICD-10*, *International Statistical Classification of Diseases, 10th Revision*; MRI, magnetic resonance imaging; NS, not specified; RDC, Research Diagnostic Criteria.

[a] Boldface indicates studies included in the meta-analysis.

Table 2. Patient and Control Demographic and Clinical Data Recorded in the Database

Variable	No. of Studies Reporting Variable	Mean (SD) Between Studies	Pooled No. of Subjects in Database
No. of patients	141	24.9 (13.1)	3509
No. of controls	141	33.2 (28.5)	4687
Patient age, mean	130	32.6 (12.4)	. . .
Patient age, SD	106	8.0 (3.6)	. . .
Control age, mean	129	31.7 (11.9)	. . .
Control age, SD	117	7.6 (3.4)	. . .
		Subjects in Each Study, %, Mean (SD)	
Female patients	129	46.0 (18.6)	1571
Female controls	130	42.0 (17.5)	1748
Bipolar I disorder:bipolar II disorder	90	89.2:8.3 (17.3:12.6)	1961:215
Current medication			
Medication free	54	25.0 (19.8)	350
Mood stabilizer	32	68.9 (23.5)	512
Lithium	55	53.1 (24.4)	700
Anticonvulsant	32	20.8 (22.7)	170
Sodium valproate	38	21.7 (23.5)	169
Carbamazepine	33	5.8 (11.1)	44
Antipsychotic	48	22.7 (26.5)	287
Antidepressant	48	14.5 (14.4)	182
Benzodiazepine	32	3.1 (6.3)	22
Lifetime ECT	17	11.6 (14.8)	49

Abbreviation: ECT, electroconvulsive therapy.

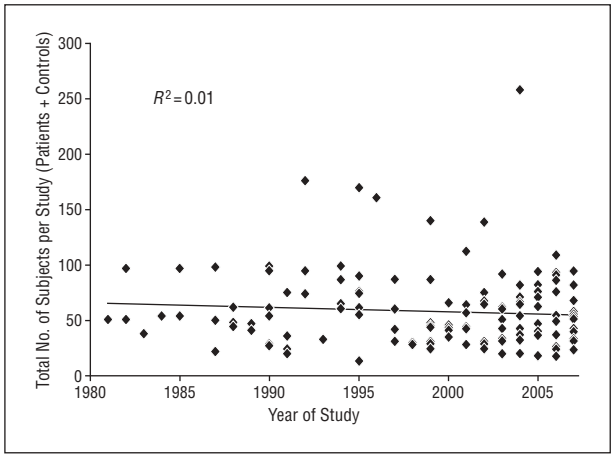

Figure 1. Total number of subjects (patients + controls) per study over time.

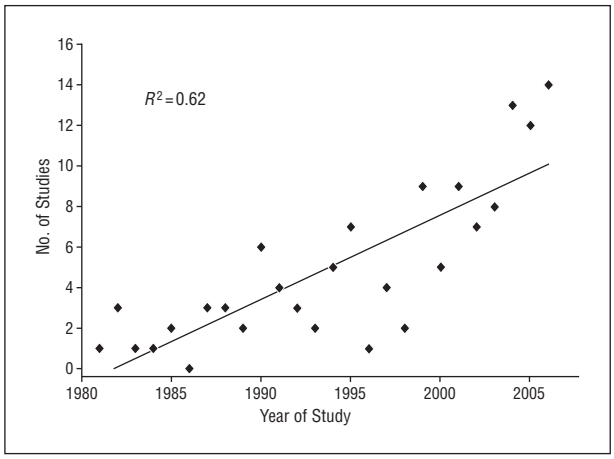

Figure 2. Number of bipolar structural imaging studies per year.

META-ANALYSIS COMPARING PATIENTS WITH BIPOLAR DISORDER TO CONTROL SUBJECTS

Patients with bipolar disorder showed increased volumes of the total lateral ventricles, right lateral ventricle, and third ventricle and decreased cross-sectional area of the corpus callosum (**Table 3**) (**Figure 3**). Hyperintensities, deep white matter hyperintensities, subcortical gray matter hyperintensities, and hyperintensities in the left hemisphere, right hemisphere, and frontal and parietal lobe were more frequently observed in patients with bipolar disorder (**Table 4**) (**Figure 4**). Analysis of the occipital and temporal lobes was not possible because of low numbers of hyperintensities reported in these regions. Increased total lateral ventricular volume, hyperintensities, deep white matter hyperintensities, and hyperintensities in the right hemisphere remained significant after Bonferroni correction.

PUBLICATION BIAS

Of the 13 affected regions/abnormalities, 10 were reported by enough studies to perform a publication bias test. There was evidence of significant publication bias for the combined hyperintensities category and hyperintensities in the right hemisphere (Table 3 and Table 4).

META-REGRESSION AND INVESTIGATION OF HETEROGENEITY

Nineteen of the 47 brain regions/abnormalities examined showed significant between-study heterogeneity, justifying the use of a random-effects model to combine the effect sizes. The following meta-regression analysis investigated possible sources of this heterogeneity. To investigate whether lateral ventricle expansion may be present at the beginning of the illness or may progress with time, we examined the effect of duration of illness and age on the difference in total lateral ventricular volume between patients and controls. No effect of mean patient age (n=15 studies; P=.66) or duration of illness (n=11 studies; P=.36) was detected. Because hyperintensities have reportedly been increased in older patients with depression and patients with a late age at onset,[157,158] we investigated the effects of these variables on the difference in incidence rates of deep white matter lesions between patients with bipolar disorder and controls. However, there was no significant effect of age (n=13 studies; P=.60) or age at onset (n=8; P=.42). The proportion of patients using lithium in a given study had no observable effect on the incidence of deep white matter hyperintensities in patients compared with controls (n=4 studies; P=.46). Because lithium has been reported to increase gray matter volume,[19] we performed a meta-regression investigating whether the number of patients taking lithium modulated the effect size of patient and control differences in total gray matter. Gray matter volume increased among patients compared with controls

Table 3. Meta-analysis of Continuous Data Comparing Patients With Bipolar Disorder to Controls[a]

Region	No. of Studies	No. of Patients With Bipolar Disorder/ No. of Controls	Comparison of Patients With Bipolar Disorder and Controls			Heterogeneity		Publication Bias *P* Value
			Effect Size (95% CI)	Effect Size *P* Value	Size vs Controls, %	I^2, %	*P* Value	
Lateral ventricles (total)	**17**	**375/589**	**0.39 (0.24 to 0.55)**	**.00000078[b]**	**117.2**	**19**	**.24**	**.42**
Lateral ventricles (MRI)	**9**	**201/285**	**0.26 (0.07 to 0.45)**	**.0071**	**109.8**	**0**	**.60**	**.40**
Lateral ventricles (CT)	**8**	**174/304**	**0.52 (0.28 to 0.76)**	**.000018[b]**	**124.2**	**29**	**.20**	**.93**
Lateral ventricle (left)	11	342/312	0.16 (–0.04 to 0.36)	.12	109.6	34	.11	. . .
Lateral ventricle (right)	**11**	**342/312**	**0.20 (0.00 to 0.39)**	**.047**	**111.8**	**29**	**.15**	**.92**
Third ventricle	**10**	**208/271**	**0.27 (0.00 to 0.53)**	**.046**	**112.8**	**46**	**.04**	**.091**
Intracranial volume	11	207/311	0.00 (–0.18 to 0.19)	.99	100.0	2	.43	. . .
Brain	15	379/470	–0.13 (–0.28 to 0.02)	.092	98.6	9	.34	. . .
Cerebrum	12	325/292	–0.15 (–0.35 to 0.06)	.15	98.4	34	.11	. . .
Gray matter (total)	13	257/310	–0.19 (–0.50 to 0.13)	.25	98.0	69	<.01	. . .
White matter (total)	12	221/284	–0.09 (–0.32 to 0.15)	.49	99.1	41	.05	. . .
Caudate (total)	10	272/225	0.07 (–0.17 to 0.32)	.55	101.2	44	.05	. . .
Caudate (left)	10	273/273	–0.03 (–0.21 to 0.15)	.72	99.8	10	.35	. . .
Caudate (right)	10	273/273	–0.07 (–0.24 to 0.10)	.39	99.4	0	.50	. . .
Putamen (total)	6	146/116	0.20 (–0.08 to 0.49)	.17	102.8	22	.26	. . .
Putamen (left)	6	197/183	–0.02 (–0.22 to 0.18)	.85	99.7	0	.57	. . .
Putamen (right)	6	197/183	0.00 (–0.20 to 0.21)	.98	99.9	0	.63	. . .
Globus pallidus (total)	5	135/106	0.50 (0.00 to 1.01)	.052	109.1	71	<.01	. . .
Globus pallidus (left)	3	69/64	0.42 (–0.03 to 0.87)	.067	106.9	40	.19	. . .
Globus pallidus (right)	3	69/64	0.23 (–0.44 to 0.91)	.50	103.9	73	.02	. . .
Thalamus (total)	9	235/207	–0.02 (–0.32 to 0.28)	.89	100.2	59	.01	. . .
Thalamus (left)	8	177/203	0.03 (–0.29 to 0.36)	.84	100.5	58	.02	. . .
Thalamus (right)	8	177/203	0.01 (–0.36 to 0.38)	.98	100.4	68	<.01	. . .
Temporal lobe (total)	3	70/48	–0.17 (–0.89 to 0.54)	.64	98.0	72	.03	. . .
Temporal lobe (left)	9	258/277	–0.08 (–0.35 to 0.20)	.60	99.0	56	.01	. . .
Temporal lobe (right)	9	258/277	–0.16 (–0.44 to 0.12)	.26	97.7	55	.01	. . .
Hippocampus (total)	8	230/209	–0.17 (–0.53 to 0.19)	.37	98.0	70	<.01	. . .
Hippocampus (left)	13	380/487	0.10 (–0.06 to 0.26)	.22	101.5	18	.23	. . .
Hippocampus (right)	13	380/487	0.02 (–0.13 to 0.17)	.83	100.3	11	.32	. . .
Amygdala-hippocampus complex (left)	3	68/82	–0.09 (–0.42 to 0.23)	.58	98.0	0	.74	. . .
Amygdala-hippocampus complex (right)	3	68/82	–0.07 (–0.39 to 0.26)	.70	98.2	0	.62	. . .
Amygdala (total)	8	192/176	–0.46 (–1.02 to 0.10)	.10	93.9	84	<.01	. . .
Amygdala (left)	10	236/354	–0.07 (–0.47 to 0.33)	.73	99.5	80	<.01	. . .
Amygdala (right)	10	236/354	–0.04 (–0.45 to 0.38)	.87	100.3	81	<.01	. . .
Anterior cingulate (left)	4	89/85	–1.17 (–2.47 to 0.13)	.078	85.9	91	<.01	. . .
Anterior cingulate (right)	4	89/85	–0.02 (–0.33 to 0.29)	.90	98.5	0	.70	. . .
Posterior cingulate (left)	3	73/70	–0.38 (–1.23 to 0.46)	.37	95.8	76	<.01	. . .
Posterior cingulate (right)	3	73/70	–0.18 (–0.64 to 0.28)	.44	96.8	29	.23	. . .
Subgenual PFC (left)	4	54/88	–0.38 (–0.89 to 0.13)	.14	88.3	49	.12	. . .
Subgenual PFC (right)	4	54/88	0.05 (–0.30 to 0.40)	.79	99.9	0	.56	. . .
Cerebellar vermis region 1	3	91/69	–0.01 (–0.32 to 0.31)	.97	99.9	0	.97	. . .
Cerebellar vermis region 2	3	91/69	0.07 (–0.38 to 0.52)	.76	101.4	48	.10	. . .
Cerebellar vermis region 3	3	91/69	–0.12 (–0.44 to 0.19)	.45	97.2	0	.58	. . .
Corpus callosum (length)	3	50/64	–0.36 (–0.74 to 0.02)	.061	97.6	0	.56	. . .
Corpus callosum (cross-sectional area)	**4**	**75/93**	**–0.43 (–0.74 to –0.12)**	**.0066**	**92.7**	**0**	**.53**	. . .

Abbreviations: CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging; PFC, prefrontal cortex.
[a] Boldface indicates significant differences.
[b] Indicates result remained significant after Bonferroni correction for multiple comparisons.

when the proportion of patients using lithium increased (n=8 studies; *P*=.004). Amygdala volume change was especially heterogeneous between studies; however, this heterogeneity was not explained by differences in patient sex or age (data not shown). There was no significant effect of study quality score for any of the structures differing between patients with bipolar disorder and controls (*P*>.15 in all cases).

Older studies measured the lateral ventricles using CT imaging, rather than MRI, and/or reported lateral ventricle to brain ratio (VBR) rather than a volume measure. To assess if these measures affected the results, we combined 9 MRI studies measuring the lateral ventricle, giving an effect size of 0.26 (95% confidence interval [CI], 0.07 to 0.45; *P*=.007), and compared this with 8 CT studies that gave a combined effect size of 0.52 (95%

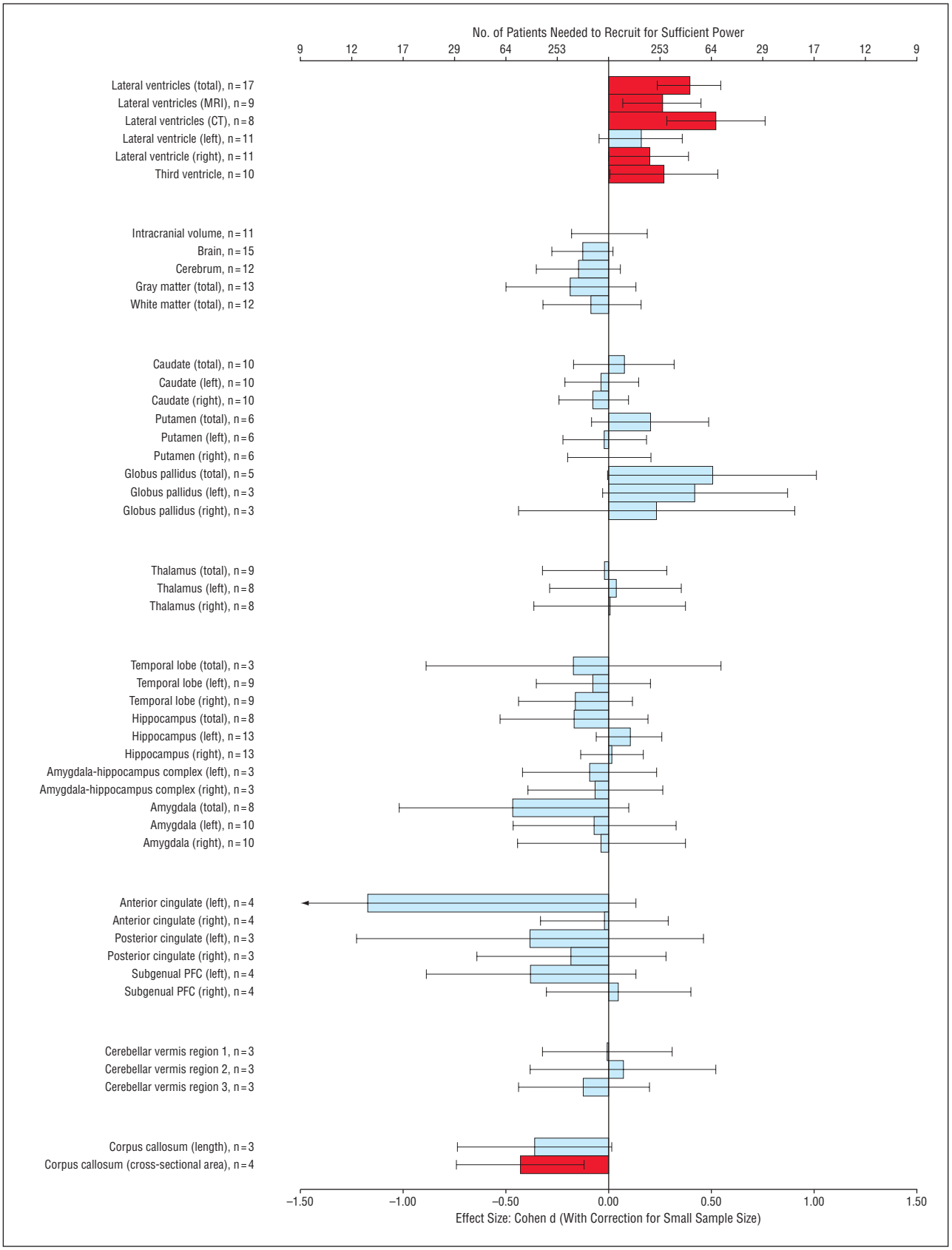

Figure 3. Continuous variables from the bipolar-control meta-analysis. Effect size is shown for each structure with 95% confidence intervals. The effect size is positive when the structure is larger in patients with bipolar disorder compared to controls and negative when the structure is smaller in patients with bipolar disorder. Red bars represent significant differences, and blue bars are nonsignificant differences. n Indicates the number of studies included in each meta-analysis. The values at the top of the figure indicate the number of required patients for a future study to be sufficiently powered, assuming within-study heterogeneity is similar to studies included in the meta-analysis.

Table 4. Meta-analysis of Binary Data Comparing Patients With Bipolar Disorder to Controls[a]

Abnormality	No. of Studies	No. of Patients With Bipolar Disorder/Controls	Comparison of Patients With Bipolar Disorder and Controls		Heterogeneity		Publication Bias *P* Value
			OR (95% CI)	Effect Size *P* Value	I^2, %	*P* Value	
Any hyperintensity	**16**	**494/587**	**3.04 (1.70 to 5.46)**	**.00019[b]**	**50**	**.01**	**.026**
Deep white matter hyperintensities	**13**	**394/456**	**2.49 (1.64 to 3.79)**	**.000020[b]**	**0**	**.69**	**.67**
Periventricular hyperintensities	8	314/249	1.25 (0.73 to 2.16)	.42	30	.19	. . .
Subcortical gray matter hyperintensities	**6**	**220/189**	**2.84 (1.29 to 6.27)**	**.010**	**0**	**.57**	**.17**
Left hemisphere hyperintensities	**5**	**96/87**	**4.05 (1.33 to 12.37)**	**.014**	**34**	**.20**	**.34**
Right hemisphere hyperintensities	**5**	**96/87**	**5.55 (2.10 to 14.64)**	**.00054[b]**	**0**	**.56**	**.024**
Frontal lobe hyperintensities	**3**	**65/65**	**6.02 (2.07 to 17.51)**	**.0010**	**0**	**.51**	. . .
Parietal lobe hyperintensities	**3**	**65/65**	**6.51 (1.30 to 32.52)**	**.022**	**0**	**.57**	. . .

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Boldface indicates significant differences.
[b] Indicates result remained significant after Bonferroni correction for multiple comparisons.

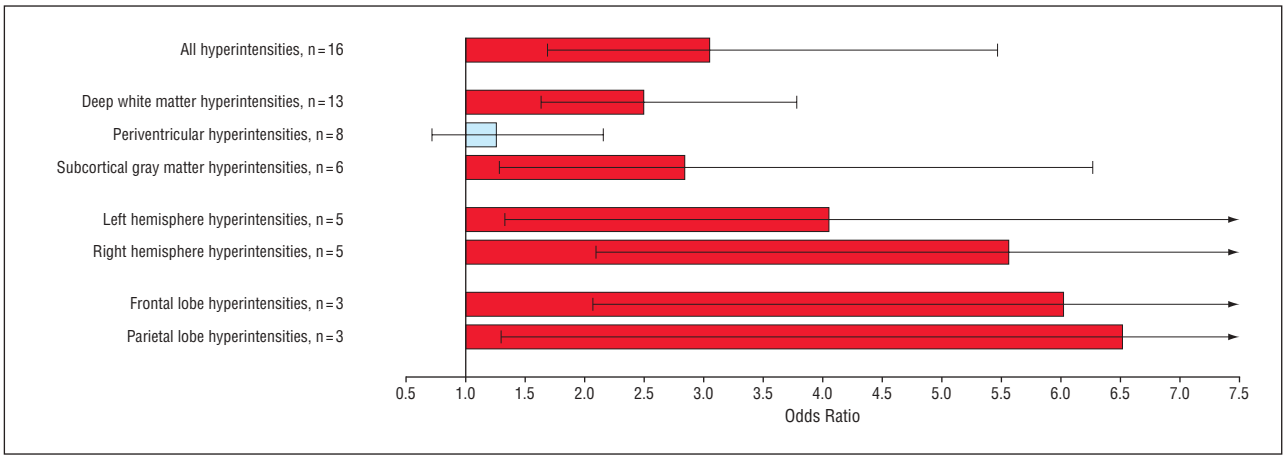

Figure 4. Binary variables from the bipolar-control meta-analysis. Odds ratios are shown for each type of hyperintensity with 95% confidence intervals. An odds ratio greater than 1 means the hyperintensity is more common in patients with bipolar disorder than controls. Red bars represent significant differences, and blue bars are nonsignificant differences. n Indicates the number of studies included in each meta-analysis.

CI, 0.28 to 0.76; $P < .001$). When combining 10 studies reporting a VBR measure, we obtained an effect size of 0.44 (95% CI, 0.20 to 0.68; $P < .001$), while 6 studies reporting a volume measure gave an effect size of 0.28 (95% CI, 0.06 to 0.49; $P = .0082$).

The results of the sensitivity analysis are shown in **Table 5**.

META-ANALYSIS COMPARING PATIENTS WITH BIPOLAR DISORDER TO PATIENTS WITH SCHIZOPHRENIA

The left lateral ventricle and third ventricle were smaller in patients with bipolar disorder compared to patients with schizophrenia (**Table 6**). Both the left and right hippocampus were larger in patients with bipolar disorder compared with patients with schizophrenia, although there was evidence of publication bias for these measures.

COMMENT

SUMMARY OF STRUCTURAL CHANGES IN BIPOLAR DISORDER

Patients with bipolar disorder had lateral ventricular enlargement (+17%) and increased rates of deep white matter hyperintensities (2.5 times more likely in patients than controls) but did not have increased rates of periventricular hyperintensities. From the meta-regression analysis, there was no evidence that age, age at onset, or use of lithium affected rates of deep white matter hyperintensities or that duration of illness increased ventricular enlargement. However, lithium use was associated with increased total gray matter volume. Meta-regression is statistically low powered and may be prone to type II errors; in addition, associations found at the level of multiple studies may not exist at the indi-

vidual-patient level.[159] Despite this, the association of lithium use with increased gray matter volume has been reported in a number of individual studies,[16,18,19] supporting our finding.

Given the size of the meta-analysis, the relatively small number of significant findings is perhaps surprising. There may be genuinely limited structural change in bipolar disorder, or between-study heterogeneity may have obscured other differences. A large number of factors may affect between-study heterogeneity, and some parameters, such as variations in brain region definitions and scanner sequences, are difficult to examine with meta-regression techniques. In this sense, meta-analyses are limited and well-controlled imaging studies with very large sample sizes may provide more definitive answers.

Table 5. Sensitivity of the Results to Different Analysis Methods

Change From Standard Analysis	Regions That Lose Significance in New Analysis	Regions That Gain Significance in New Analysis
Percentage volume difference used as effect size rather than Hedges g	Right lateral ventricle	Left globus pallidus larger in bipolar disorder; right posterior cingulate smaller in bipolar disorder
Exclusion of ratio, area, and length measures	Right lateral ventricle; third ventricle	None
Exclusion of studies with patients with bipolar II disorder	None	Gray matter volume reduced in bipolar disorder; left subgenual prefrontal cortex smaller in bipolar disorder; left and right globus pallidus larger in bipolar disorder

BIOLOGICAL IMPLICATIONS OF MAIN FINDINGS

Ventricular enlargement has been extensively documented in schizophrenia,[26] although it is not clear if the expansion is due to diffuse or focal gray/white matter volume reduction. Although the neuropathological mechanism for this change is not known, the volume loss may be due in part to smaller neuronal cell bodies and fewer dendritic spines and dendritic arborizations on pyramidal neurones reportedly found in patients with schizophrenia.[160] In bipolar disorder, ventricular expansion and corresponding reduction in brain volume may be linked to the reduced population of glial cells and neuronal density observed in this condition.[161] It is not clear if ventricular enlargement occurs before, during, or after illness onset, although our meta-regression suggests enlargement does not progress with illness duration and so may be present near the beginning of the illness.

Increased rates of hyperintensities are not specific to bipolar disorder, being associated with major depressive disorder, normal aging, dementia, cardiovascular disease, and elevated diastolic blood pressure.[162] Postmortem studies of subjects with depression using in vitro MRI have reported that hyperintensities represent dilated perivascular spaces, oligemic demyelination, and ischemic demyelination.[163]

INDIVIDUAL STUDIES HAVE HIGH RATES OF TYPE I AND TYPE II ERRORS

To provide sufficient statistical power, studies that measured a large number of regions would also need to recruit a large number of subjects. Indeed, if there were a consensus for the expected effect size for differences in cerebral structures between patients with bipolar disorder and control subjects, and a consensus for controlling multiple comparisons, one would expect to see a positive correlation between the number of subjects in a study

Table 6. Meta-analysis of Continuous Data and Binary Data Comparing Patients With Bipolar Disorder With Patients With Schizophrenia[a]

Region	No. of Studies	No. of Patients With Bipolar Disorder/ Schizophrenia	Comparison of Patients With Bipolar Disorder and Patients With Schizophrenia: Effect Size (95% CI)	Effect Size *P* Value	Size vs Schizophrenia, %	Heterogeneity: I^2, %	Heterogeneity: *P* Value	Publication Bias *P* Value
Lateral ventricles (total)	10	207/432	−0.17 (−0.36 to 0.02)	.08	92.5	13	.32	. . .
Lateral ventricle (left)	**4**	**120/131**	**−0.33 (−0.58 to −0.07)**	**.011**	**83.9**	**0**	**.59**	. . .
Lateral ventricle (right)	4	120/131	−0.21 (−0.46 to 0.04)	.10	89.5	0	.47	. . .
Third ventricle	**5**	**102/135**	**−0.27 (−0.53 to −0.01)**	**.041**	**88.4**	**0**	**.85**	**.60**
Brain	5	121/236	−0.09 (−0.45 to 0.28)	.64	98.3	54	.03	. . .
Gray matter (total)	3	50/78	0.38 (−0.15 to 0.90)	.16	104.9	44	.17	. . .
White matter (total)	3	50/78	0.38 (−0.39to1.14)	.34	104.3	75	<.01	. . .
Temporal lobe (left)	5	121/150	0.20 (−0.09 to 0.48)	.17	102.5	19	.29	. . .
Temporal lobe (right)	5	121/150	0.15 (−0.10 to 0.39)	.24	102.0	0	.65	. . .
Hippocampus (left)	**6**	**185/308**	**0.35 (0.11 to 0.59)**	**.0045**	**106.1**	**31**	**.16**	**<.001**
Hippocampus (right)	**6**	**185/308**	**0.29 (0.03 to 0.55)**	**.026**	**104.8**	**39**	**.10**	**.029**
			OR (95% CI)					
Any hyperintensity	5	167/277	1.81 (0.62 to 5.28)	.28	. . .	60	.04	. . .

Abbreviations: See Table 4.
[a] Boldface indicates significant differences.

and the number of measurements made. In contrast, there was a significant negative correlation, suggesting there is no consensus in one or both of these issues.

Typically, 8 regions were investigated per study, giving the probability of a type I error as 0.34 (calculation from Bonferroni equation), unless a correction for multiple comparisons is made. This estimate is an upper boundary for false-positive error rates, assuming regional brain measures are independent. Studies are not only at risk for type I errors; for example, if a study measured the volume of the lateral ventricles, which was associated with one of the largest effect sizes in the meta-analysis (effect size=0.39), and recruited the mean number of patients and controls per study calculated from the database (25 and 33 respectively), the study would have a 70% chance of making a type II error. If the effect size for lateral ventricle dilation is calculated from MRI studies only, a representative study has an 84% chance of making a type II error. Hence, a typical structural imaging study is underpowered to detect one of the largest effect sizes found in the meta-analysis. To combat these problems, studies will need to recruit larger numbers of patients and controls and have a consistent way of dealing with multiple comparisons.

Despite the aforementioned problems, recruitment size has not changed during the last 25 years and studies remain underpowered. It is possible type I errors have actually misled researchers into believing that 20 to 30 patients and controls is a sufficient sample size because previous studies have "obtained results" with these numbers of participants. For a future study to be sufficiently powered, the required number of subjects may be readily calculated from the effect sizes given in Table 3. For example, for a study to be sufficiently powered to detect a difference in lateral ventricle volume, 105 patients and 105 controls would be required (power=0.8; $\alpha = .05$, 2-tailed *t* test). The power calculations and effect sizes are based on studies included in the meta-analysis, and the prediction of required sample sizes for future studies assumes within-study heterogeneity will remain constant. However, if future studies were to minimize within-study heterogeneity through refined phenotype selection and improved imaging methods, the effect sizes may increase, leading to smaller required sample sizes. In addition, where a structure strongly correlates with age and brain volume, the required number of subjects may also be smaller because using these variables as nuisance covariates will increase the power of the analysis. Small studies are still important but should perhaps be cautious in their conclusions and combine their result with previous studies and report an "updated effect size."

COMPARISON WITH PREVIOUSLY PUBLISHED META-ANALYSES

Our study was in good agreement with previous meta-analyses of brain structure in bipolar disorder. Previously reported odds ratios of increased rates of hyperintensities among patients with bipolar disorder were 3.29[6] and 3.3,[7] which are in close agreement with the odds ratio of 3.04 calculated in this study. We extended these findings by performing meta-analyses on the location and subtype of hyperintensities. Compared with a previous meta-analysis of patients with affective disorder,[8] we found a similar effect size for increased total lateral ventricular volume among patients with bipolar disorder (d=0.42 and d=0.39, respectively). Our results also concur with a previous meta-analysis showing right lateral ventricle enlargement in bipolar disorder.[9]

In our study, patients with schizophrenia compared to bipolar disorder showed enlargement of the left lateral ventricle and third ventricle and decreased hippocampal volume. However, relatively few brain structures were included because of the small number of studies directly comparing these diagnostic groups. For a more comprehensive comparison, we compared our bipolar-control meta-analysis with a previous meta-analysis by Wright et al[26] comparing patients with schizophrenia with controls (**Figure 5**). This comparison supports our own findings as well as suggests that patients with schizophrenia show increased volume of the total and right lateral ventricle, reduced volume of the amygdala, and perhaps increased volume of the globus pallidus compared to patients with bipolar disorder. For cortical structures, both our meta-analysis and the Wright et al meta-analysis pooled studies that measured gray matter volume alone with studies that combined gray and white matter. Combining such studies may dilute the effect of regional reductions in cortical gray matter, an example being superior temporal lobe volumes in schizophrenia, where reviews by Shenton et al[164] and McCarley et al[165] have highlighted that gray matter reductions are obscured when gray and white matter are analyzed together. However, when we separated studies based on this criterion, results in our meta-analysis did not change (data not shown). Two meta-analyses of hippocampus volume in major depressive disorder[166,167] report a volumetric reduction, which contrasts with our null finding in bipolar disorder. The possible neuroprotective effects of lithium use may have masked the reduction in hippocampal volume in bipolar disorder.[19,168] To test this hypothesis, we performed a meta-regression of the proportion of patients using lithium on the effect size of total hippocampal volume. The effect was close to significant (n=4 studies; $P = .051$); as the number of patients using lithium increased, the volume of the hippocampus compared with controls also increased, supporting our hypothesis. Individual structural imaging studies in bipolar disorder that have directly investigated correlations between lithium use and hippocampus volume are equivocal, with 4 studies reporting that lithium use was associated with hippocampus enlargement,[4,148,155,156] while 2 reported no effect.[108,116]

A meta-analysis involving more studies may have increased power to detect significant differences; however, studies included may be more heterogeneous, increasing the variance and hence reducing the chance of detecting a significant difference. The rationale used for the present meta-analysis was that the advantage of including more studies outweighed the disadvantage from increased heterogeneity due to different types of measurement. Where the number of studies was large enough, we attempted subanalyses, such as volume and ratio measures of lateral ventricle volume, to reduce heterogeneity and give further specificity to the findings and also

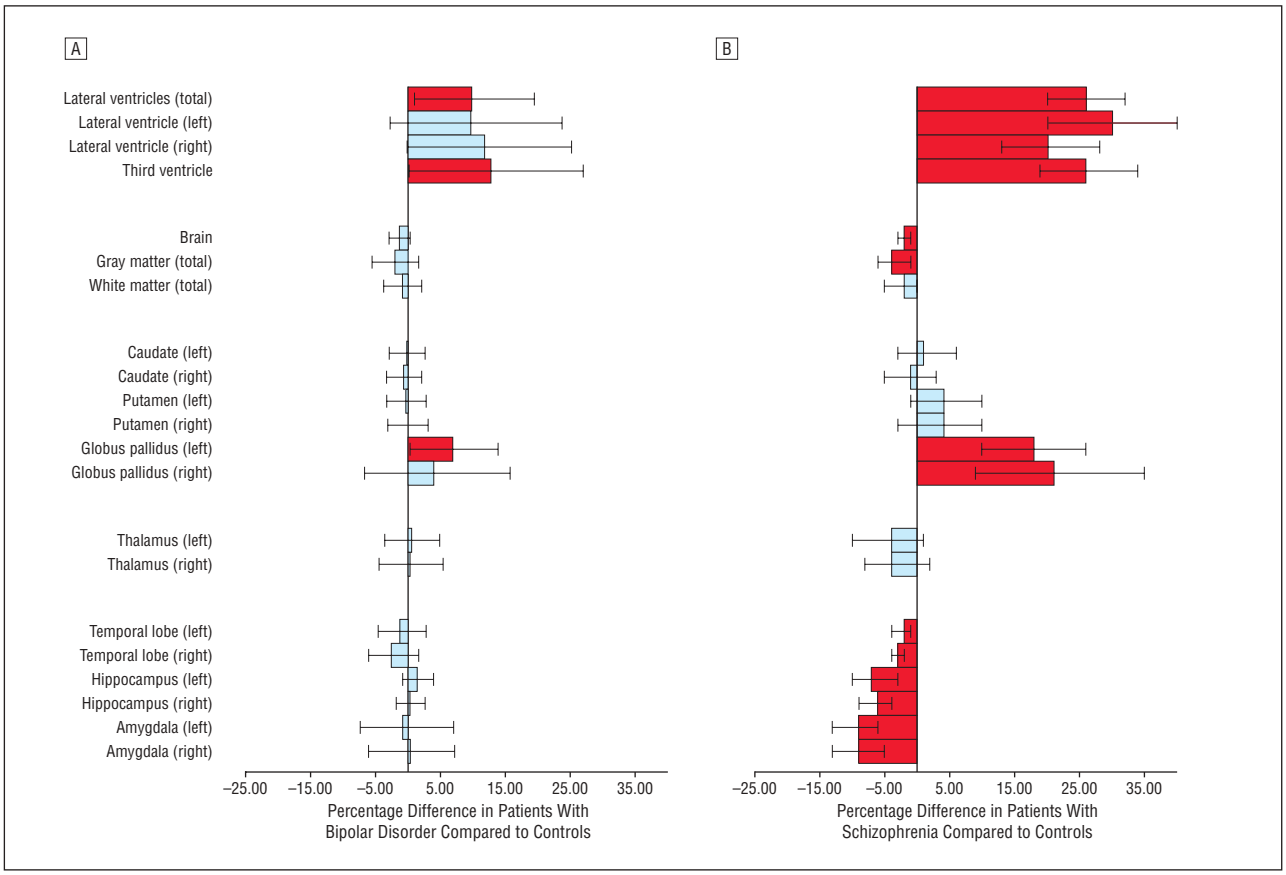

Figure 5. Comparison of our meta-analysis (A) and the meta-analysis of patients with schizophrenia by Wright et al[26] (B). Only regions investigated by both studies are shown. Computed tomographic studies have been excluded from our analysis, and effect sizes are calculated from percentage increase or decrease in structure size compared with the control group to match the methods used by Wright et al; as such, the significance of results may vary from Figure 3 (see also "Sensitivity Analysis" subsection in the text). Red bars represent significant differences, and blue bars are nonsignificant differences.

attempted to account for study heterogeneity by implementing a meta-regression analysis. Lateral ventricular volume measured using CT was associated with a larger effect size than MRI studies. This may be because older CT studies were less stringent in controlling for possible confounds, such as alcohol and drug abuse/dependence, which are relatively common in bipolar disorder[169] and are associated with brain volume change.[170] Computed tomographic studies were also more likely to report the VBR measure; because this measurement reduces variance due to brain volume, it may be more sensitive to ventricular dilation in bipolar disorder compared with absolute volume measures.

The results database and meta-analysis are publicly available on the Internet for the purpose of allowing researchers to verify the methods used, aiding upcoming studies and reviews, and enabling further meta-analyses. Customized meta-regressions may be carried out on the data by individual researchers interested in the effect of various combinations of demographic and clinical variables on a region of interest (eg, the effect of age and sex on temporal lobe volume in bipolar disorder).

In conclusion, there are robust but limited changes in brain structure in bipolar disorder and evidence that lithium medication increases gray matter volume. Without refinements in phenotypic selection and imaging methods or increased sample size, type I and type II errors will remain appreciable. Future studies would benefit by providing comprehensive patient clinical data as well as continuing to provide raw structural measures to facilitate future meta-analyses. The publicly available results database and meta-analysis from this article may prove to be a useful resource for planning future structural imaging studies.

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